PMSS Information

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Research question and objectives	The primary objective of this study is to describe the incidence of adverse events (AEs) and serious adverse events (SAEs) over a period of 12 weeks after receiving Olumiant (baricitinib) among adult Chinese patients with moderate to severe active rheumatoid arthritis. The secondary objectives are to describe the incidence of AEs and SAEs over a period of 24 weeks and to describe effectiveness and patient-reported outcomes of baricitinib in the study population.
Country(-ies) of study	China
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1. Abstract

Title

Post-Marketing Safety Study on Olumiant® (Baricitinib) Use Among Moderate to Severe Active Rheumatoid Arthritis Patients in China

Keywords

Pharmacovigilance (or drug safety), effectiveness, rheumatoid arthritis (RA), baricitinib, Janus kinase (JAK) inhibitor

Rationale and background

The data from Phase 3 clinical studies with baricitinib demonstrated the drug to be effective and generally well tolerated. In order to understand the safety data in the real world and with the aim of identifying, characterizing, or quantifying a safety hazard, confirming the safety profile of the medicinal product, the current study investigated the safety and effectiveness of baricitinib as a treatment in Chinese patients with moderate to severe active RA. This study was performed as an additional pharmacovigilance activity of the China Risk Management Plan (RMP) for baricitinib, which is required by the National Medical Products Administration (NMPA) according to local regulations.

Research question and objectives

The primary objective of the study was to describe the incidence of adverse events (AEs) and serious adverse events (SAEs) over a period of 12 weeks.

The secondary objectives were to describe the incidence of AEs and SAEs over a period of 24 weeks, and to describe the effectiveness and patient-reported outcomes (PROs) of baricitinib in the study population:

- change from baseline to Weeks 12 and 24 in 28 diarthrodial joint count (DAS28)-C-reactive protein (CRP)
- change from baseline to Weeks 12 and 24 in Simplified Disease Activity Index (SDAI) score
- change from baseline to Weeks 12 and 24 in Clinical Disease Activity Index (CDAI) score
- proportion of patients achieving DAS28-CRP <2.6 and ≤3.2 at Weeks 12 and 24, respectively
- proportion of patients achieving SDAI score ≤3.3 and ≤11 at Weeks 12 and 24, respectively
- proportion of patients achieving CDAI score ≤2.8 and ≤10 at Weeks 12 and 24, respectively
- mean duration of morning joint stiffness (MJS) in Weeks 12 and 24 as collected in electronic diaries (e-diaries)
- mean visual analogue scale (VAS) for pain in Weeks 12 and 24 as collected in e-diaries

Study design

This postmarketing safety study (PMSS) was a single country, prospective, single arm, noninterventional study designed to collect all AEs and SAEs regardless of their relatedness to baricitinib and monitor the effectiveness and PROs of baricitinib at Weeks 12 and 24.

Setting

The study was conducted in China and considered representation of Chinese patient population with moderate to severe active RA during the period 27 Aug 2020 to 25 Nov 2022.

Subjects and study size, including dropouts

The population included patients of at least 18 years age who were diagnosed with moderate to severe active RA and have been prescribed baricitinib according to the approved label in a routine clinical care setting by the investigator. At least 600 patients were required to be analysed and reported as the safety analysis population for this study. Approximately 667 patients were required to be enrolled given the expected 10% drop-out rate.

Variables and data sources

Patient demographics, diagnosis information, initial history and pre-existing conditions, study drug administration, concomitant medications, tender/swollen joint count, patient and physician global assessments, duration of MJS, pain VAS, AEs, SAEs, AEs of special interest (AESIs; serious infection, hepatotoxicity and venous thromboembolism [VTE], including deep venous thrombosis [DVT], and pulmonary embolism [PE] were considered as AESIs and were recorded in the case report form [CRF] as judged by investigators), and treatment information were collected.

Results

A total of 667 patients were enrolled in this study and the major proportion of whom were female (82.3%). Mean age was 53.3 years, and 15.9% was 65 years or older. The safety analysis population included 667 (100%) patients, and effectiveness population included 514 (77.1%) patients.

A total of 290 patients (43.5%) in the safety analysis population had at least 1 prespecified medical history or concomitant disease (which included cardiovascular disease/recent or active infections/fragility fracture/malignancy/renal impairment/hepatic impairment/allergy and VTE). Cardiovascular disease (168 patients, 25.2%) and allergy (74 patients, 11.1%) were reported by >10% of the population. A total of 436 patients (65.4%) in the safety analysis population had at least 1 other pre-existing conditions/medical history or other concomitant disease. Osteoporosis (101 patients, 15.1%) and anaemia (73 patients, 10.9%) were the preferred terms (PTs) reported by >10% of the population.

A total of 480 patients (72.0%) had been on RA medications prior to the study entry. Most of these patients had been on conventional synthetic disease modifying antirheumatic drugs (csDMARDs) (468/480 patients). Within this group of medications, methotrexate (MTX;

41.7%), leflunomide (31.3%), and hydroxychloroquine (hydroxychloroquine sulfate) (20.2%) were the most commonly reported prior RA medications. A total of 35 patients (5.2%) had been on targeted synthetic disease modifying antirheumatic drugs (tsDMARDs), and 29 patients (4.3%) had been on biologic disease modifying antirheumatic drugs (bDMARDs) prior to the study entry. A total of 579 patients (86.8%) received concomitant RA medications on entry to the study. Most of these patients were taking csDMARDs (579/580 patients). Within this group of medications, MTX (54.3%), leflunomide (35.5%), and hydroxychloroquine (hydroxychloroquine sulfate) (24.9%) were the most commonly reported concomitant RA medications.

The mean (SD) duration of RA was 86.9 (99.9) years and similar across safety analysis population and effectiveness analysis population. Duration of RA varied from 1 year to >10 years in both the populations. Approximately 22% of both the populations had RA for ≤1 year, and 27% of both the populations had RA for >10 years.

Overall mean (SD) baricitinib exposure in the safety analysis population was 143.9 (56.6) days and in the effectiveness analysis population was 164.3 (32.5) days. When considering the days of baricitinib exposure across all patients, total patient year exposure in the safety analysis population was 262.1 years and in effectiveness analysis population was 230.8 years. In the safety analysis population, 87.0% of patients were administered with 2 mg, while 7.9% with 4 mg and 5.1% with both dosages. The proportion of patients in terms of dosages of baricitinib across the safety and effectiveness populations were similar.

Safety

A total of 214 patients (32.1%; incidence rate [IR] – 165.2 and exposure adjusted incidence rate [EAIR] – 172.5) reported 329 AEs over a period of 12 weeks, and 95 patients (14.2%; IR – 64.7 and EAIR – 67.9) reported 111 AEs related to study treatment. A total of 250 patients (37.5%; IR – 119.9 and EAIR – 125.9) reported 428 AEs over a period of 24 weeks, and 120 patients (18.0%; IR – 48.1 and EAIR – 50.7) reported 147 AEs related to study treatment. Most AEs were mild or moderate in severity. The most common AEs were hepatic function abnormal, upper respiratory tract infection, and platelet count increased.

There were 2 deaths reported during the study. One patient died because of severe pneumonia, and the cause of death for the second patient was unknown. Both were >65 years with multiple concomitant diseases and had taken baricitinib 2 mg. The Investigator assessed the event of death due to pneumonia as possibly related to baricitinib, and the second event of death was assessed to be unrelated to baricitinib.

A total of 22 patients (3.3%; IR – 14.2 and EAIR – 15.0) reported 23 SAEs over a period of 12 weeks and of whom 8 patients (1.2%; IR – 5.1 and EAIR – 5.4) reported 8 SAEs related to study treatment. A total of 28 patients (4.2%; IR – 10.3 and EAIR – 10.9) reported 31 SAEs over a period of 24 weeks and of whom 10 patients (1.5%; IR – 3.6 and EAIR – 3.8) reported 10 SAEs possibly related to study treatment. The only SAEs reported by >1 patient in the population were pneumonia (4 patients, 0.6%), rheumatoid arthritis (3 patients, 0.4%), and arthralgia (2 patients, 0.3%). All the pneumonia cases were reported as possibly related to study

treatment. Other SAEs reported as possibly related to study treatment were appendicitis, arthralgia, drug-induced liver injury (DILI), influenza, otitis media, and tonsillitis (single events).

A total of 20 patients (3.0%; IR – 12.9 and EAIR – 13.5) reported 22 events that led to permanent drug discontinuation over 12 weeks. A total of 24 patients (3.6%; IR – 8.7 and EAIR – 9.2) reported 26 events that led to permanent drug discontinuation over 24 weeks. RA and arthralgia were the only events reported by at least 2 patients that led to permanent drug discontinuation over 12 weeks and 24 weeks.

A total of 6 patients (0.9%) reported SAEs within the infections and infestations system organ class (SOC), meeting International Council for Harmonisation (ICH) criteria for seriousness, such as hospitalization over 12 weeks. Only 3 serious pneumonia events of these were reported by the investigator as an AESI. A total of 8 patients (1.2%) reported SAEs within the infections and infestations SOC over 24 weeks. Appendicitis was the only additional serious event reported by the investigators as an AESI after 12 weeks until 24 weeks.

A total of 16 patients reported 17 hepatotoxicity events over 12 weeks. The events were hepatic function abnormal (14 patients), alanine aminotransferase (ALT) increased (1 patient), and DILI (1 patient). One event of DILI was an SAE; (a 63-year-old female patient with relevant medical history including fatty liver, experienced hepatic enzyme increased with peak ALT at 351 U/L [0 to 40] and aspartate aminotransferase [AST] at 172 U/L [0 to 40] on Study Day 27. Bilirubin was in normal range and was admitted to hospital. The patient did not have symptoms/signs in association with the event. There is no evidence of viral hepatitis. After corrective treatment was given to protect the liver, ALT and AST returned back to normal approximately 38 days later. Baricitinib was temporarily discontinued and restarted after. In the opinion of investigator, the event was related to the combined use of baricitinib, leflunomide, MTX, and aceclofenac). A total of 23 patients reported 26 hepatoxicity events over 24 weeks. Hepatic function abnormal (17 patients, 19 events) and DILI (2 patients, 3 events) were the events reported by at least 2 patients. No one met laboratory criteria for potential Hy's Law (ALT/AST ≥3 × upper limit of normal [ULN] and total bilirubin [TBIL] ≥2 × ULN).

No VTE event was reported during the study.

A total of 542 patients (81.2%) were <65 years, 106 patients (15.9%) were ≥65 and <75 years, and 19 patients (2.8%) were ≥75 years. Based on subgroup analyses, safety observations were generally similar between different age subgroups at 12 and 24 weeks. Incidence of SAEs was numerically higher in the ≥65-and-<75–years group (10.4% at 12 and 24 weeks) compared to <65-years (1.8% and 3.0% at 12 and 24 weeks). The ≥75-year group included too few patients (n=19) to make relevant comparisons. Incidence of AEs leading to permanent drug discontinuation was similar in the ＜65-years (2.6% and 3.0% at 12 and 24 weeks) and ≥65-and-<75–years groups (4.7% at 12 and 24 weeks). Incidence of serious infection was higher in the ≥65-and-<75–years group (1.9% at 12 and 24 weeks) compared to the ＜65-years (0.2% and 0.4% at 12 and 24 weeks). Incidence of hepatotoxicity was similar in the ＜65-years (2.2% and 3.5% at 12 and 24 weeks) and ≥65-and-<75–years groups (1.9% at 12 and 24 weeks).

Considering that the number of patients with events were small, the interpretability of data is limited.

A total of 580 patients (86.9%) received 2-mg baricitinib, 53 patients (7.9%) received 4 mg, and 34 patients (5.1%) received both dosages. Overall safety observations were similar between different dosage groups, although incidence of AEs leading to permanent drug discontinuation was numerically higher in the 4-mg–only group (7.6% at 12 and 24 weeks) compared to 2-mg only (2.8% and 3.5% at 12 and 24 weeks).

Effectiveness

For DAS28-CRP, at baseline, most patients belonged to >3.2 category (83.3%). At 12 weeks (54.2%) and 24 weeks (66.6%), more than half of the effectiveness analysis population belonged to ≤3.2. For DAS28–erythrocyte sedimentation rate (ESR), at baseline, majority of the population (86.9%) had >3.2 score and more than half of the population (58.4%) belonged to >5.1 score category. At 12 weeks, most patients belonged to >3.2 score (58.0%). At 24 weeks as well, most patients belonged to ≤3.2 score (54.0%) and >3.2 score (46.0%) categories. For SDAI, at baseline, most patients belonged to the >11.0 category (87.5%). At 12 weeks (52.3%) and 24 weeks (64.6%), more than half of the effectiveness analysis population belonged to ≤11.0. For CDAI, at baseline, most patients belonged to the >10.0 category (88.0%). At 12 weeks (50.3%) and 24 weeks (63.5%), more than half of the effectiveness analysis population belonged to ≤10.0. At baseline, mean (SD) MJS score was 44.7 (52.3). At 12 weeks, mean (SD) change from baseline was −20.6 (78.9), and at 24 weeks, mean (SD) change from baseline was −28.3 (47.0). At baseline, mean (SD) VAS score of patients' pain was 5.9 (2.0). At 12 weeks, mean (SD) change from baseline was −2.4 (2.2), and at 24 weeks, mean (SD) change from baseline was −3.0 (2.5).

Overall, baricitinib demonstrated effectiveness in reducing DAS28-ESR, CDAI, and SDAI scores, and showed to be effective when measured through the PROs (pain VAS and MJS).

The DAS28-CRP, SDAI, and CDAI scores at baseline and at 24 weeks were significantly different in the age subgroup and baseline SDAI subgroup. DAS28-CRP score at baseline was significant for tumour necrosis factor-inhibitor receiver (TNFi-IR) subgroup. All other efficacy observations were similar between the subgroups.

Discussion

This final report summarizes safety and effectiveness data from patients with moderate-to-severe RA who were prescribed baricitinib across 31 sites in China, comprising a PMSS. This PMSS programme was able to provide information on safety, effectiveness, and utilisation of baricitinib in the real-world setting.

Analysis of results from this study indicated that the safety profile of baricitinib in clinical settings was generally consistent with the safety profile observed in the clinical trial (RA-BALANCE [a Phase 3 randomised controlled trial (RCT) containing 80% Chinese population], global RA integrated safety analysis (including long-term data from nine Phase 3, Phase 2, and Phase 1b clinical trials, and 1 completed long-term extension study) and Japan all-

case postmarketing surveillance (PMS) study involving all patients with RA who started baricitinib treatment (Li Z et al. 2020, Genovese et al. 2020, Takagi et al. 2022, Taylor et al. 2021).

Around 29.5% of patients discontinued the study mainly for patient's decision (n = 101) and lost to follow-up (n = 47), which was higher than observed in the clinical trial RA-BALANCE study (<10%) (Li Z et al. 2020), but comparable to the Japan noninterventional, observational PMS study (24.8% discontinued up to Week 24) (Takagi et al. 2022).

The proportion of patients reporting AEs over 24 weeks in this PMSS (37.5%) was lower than in the RA-BALANCE study (74.5%) and similar to the incidence in Japan PMS study (26.9%) (Takagi et al. 2022). The incidence of SAEs over 24 weeks in this study (4.2%, EAIR: 10.9) was similar to that in the Japan PMS study (4.3%, IR: 13.4) and global RA integrated safety analysis 0-to-24–week placebo-controlled dataset (EAIR 9.7 for baricitinib 2 mg/EAIR 12.3 for baricitinib 4 mg) (Takagi et al. 2022, Genovese et al. 2020). Incidence of AEs leading to drug permanent discontinuation over 24 weeks in this study (EAIR 9.2) was similar to that in the global RA integrated safety analysis 0-to-24–week placebo-controlled dataset (EAIR 10.8 for baricitinib 2 mg/EAIR 10.6 for baricitinib 4 mg) (Genovese et al. 2020).

Deaths reported in this study (2 patients [0.3%], IR 0.7) occurred in patients >65 years with multiple concomitant diseases. The IR of death was similar to the IR in the global RA integrated safety analysis treated with baricitinib 4 mg for 24 weeks (0.6) and the IR in the Japan PMS (0.4%, IR:0.85); it was within the reported IR of 1.5 to 2.4/100 patient-years in epidemiological studies of RA (Taylor et al. 2021).

The most common AEs in this study (for 24 weeks) were hepatic function abnormal (3.3%), upper respiratory tract infection (2.7%), and platelet count increased (2.4%). The common AEs (≥1% of population) reported were in line with the safety profile of baricitinib as presented in the current label in China. Terms from Adverse Reactions in Table 1 of current Chinese label observed in this study were also within the corresponding frequency range mentioned in the label.

A total of 8 patients (1.2%) reported SAE within infections and infestations SOC, similar with the proportion reported in Japan PMSS or clinical trial. However, only 4 of these were reported by the investigator as an AESI (serious events of influenza, otitis media and tonsillitis, and 1 pneumonia were not reported as AESIs).

Incidence of hepatotoxicity (3.4%, IR 8.5) was similar with Japan PMS study (2.8%, IR 7.2). Postbaseline ALT/AST change to ≥3 × ULN (1.2% and 0.9%, respectively) were similar to the results observed in clinical trials (1.5% for ALT ≥3 × ULN) (Smolen et al 2019) and Japan PMS study result (0.8% and 0.7%, respectively) over 24 weeks (Takagi et al. 2022). Though 2 AEs with reported term as DILI observed in the study, no one met potential Hy's law criteria (ALT/AST ≥3 × ULN, TBIL ≥2 × ULN) or reported symptoms/signs in association with the event.

No VTE or major adverse cardiovascular events (MACE; including myocardial infarction, cardiovascular death, and stroke) occurred in this study. Only 1 malignancy of thyroid cancer (53-year-old female with medical history of thyroid nodules, not related to baricitinib as judged by the investigator) occurred in the study. However, these findings should be interpreted with caution given that exposure (24-week observation period) and sample size of this study (N=667) is limited to observe these AEs with a long latency time.

Safety subgroup analysis for this study suggested that the safety profile of baricitinib 2 mg was generally similar to 4 mg. Incidence of AEs leading to permanent drug discontinuation was higher in the 4-mg–only group compared to 2-mg–only, but as these dose groups were not randomized and may differ in disease severity and risk factors, one cannot interpret this comparison. Safety observations were generally similar between different age subgroups at 12 and 24 weeks, although patients from ≥65 years groups showed numerically differences with some events. These findings should be interpreted with caution, given that sample size of other groups was limited and imbalance. In summary, no clinically meaningful differences were noted in AEs by age and dosage.

Given the broad inclusion criteria of the present study, these real-world findings support the safety profile of baricitinib reported in the randomized Phase 3 trials. No new safety signals were observed, and no additional risk minimization activities are required for Chinese patients.

In this study, patients showed improvements in disease activity and PROs from baseline to Week 24 during baricitinib treatment. Similar to the observations from BALANCE study and the Japan PMS study, with baricitinib treatment, in this study, DAS28-CRP scores kept reducing from baseline to Week 24. The proportion of patients with SDAI score ≤11 at Week 24 in the BALANCE study was 27.6% (Li Z et al. 2020) and in the current study it was 64.6%. The proportion of patients with CDAI score ≤10 in the BALANCE study at Week 24 was 26.9% (Li Z et al. 2020) and in the current study it was 63.5%. However, these findings should be interpreted with caution, given that almost 30% of all patients discontinued the study, mainly for patient's decision and lost to follow-up. Some of these patients may have stopped because of lack of effectiveness. Similar improvements in achieving remission/low disease activity (LDA) were also observed in Japan PMS study with a discontinuation around 25% (Takagi et al. 2022).

Subgroup analysis for effectiveness suggested that baseline characteristics did not substantially affect treatment response. Significant differences were observed in the following: age subgroup for DAS28-CRP scores at baseline and change at 24 weeks, SDAI score at baseline and change at 24 weeks and CDAI score at baseline; baseline SDAI subgroup for DAS28-CRP, SDAI score and CDAI score at baseline and change at 24 weeks, and TNFi-IR for DAS28-CRP score at baseline. All other effectiveness results across patients with different gender, age, disease duration, dosage, previous tumour necrosis factor inhibitor (TNFi) use, were similar.

Conclusion

This observational study was conducted to investigate and describe the incidence of AEs and SAEs and to monitor effectiveness among adult Chinese patients with moderate to severe active RA after receiving baricitinib for a period of 12 and 24 weeks.

The study results did not identify any new safety concern or signal. Baricitinib was effective in reducing disease activity and improving PROs in the real world.

The real-world usage of baricitinib confirmed both safety and effectiveness of baricitinib when used up to 24 weeks in Chinese patients with moderate to severe active RA.

Marketing Authorisation Holder(s)

Eli Lilly and Company

Names and affiliations of principal investigators

There were 31 sites and principal investigators.

Leading Principal Investigator: Xiaofeng Zeng, Peking Union Medical College Hospital

2. List of abbreviations

Term	Definition
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
bDMARD	biologic disease modifying anti-rheumatic drug
BMI	body mass index
CCP	cyclic peptide containing citrulline
cDMARD	conventional disease modifying anti-rheumatic drug
CI	confidence interval
csDMARD	conventional synthetic disease modifying anti-rheumatic drug
CDAI	Clinical Disease Activity Index
CPK	creatine phosphokinase
Cr	creatinine
CREDIT	Chinese registry of rheumatoid arthritis
CRF	case report form
CRP	C-reactive protein
CTCAE	common terminology criteria for adverse events
DAS28	Disease Activity Score modified to include the 28 diarthrodial joint count
DILI	drug-induced liver injury
DMARD	disease-modifying antirheumatic drug
DVT	deep venous thrombosis
EAIR	exposure adjusted incidence rate

eCRF	electronic case report form
EDC	electronic data capture
e-diaries	electronic diaries
ESR	erythrocyte sedimentation rate
ICF	informed consent form
ICH	International Council for Harmonisation
IR	incidence rate
JAK	janus kinase
LDA	low disease activity
LS	least-squares
LYM	lymphocyte count
MACE	major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
MJS	morning joint stiffness
MMRM	mixed-effects model of repeated measures
MTX	methotrexate
NEUT	absolute neutrophil count
nmiss	number of data missing patients
NMPA	National Medical Products Administration
PE	pulmonary embolism
PMS	postmarketing surveillance
PMSS	postmarketing safety study
PPD	purified protein derivative
PRO	patient-reported outcome
PT	preferred term
PYE	patient-years of exposure
Q1 and Q3	interquartile range

QD	once daily
RA	rheumatoid arthritis
RCT	randomised controlled trial
RF	rheumatoid factor
RMP	Risk Management Plan
SAE	serious adverse event
SAP	Statistical Analysis Plan
SDAI	Simplified Disease Activity Index
SJC	swollen joint count
SOC	system organ class
TB	tuberculosis
TBIL	total bilirubin
TEAE	treatment-emergent adverse event
TJC	tender joint count
TNF	tumour necrosis factor
TNFi	tumour necrosis factor inhibitor
TNFi-IR	tumour necrosis factor-inhibitor receiver
tsDMARD	targeted synthetic disease modifying antirheumatic drugs
URTI	upper respiratory tract infections
ULN	upper limit of normal
UTI	urinary tract infections
VAS	visual analogue scale
VTE	venous thromboembolism
WBC	white blood cell

3. Investigators

Leading Principal Investigator

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A complete list of investigators is provided in Annex 4.

4. Other responsible parties

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5. Milestones

Milestone	Planned date	Actual date
Start of data collection	31 Jun 2020	27 Aug 2020
End of data collection	31 Aug 2022	25 Nov 2022
Study progress report 1	31 Jan 2021	07 Apr 2021
Study progress report 2	31 Jan 2022	08 Apr 2022
Final report of study results	31 Dec 2022	See Page 1

The start of data collection means the date that the first study subject was enrolled to the study, the end date of data collection means the date from which the analytical dataset was completely available. Study progress report refers to the Periodic Safety Update Report (PSUR).

6. Rationale and background

Baricitinib is an orally available, selective JAK inhibitor (JAK1/JAK2) (Fridman et al. 2010) approved in Europe, United States, Japan, and in many other countries for the treatment of patients with moderate to severe active RA. In June 2019, Olumiant® (baricitinib) 2 mg QD was approved in China for the treatment of moderate to severe active RA in adult patients who have responded inadequately to or who are intolerant to 1 or more DMARDs. In December 2020, baricitinib 4 mg QD was approved for the treatment of moderate to severe active RA in adult patients who have an inadequate response to initiating 2 mg QD for 3 months, or adult patients who have had an inadequate response to TNFi therapy. Baricitinib may be used in combination with MTX or other non–biological DMARDs according to approved China label.

In the completed Phase 3 studies, compared to placebo as well as approved oral cDMARDs and injectable bDMARDs, which represent the established standards of care in RA, baricitinib demonstrated clear, consistent, and clinically meaningful improvements across all relevant domains of efficacy related disease activity, physical function, radiographic progression of structural joint damage, and relevant PRO measures (Taylor et al. 2017, Genovese et al. 2016). Treatment effects were robust as measured by sensitivity analyses of primary efficacy endpoints and across subgroups. In addition, the results observed in study RA-BALANCE (I4V-CR-JAGS, a Phase 3 RCT containing 80% Chinese population) are consistent with those observed in the global Phase 3 study for the majority of efficacy measures and IRs of SAEs, including serious infections were similar among patients receiving either baricitinib or placebo.

For the integrated analysis of data from the RA clinical development program, consistent with the immunomodulatory mode of action of baricitinib, treatment-emergent infections were more commonly observed in baricitinib-treated patients. The most frequently reported infections were URTI, viral URTI, UTI, bronchitis, pharyngitis, gastroenteritis, herpes zoster, influenza, sinusitis, and herpes simplex. The majority of the commonly reported AEs were anticipated events in the RA population (for example, infections, including URTI) or laboratory abnormalities consistent with the pharmacology of JAK inhibitors (for example, increases in CPK and lipids, including total cholesterol, low density lipoprotein-cholesterol, and high density lipoprotein-cholesterol). Of these AEs, URTIs (including viral URTIs and bronchitis), herpes zoster, lipid increases, and increased CPK were considered ADRs. In the RA clinical development program, no increased risk for SAEs (including serious infections, malignancies, or MACE) was observed for either the baricitinib 4-mg or 2-mg group compared to placebo control. The safety profile of baricitinib at both the 2-mg and 4-mg QD dose has remained consistent with long-term treatment. Deaths have been reported infrequently in patients taking baricitinib and are not considered a risk with baricitinib use (Lilly 2019).

In order to understand the safety data in the real world and with the aim of identifying, characterizing or quantifying a safety hazard, confirming the safety profile of the medicinal product, Study I4V-GH-B021 investigated the safety and effectiveness of baricitinib as a treatment in Chinese patients with moderate to severe active RA. This study performed as an additional pharmacovigilance activity of the China RMP for baricitinib, which is required by the

NMPA according to local regulations. In Study I4V-CR-JAGS, 59.5% and 75.9% of Chinese patients reported at least 1 TEAE through Weeks 12 and 24, respectively (Lilly 2018). Thus, B021 is designed to capture majority of the events during an observation period of 12 and 24 weeks. In addition, according to a real-world large-scale study in China, the median treatment duration of bDMARD therapies was less than 24 weeks, maybe because of poor socioeconomic condition and/or poor patient compliance (An et al. 2017). Therefore, in this study, AEs were collected over a period of 12 and 24 weeks.

This is a single-country, single arm, prospective, noninterventional PMSS conducted in Chinese RA patients in clinical practice setting to describe the incidence of AEs and SAEs, including the incidence of AEs/SAE related to baricitinib as assessed by investigator, and monitor the effectiveness and PROs of baricitinib at Weeks 12 and 24.

7. Research question and objectives

Primary objective

The primary objective of this study was to describe the incidence of AEs and SAEs over a period of 12 weeks.

Secondary objectives

The secondary objectives were to describe the incidence of AEs and SAEs over a period of 24 weeks and to describe the effectiveness and PROs of baricitinib in the study population

- change from baseline to Weeks 12 and 24 in DAS28-CRP
- change from baseline to Weeks 12 and 24 in SDAI score
- change from baseline to Weeks 12 and 24 in CDAI score
- proportion of patients achieving DAS28-CRP <2.6 and ≤3.2 at Weeks 12 and 24, respectively
- proportion of patient achieving SDAI score ≤3.3 and ≤11 at Weeks 12 and 24, respectively
- proportion of patients achieving CDAI score ≤2.8 and ≤10 at Weeks 12 and 24, respectively
- mean duration of MJS in Weeks 12 and 24 as collected in e-diaries
- mean VAS for pain in Weeks 12 and 24 as collected in e-diaries.

8. Amendments and updates

Not applicable.

9. Research methods

9.1. Study design

This PMSS was a single-country, single arm, prospective, noninterventional, single arm study designed to collect all AEs and SAEs regardless of their relatedness to baricitinib over a period of approximately 12 weeks and 24 weeks. Based on collected AE and SAE data, the incidence of TEAEs and SAEs, including relatedness to administration of baricitinib, was evaluated.

This PMSS was also designed to monitor the effectiveness and PROs of baricitinib by evaluating change from baseline to Weeks 12 and 24 in DAS28-CRP, SDAI score, and CDAI score; proportion of patients achieving DAS28-CRP <2.6 and ≤3.2, SDAI score ≤3.3 and ≤11, and CDAI score ≤2.8 and ≤10 at Weeks 12 and 24; and mean duration of MJS and mean VAS for pain assessed in Weeks 12 and 24 as collected in the e-diaries, among patients in China with moderate to severe active RA receiving treatment with baricitinib.

The observation period for each case was either until 30 days after the last dose, or until patients switched to a new RA medication (in case patients stopped taking baricitinib before 24 weeks), or up to 24 weeks.

9.2. Setting

Primary data collection for the study was through the CREDIT platform, which includes both physician evaluation and PROs records.

First patients were enrolled from 27 Aug 2020, and the analytical dataset was completely available on 25 Nov 2022.

9.3. Subjects

The patient population for this study consisted of patients who were diagnosed with moderate to severe active RA and initiated treatment with baricitinib according to the approved label. There were no other treatment groups for the study.

The decision to enrol a patient in the study was at the discretion of the investigator, based on the inclusion/exclusion criteria.

The study team selected sites in consideration of Chinese moderate to severe active RA patient population representation.

Patients were eligible to be included in the study if they met all the following inclusion criteria and none of the exclusion criteria.

Inclusion criteria

- were at least 18 years old
- diagnosed with moderate to severe active RA
- prescribed with baricitinib according to the approved label by the investigator in the routine care of the patient

- provided written consent to the release of their data after being informed of the study.

Exclusion criteria

- were simultaneously participating in a different study that included a treatment intervention and/or an investigational drug
- contradicted for the use of baricitinib according to the approved label.

9.4. Variables

Table 9.1 shows data collection schedule.

Table 9.1 Data Collection Schedule

Procedure	Baseline Visit 1 Day 0 Predose	Recommend Postbaseline Visit 2 Day 28±14 (4±2 wks)	Recommend Postbaseline Visit 3 Day 84±14 (12±2 wks)	Recommend Postbaseline Visit 4 Day 168±14 (24±2 wks)
Confirmation of eligibility and consent to release information	X			
Demographics	X			
Diagnosis	X			
Initial history/pre-existing conditions	X			
Treatment information	X	X	X	X
Concomitant medications	X	X	X	X
Effectiveness assessment	X		X	X
Safety assessment		X	X	X

Abbreviations: eCRF = electronic case report form; wks = weeks.
Notes:

- Baseline was the visit where the patient's data was collected prior to the administration of first dose of study drug.
- Name of the investigational institute and investigator, contract date with the investigator, and patient identification number were recorded in each eCRF.

9.4.1. Baseline variables

The following variables were collected during baseline:

- Demographics information (including, but not limited to initials, year of birth/age, sex [female/male], BMI [derived from weight and height])
- Disease diagnosis data: information including but not limited to date of initial diagnosis of moderate to severe active RA, RF (from the medical record at the time of enrolment)
- Initial history/pre-existing conditions information: including but not limited to previous history of DMARDs for RA (name of treatment, start date, and stop date), prespecified

medical history/concomitant disease terms include cardiovascular disease, recent or active infection, fragility fracture, malignancy, renal impairment, hepatic impairment, allergy and VTE (diagnosis, start date, and end date, if the term is renal impairment or hepatic impairment, the severity will be recorded), and other pre-existing conditions, medical histories and concomitant diseases other than those that are prespecified

- Concomitant medication information (at baseline and at post-baseline visits): medication name, dose and frequency, indication for use, start and stop date

9.4.2. Exposure

Baricitinib treatment information was collected at each visit and included dose and frequency, start date, and stop date, and reason for dose change or discontinuation.

9.4.3. Safety variables

Safety assessment information collected during the study is presented in Table 9.1.

The following safety variables were evaluated during the study:

- AEs

AEs are any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment.

All AEs will be collected. These include suspected drug interactions and events associated with other drugs that are suspected of significantly affecting a patient's management, including those that could cause death, danger to life, admission to hospital, prolongation of hospitalization, persistent or significant disability/incapacity, and birth defects. The MedDRA SOC and PT, classified from verbatim terms, will be used for coding the AE terms whether serious or nonserious.

AEs were continually collected during the whole study period except for baseline visit, so the AEs collected in this study were all TEAEs.

- AEs related to study treatment as judged by the Investigator

These are AEs suspected to be causally related to the medicinal product.

Relationship of AE to baricitinib was recorded as 'Yes' or 'No' in CRF directly.

- SAEs

The study personnel reported to Lilly or its designee any protocol-defined SAE arising in temporal association with the Lilly product(s) under evaluation within 24 hours of awareness of the event via a sponsor-approved method. A protocol-defined SAE is any AE from this study that results in one of the following outcomes:

- Death
- Initial or prolonged inpatient hospitalization

- A life-threatening experience (immediate risk of dying)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect, or
- Is an important medical event that could not be immediately life-threatening or result in death or hospitalization but could jeopardize the patient or could require intervention to prevent one of the other outcomes listed above. Previously (prior to start of baricitinib) planned surgeries were not reported as SAEs unless the underlying medical condition has worsened during treatment with baricitinib.

SAEs were recorded by investigator in the CRF directly.

- AESIs

As defined in the China RMP (version 1.0), important identified/potential risk included serious infections, hepatotoxicity, foetal malformation following exposure in utero, and VTE. Consistent with RMP, the followings were considered as AESIs:

  - Serious infection
  - Hepatotoxicity
  - VTE including DVT and PE

AESIs were recorded in the CRF as 'Whether it is an adverse event of special interest' = 'Yes'

- AEs leading to drug adjustment

AEs leading to drug adjustment included AEs leading to dose increased/dose reduced/dose interrupted.

- Severity of AEs

For each AE, the severity level was recorded according to the investigator's perceived severity of the event (mild, moderate, or severe).

Regardless of their severity or relatedness to baricitinib, any AEs and SAEs arising in temporal association with baricitinib were collected and recorded by the investigators using the Safety Assessment Section in the electronic CRF throughout the whole observation period.

9.4.4. Effectiveness variables

The following efficacy variables were assessed during the study:

- Disease Activity Score modified to include the 28 diarthrodial joint count (DAS28-CRP)

The DAS28-CRP is a measure of disease activity in 28 joints that consists of a composite numeric score of the following variables: TJC, SJC, CRP, and Patient's Global Assessment of Disease Activity (Vander Cruyssen et al. 2005). The 28 joints to be examined and assessed as tender or not tender for TJC and as swollen or not swollen for SJC include: 2 shoulders, 2 elbows, 2 wrists, 10 metacarpophalangeal joints, 10 proximal interphalangeal joints, and 2 knees (Smolen et al. 1995).

Remission is defined as a DAS28-CRP score of <2.6. LDA is defined as a DAS28-CRP score of ≥2.6 to ≤3.2.

- SDAI score

The SDAI is a tool for measurement of disease activity in RA that integrates measures of physical examination, acute phase response, patient self-assessment, and evaluator assessment. The SDAI is calculated by adding together scores from the following assessments (Aletaha and Smolen 2005):

- Number of swollen joints (0 to 28)
- Number of tender joints (0 to 28)
- CRP in mg/dL (0.1 to 10.0)
- Patient global assessment of disease activity on VAS (0 to 10.0)
- Physician (evaluator) global assessment of disease activity on VAS (0 to 10.0)

Remission is defined as an SDAI score of ≤3.3. LDA is defined as a SDAI score of >3.3 to ≤11.0 (Singh et al. 2016).

- CDAI

The CDAI is a tool for measurement of disease activity in RA allowing for immediate scoring because it does not use a laboratory result (Aletaha and Smolen 2005). The CDAI is calculated by adding together scores from the following assessments:

- Number of swollen joints (0 to 28)
- Number of tender joints (0 to 28)
- Patient global assessment of disease activity on VAS (0 to 10.0)
- Physician (evaluator) global assessment of disease activity on VAS (0 to 10.0)

Remission is defined as a CDAI score of ≤2.8. LDA is defined as a CDAI score of >2.8 to ≤10.0 (Singh et al. 2016).

- MJS

The duration of MJS was reported by the patients as the length of time in hours and minutes that their MJS lasted each day.

- Pain VAS

The pain VAS is a single-item PRO. It's a continuous scale comprised of a horizontal line, usually 10 centimetres in length, anchored by "no pain" (score of 0) and "pain as bad as it could be" or "worst imaginable pain" (score of 10.0). Patients were asked to report pain intensity in the last 24 hours and mark on the electronic scale. The score automatically transferred based on a presetting ratio on the electronic system.

9.5. Data sources

This was a site-based prospective study, analysing identified patient-level data. All patients were collected from hospitals and were followed based on protocol requirements. All variables were

collected through a data platform named "Chinese registry of rheumatoid arthritis (CREDIT)" as a part of routine clinical data collection (Yu et al. 2018). The CREDIT, which was established in November 2016, is the first nationwide online multi-centre registry for RA in China. It was set up as a registry and has been installed on the investigators' clinical computers. Until 2022, RA patients who fulfilled the 2010 ACR/EULAR classification criteria for RA were recruited into the registry by their rheumatologists from more than 500 clinical centres in 31 provinces across China (Jiang et al. 2022). All the hospitals were Class A tertiary hospitals, with independent departments of rheumatology and immunology, and the doctors participating in the evaluation were rheumatic specialists. Safety and effectiveness data were recorded by investigators in the CREDIT. PROs data were collected in e-diaries through an application installed on patients' smartphones and automatically transferred to the CREDIT.

9.6. Bias

This section highlights 2 common sources of bias seen in observational studies, including mitigating measures used to minimize or rationale for why it is unlikely to impact the current study.

Patient selection bias

In order to reduce potential bias in patient selection, participating physicians located in different cities were asked to invite all patients from CREDIT platform who met the study criteria to participate in the study.

Because this is an observational study that patients' treatments were not intervened, it was highly possible that comparatively higher rates of loss-of-follow-up could be observed than in clinical trials.

Information bias

Information bias arises when any information used in a study (exposure, outcome, or covariates) is either measured or recorded inaccurately. In this study, information on the disease status, safety endpoints, and treatment received has a high probability of accuracy because it is directly provided by treating physicians.

9.7. Study size

The study was conducted based on CREDIT, which include around 80,000 registered RA patients and an estimate of 20,000 more patients were enrolled during this period. Moreover, around 75% RA patients in China was reported as moderate to severe in severity (Yu et al. 2018). Considering the proportion of patients applicable to JAK inhibitors, the number of potential users of baricitinib, which was the target population of this study, was estimated at approximately 562. The sample size was considered focusing on serious infection. The incidence of serious infection of 24 week was 1.4% in Clinical Trial I4V-CR-JAGS (I4V-CR-JAGS Clinical Study Report). Assuming that the incidence of the study was the same of 1.6% based on the trial finding, a sample size of 530 patients would provide the width of 95% CI with 0.02, such as 95% CI (0.4%, 2.4%). The narrow width of 95% CI would be used to estimate incidence of AEs of the total population with an accurate statistical judge. Therefore, it was considered that

600 patients were needed for a final sample size of safety analysis for this PMSS. This would require enrolling 667 patients considering an assumptive safety follow-up drop-out rate of 10%.

9.8. Data transformation

For time conversion, 1 month equals 30.4375 days and 1 year equals 365.25 days.

BMI (kg/m^2) = Weight (kg) / height $(m)^2$

The duration of RA (months) = (Date of informed consent – date of diagnosis of RA) / 30.4375.

Months from the onset date of RA to ICF (months) = (Date of informed consent –the onset date of RA) / 30.4375.

Days from first study drug to completion or early termination of the study = completion or early termination date in study termination page – the date of first study drug + 1.

9.9. Statistical methods

9.9.1. Main summary measures

Statistical descriptive methods

For continuous data, descriptive statistics were calculated as number of nonmissing patients, number of missing patients (nmiss), mean, standard deviation (SD), median, Q1, Q3, minimum, and maximum. The minimum and maximum had the same decimal place as the raw data, while mean, median, Q1 and Q3 had 1 more decimal place, and standard deviation had 2 more decimal places. For categorical data, the frequency and/or percentage of patients in each category was presented. Counts that were zero were displayed as "0". Percentages were based on nonmissing data unless otherwise specified. Two-sided 95% CI was calculated for the estimated incidence wherever appropriate. If the calculated value was greater than or equal to 0.01, 2 decimal places were retained. Otherwise, 3 decimal places were retained. Two-sided significance level of 0.05 was used. For p-values, 4 decimals were retained.

Statistical test wherever required

For continuous variable, paired t test or Wilcoxon signed-rank test, analysis of variance test, Wilcoxon rank sum test, or Kruskal-Wallis test were used. For categorical variables, McNemar test, Bowker's symmetry test, Chi-square test, or Fisher's exact test was used. P-values were rounded to 4 decimal places. '<.0001' was displayed when the p-value was less than 0.0001 and '>.9999' was displayed when the p-value was greater than 0.9999.

Statistical analysis was performed under the bilateral significance level of 0.05 whenever required.

Statistical programming used SAS™ 9.4 or higher version.

The baseline values for all variables (if applicable) were defined as the latest measurement or examination result before the first dose of study drug.

Generally, statistical description by visits was performed on the scheduled visits unless it was specified otherwise. For shift of clinical evaluation of safety data, for example, abnormal with/without clinical significance of laboratory test, the data on scheduled and unscheduled visits were all included in the analyses.

Patient screening ID (USUBJID) was used as a unique identifier in all listing.

9.9.2. Main statistical methods

9.9.2.1. Patient disposition and protocol deviation

The following summaries were tabulated:

- Number and percentage of patients screened and reasons for screen failure
- Number and percentage of patients who were enrolled into the study and completed the study
- Number and percentage of patients who prematurely withdrew from the study and reasons of discontinuation

Detailed information regarding disposition of each patient were listed.

Flow chart of patient disposition was shown.

All protocol deviations were also be listed by patient.

9.9.2.2. Analysis datasets

For all enrolled patients, the number of patients in each analysis population was summarized together with the number of patients excluded from each analysis population and the corresponding reasons.

Detailed information of analysis populations was listed by patient.

Safety analyses population

The safety population consisted of all patients who took at least 1 dose of baricitinib as prescribed by the investigator in the routine care of the patient and provided safety information.

Effectiveness analyses population

The effectiveness analysis population consisted of all patients included in the safety analyses population, who participated in the follow-up visit within the protocol-defined visit window, thus having a baseline and at least 1 postbaseline effectiveness observation. If data were missing or if a patient discontinued from the study, there was no imputation applied.

Patients who had been administered baricitinib for less than 10 weeks had to be excluded from the effectiveness analysis set.

9.9.2.3. Demographics and baseline characteristics

Demographics and baseline characteristics were performed on the safety analyses population and effectiveness analyses population, unless expressly stated otherwise.

Demographics

Demographics, including age, gender, height, weight, BMI, and smoking history, were summarized using descriptive statistics. Age and BMI were summarized as both continuous and categorical variables. The categories of age were 18 to 34 years, 35 to 44 years, 45 to 64 years, 65 to 74 years, and ≥75 years. The categories of BMI were <18.5 kg/m^2, ≥18.5 to <24 kg/m^2, ≥24 to <28 kg/m^2, and ≥28 kg/m^2.

Detailed information of demographic was listed by patient.

Diagnosis information of RA

Number and percentage of patients who met the ACR1987/ACR/EULAR 2010 criteria, number of items met or the number of points for each patient, months from the onset date of RA to ICF, and the duration of RA (also category by ≤1 year, >1 to ≤3 years, >3 to ≤10 years, and >10 years) were summarized using descriptive statistics.

Detailed diagnosis information of RA was listed by patient.

Prespecified medical history and concomitant disease

Number and percentage of patients with at least 1 prespecified medical history and concomitant disease, which included cardiovascular disease/recent or active infections/fragility fracture/malignancy/renal impairment/hepatic impairment/allergy and VTE, were summarized overall and for each kind of specific disease. Number and percentage of patients in each severity (mild, moderate, severe) of renal and hepatic impairment were also presented. Detailed information was listed by patient.

Other pre-existing conditions/medical history and concomitant disease

Number and percentage of patients who had any allergy, family history, experienced any historical illnesses, pre-existing conditions, or past surgeries, and had any concomitant disease other than those in prespecified medical history were summarized. All the terms of other pre-existing conditions/medical history and concomitant disease were coded using the latest version of MedDRA. All pre-existing conditions and medical history were also summarized by SOC and PT. Because the start and end date of some TB were unknown, these were additionally classified and merged with analysis datasets in the form of external data.

Detailed information of pre-existing conditions and medical history were listed by patient.

Chest radiography

Detailed information of chest radiography (if available) was listed by patient.

Tuberculosis test

The results of PPD skin test and T-Spot TB test were summarized. Detailed information of TB test (if available) was listed by patient.

Baseline DAS 28/CDAI/SDAI

Baseline DAS 28-CRP, DAS 28-ESR, CDAI, and SDAI were summarized using descriptive statistics for continuous variable.

Baseline DAS28-CRP/DAS28-ESR/SDAI/CDAI were summarized for safety analyses population as both continuous variables and categorical variables whenever applicable. The categories for these variables were as following: DAS28-CRP and DAS28-ESR (<2.6, ≥2.6 to ≤3.2, >3.2 to ≤5.1, >5.1, ≤3.2, and >3.2), SDAI (≤3.3, >3.3 to ≤11.0, >11.0 to ≤26.0, >26.0, ≤11.0, and >11.0), CDAI (≤2.8, >2.8 to ≤10.0, >10.0 to ≤22.0, >22.0, ≤10.0, and >10.0).

Baseline key indicator

Baseline key indicators (CRP, ESR, RF, and anti-CCP) were summarized using descriptive statistics for continuous variable.

9.9.2.4. Prior and concomitant medications

Prior and concomitant medications were coded by the latest version of the WHO Drug Dictionary. Prior and concomitant medications were summarized by ATC classification and WHO Drug PT, respectively. The summary was sorted in decreasing order of percentage of ATC classification firstly and then sorted in decreasing order of percentage of drug name in safety analyses population. Some RA medications of special interest were summarized, including bDMARDs and tsDMARDs. All the bDMARDs and tsDMARDs medication will be additionally classified as prior or concomitant medication and merged with analysis datasets in the form of external data. Detailed information of prior and concomitant medications was listed by patient.

9.9.2.5. Safety analyses

Analysis was performed on the safety analyses population.

Detailed information of all AEs was listed. Detailed information of AEs later than 24 weeks after first dose date was listed separately by patient.

9.9.2.5.1. Primary safety endpoint

The EAIR was calculated as the number of patients with an event per 100 patient-years of overall baricitinib exposure time. The IRs will be calculated as the number of patients with an event per 100 patient-years of observation time.

The number of events, number of patients, percentage, IR, and EAIR of AEs/SAEs over a period of 12 weeks was summarized. The 95% CIs, which were based on Poisson distribution, around the IR and EAIR were also reported.

All the terms of AEs/SAEs over a period of 12 weeks were coded using the latest version of the MedDRA. All AEs and SAEs over a period of 12 weeks were also summarized by SOC and PT.

AEs/SAEs over a period of 12 weeks were summarized by severity. In the table, the number of events, number of patients, and percentage were summarized. In the AEs/SAEs summary by patients, the worst severity for the same SOC and PT were used for each patient. In the

AEs/SAEs summary by events, all AEs/SAEs were presented. Summarized AEs/SAEs were sorted by descending overall percentage regarding SOC and PT within.

AEs/SAEs over a period of 12 weeks were also summarized by the relatedness to administration of baricitinib. In the table, the number of events, number of patients, and percentage were summarized. Summarized AEs/SAEs were sorted by descending overall percentage regarding SOC and PT within.

9.9.2.5.2. Secondary safety endpoint

The number of events, number of patients, percentage, IRs, and EAIR of AEs/SAEs over a period of 24 weeks were summarized. The 95% CIs around the IR and EAIR were also reported. The calculation formulae of the 95% CIs around the IR and EAIR were similar to the primary safety endpoints.

All the terms of AEs/SAEs over a period of 24 weeks were coded using the latest version of the MedDRA. All AEs and SAEs over a period of 24 weeks were also summarized by SOC and PT.

AEs/SAEs over a period of 24 weeks were summarized by severity. In the table, the number of events, number of patients, and percentage were summarized. In the AEs/SAEs summary by patients, the worst severity for the same SOC and PT were used for each patient. In the AEs/SAEs summary by events, all AEs/SAEs were presented. AEs/SAEs summarized were sorted by descending overall percentage regarding SOC and PT within.

AEs/SAEs over a period of 24 weeks were also summarized by the relatedness to administration of baricitinib. In the table, the number of events, number of patients, and percentage were summarized. AEs/SAEs summarized were sorted by descending overall percentage regarding SOC and PT within.

9.9.2.5.3. Other kinds of AEs over a period of 12/24 weeks

The percentage, IRs, and EAIR of the following kind of AEs were calculated. The calculation formulae were similar to the primary and secondary safety endpoints.

- AEs related to study treatment as judged by the investigator over a period of 12/24 weeks
- SAEs related to study treatment as judged by the investigator over a period of 12/24 weeks
- AESIs over a period of 12/24 weeks
- AESIs related to study treatment as judged by the investigator over a period of 12/24 weeks
- SAEs with special interest over a period of 12/24 weeks
- AEs leading to drug adjustment over a period of 12/24 weeks
- AEs leading to drug permanent discontinuation over a period of 12/24 weeks.

Analyses of the above were similar to the primary safety endpoints (Section 9.9.2.5.1).

9.9.2.5.4. Exposure

Intended baricitinib exposure days and actual baricitinib exposure days, and total patient year exposure were summarized using descriptive statistics.

Detailed information of exposure was listed by patient.

9.9.2.5.5. Laboratory test

The laboratory tests were summarized using descriptive statistics for continuous variable by visit, including white blood cell, haemoglobin, platelet count, neutrophils, LYM, ALT, AST, ALP, TBIL, Cr, CPK, and so on. Various units of a continuous variable were converted to the same unit before analysis.

A shift table was also provided to summarize the shift between baseline grades and worst postbaseline grades. These laboratory tests in unscheduled visits were included in the summary of shift table. The grades for above laboratory tests are listed in the SAP.

The change of grade (decreased, same, increased, from <Grade 3 to ≥Grade 3, from <K × ULN to ≥K × ULN where K× stands for a specific times of ULN such as 5 × ULN) between baseline value and minimum or maximum value of all postbaseline visits was summarized for the above laboratory tests. These laboratory tests in unscheduled visits were included in these summary tables.

Coagulation tests were summarized using descriptive statistics for continuous variable by visit. Urinalysis and hepatitis were summarized using change from baseline value to worst case of all postbaseline visits.

Detailed information of laboratory tests was listed by patient. Patients with abnormal laboratory tests were listed in the listings following the corresponding summary tables.

9.9.2.6. Effectiveness analyses

9.9.2.6.1. DAS28-CRP score

At baseline and at Weeks 12 and 24, the DAS28-CRP score was summarized using descriptive statistics. Change from baseline to Weeks 12 and 24 in the DAS28-CRP score was also summarized and compared using paired t test or Wilcoxon signed-rank test.

A frequency table was provided to show the frequency in each category of the DAS28-CRP score (<2.6, ≥2.6 to ≤3.2, >3.2 to ≤5.1, >5.1, ≤3.2 and >3.2) at each visit.

Additionally, the MMRM analysis was used to present the LS mean of the DAS28-CRP during 12 and 24 weeks; for the change from baseline value of effectiveness measures by the scheduled week(s), the MMRM was applied by using the effectiveness measure as the response variable, the fixed effects including categorical week and the continuous fixed covariates of baseline DAS28 score and baseline DAS28 score-by-week-interaction, to estimate the difference from baseline across postbaseline visits. An unstructured covariance structure was used to model the within-patient errors. LS mean and 95% CI at the scheduled week(s) was provided.

9.9.2.6.2. SDAI score

At baseline and at Weeks 12 and 24, the SDAI score was summarized using descriptive statistics. Change from baseline to Weeks 12 and 24 in the SDAI score was also summarized and compared using paired t test or Wilcoxon signed-rank test.

A frequency table was provided to show the frequency in each category of SDAI score (≤3.3, >3.3 to ≤11.0, >11.0 to ≤26.0, >26.0, ≤11.0 and >11.0) at each visit. Additionally, the MMRM analysis was applied to the SDAI score to present the LS mean of the SDAI score during 12 and 24 weeks.

9.9.2.6.3. CDAI score

At baseline and at Weeks 12 and 24, the CDAI score was summarized using descriptive statistics. Change from baseline to Weeks 12 and 24 in the CDAI score was also summarized and compared using paired t test or Wilcoxon signed-rank test.

A frequency table was provided to show the frequency in each category of the CDAI score (≤2.8, >2.8 to ≤10.0, >10.0 to 22.0, >22.0, ≤10.0 and >10.0) at each visit. Additionally, the MMRM analysis was applied to the CDAI score to present the LS mean of the CDAI score during 12 and 24 weeks.

9.9.2.6.4. MJS

At baseline and at Weeks 12 and 24, MJS (minutes) was summarized using descriptive statistics. Change from baseline to Weeks 12 and 24 in MJS (minutes) was also summarized and compared using paired t test or Wilcoxon signed-rank test.

A TJC and SJC was summarized using descriptive statistics.

9.9.2.6.5. VAS score for pain

At Baseline and at Weeks 12 and 24, the VAS score (VAS score of patients' pain, VAS score of overall disease status of patients, VAS score of overall disease status of doctors) was summarized using descriptive statistics. Change from baseline to Weeks 12 and 24 in the VAS score was also summarized and compared using paired t test or Wilcoxon signed-rank test.

9.9.2.6.6. Other analyses

At baseline and at Weeks 12 and 24, the DAS28-ESR score was summarized using descriptive statistics. Change from baseline to Weeks 12 and 24 in DAS28-ESR score was also summarized and compared using paired t test or Wilcoxon signed-rank test.

A frequency table was provided to show the frequency in each category of the DAS28-ESR score (<2.6, ≥2.6 to ≤3.2, >3.2 to ≤5.1, >5.1, ≤3.2 and >3.2) at each visit.

At baseline and at Weeks 12 and 24, key indicators (CRP, ESR, RF, and anti-CCP) were summarized using descriptive statistics. Change from baseline to Weeks 12 and 24 was also summarized.

9.9.2.7. Subgroup analyses

For effectiveness purpose, demographics, RA diagnosis, drug dosages, DAS28-CRP, SDAI score, and CDAI score will be analysed for the following subgroups:

- Gender subgroups (Male, Female)
- Age subgroups (<65 years, ≥65 and <75 years, ≥75 years)
- Baseline SDAI subgroups (<Q1, ≥Q1 and <Q3, ≥Q3)
- RF and anti-CCP subgroups (both negative, any positive)
- TNF-IR subgroups (yes, no)
- Dosage subgroups (2 mg only, 4 mg only, both dosages)
- RA duration subgroups (≤1 year, >1 and ≤5 years, >5 and ≤10 years, >10 years).

For the TNF-IR subgroups, all the patients with prior or concomitant use of following agents were considered as yes subgroup: TNF receptor 2 –igg, TNF alpha inhibitors, Enbrel® (etanercept), Humira® (adalimumab), Remicade® (infliximab), Cimzia® (certolizumab pegol), and Simponi® (golimumab).

For safety purpose, demographics, RA diagnosis, drug exposure, AE summary, AESI summary, and AE summary by SOC and PT were analysed for the following subgroups:

- Age subgroups (<65 years, ≥65 and <75 years, ≥75 years)
- Drug dosage subgroups (2 mg only, 4 mg only, both dosages)
- Renal impairment subgroups (yes, no) (only for AE summary).

9.9.2.8. Periodic analyses

A periodic analysis was conducted 1 year after first patient visit.

Because the first patient was enrolled on 27 Aug 2020, the cut-off date of the periodic analysis was set as 27 Aug 2021. All patients enrolled after the cut-off date were not analysed. For patients enrolled before the cut-off date, the visits, including all data belonging to this visit, were not analysed when the visit dates were later than the cut-off date. AEs, medications, or any other data with a start date later than the cut-off date were not analysed.

9.9.3. Missing values

As a general rule, missing data values were not imputed unless otherwise specified.

The missing date of an AE was imputed as follows. The imputed date of an AE was only used to classify the AE, and the original incomplete or missing dates were presented in the listings.

The original incomplete or missing start dates of AE were imputed as below:

- Missing day, year, and month before the year and month of first dose: the last day of the month was used.
- Missing day, year, and month same as the year and month of first dose: the first dose date was used.
- Missing day, year, and month after the year and month of first dose: the first day of the month was used.

- Missing day and month, year before the year of first dose: “31 Dec” was used.
- Missing day and month, year same as the year of first dose: the first dose date was used.
- Missing day and month, year after the year of first dose: “01 Jan” was used.
- Completely missing: the first dose date was used.

The original incomplete or missing end dates of AE were imputed as below:

- Only day was missing: the last day of the month was used.
- Missing day and month: “31 Dec” was used.
- Completely missing: end date was not imputed

If the imputed start date was after the imputed end date, the imputed end date was used to impute the start date.

The incomplete or missing RA diagnosis date, RA onset date, first start date of baricitinib, last end date of baricitinib, and discontinuation date of baricitinib were imputed as below when no confliction was found. The imputed date was only used to derive the variable. The original incomplete or missing dates were presented in the listings.

- Missing day: the first day of the month was used.
- Missing day and month: “01 Jan” was used.
- Completely missing: date was not be imputed.

9.9.4. Sensitivity analyses

Not applicable. No sensitivity analyses were performed for this study.

9.9.5. Amendments to the statistical analysis plan

The SAP Version 1.0 dated 11 Oct 2021 was updated to Version 2.0 dated 25 Nov 2022 and the following key updates were made:

- The observation periods of Weeks 12 and 24 were modified.
- Subgroup analyses were added.
- ADR were changed to AE related to study treatment judged by investigator.
- The decimal places of derived results were changed.

The SAP Version 2.0 dated 25 Nov 2022 was updated to Version 3.0 dated 02 Dec 2022 and the following key update was made:

- The upgrading changed the description about the rule of classification of prior and concomitant medication.

9.10. Quality Control

Data quality control was performed on 30 sites (which have enrolled at least 1 patient) by qualified designated personnel.

To ensure accurate, complete, and reliable data, Lilly or its representatives did the following:

- Provided instructional material to the study sites, as appropriate

- Sponsored a start-up training session to instruct the investigators and study coordinators. This session gave instructions on the protocol, the completion of the eCRFs, and study procedures.
- Made periodic visits to the study site
- Was available for consultation and stayed in contact with the study site personnel by mail, telephone, and/or fax
- Reviewed and evaluated eCRF data and used standard computer edits to detect errors in data collection
- Conducted a quality review of the database

In addition, Lilly or its representatives could periodically check a sample of the patient data recorded against source documents at the study site. The study could have been audited by Lilly or its representatives, and/or regulatory agencies at any time. Investigators were given notice before an audit occurred.

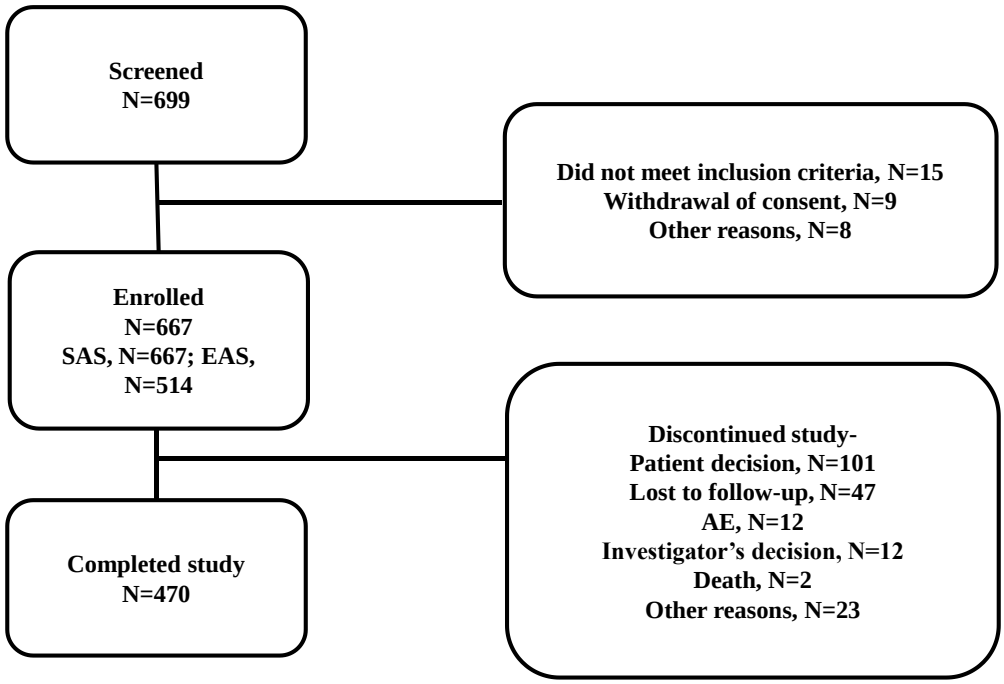
To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the investigator kept records of clinical notes and patient medical records as original source documents for the study. If requested, the investigator provided the sponsor, applicable regulatory agencies, and applicable ethical review boards with direct access to original source documents.

10. Results

10.1. Participants

Overall, 699 patients were consented for participation in this study of whom, 667 patients were enrolled (Table ANN. 1, Figure 10.1) from 31 sites in 17 provinces of China. A total of 470 (70.5%) patients completed the 24 weeks observational periods. Of the 197 (29.5%) patients who discontinued the study, patient's decision (101 patients, 51.3%), lost to follow-up (47 patients, 23.9%), and other reasons (23 patients, 11.7%) were reported by >10% of patients. All other reasons were reported by <7% of patients.

The definitions of analyses populations are provided in Section 9.9.2.2.



Abbreviations: AE = adverse event; EAS = efficacy analysis set; N = Number of patients; SAS = safety analysis set.
Sources: Table ANN. 1.

Figure 10.1 Patient disposition.

The safety analysis population included 667 (100%) patients and effectiveness population included 514 (77.1%) patients (Table ANN. 1). A total of 153 (22.9%) patients were excluded from the effectiveness analysis population because of lack of effectiveness outcomes after study treatment (113 patients, 73.9%) and study treatment was less than 10 weeks (101 patients, 66.0%).

A total of 29 (4.3%) patients reported at least 1 protocol deviation; 17 patients (58.6%) had problems with ICF and 9 patients (31.0%) had missing visits (Table ANN. 2).

10.2. Descriptive data

10.2.1. Demographics

As shown in Table 10.1, the major proportion of patients were female (82.3%). The average age of the study population was 53.3 years.

A detailed summary of demographic characteristics for safety and effectiveness analysis populations is provided in Table ANN. 4 and Table ANN. 5, respectively.

Table 10.1. Demographic Characteristics – Safety Analysis Population

		Safety Analyses Population (N=667)
Age (years)	n (nmiss)	667 (0)
	Mean (Std)	53.25 (12.51)
	Median (Q1, Q3)	54.00 (46.00, 62.00)
Age category (%)	18-34	61 (9.15%)
	35-44	92 (13.79%)
	45-64	389 (58.32%)
	65-74	106 (15.89%)
	≥75	19 (2.85%)
	Total	667 (100.00%)
Sex	Male	118 (17.69%)
	Female	549 (82.31%)
	Total	667 (100.00%)
BMI (kg/m^2)	n (nmiss)	666 (1)
	Mean (Std)	22.32 (3.42)
	Median (Q1, Q3)	21.84 (19.84, 24.24)
BMI category (kg/m^2)	<18.5	76 (11.41%)
	≥18.5-<24	399 (59.91%)
	≥24-<28	151 (22.67%)
	≥28	40 (6.01%)
	Total	666 (100.00%)
	Missing	1

Abbreviations: BMI = body mass index; N = total number of patients; n = number of patients with data; nmiss = number of data missing patients; Std = standard deviation; Q1 and Q3 = interquartile range.
Note: The percentage denominator is the number of patients with non-missing value.
Source: Table ANN. 4.

10.2.2. Medical history and concomitant medications

10.2.2.1. Prespecified medical history and concomitant disease

A total of 290 patients (43.5%) in the safety analysis population had at least 1 prespecified medical history or concomitant disease. Cardiovascular disease (168 patients, 25.2%) and allergy (74 patients, 11.1%) were reported by >10% of the population (Table ANN. 10).

A summary of prespecified medical history and concomitant disease for effectiveness analysis population is provided in Table ANN. 11. A detailed summary of prespecified concomitant disease in both safety analysis population and effectiveness analysis population is provided in Table ANN. 8 and Table ANN. 9, respectively. A detailed summary of prespecified medical history in both safety analysis population and effectiveness analysis population is provided in Table ANN. 6 and Table ANN. 7.

10.2.2.2. Other pre-existing conditions

A total of 436 patients (65.4%) in the safety analysis population had at least 1 other pre-existing condition/medical history or other concomitant disease. Osteoporosis (101 patients, 15.1%), and anaemia (73 patients, 10.9%) were the PTs reported by >10% of the population (Table ANN. 16).

A summary of other pre-existing conditions/medical history and other concomitant diseases for effectiveness analysis population is presented in Table ANN. 17. A detailed summary of pre-existing condition/medical history in both safety analysis population and effectiveness analysis population is provided in Table ANN. 12 and Table ANN. 13, respectively. A detailed summary of other concomitant disease in both the safety analysis population and effectiveness analysis population is provided in Table ANN. 14 and Table ANN. 15, respectively.

10.2.2.3. Prior and concomitant medications

Prior medications

Overall, 535 patients (80.2%) in the safety analysis population had been taking at least 1 prior medication. The most commonly received (>30% of the population) prior medications belonged to the below listed groups of medications, and the top 3 medication names taken by the patients are also listed below (Table ANN. 18):

- antineoplastic and immunomodulating agents (72.6%)
  - MTX (41.7%)
  - leflunomide (31.3%)
  - iguratimod (12.4%)
- alimentary tract and metabolism (44.7%)
  - alfacalcidol (15.1%)

  - calcitriol (13.2%)
  - calcium carbonate and vitamin d3 (7.1%)
- musculoskeletal system (44.1%)
  - methylene diphosphonate (12.4%)
  - total glucosides of white paeony (10.3%)
  - celecoxib (6.8%)
- systemic hormonal preparations, excluding sex hormones and insulins (30.6%)
  - methylprednisolone (13.5%)
  - prednisone acetate (11.1%)
  - prednisone (2.3%)

Concomitant medications

The majority of the population (94.8%) was taking at least 1 concomitant medication (Table ANN. 20).

The most commonly received (>30% of the population) concomitant medications belonged to the below listed groups of medications, and the top 3 medication names taken by the patients are also listed below (Table ANN. 20):

- antineoplastic and immunomodulating agents (87.3%)
  - MTX (54.3%)
  - leflunomide (35.5%)
  - hydroxychloroquine sulfate (14.5%)
- alimentary tract and metabolism (69.1%)
  - calcitriol (23.4%)
  - alfacalcidol (22.6%)
  - calcium carbonate and vitamin d3 (14.1%)
- musculo-skeletal system (57.1%)
  - total glucosides of white paeony (13.2%)
  - methylene diphosphonate (10.3%)
  - celecoxib (7.8%)
- blood and blood forming organs (41.1%)
  - folic acid (32.7%)
  - mecobalamin (3.6%)
  - folate (1.1%)
- systemic hormonal preparations, excluding sex hormones and insulins (40.5%)
  - methylprednisolone (19.3%)
  - prednisone acetate (15.0%)
  - prednisone (3.3%)

A summary of concomitant medications for the effectiveness analyses population is provided in Table ANN. 21.

Specific prior and concomitant medications

A total of 480 patients (72.0%) had been on RA medications prior to the study entry (Table ANN. 22). Most of these patients had been on csDMARDs (468/480 patients). Within this group of medications, MTX (41.7%), leflunomide (31.3%), and hydroxychloroquine (hydroxychloroquine sulfate) (20.2%) were the most commonly reported prior RA medications. A total of 35 patients (5.3%) had used tsDMARDs other than baricitinib, and 29 patients (4.4%) had used bDMARDs.

A total of 579 patients (86.8%) received concomitant RA medications on entry of the study (Table ANN. 22). Most of these patients were taking csDMARDs (579/580 patients). Within this group of medications, MTX (54.3%), leflunomide (35.5%), and hydroxychloroquine (hydroxychloroquine sulfate) (24.9%) were the most commonly reported concomitant RA medications.

The summary of specific prior and concomitant medication for effectiveness analyses population is provided in (Table ANN. 23).

10.2.2.4. Tuberculosis testing

A total of 6 patients (0.9%) and 81 patients (12.1%) from the safety analysis population had the PPD skin test and T-spot TB test performed, respectively. Four out of 6 patients reported negative PPD results and 2 out of 6 patients reported positive PPD results.

A total of 71/81 (87.7%) patients reported negative T-spot TB results, and 10/81(12.3%) patients reported positive T-spot TB results (Table ANN. 24).

Results of TB testing in effectiveness analysis population is summarized in Table ANN. 25.

10.2.3. Baseline characteristics

10.2.3.1. Rheumatoid arthritis history

The mean (SD) duration of RA was 86.9 (99.9) months in the safety analysis population.

The mean (SD) duration of RA was similar across safety analysis population and effectiveness analysis population. Duration of RA varied from 1 year to >10 years in both of the populations (Table 10.2).

Table 10.2. Rheumatoid Arthritis Diagnosis

		Safety Analyses Population (N=667)	*Effectiveness Analyses Population (N=514)*
Months from the onset date of RA to ICF (months)	n (nmiss)	667 (0)	514 (0)
	Mean (Std)	101.96 (104.28)	101.47 (104.61)
	Median	62.39	62.56
	Q1, Q3	23.46, 145.91	22.83, 143.74
	Min, Max	0, 623.67	0, 623.67
Duration of RA (months)	n (nmiss)	667 (0)	514 (0)

		Safety Analyses Population (N=667)	*Effectiveness Analyses Population (N=514)*
	Mean (Std)	86.91 (99.94)	88.02 (100.98)
	Median	46.88	48.65
	Q1, Q3	13.86, 129.08	13.80, 128.69
	Min, Max	0, 623.67	0, 623.67
	≤1 year	144 (21.59%)	113 (21.98%)
	>1-≤3 years	140 (20.99%)	103 (20.04%)
	>3-≤10 years	203 (30.43%)	159 (30.93%)
	>10 years	180 (26.99%)	139 (27.04%)
	Total	667 (100.00%)	514 (100.00%)
Meeting the ACR/EULAR 2010 criteria for RA diagnosis and number of points	Yes	667 (100.00%)	514 (100.00%)
	n (nmiss)	667 (0)	514 (0)
	Mean (Std)	8.34 (1.51)	8.42 (1.47)
	Median	8.00	8.00
	Q1, Q3	7.00, 10.00	7.00, 10.00
	Min, Max	6, 10	6, 10
	Total	667 (100.00%)	514 (100.00%)

Abbreviations: ICF = informed consent form; Max = maximum; Min = minimum; N = total number of patients; n = number of patients with data; nmiss = number of data missing patients; Std = standard deviation; Q1 and Q3 = interquartile range; RA = rheumatoid arthritis.

Notes: The percentage denominator is the number of patients with non-missing value.
The duration of RA (months) = (Date of informed consent – date of diagnosis of RA) / 30.4375, round to 2 decimal places. Months from the onset date of RA to ICF (months) = (Date of informed consent –the onset date of RA) / 30.4375, round to 2 decimal place.

10.2.3.2. PDAS28/CDAI/SDAI

At baseline, the mean (SD) DAS28-CRP score was 4.6 (1.9). Most patients in the safety analysis population had their scores in the range of >3.2 to ≤5.1 (41.6%) and >5.1 (40.8%) (Table ANN. 26).

At baseline, the mean (SD) DAS28-ESR score was 5.2 (2.0). Most patients in the safety analysis population had their scores in the range of >3.2 to ≤5.1 (27.7%) and >5.1 (58.5%) (Table ANN. 26).

At baseline, the mean (SD) SDAI score was 30.8 (18.4). Most patients in the safety analysis population had their scores in the range of >11.0 to ≤26.0 (29.8%) and >26.0 (56.0%) (Table ANN. 26).

At baseline, the mean (SD) CDAI score was 28.7 (17.1). Most patients in the safety analysis population had their scores in the range of >22.0 (61.6%) (Table ANN. 26).

Baseline DAS28/CDAI/SDAI scores for the effectiveness analyses population is provided in (Table ANN. 27).

10.2.3.3. Key indicator

At baseline, the mean (SD) values of ESR, CRP, RF, and anti-CCP are listed below (Table ANN. 28):

- ESR – 44.4 (29.9)
- CRP – 23.4 (30.9)
- RF – 243.1 (400.2)
- Anti-CCP – 308.1 (508.6)

Baseline key indicators are summarized for the effectiveness analysis population in Table ANN. 29.

10.3. Outcome data

Section 10.4 includes summaries of main study results.

10.4. Main results

10.4.1. Study drug exposure

Overall mean (SD) baricitinib exposure in the safety analysis population was 143.9 (56.6) days (Table ANN. 30) and in the effectiveness analysis population was 164.3 (32.5) days (Table ANN. 31). Total patient year exposure in the safety analysis population was 262.1 and in effectiveness analysis population was 230.8.

A total of 580 patients (87.0%) were administered with 2 mg, 53 patients (7.9%) were administered with 4 mg, and 34 patients (5.1%) received both dosages of baricitinib (Table ANN. 30). The proportion of patients who were administered with 2 mg, 4 mg, and both dosages of baricitinib across the 2 populations were similar.

10.4.2. Safety

10.4.2.1. Adverse events

A total of 214 patients (32.1%; IR – 165.2 and EAIR – 172.5) reported 329 AEs over a period of 12 weeks, and 95 patients (14.2%; IR – 64.7 and EAIR – 67.9) reported 111 AEs as related to study treatment. Twenty-two patients (3.3%; IR – 14.2 and EAIR – 15.0) reported 23 SAEs during the 12-week period, and 8 patients (1.2%; IR – 5.1 and EAIR – 5.4) reported SAEs as related to the study treatment (Table 10.3).

A total of 250 patients (37.5%; IR – 119.9 and EAIR – 125.9) reported 428 AEs over a period of 24 weeks, and 120 patients (18.0%; IR – 48.1 and EAIR – 50.7) reported 147 AEs related to study treatment. Twenty-eight patients (4.2%; IR – 10.3 and EAIR – 10.9) reported 31 SAEs during the 24-week period and 10 patients (1.5%; IR – 3.6 and EAIR – 3.8) reported SAEs related to the study treatment (Table 10.3).

Two patients (0.3%; IR – 0.7 and EAIR – 0.8) died during the study.

Table 10.3 AE Summary – Safety Analyses Population

	Safety Analyses Population (N=667)						
	Event	*n*	*Patient-year of Observation Time*	*Patient-year of Exposure Time*	*Percentage and 95% CI*	*Incidence Rate (per 100Patient-years) and 95% CI*	*EAIR (per 100 Patient-years) and 95% CI*
AEs over a period of 12 weeks	329	214	129.56	124.04	32.08% (28.55%, 35.77%)	165.17 (143.78, 188.85)	172.52 (150.18, 197.25)
AEs over a period of 24 weeks	428	250	208.55	198.58	37.48% (33.80%, 41.28%)	119.88 (105.47, 135.69)	125.89 (110.77, 142.51)
AEs related to study treatment as judged by the investigator over a period of 12 weeks	111	95	146.87	139.99	14.24% (11.68%, 17.13%)	64.68 (52.33, 79.07)	67.86 (54.90, 82.96)
AEs related to study treatment as judged by the investigator over a period of 24 weeks	147	120	249.25	236.65	17.99% (15.15%, 21.12%)	48.14 (39.92, 57.57)	50.71 (42.04, 60.63)
Death	2	2	276.44	261.30	0.30% (0.04%, 1.08%)	0.72 (0.09, 2.61)	0.77 (0.09, 2.76)
SAEs over a period of 12 weeks	23	22	154.74	147.03	3.30% (2.08%, 4.95%)	14.22 (8.91, 21.53)	14.96 (9.38, 22.65)
SAEs over a period of 24 weeks	31	28	270.94	256.72	4.20% (2.81%, 6.01%)	10.33 (6.87, 14.94)	10.91 (7.25, 15.76)
SAEs related to study treatment as judged by the investigator over a period of 12 weeks	8	8	156.38	148.32	1.20% (0.52%, 2.35%)	5.12 (2.21, 10.08)	5.39 (2.33, 10.63)
SAEs related to study treatment as judged by the investigator over a period of 24 weeks	10	10	275.17	260.30	1.50% (0.72%, 2.74%)	3.63 (1.74, 6.68)	3.84 (1.84, 7.07)
AEs leading to drug adjustment over a period of 12 weeks	36	30	152.98	145.21	4.50% (3.05%, 6.36%)	19.61 (13.23, 28.00)	20.66 (13.94, 29.49)
AEs leading to drug adjustment over a period of 24 weeks	45	39	267.44	253.47	5.85% (4.19%, 7.91%)	14.58 (10.37, 19.94)	15.39 (10.94, 21.03)

	Safety Analyses Population (N=667)						
	Event	*n*	*Patient-year of Observation Time*	*Patient-year of Exposure Time*	*Percentage and 95% CI*	*Incidence Rate (per 100Patient-years) and 95% CI*	*EAIR (per 100 Patient-years) and 95% CI*
AEs leading to drug permanent discontinuation over a period of 12 weeks	22	20	155.38	148.18	3.00% (1.84%, 4.59%)	12.87 (7.86, 19.88)	13.50 (8.24, 20.85)
AEs leading to drug permanent discontinuation over a period of 24 weeks	26	24	274.44	260.79	3.60% (2.32%, 5.31%)	8.75 (5.60, 13.01)	9.20 (5.90, 13.69)

Abbreviations: AE = adverse event; CI = confidence interval; EAIR = exposure adjusted incidence rate; N = number of patients in population; n = the number of patients with events; SAE = serious adverse event; SAP =Statistical Analysis Plan.

Notes: The number of events for each patient counts the events that happened during the 12-week/24-week observation time.

The percentage denominator is the number of analyses population and the numerator is the number of patients with corresponding events.

The percentage of AEs/SAEs over a period of 12/24 weeks = Number of patients with at least 1 AE/SAE over a period of 12/24 weeks ÷ number of patients in safety analyses population × 100, results round to 2 decimal places.

The incidence rates of AEs/SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least 1 AE/SAE over an observation period of 12/24 weeks ÷ observation time of AEs/SAEs over a period of 12/24 weeks (years) × 100, results round to 2 decimal places. The EAIR of AEs/SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least 1 AE/SAE over an observation period of 12/24 weeks ÷ overall exposure time of AEs/SAEs over a period of 12/24 weeks (years) × 100, results round to 2 decimal places.

The calculation of observation time and exposure time could refer to definition in the main body of SAP.

AEs related to study treatment as judged by the investigator are the AEs whose relationship with baricitinib are not ‘’N’’. Drug adjustment includes dose increase, dose reduction, and temporary discontinuation.

Death is from the SAE for which the reason is death or the AE whose outcome is fatal or death recorded in the page of study termination.

AEs by maximum severity

12-week period

Overall, 214 patients (32.1%) reported 329 events in the 12-week period. A total of 136 patients reported events that were mild in severity (20.4%) (Table ANN. 32). Most commonly reported (>5% of the population) events belonged to the following SOCs, and the top 3 PTs are listed below (Table ANN. 33):

- Infections and infestations (7.3%)
  - Upper respiratory tract infection (2.5%)
  - Urinary tract infection (1.6%)
  - Pneumonia (0.9%)
- Investigations (7.3%)
  - Platelet count increased (2.1%)
  - White blood cell count increased (1.3%)
  - LYM decreased (1.0%)

The PTs reported by >2% of the population were hepatic function abnormal (2.7%), upper respiratory tract infection (2.5%), and platelet count increased (2.1%).

A total of 20 patients (3.0%) reported severe AEs. Rheumatoid arthritis (4 patients, 0.6%) and pneumonia (3 patients, 0.4%) were the only PTs reported by more than 1 patient.

24-week period

Overall, 250 patients (37.5%) reported 428 events in the 24-week period. A total of 158 patients reported events that were mild in severity (23.7%) (Table ANN. 34). The most commonly reported (>5% of the population) events belonged to the following SOCs, and the top 3 PTs are listed below (Table ANN. 35):

- Infections and infestations (9.6%)
  - Upper respiratory tract infection (2.7%)
  - Urinary tract infection (2.3%)
  - Pneumonia (1.4%)
- Investigations (9.3%)
  - Platelet count increased (2.4%)
  - White blood cell count increased (1.5%)
  - LYM decreased (1.5%)
- Metabolism and nutrition disorders (5.3%)
  - Hyperlipidaemia (1.7%)
  - Hyperuricaemia (0.9%)
  - Decreased appetite (0.8%)

The PTs reported by >2% of the population in the 24-week period were hepatic function abnormal (22 patients, 3.3%), upper respiratory tract infection (18 patients, 2.7%), platelet count

increased (16 patients, 2.4%), urinary tract infection (15 patients, 2.2%), and anaemia (14 patients, 2.1%) (Table ANN. 35).

A total of 25 patients (3.7%) reported severe AEs. Rheumatoid arthritis (4 patients, 0.6%), pneumonia (3 patients, 0.4%), and arthralgia (2 patients, 0.3%) were the PTs reported by more than 1 patient.

10.4.2.2. Adverse events related to study treatment

12-week period

Overall, 95 patients (14.2%) reported 111 AEs related to study treatment in the 12-week period as judged by the investigator. A total of 60 patients reported AEs related to study treatment were mild (9.0%) in severity (Table ANN. 36). Most commonly reported AEs related to study treatment belonged to the SOCs (reported by >2% patients) infections and infestations (33 patients, 5.0%) and investigations (17 patients, 2.6%), and AEs related to study treatment reported by >1% patients were hepatic function abnormal (12 patients, 1.8%), upper respiratory tract infection (9 patients, 1.4%), and urinary tract infection (8 patients, 1.2%) (Table ANN. 37). The only severe AE related to study treatment reported by more than 1 patient was pneumonia (3 patients, 0.5%) (Table ANN. 36).

24-week period

Overall, 120 patients (18.0%) reported 147 AEs related to study treatment in the 24-week period as judged by the investigator. A total of 76 patients reported AEs related to study treatment were mild (11.4%) in severity (Table ANN. 38). Most commonly reported AEs related to study treatment belonged to SOCs (reported by >2% of patients) infections and infestations (6.9%), investigations (3.3%), and hepatobiliary disorders (2.7%), and AEs related to study treatment reported by >1% patients were hepatic function abnormal (2.3%), urinary tract infection (1.8%), upper respiratory tract infection (1.4%), pneumonia (1.2%), anaemia (1.2%), and herpes zoster (1.1%) (Table ANN. 39). The only severe AE related to study treatment reported by more than 1patient was pneumonia (3 patients, 0.5%) (Table ANN. 38).

10.4.2.3. Deaths

There were 2 deaths reported during the study:

0076-010001

A 73-year-old male patient with low BMI (15.9) died from severe pneumonia 69 days after receiving baricitinib 2 mg orally, daily for the treatment of RA. Relevant medical history included hypoalbuminaemia, hyperglobulinemia, duodenal ulcer, anaemia, and increased tumour marker. Concomitant medications included leflunomide, MTX, diclofenac sodium, and tripterygium wilfordii. On Study Day 66, the patient underwent a computerized tomography that revealed: double lung emphysema with double lung agical bullae, signs of interstitial pneumonia in the lower lobes of both lungs, and middle lobes of right lung. A SAE of severe pneumonia was reported. On Day 68, the patient was transferred to a different hospital because of “dyspnea, cough, and aggravation for 3 days” with poor general condition, coma states. Admission

diagnosis included: 1. Severe pneumonia; 2. Failure respiratory; 3. Hypoglycaemic coma; 4. Liver failure; 5. Hepatic encephalopathy; 6. Metabolic acidosis; 7. Rheumatoid arthritis; 8. Duodenal ulcer; 9. Hyperlactacidaemia; and 10. Troponin increased. The patient was treated with meropenem to anti-infection, compound glycyrrhizin to protect liver, methylene blue to improve vascular paralysis, acid-suppressive drugs to protect stomach and maintain balance of water salt electrolyte, and nutrition support; the patient had continuous anuria, high blood potassium and poor coagulation function, and received continuous renal replacement therapy, plasma infusion, and fibrinogen infusion. The patient died 1 day after. Cause of death: circulatory failure, sepsis, multiple organ failure, and severe pneumonia. In opinion of study investigator, the association with baricitinib could not be ruled out, so it was judged to be possible.

0223-011020

Unexplained death was reported in a 69-year-old male patient receiving baricitinib 2 mg orally, daily for the treatment of RA. Medical history included cerebral infarction, coronary artery disease, angina unstable, arrhythmia, ventricular extrasystoles, ventricular tachycardia, type 2 diabetes mellitus, lipoma, gastric ulcer, and duodenal ulcer haemorrhage. The patient was in poor condition. On Study Day 10, the patient had difficulty eating (related to gastric ulcer combined with duodenal ulcer) and decided to discontinue all drugs and refused to return to hospital for treatment and was gradually unable to eat. Twenty-one days after receiving first dose of baricitinib 2 mg and 11 days after last dose of baricitinib, the patient died at home (unexplained death), without relevant examination. An autopsy was not performed, hence the cause of death was unclear. In the opinion of the study investigator the event of death was unrelated to study drug baricitinib.

10.4.2.4. SAEs

12-week period

A total of 22 patients (3.3%) reported 23 SAEs over a period of 12 weeks and of whom 8 patients reported 8 SAEs related to study treatment (Table ANN. 40, Table ANN. 41).

The most commonly reported SOCs (reported by ≥5 patients) were infections and infestations (6 patients, 0.9%) and musculoskeletal and connective tissue disorders (6 patients, 0.9%) (Table ANN. 40).

Pneumonia (4 patients, 0.6%) and rheumatoid arthritis (3 patients, 0.5%) are the only SAEs reported by >1 patient in the population. All other SAEs were reported by single patients (Table ANN. 42). All the pneumonia cases were reported as possibly related to study treatment. Other SAEs related to study treatment were arthralgia, otitis media, tonsillitis and DILI (single events) (Table ANN. 43).

24-week period

A total of 28 patients (4.2%) reported 31 SAEs over a period of 24 weeks and of whom 10 patients reported 10 SAEs related to study treatment (Table ANN. 44, Table ANN. 45).

The most commonly reported SOCs (reported by ≥5 patients) were infections and infestations (8 patients, 1.2%) and musculoskeletal and connective tissue disorders (8 patients, 1.2%) (Table ANN. 44).

The only SAEs reported by >1 patient in the population were pneumonia (4 patients, 0.6%), rheumatoid arthritis (3 patients, 0.5%), and arthralgia (2 patients, 0.3%). All other SAEs were reported by single patients (Table ANN. 46). All the pneumonia cases were reported as possibly related to study treatment. Other SAEs related to study treatment were appendicitis, arthralgia, DILI, influenza, otitis media, and tonsillitis (single events) (Table ANN. 47).

10.4.2.5. AEs leading to drug adjustment/discontinuation

A total of 30 patients (4.5%) reported 36 events that led to drug adjustment (Table ANN. 48), and 20 patients (3.0%) reported 22 events that led to permanent drug discontinuation over 12 weeks (Table ANN. 49).

A total of 39 patients (5.9%) reported 45 events that led to drug adjustments (Table ANN. 50), and 24 patients (3.6%) reported 26 events that led to permanent drug discontinuation over 24 weeks (Table ANN. 51).

The events that led to drug adjustments reported by at least 2 patients over 12 weeks and 24 weeks were herpes zoster, hepatic function abnormal, pneumonia, and upper respiratory tract infection (Table ANN. 48, Table ANN. 50). Rheumatoid arthritis and arthralgia were the only events reported by at least 2 patients that led to permanent drug discontinuation over 12 weeks and 24 weeks (Table ANN. 49, Table ANN. 51).

10.4.2.6. Adverse events of special interest (as judged by the investigator)

A total of 19 patients reported 21 AESIs in 12 weeks (IR – 12.3; EAIR – 12.9), and 26 patients reported 31 AESIs in 24 weeks (IR – 9.6; EAIR – 10.1) (Table 10.4). Most of these events were related to study treatment and very few of these were SAEs. These AESIs are summarized below.

Table 10.4. Summary of AEs with Special Interest as Based on Investigators' Judgement – Safety Analyses Population

	Safety Analyses Population (N=667)						
	Event	*n*	*Patient-year of Observation Time*	*Patient-year of Exposure Time*	*Percentage and 95% CI*	*Incidence Rate and 95% CI*	*EAIR and 95% CI*
AEs of special interest over a period of 12 weeks	21	19	155.09	147.02	2.85% (1.72%, 4.41%)	12.25 (7.38, 19.13)	12.92 (7.78, 20.18)
Serious infection	4	3	156.74	148.52	0.45% (0.09%, 1.31%)	1.91 (0.39, 5.59)	2.02 (0.42, 5.90)
Hepatotoxicity	17	16	155.37	147.13	2.40% (1.38%, 3.87%)	10.30 (5.89, 16.72)	10.87 (6.22, 17.66)
VTE	0	0	157.02	148.63	0.00% (0%, 0.55%)	0.00 (NA, 2.35)	0.00 (NA, 2.48)
AEs of special interest over a period of 24 weeks	31	26	271.34	256.65	3.90% (2.56%, 5.66%)	9.58 (6.26, 14.04)	10.13 (6.62, 14.84)
Serious infection	5	4	276.02	260.99	0.60% (0.16%, 1.53%)	1.45 (0.39, 3.71)	1.53 (0.42, 3.92)
Hepatotoxicity	26	23	271.70	256.76	3.45% (2.20%, 5.13%)	8.47 (5.37, 12.70)	8.96 (5.68, 13.44)
VTE	0	0	276.57	261.30	0.00% (0%, 0.55%)	0.00 (NA, 1.33)	0.00 (NA, 1.41)
AEs of special interest related to study treatment as judged by the investigator over a period of 12 weeks	17	15	155.45	147.38	2.25% (1.26%, 3.68%)	9.65 (5.40, 15.92)	10.18 (5.70, 16.79)
Serious infection	4	3	156.74	148.52	0.45% (0.09%, 1.31%)	1.91 (0.39, 5.59)	2.02 (0.42, 5.90)
Hepatotoxicity	13	12	155.73	147.50	1.80% (0.93%, 3.12%)	7.71 (3.98, 13.46)	8.14 (4.20, 14.21)
VTE	0	0	157.02	148.63	0.00% (0%, 0.55%)	0.00 (NA, 2.35)	0.00 (NA, 2.48)
AEs of special interest related to study treatment as judged by the investigator over a period of 24 weeks	25	21	272.47	257.60	3.15% (1.96%, 4.77%)	7.71 (4.77, 11.78)	8.15 (5.05, 12.46)
Serious infection	5	4	276.02	260.99	0.60% (0.16%, 1.53%)	1.45 (0.39, 3.71)	1.53 (0.42, 3.92)
Hepatotoxicity	20	18	272.83	257.71	2.70% (1.61%, 4.23%)	6.60 (3.91, 10.43)	6.98 (4.14, 11.04)
VTE	0	0	276.57	261.30	0.00% (0%, 0.55%)	0.00 (NA, 1.33)	0.00 (NA, 1.41)

	Safety Analyses Population (N=667)						
	Event	*n*	*Patient-year of Observation Time*	*Patient-year of Exposure Time*	*Percentage and 95% CI*	*Incidence Rate and 95% CI*	*EAIR and 95% CI*
SAEs with special interest over a period of 12 weeks	4	4	156.60	148.45	0.60% (0.16%, 1.53%)	2.55 (0.70, 6.54)	2.69 (0.73, 6.90)
Serious infection	3	3	156.76	148.53	0.45% (0.09%, 1.31%)	1.91 (0.39, 5.59)	2.02 (0.42, 5.90)
Hepatotoxicity	1	1	156.87	148.55	0.15% (0.004%, 0.83%)	0.64 (0.02, 3.55)	0.67 (0.02, 3.75)
VTE	0	0	157.02	148.63	0.00% (0%, 0.55%)	0.00 (NA, 2.35)	0.00 (NA, 2.48)
SAEs with special interest over a period of 24 weeks	5	5	275.87	260.92	0.75% (0.24%, 1.74%)	1.81 (0.59, 4.23)	1.92 (0.62, 4.47)
Serious infection	4	4	276.03	261.00	0.60% (0.16%, 1.53%)	1.45 (0.39, 3.71)	1.53 (0.42, 3.92)
Hepatotoxicity	1	1	276.42	261.22	0.15% (0.004%, 0.83%)	0.36 (0.01, 2.02)	0.38 (0.01, 2.13)
VTE	0	0	276.57	261.30	0.00% (0%, 0.55%)	0.00 (NA, 1.33)	0.00 (NA, 1.41)

Abbreviations: AE = adverse event; CI = confidence interval; EAIR = exposure adjusted incidence rate; EDC = electronic data capture; N = number of patients in population; n = the number of patients with events; NA = not applicable; SAE = serious adverse event; SAP = Statistical Analysis Plan; VTE = venous thromboembolism.

Notes: The percentage denominator is the number of analyses population and the numerator is the number of patients with corresponding events.

The percentage of AEs/SAEs over a period of 12/24 weeks = Number of patients with at least 1 AE/SAE over a period of 12/24 weeks ÷ number of patients in safety analyses population × 100, results round to 2 decimal places.

The incidence rates of AEs/SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least 1 AE/SAE over an observation period of 12/24 weeks ÷ observation time of AEs/SAEs over a period of 12/24 weeks (years) × 100, results round to 2 decimal places.

The EAIR of AEs /SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least 1 AE/SAE over an observation period of 12/24 weeks ÷ overall exposure time of AEs/SAEs over a period of 12/24 weeks (years) × 100, results round to 2 decimal places.

The calculation of observation time and exposure time could refer to definition in the main body of SAP.

AEs related to study treatment as judged by the investigator are the AEs whose relationship with baricitinib are not 'No'.

AE of special interest is based on the judgement of investigator recorded in EDC.

10.4.2.6.1. Serious infection

For 12 weeks, a total of 6 patients (0.9%) reported SAEs within the infections and infestations SOC, meeting ICH criteria for seriousness, such as hospitalization (Table ANN. 40). Only 3 serious pneumonia events of these were reported by the investigators as AESIs. These events were related to the study treatment (Table ANN. 53) (Table ANN. 54).

For 24 weeks, a total of 8 patients (1.2%) reported SAEs within the infections and infestations SOC (Table ANN. 44). Appendicitis was the only additional serious event reported by the investigators as an AESI after 12 weeks until 24 weeks (Table ANN. 55). It was also related to the study treatment (Table ANN. 56).

10.4.2.6.2. Hepatotoxicity

A total of 16 patients (2.4%) reported 17 hepatotoxicity events over 12 weeks. The events were hepatic function abnormal (14 patients), ALT increased (1 patient), and DILI (1 patient) (Table ANN. 58). In 10 patients the event of hepatic function abnormal was related to the study treatment. One event each of ALT increased and DILI were also related to the study treatment (Table ANN. 59). One event of DILI was a SAE (Table ANN. 60) (Table ANN. 63).

A total of 23 patients (3.5%) reported 26 hepatoxicity events over 24 weeks. Hepatic function abnormal (17 patients, 19 events) and DILI (2 patients, 3 events) were the events reported by at least 2 patients (Table ANN. 61). ALT increased, AST increased, blood bilirubin increased, and liver function test abnormal were all reported by single patients (Table ANN. 61). In 13 patients, the event of hepatic function abnormal was related to the study treatment. The event of DILI was reported by 2 patients, which is summarized below. One patient each reported ALT increased, blood bilirubin increased, and liver function test abnormal that were related to the study treatment (Table ANN. 62).

An overview of patients reported hepatotoxicity events with available lab values (ALT or AST >3 × ULN, or TBIL >2 × ULN) over 24 weeks is provided in Table 10.5.

Table 10.5. AESIs of Hepatotoxicity over a Period of 24 Weeks for Patients with Posttreatment AST or ALT >3 ULN or TBIL >2 ULN – Safety Analysis Population

Patient No.	*PT*	*Severity*	*Outcome*	*Relationship to baricitinib*	*Action taken for baricitinib*	*Serious*	*Maximum Posttreatment ALT (U/L)/ULN*	*Maximum Posttreatment AST (U/L)/ULN*	*Maximum Posttreatment TBIL (U/L)/ULN*
0082-022006	Hepatic function abnormal	Mild	Persisted	Yes	Dose not changed	No	100/40	123/35	12.4/24
0121-009005	Hepatic function abnormal	Mild	Disappeared	Yes	Dose reduced	No	149.1/45	166.1/40	21.5/25
0402-014012	Hepatic function abnormal	Mild	Disappeared	No	Permanently discontinue medication	No	136/40	92/35	10.1/23
1100-003005	Hepatic function abnormal	Moderate	Disappeared	Yes	Dose not changed	No	197/40	137/40	14.19/20
	Hepatic function abnormal	Moderate	Disappeared	Yes	Temporarily discontinue medication	No			
1100-003010	Drug-induced liver injury	Moderate	Disappeared	Yes	Dose not changed	No	125/40	110/40	11.62/20
1100-003024	Drug-induced liver injury	Severe	Disappeared	Yes	Temporarily discontinue medication	Yes	351/40	172/40	8.87/20
	Drug-induced liver injury	Severe	Disappeared	Yes	Temporarily discontinue medication	No			
1100-003062	Hepatic function abnormal	Mild	Turned for the better	No	Dose not changed	No	145/40	50/40	10.05/20

Abbreviations: AESI = adverse event of special interest; ALT = alanine aminotransferase; AST = aspartate aminotransferase; No. = number; PT = preferred term; TBIL = total bilirubin; ULN = upper limit normal.

There are 2 patients with report term of DILI; however, none of them met laboratory criteria for potential Hy's Law, with ALT/AST ≥3 × ULN and TBIL ≥2 × ULN and have symptoms/signs in association with the event. Brief narratives for the 2 cases are presented below:

1100-003024: a 63-year-old female patient reported the SAE of severe drug-induced liver injury 28 days after receiving baricitinib 2 mg, orally, daily for the treatment of RA. Relevant medical history included fatty liver. Concomitant medication included MTX, leflunomide, and aceclofenac. Baseline AST, ALT, and TBIL were in normal range. On Study Day 27, the patient had hepatic enzyme increased with peak ALT at 351 U/L (0 to 40) and AST at 172 U/L (0 to 40), bilirubin was in normal range, and the patient was admitted to hospital after 1 day. The patient did not have symptoms/signs in association with the event. As corrective treatment, glutathione, magnesium isoglycyrrhizinate, compound diisopropyl dichloroacetate, and glucurolactone were given temporarily to protect the liver, and human interleukin-2 was given for immune regulation. ALT and AST returned to normal approximately 38 days later. Action taken with baricitinib in response to the SAE was study drug temporarily discontinued on Day 28 and restarted after. The event did not occur after drug restart. The opinion of investigator, the event was related to the combined use of baricitinib, leflunomide, MTX, and aceclofenac.

1100-003010: a 59-year-old female patient reported the AEs of moderate drug-induced liver injury and hepatic functional abnormal 156 days after receiving baricitinib 2 mg, orally, daily for the treatment of RA. Concomitant medication included MTX and iguratimod. The patient had hepatic enzyme increased with peak ALT at 125 U/L (0 to 40), AST at 110 U/L (0 to 40), and bilirubin was in normal range. The patient recovered from the event 2 months later. There was no change with baricitinib (dose not changed) in response to the events. The investigator stated that the events may be related to baricitinib, MTX, and iguratimod.

There were no patients in the upper right quadrant of the DILI screening plot (ALT/AST ≥3 × ULN and TBIL ≥2 × ULN).

10.4.2.6.3. VTE

No event was reported in 12 weeks or 24 weeks.

10.4.2.7. Laboratory

Haematology

Hematologic changes were generally small. The summary of baseline values, values at 4 weeks, 12 weeks, and 24 weeks and corresponding changes from baseline at these visits are provided in Table ANN. 65. Shifts in CTCAE grades of haematology parameters from baseline to postbaseline are summarized in Table ANN. 67.

Table 10.6 summarizes treatment-emergent changes in haematology parameters. Treatment-emergent change from <CTCAE Grade 3 to Grade 3 or higher was observed in 2 patients (0.4%) in neutrophils and in 3 patients (0.6%) in lymphocytes. No one changed to CTCAE Grade 4. Thrombocytosis (platelets change to >600 × 10^9/L) was observed in 2 patients (0.4%) (Table 10.6).

Table 10.6. Treatment Emergent Changes in Laboratory Parameters, Haematology — Safety Analyses Population

Parameter	CTCAE Grade Shift Between Baseline and Minimum Postbaseline Value	Safety Analyses Population (N=667) n/Nx (%)
Leukocytes	Any grade increased	26/506 (5.14)
	Change from <Grade 3 to ≥Grade 3	0
Haemoglobin	Any grade increased	51/505 (10.10)
	Change from <Grade 3 to ≥Grade 3	0
Neutrophils	Any grade increased	34/503 (6.76)
	Change from <Grade 3 to ≥Grade 3	2/503 (0.40)
Lymphocytes	Any grade increased	70/503 (13.92)
	Change from <Grade 3 to ≥Grade 3	3/503 (0.60)
Platelets	Any grade increased	6/506 (1.19)
	Change from <Grade 3 to ≥Grade 3	0
	Thrombocytosis: Change from ≤600 × 10^9/L to >600 × 10^9/L	2/506 (0.40)

Abbreviations: CTCAE = common terminology criteria for adverse events; N = number of patients in the analysis population; n = number of patients in the specified category; Nx = number of patients with baseline and at least 1 postbaseline value.

Notes: Percentage is calculated by n/Nx × 100%.

CTCAE uses Version 5.0.

Decreased: minimum postbaseline value category < baseline category. Same: minimum post-baseline value category = baseline category. Increased: minimum post-baseline value category > baseline category.

Source: Table ANN. 68.

Chemistry

Chemistry changes were generally small. The summary of baseline values, values at 4 weeks, 12 weeks, and 24 weeks and corresponding changes from baseline at these visits is provided in Table ANN. 69.

Shifts between baseline and maximum postbaseline values in chemistry parameters are summarized in Table ANN. 70 through Table ANN. 73. Shifts in terms of CTCAE grades are summarized in Table ANN. 74 and Table ANN. 75.

Treatment-emergent changes in chemistry parameters are summarized in (Table 10.7). Six patients (1.2%) had change to ≥3 × ULN in ALT and 4 patients (0.9%) in AST, and 1 patient had change to ≥ 5× ULN in ALT (Case 1100-003024 presented in Section 10.4.2.6.2). No patient experienced change in TBIL to ≥2 × ULN. No patient experienced Cr or CPK change to ≥CTCAE Grade 3.

Treatment-emergent abnormalities in chemistry parameters are summarized in Table ANN. 76.

Table 10.7. Treatment Emergent Changes in Laboratory Parameters, Chemistry — Safety Analyses Population

Parameter	Category Shift between Baseline and Maximum Postbaseline Value	Safety Analyses Population (N=667) n/Nx (%)
ALT	Any category increased	40/488 (8.20)
	Change from <3 × ULN to ≥3 × ULN	6/488 (1.23)
	Change from <5 × ULN to ≥5 × ULN	1/488 (0.20)
AST	Any category increased	50/462 (10.82)
	Change from <3 × ULN to ≥3 × ULN	4/462 (0.87)
	Change from <5 × ULN to ≥5 × ULN	0
ALP	Any category increased	16/313 (5.11)
	Change from <1.5 × ULN to ≥1.5 × ULN	4/313 (1.28)
TBIL	Any category increased	23/435 (5.29)
	Change from <2 × ULN to ≥2 × ULN	0
Creatinine	Any CTCAE grade increased	17/408 (4.17)
	Change from <Grade 3 to ≥Grade 3	0
CPK	Any CTCAE grade increased	4/40 (10.00%)
	Change from <Grade 3 to ≥Grade 3	0

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; Cr = creatinine; CTCAE = common terminology criteria for adverse events; N = number of patients in the analysis population; n = number of patients in the specified category; Nx = number of patients with baseline and at least 1 post baseline value; TBIL = total bilirubin; ULN = upper limit of normal.

Notes: CTCAE uses Version 5.0.

Percentage is calculated by n/Nx × 100%.

Decreased: maximum postbaseline value category < baseline category. Same: maximum postbaseline value category = baseline category. Increased: maximum postbaseline value category > baseline category.

Source: Table ANN. 77.

Urinalysis

Treatment-emergent abnormalities in urinalysis parameters are summarized in Table ANN. 77.

10.4.3. Effectiveness

10.4.3.1. DAS28-CRP

At baseline, the mean (SD) values were 4.7 (1.8). At 12 weeks, mean (SD) change from baseline was −1.6 (1.6), and at 24 weeks, mean (SD) change from baseline was −2.0 (1.7) (Table ANN. 78).

At baseline, most patients belonged to the >3.2 category (83.3%). At 12 weeks (54.2%) and 24 weeks (66.6%), more than half of the effectiveness analysis population belonged to the ≤3.2 category (Table ANN. 79).

Based on MMRM analysis, the LS mean (SE) change in score at 12 weeks was −1.5 (0.1) (p<.0001) and at 24 weeks was −1.9 (0.1) (p<.0001) (Table ANN. 80).

10.4.3.2. DAS28-ESR

At baseline, the mean (SD) score was 5.2 (2.0) (Table ANN. 89). At baseline, majority of the population (86.9%) had a >3.2 score, and more than half of the population (58.4%) belonged to the >5.1 score category (Table ANN. 90).

At 12 weeks, mean (SD) change from baseline was −1.5 (1.6), and at 24 weeks, mean (SD) change from baseline was −1.9 (1.7).

At 12 weeks, most patients belonged to the >3.2 score (58.0%) and ≤3.2 score (42.0%) categories. At 24 weeks as well, most patients belonged to the ≤3.2 score (54.0%) and >3.2 score (46.0%) categories.

10.4.3.3. SDAI

At baseline, the mean (SD) SDAI score was 31.5 (18.4) (Table ANN. 81). At 12 weeks, mean (SD) change from baseline was −15.6 (16.1), and at 24 weeks, mean (SD) change from baseline was −19.4 (17.7).

At baseline, most patients belonged to the >11.0 category (87.5%). At 12 weeks (52.3%) and 24 weeks (64.6%), more than half of the effectiveness analysis population belonged to the ≤11.0 category (Table ANN. 82).

Based on MMRM analysis, the LS mean (SE) change in scores at 12 weeks was −15.4 (0.6) (p<.0001) and at 24 weeks was −19.3 (0.6) (p<.0001) (Table ANN. 83).

10.4.3.4. CDAI

At baseline, the mean (SD) CDAI score was 29.2 (17.3) (Table ANN. 84). At 12 weeks, mean (SD) change from baseline was −14.3 (14.9) and at 24 weeks, mean (SD) change from baseline was −17.8 (16.2).

At baseline, most patients belonged to the >10.0 category (88.0%). At 12 weeks (50.3%) and 24 weeks (63.5%), more than half of the effectiveness analysis population belonged to the ≤10.0 category (Table ANN. 85).

Based on MMRM analysis, the LS mean (SE) change in scores at 12 weeks was −14.2 (0.6) (p<.0001) and 24 weeks was −17.7 (0.6) (p<.0001) (Table ANN. 86).

10.4.3.5. MJS

At baseline, the mean (SD) MJS score was 44.7 (52.3) (Table ANN. 86). At 12 weeks, mean (SD) change from baseline was −20.6 (78.9), and at 24 weeks, mean (SD) change from baseline was −28.3 (47.0).

At baseline, mean (SD) TJCs were 10.5 (8.2). At 12 weeks, mean (SD) change from baseline was −5.6 (7.5), and at 24 weeks, mean (SD) change from baseline was −6.6 (7.6).

At baseline, mean (SD) SJC was 9.5 (7.6). At 12 weeks, mean (SD) SJC was −5.2 (6.7), and at 24 weeks, mean (SD) change from baseline was −6.4 (7.3).

10.4.3.6. Pain VAS

At baseline, the mean (SD) VAS score of patients' pain was 5.9 (2.0) (Table ANN. 88). At 12 weeks, mean (SD) change from baseline was −2.4 (2.2), and at 24 weeks, mean (SD) change from baseline was −3.0 (2.5).

At baseline, the mean (SD) VAS score of overall disease status was 6.0 (2.0). At 12 weeks, mean (SD) change from baseline was −2.4 (2.2), and at 24 weeks, mean (SD) change from baseline was −3.1 (2.4).

At baseline, the mean (SD) VAS score of overall disease status of doctors was 6.0 (1.9). At 12 weeks, mean (SD) change from baseline was −2.4 (2.1), and at 24 weeks, mean (SD) change from baseline was −3.0 (2.3).

10.4.3.7. Key Indicator

Key indicators, such as ESR, CRP, and RF, showed reduction in their values over time from baseline (Table ANN. 91).

10.5. Other analyses

10.5.1. Subgroup analyses

Demographic data, baseline characteristics data, and efficacy and safety observations by subgroups are presented in Table ANN. 92 to Table ANN. 337.

10.5.1.1. Safety

All analyses in safety were descriptive and there were no statistical comparisons.

Safety observations were generally similar between different age subgroups at 12 and 24 weeks. The ≥75-year group included too few patients (n=19) to make relevant comparisons. Though incidence of SAEs was numerically higher in the ≥65-and-<75–years group (10.4% at 12 and 24 weeks) compared to ＜65-years (1.9% and 3.0% at 12 and 24 weeks) (Table 10.8), incidence of related SAEs was similar among groups. Incidence of AEs leading to permanent drug discontinuation was similar in the＜65-years (2.6% and 3.0% at 12 and 24 weeks) and ≥65-and-<75-years groups (4.7% at 12 and 24 weeks). Incidence of serious infection was higher in the ≥65-and-<75-years group (1.9% at 12 and 24 weeks) compared to the ＜65-years (0.2% and 0.4% at 12 and 24 weeks). Incidence of hepatotoxicity was similar in the ＜65-years (2.2% and 3.5% at 12 and 24 weeks) and ≥65-and-<75-years groups (1.9% at 12 and 24 weeks). These differences were not clinically meaningful considering that the number of patients with events were small and the interpretability of data is limited.

Overall safety observations were generally similar between different dosage groups (Table 10.9). Incidence of AEs leading to permanent drug discontinuation was numerically higher in the 4-mg–only group (7.6% at 12 and 24 weeks) compared to 2-mg–only (2.8% and 3.5% at 12 and 24 weeks), but as these dose groups were not randomized and may be different in disease severity and risk factors, this finding cannot be interpreted.

For renal impairment safety subgroups, there were no obvious differences observed between the groups (Table ANN. 358).

Table 10.8 Subgroup Analysis by Age — Safety Analysis Population

n (%) PYE [EAIR]	Safety Analyses Population (N=667)						Source
	<65 Years (Nx=542)		≥65 and <75 Years (Nx=106)		≥75 Years (Nx=19)		
	12 Weeks	24 Weeks	12 Weeks	24 Weeks	12 Weeks	24 Weeks	
AEs	165 (30.44) 102.54 [160.91]	196 (36.16) 164.08 [119.45]	41 (38.68) 17.99 [227.90]	45 (42.45) 29.38 [153.17]	8 (42.11) 3.51 [227.92]	9 (47.37) 5.1 [175.78]	Table ANN. 293
AEs related to study treatment as judged by the investigator	73 (13.47) 114.70 [63.64]	93 (17.16) 194.34 [47.85]	18 (16.98) 21.32 [84.43]	20 (18.87%) 36.33 [55.05]	4 (21.05%) 3.97 [100.76]	7 (36.84) 5.97 [117.25]	
Death	0 213.14 [0.00]		2 (1.89%) 40.91 [4.89]		0 7.24 [0.00]		
SAEs	10 (1.85) 120.30 [8.31]	16 (2.95) 210.6 [7.60]	11 (10.38) 22.34 [49.24]	11 (10.38) 39.20 [28.06]	1 (5.26) 4.39 [22.78]	1 (5.26) 6.89 [14.51]	
SAEs related to study treatment as judged by the investigator	5 (0.92) 120.76 [4.14]	7 (1.29) 212.35 [3.30]	3 (2.83) 23.10 [12.99]	3 (2.83) 40.70 [7.37]	0 4.46 [0.00]	0 7.24 [0.00]	
AEs leading to permanent drug discontinuation	14 (2.58) 120.84 [11.59]	16 (2.95) 212.87 [7.52]	5 (4.72) 22.89 [21.84]	5 (4.72) 40.68 [12.29]	1 (5.26) 4.46 [22.42]	3 (15.79) 7.24 [41.44]	
AESI	13 (2.40) 119.67 [10.86]	20 (3.69) 209.38 [9.55]	4 (3.77) 23.01 [17.38]	4 (3.77) 23.01 [17.38]	2 (10.53) 4.33 [46.19]	2 (10.53) 6.84 [29.24]	Table ANN. 294, Table ANN. 295, and Table ANN. 296
Serious infection	1 (0.18) 120.95 [0.83]	2 (0.37) 212.84 [0.94]	2 (1.89) 23.11 [8.65]	2 (1.89) 23.11 [8.65]	0 4.46 [0.00]	0 7.24 [0.00]	
Hepatotoxicity	12 (2.21) 119.77 [10.02]	19 (3.51) 209.48 [9.07]	2 (1.89) 23.03 [8.68]	2 (1.89) 23.03 [8.68]	2 (10.53) 4.33 [46.19]	2 (10.53) 6.84 [29.24]	
VTE	0 121.05 [0.00]	0 213.14 [0.00]	0 23.12 [0.00]	0 23.12 [0.00]	0 4.46 [0.00]	0 7.24 [0.00]	

Abbreviations: AE = adverse event; AESI = adverse event of special interest; EAIR = exposure-adjusted incidence rate; N = number of patients in the safety analysis set; n = number of patients with events; Nx = number of patients in population; PYE = patient-years of exposure; SAE = serious adverse event; VTE = venous thromboembolism.

Notes: Used EAIR per 100 PYE (patient exposure censored at the event).

AESI was based on the judgement of investigator recorded in the electronic case report form (eCRF).

Table 10.9 Subgroup Analysis by Dosage — Safety Analysis Population

n (%) PYE [EAIR]	Safety Population (N=667)						Source
	2 mg only (Nx=580)		4 mg only (Nx=53)		Both dosage (Nx=34)		
	12 weeks	24 weeks	12 weeks	24 weeks	12 weeks	24 weeks	
AEs	187 (32.24) 108.11 [172.97]	221 (38.10) 173.71 [127.22]	14 (26.42) 10.62 [142.42]	14 (26.42) 15.45 [90.61]	13 (38.24) 6.09 [213.46]	15 (44.12) 9.42 [159.24]	Table ANN. 320 Table ANN. 321
AEs related to study treatment as judged by the investigator	84 (14.48) 121.79 [68.97]	108 (18.62) 206.58 [52.28]	3 (5.66) 11.09 [27.05]	4 (7.55) 18.26 [21.91]	8 (23.53) 7.11 [112.52]	8 (23.53) 11.81 [67.74]	
Death	2 (0.34) 228.59 [0.87]		0 18.71 [0.00]		0 14.00 [0.00]		
SAEs	17 (2.93) 128.62 [13.22]	23 (3.97) 225.52 [10.20]	3 (5.66) 10.87 [27.60]	3 (5.66) 17.69 [16.96]	2 (5.88) 7.54 [26.53]	2 (5.88) 13.51 [14.80]	
SAEs related to study treatment as judged by the investigator	6 (1.03) 129.37 [4.64]	8 (1.38) 227.69 [3.51]	1 (1.89) 11.25 [8.89]	1 (1.89) 18.71 [5.34]	1 (2.94) 7.70 [12.99]	1 (2.94) 13.91 [7.19]	
AEs leading to permanent drug discontinuation	16 (2.76) 129.15 [12.39]	20 (3.45) 228.09 [8.77]	4 (7.55) 11.2 [35.59]	4 (7.55) 18.69 [21.40]	0 7.80 [0.00]	0 14.00 [0.00]	
AESIs	15 (2.59) 128.29 [11.69]	22 (3.79) 224.71 [9.79]	1 (1.89) 11.25 [8.89]	1 (1.98) 18.71 [5.34]	3 (8.82) 7.5 [40.11]	3 (8.82) 13.23 [22.68]	Table ANN. 323 Table ANN. 324 Table ANN. 325
Serious infection	2 (0.34) 129.57 [1.54]	3 (0.52) 228.37 [1.31]	0 11.25 [0.00]	0 18.71 [0.00]	1 (2.94) 7.70 [12.99]	1 (2.94) 13.91 [7.19]	
Hepatotoxicity	13 (2.24) 128.30 [10.13]	20 (3.45) 224.72 [8.9]	1 (1.89) 11.25 [8.17]	1 (1.89) 18.71 [5.34]	2 (5.88) 7.58 [26.39]	2 (5.88) 13.33 [15.00]	
VTE	0 129.58 [0.00]	0 228.59 [0.00]	0 11.25 [0.00]	0 18.71 [0.00]	0 7.80 [0.00]	0 14.00 [0.00]	

Abbreviations: AE = adverse event; AESI = adverse event of special interest; EAIR = exposure-adjusted incidence rate; N = number of patients in the safety analysis set; n = number of patients with events; Nx = number of patients in population; PYE = patient-years of exposure; SAE = serious adverse event; VTE = venous thromboembolism.

Notes: Used EAIR per 100 PYE (patient exposure censored at the event).

AESI was based on the judgement of investigator recorded in electronic case report form (eCRF).

10.5.1.2. Effectiveness

Results of subgroup analysis of efficacy parameters are presented in Table 10.10.

The following subgroups had significant differences:

- Age subgroups: p<.05
  - DAS28-CRP score at baseline and change at 24 weeks
  - SDAI score at baseline and change at 24 weeks
  - CDAI score at baseline
- Baseline SDAI subgroups: p<.05
  - DAS28-CRP score at baseline and change at 24 weeks
  - SDAI score at baseline and change at 24 weeks
  - CDAI score at baseline and change at 24 weeks
- TNFi-IR: p<.05
  - DAS28-CRP score at baseline

Table 10.10. Subgroup Analysis — Effectiveness Analyses Population

Subgroup	Outcome			Effectiveness Analyses Population				Source
				Male (N=86)	Female (N=428)		P-value*	
Gender	DAS28-CRP score	Baseline	Mean (Std)	4.92 (1.83)	4.63 (1.84)		.1764	Table ANN. 95
		Change at 24-weeks	Mean (Std)	−2.19 (1.73)	−1.92 (1.65)		.2242	
		LDA/remission rate (≤3.2) at baseline	n (%)	11 (13.10%)	73 (17.46%)			Table ANN. 98 Table ANN. 99
		LDA/remission (≤3.2) at 24-weeks	n (%)	36 (66.67%)	199 (66.56%)			
	SDAI score	Baseline	Mean (Std)	33.40 (18.86)	31.06 (18.34)		.3001	Table ANN. 101
		Change at 24-weeks	Mean (Std)	−22.22 (18.74)	−18.85 (17.54)		.2133	
		LDA/remission rate (≤11) at baseline	n (%)	7 (8.33%)	56 (13.40%)			Table ANN. 103 Table ANN. 104
		LDA/remission rate (≤11) at 24-weeks	n (%)	34 (62.96%)	194 (64.88%)			
	CDAI score	Baseline	Mean (Std)	30.13 (17.14)	28.99 (17.30)		.5180	Table ANN. 107
		Change at 24-weeks	Mean (Std)	−19.90 (16.06)	−17.40 (16.17)		.2660	
		LDA/remission rate (≤10) at baseline	n (%)	6 (7.14%)	55 (12.97%)			Table ANN. 109 Table ANN. 110
		LDA/remission (≤10) at 24-weeks	n (%)	39 (65.00%)	203 (63.24%)			
				<65 years (N=422)	≥65 and <75 years (N=78)	≥75 years (N=14)	P-value*	
Age	DAS28-CRP score	Baseline	Mean (Std)	4.55 (1.88)	5.16 (1.53)	5.93 (1.31)	.0015	Table ANN. 116
		Change at 24-weeks	Mean (Std)	−1.86 (1.64)	−2.39 (1.66)	−2.74 (2.03)	.0288	
		LDA/remission rate (≤3.2) at baseline	n (%)	77 (18.64%)	7 (9.33%)	0		Table ANN. 118 Table ANN. 119
		LDA/remission (≤3.2) at 24-weeks	n (%)	195 (67.01%)	34 (65.38%)	6 (60.00%)		Table ANN. 120
	SDAI score	Baseline	Mean (Std)	30.45 (18.47)	34.20 (16.99)	46.39 (17.74)	.0028	Table ANN. 124
		Change at 24-weeks	Mean (Std)	−18.29 (17.07)	−23.08 (18.74)	−31.36 (25.63)	.0400	

Subgroup	Outcome			Effectiveness Analyses Population				Source
				Male (N=86)	Female (N=428)		P-value*	
		LDA/remission rate (≤11) at baseline	n (%)	59 (14.29%)	4 (5.33%)	0		Table ANN. 126 Table ANN. 127
		LDA/remission rate (≤11) at 24-weeks	n (%)	192 (65.98%)	32 (61.54%)	4 (40.00%)		Table ANN. 128
	CDAI score	Baseline	Mean (Std)	28.39 (17.27)	30.93 (16.24)	43.02 (17.04	.0071	Table ANN. 132
		Change at 24-weeks	Mean (Std)	−17.13 (15.49)	−20.27 (17.23)	−23.32 (25.34)	.2454	
		LDA/remission rate (≤10) at baseline	n (%)	56 (13.43%)	5 (6.49%)	0		Table ANN. 134 Table ANN. 135
		LDA/remission (≤10) at 24-weeks	n (%)	206 (66.03%)	32 (56.14%)	4 (33.33%)		Table ANN. 136
				<Q1 (N=125)	≥Q1 and <Q3 (N=251)	≥Q3 (N=126)	P-value*	
Baseline SDAI	DAS28-CRP score	Baseline	Mean (Std)	2.24 (1.38)	4.86 (0.72)	6.74 (0.63)	<.0001	Table ANN. 143
		Change at 24-weeks	Mean (Std)	−0.67 (0.92)	−1.98 (1.42)	−3.29 (1.72)	<.0001	
		LDA/remission rate (≤3.2) at baseline	n (%)	80 (64.00%)	4 (1.59%)	0		Table ANN. 145, Table ANN. 146
		LDA/remission (≤3.2) at 24-weeks	n (%)	79 (89.77%)	111 (62.36%)	43 (51.19%)		Table ANN. 147
	SDAI score	Baseline	Mean (Std)	9.74 (5.76)	29.39 (6.68)	57.10 (9.79)	<.0001	Table ANN. 151
		Change at 24-weeks	Mean (Std)	−4.38 (6.84)	−17.72 (11.69)	−38.56 (19.14)	<.0001	
		LDA/remission rate (≤11) at baseline	n (%)	63 (50.40%)	0	0		Table ANN. 153 Table ANN. 154
		LDA/remission rate (≤11) at 24-weeks	n (%)	79 (89.77%)	105 (58.99%)	42 (50.00%)		Table ANN. 155
	CDAI score	Baseline	Mean (Std)	9.16 (5.43)	26.88 (6.44)	53.36 (9.52)	<.0001	Table ANN. 159
		Change at 24-weeks	Mean (Std)	−4.36 (6.42)	−15.95 (11.13)	−33.67 (17.34)	<.0001	
		LDA/remission rate (≤10) at baseline	n (%)	61 (48.80%)	0	0		Table ANN. 161 Table ANN. 162
		LDA/remission (≤10) at 24-weeks	n (%)	82 (91.11%)	114 (60.64%)	44 (44.44%)		Table ANN. 163

Subgroup	Outcome			Effectiveness Analyses Population				Source
				Male (N=86)	Female (N=428)		P-value*	
				2 mg only (N=458)	4 mg only (N=28)	Both dosage (N=28)	P-value*	
Dosage	DAS28-CRP score	Baseline	Mean (Std)	4.69 (1.83)	4.53 (2.04)	4.67 (1.86)	.9240	Table ANN. 215
		Change at 24-weeks	Mean (Std)	−1.95 (1.68)	−2.13 (1.73)	−2.07 (1.37)	.9132	
		LDA/remission rate (≤3.2) at baseline	n (%)	72 (16.11%)	7 (25.93%)	5 (17.86%)		Table ANN. 219 Table ANN. 220
		LDA/remission (≤3.2) at 24-weeks	n (%)	204 (65.38%)	19 (90.48%)	12 (60.00%)		Table ANN. 221
	SDAI score	Baseline	Mean (Std)	31.60 (18.38)	29.89 (20.49)	30.61 (17.62)	.8769	Table ANN. 229
		Change at 24-weeks	Mean (Std)	−19.13 (17.93)	−22.02 (19.23)	−20.25 (13.15)	.7439	
		LDA/remission rate (≤11) at baseline	n (%)	52 (11.63%)	6 (22.22%)	5 (17.86%)		Table ANN. 231 Table ANN. 233
		LDA/remission rate (≤11) at 24-weeks	n (%)	197 (63.14%)	19 (90.48%)	12 (60.00%)		Table ANN. 233 Table ANN. 235
	CDAI score	Baseline	Mean (Std)	29.39 (17.27)	26.84 (18.81)	28.04 (15.97)	.7232	Table ANN. 243
		Change at 24-weeks	Mean (Std)	−17.56 (16.24)	−20.08 (17.94)	−19.00 (13.07)	.7374	
		LDA/remission rate (≤10) at baseline	n (%)	50 (11.04%)	6 (22.22%)	5 (17.86%)		Table ANN. 247 Table ANN. 248
		LDA/remission (≤10) at 24-weeks	n (%)	208 (61.72%)	21 (95.45%)	13 (59.09%)		Table ANN. 249
				Both negative (N=19)	Any positive (N=355)		P-value*	
Baseline RF and anti-CCP	DAS28-CRP score	Baseline	Mean (Std)	3.71 (2.95)	4.72 (1.80)		.4960	Table ANN. 170
		Change at 24-weeks	Mean (Std)	−1.82 (1.82)	−2.06 (1.57)		.4491	
		LDA/remission rate (≤3.2) at baseline	n (%)	9 (47.37%)	11 (78.57%)			Table ANN. 172 Table ANN. 173
		LDA/remission (≤3.2) at 24-weeks	n (%)	56 (15.91%)	169 (68.42%)			
	SDAI score	Baseline	Mean (Std)	27.90 (24.54)	31.34 (18.37)		.3911	Table ANN. 176
		Change at 24-weeks	Mean (Std)	−20.42 (18.72)	−19.95 (16.95)		.9927	
		LDA/remission rate (≤11) at baseline	n (%)	9 (47.37%)	40 (11.36%)			Table ANN. 178 Table ANN. 179

Subgroup	Outcome			Effectiveness Analyses Population			Source
				Male (N=86)	Female (N=428)	P-value*	
		LDA/remission rate (≤11) at 24-weeks	n (%)	11 (78.57%)	164 (66.40%)		
	CDAI score	**Baseline**	Mean (Std)	26.04 (22.99)	28.79 (17.19)	.3692	Table ANN. 182
		Change at 24-weeks	Mean (Std)	−19.40 (16.33)	−18.41 (15.25)	.8546	
		LDA/remission rate (≤10) at baseline	n (%)	8 (42.11%)	40 (11.33%)		Table ANN. 184 Table ANN. 185
		LDA/remission (≤10) at 24-weeks	n (%)	12 (75.00%)	174 (66.67%)		
				Yes (N=23)	**No (N=491)**	**P-value***	
TNFi-IR	**DAS28-CRP score**	**Baseline**	Mean (Std)	5.31 (1.91)	4.65 (1.84)	.0326	Table ANN. 191
		Change at 24-weeks	Mean (Std)	−2.60 (1.74)	−1.93 (1.66)	.1144	
		LDA/remission rate (≤3.2) at baseline	n (%)	3 (13.04%)	81 (16.91%)		Table ANN. 193 Table ANN. 194
		LDA/remission (≤3.2) at 24-weeks	n (%)	12 (66.67%)	223 (66.57%)		
	SDAI score	**Baseline**	Mean (Std)	39.39 (21.46)	31.07 (18.21)	.0612	Table ANN. 197
		Change at 24-weeks	Mean (Std)	−27.16 (21.26)	−18.94 (17.47)	.0996	
		LDA/remission rate (≤11) at baseline	n (%)	2 (8.70%)	61 (12.73%)		Table ANN. 199 Table ANN. 200
		LDA/remission rate (≤11) at 24-weeks	n (%)	11 (61.11%)	217 (64.78%)		
	CDAI score	**Baseline**	Mean (Std)	35.90 (18.58)	28.86 (17.15)	.0604	Table ANN. 203
		Change at 24-weeks	Mean (Std)	−23.31 (16.05)	−17.50 (16.13)	.1282	
		LDA/remission rate (≤10) at baseline	n (%)	2 (8.70%)	59 (12.16%)		Table ANN. 205 Table ANN. 206
		LDA/remission (≤10) at 24-weeks	n (%)	11 (57.89%)	231 (63.81%)		

Abbreviations: CCP = cyclic peptide containing citrulline; CDAI = Clinical Disease Activity Index; DAS28-CRP = Disease Activity Score modified to include the 28 diarthrodial joint count-C-reactive protein; LDA = low disease activity; N = number of patients in a subgroup; n = number of patients with data; SDAI = Simplified Disease Activity Index; Q1 and Q3 = interquartile range; RF = rheumatoid factor; Std = standard deviation; TNFi-IR = tumour necrosis factor-inhibitor receiver.

* P-value for continuous values from Kruskal-Wallis tests.

10.6. Adverse events/adverse reactions

AEs are summarized in Section 10.4.2.1 and AEs related to study treatment are summarized in Section 10.4.2.2.

11. Discussion

11.1. Key results

A total of 667 patients were enrolled in this study and the major proportion of whom were female (82.3%). Mean age was 53.3 years and 15.9% was 65 years or older. The safety analysis population included 667 (100%) patients and effectiveness population included 514 (77.1%) patients.

A total of 290 patients (43.5%) in the safety analysis population had at least 1 prespecified medical history or concomitant disease. Cardiovascular disease (168 patients, 25.2%) and allergy (74 patients, 11.1%) were reported by >10% of the population. A total of 436 patients (65.4%) in the safety analysis population had at least 1 other pre-existing condition/medical history or other concomitant disease. Osteoporosis (101 patients, 15.1%) and anaemia (73 patients, 10.9%) were the PTs reported by >10% of the population.

A total of 480 patients (72.0%) had been on RA medications prior to the study entry. Most of these patients had been on csDMARDs (468/480 patients). Within this group of medications, MTX (41.7%), leflunomide (31.3%), and hydroxychloroquine (hydroxychloroquine sulfate) (20.2%) were the most commonly reported prior RA medications. A total of 35 patients (5.2%) had been on tsDMARDs and 29 patients (4.3%) had been on bDMARDs prior to the study entry. A total of 579 patients (86.8%) received concomitant RA medications on entry to the study. Most of these patients were taking csDMARDs (579/580 patients). Within this group of medications, MTX (54.3%), leflunomide (35.5%), and hydroxychloroquine (hydroxychloroquine sulfate) (24.9%) were the most commonly reported concomitant RA medications.

The mean (SD) duration of RA was 86.9 (99.9) years and similar across the safety analysis population and effectiveness analysis population. Duration of RA varied from 1 year to >10 years in both the populations. Approximately 22% of both the populations had RA for ≤1 year and 27% of both the populations had RA for >10 years.

Overall mean (SD) baricitinib exposure in the safety analysis population was 143.9 (56.6) days and in the effectiveness analysis population was 164.3 (32.5) days. When considering the days of baricitinib exposure across all patients, total patient year exposure in the safety analysis population was 262.1 and in effectiveness analysis population was 230.8. In the safety analysis population, 87.0% of patients were administered with 2 mg, while 7.9% with 4 mg and 5.1% with both dosages. The proportion of patients in terms of dosages of baricitinib across the safety and effectiveness populations were similar.

Safety

A total of 214 patients (32.1%; IR – 165.2 and EAIR – 172.5) reported 329 AEs over a period of 12 weeks, and 95 patients (14.2%; IR – 64.7 and EAIR – 67.9) reported 111 AEs related to study treatment. A total of 250 patients (37.5%; IR – 119.9 and EAIR – 125.9) reported 428 AEs over a period of 24 weeks, and 120 patients (18.0%; IR – 48.1 and EAIR – 50.7) reported 147 AEs

related to study treatment. Most AEs were mild or moderate in severity. The most common AEs were hepatic function abnormal, upper respiratory tract infection, and platelet count increased.

There were 2 deaths reported during the study. One patient died because of severe pneumonia, and the cause of death for the second patient was unknown. Both were >65 years with multiple concomitant diseases and had taken baricitinib 2 mg. The Investigator assessed the event of death due to pneumonia as possibly related to baricitinib, and the second event of death was assessed to be unrelated to baricitinib.

A total of 22 patients (3.3%; IR – 14.2 and EAIR – 15.0) reported 23 SAEs over a period of 12 weeks and of whom 8 patients (1.2%; IR – 5.1 and EAIR – 5.4) reported 8 SAEs related to study treatment. A total of 28 patients (4.2%; IR – 10.3 and EAIR – 10.9) reported 31 SAEs over a period of 24 weeks and of whom 10 patients (1.5%; IR – 3.6 and EAIR – 3.8) reported 10 SAEs possibly related to study treatment. The only SAEs reported by >1 patient in the population were pneumonia (4 patients, 0.6%), rheumatoid arthritis (3 patients, 0.4%), and arthralgia (2 patients, 0.3%). All the pneumonia cases were reported as possibly related to study treatment. Other SAEs reported as possibly related to study treatment were appendicitis, arthralgia, DILI, influenza, otitis media, and tonsillitis (single events).

A total of 20 patients (3.0%; IR – 12.9 and EAIR – 13.5) reported 22 events that led to permanent drug discontinuation over 12 weeks. A total of 24 patients (3.6%; IR – 8.7 and EAIR – 9.2) reported 26 events that led to permanent drug discontinuation over 24 weeks. Rheumatoid arthritis and arthralgia were the only events reported by at least 2 patients that led to permanent drug discontinuation over 12 weeks and 24 weeks.

A total of 6 patients (0.9%) reported SAEs within the infections and infestations SOC, meeting ICH criteria for seriousness such as hospitalization over 12 weeks. Only 3 serious pneumonia events of these were reported by the investigator as an AESI. A total of 8 patients (1.2%) reported SAEs within the infections and infestations SOC over 24 weeks. Appendicitis was the only additional serious event reported by the investigators as AESI after 12 weeks until 24 weeks.

A total of 16 patients reported 17 hepatotoxicity events over 12 weeks. The events were hepatic function abnormal (14 patients), ALT increased (1 patient), and DILI (1 patient). One event of DILI was an SAE; (a 63-year-old female patient with relevant medical history included fatty liver, experienced hepatic enzyme increased with peak ALT at 351 U/L (0 to 40) and AST at 172 U/L (0 to 40) on Study Day 27. Bilirubin was in normal range and was admitted to hospital. The patient did not have symptoms/signs in association with the event. There is no evidence of viral hepatitis. After corrective treatment was given to protect the liver, ALT and AST returned to normal approximately 38 days later. Baricitinib was temporarily discontinued and restarted after. The opinion of investigator, the event was related to the combined use of baricitinib, leflunomide, MTX, and aceclofenac. A total of 23 patients reported 26 hepatoxicity events over 24 weeks. Hepatic function abnormal (17 patients, 19 events) and DILI (2 patients, 3 events) were the events reported by at least 2 patients. No one met laboratory criteria for potential Hy's Law (ALT/AST ≥3 × ULN and TBIL ≥2 × ULN).

No event related to VTE was reported during the study.

A total of 542 patients (81.2%) were <65 years, 106 patients (15.9%) were ≥65 and <75 years, and 19 patients (2.8%) were ≥75 years. Based on subgroup analyses, safety observations were generally similar between different age subgroups at 12 and 24 weeks. Incidence of SAEs was numerically higher in the ≥65-and-<75–years group (10.4% at 12 and 24 weeks) compared to <65-years (1.8% and 3.0% at 12 and 24 weeks). The ≥75-year group included too few patients (n=19) to make relevant comparisons. Incidence of AEs leading to permanent drug discontinuation was similar in the <65-years (2.6% and 3.0% at 12 and 24 weeks) and ≥65-and-<75–years groups (4.7% at 12 and 24 weeks). Incidence of serious infection was higher in the ≥65-and-<75–years group (1.9% at 12 and 24 weeks) compared to the <65-years (0.2% and 0.4% at 12 and 24 weeks). Incidence of hepatotoxicity was similar in the <65-years (2.2% and 3.5% at 12 and 24 weeks) and ≥65-and-<75–years groups (1.9% at 12 and 24 weeks). Considering that the number of patients with events were small, the interpretability of data is limited.

A total of 580 patients (86.9%) received 2-mg baricitinib, 53 patients (7.9%) received 4 mg, and 34 patients (5.1%) received both dosages. Overall safety observations were similar between different dosage groups, although incidence of AEs leading to permanent drug discontinuation was numerically higher in the 4-mg–only group (7.6% at 12 and 24 weeks) compared to 2-mg–only (2.8% and 3.5% at 12 and 24 weeks).

Effectiveness

For DAS28-CRP, at baseline, most patients belonged to the >3.2 category (83.3%). At 12 weeks (54.2%) and 24 weeks (66.6%), more than half of the effectiveness analysis population belonged to ≤3.2. For DAS28-ESR, at baseline, majority of the population (86.9%) had a >3.2 score and more than half of the population (58.4%) belonged to the >5.1 score category. At 12 weeks, most patients belonged to the >3.2 score (58.0%). At 24 weeks as well, most patients belonged to the ≤3.2 score (54.0%) and >3.2 score (46.0%) categories. For SDAI, at baseline, most patients belonged to the >11.0 category (87.5%). At 12 weeks (52.3%) and 24 weeks (64.6%), more than half of the effectiveness analysis population belonged to ≤11.0. For CDAI, at baseline, most patients belonged to the >10.0 category (88.0%). At 12 weeks (50.3%) and 24 weeks (63.5%), more than half of the effectiveness analysis population belonged to ≤10.0. At baseline, mean (SD) MJS score was 44.7 (52.3). At 12 weeks, mean (SD) change from baseline was −20.6(78.9), and at 24 weeks, mean (SD) change from baseline was −28.3 (47.0). At baseline, mean (SD) VAS score of patients' pain was 5.9 (2.0). At 12 weeks, mean (SD) change from baseline was −2.4 (2.2), and at 24 weeks, mean (SD) change from baseline was −3.0 (2.5).

Overall, baricitinib demonstrated effectiveness in reducing DAS28-ESR, CDAI, and SDAI scores, and showed to be effective when measured through the PROs (pain VAS and MJS).

The DAS28-CRP, SDAI, and CDAI scores at baseline and at 24 weeks were significantly different in the age subgroup and baseline SDAI subgroup. The DAS28-CRP score at baseline was significant for the TNFi-IR subgroup. All other efficacy observations were similar between the subgroups.

11.2. Limitations

As a noninterventional, observational study, I4V-GH-B021(b) has advantages, as a reflection of real-world experience, and limitations. Because it was a single-arm study, it is not feasible to assess the safety and effectiveness of baricitinib compared to other agents. Thus, this study is limited in that the results are only descriptive and must be interpreted in the context of known external information regarding baricitinib and the patient population.

As this was an observational study conducted from 2020 onwards, prescribing physicians followed Chinese recommendations for dosage at the time. The first patient was enrolled on 27 Aug 2020, and the last patient was enrolled on 24 Jan 2022. At the time the study began, patients were required to initiate baricitinib at 2 mg QD as the only approved dosage. However, the protocol was amended in March 2021 to reflect the approval of the 4-mg dose in China, used in patients who have inadequately responded to baricitinib 2 mg QD (for 3 months) or TNFi. Consistent with approved label options, 87% of patients in this study received the 2-mg dose. Only 17 patients with inadequate efficacy after 3 months of treatment had the dosage increased from 2 mg to 4 mg. As few enrolled patients had used prior bDMARDs (4.3%), the majority of the patients (580 [87.0%]) were administered only 2-mg baricitinib, in line with the China label guidance.

The 24-week treatment period is relatively short for the assessment of safety and effectiveness considering the chronic nature of moderate-to-severe active RA. Thus, safety events requiring long-term exposure or events with a long latency period cannot be fully assessed.

A higher rate of loss-of-follow-up (7.0%) was observed in this study compared to clinical trials.

Selection bias:

In this study, in order to reduce potential bias in patient selection, physicians located in different regions invited all patients from the CREDIT platform who met the study criteria to participate in the study.

Information bias:

This observational study was based on primary data collection.

Although the accuracy and completeness of the information entered into the database primarily depended on the reporting physician, the database was built to minimize illogical data entries, and consistency checks were performed between different pieces of data whenever possible by the Sponsor or its representatives. However, this noninterventional study in the real world also reflects some situations that exist in practice, source data verification is delayed because of data entry delay in some sites.

In the electronic data capture (EDC) system, recording bias can result if the information is not systematically recorded or captured inaccurately. For example, physicians tend to register abnormal values more often than normal ones. In this study, however, the extent of this bias was likely to be minimal, as the data that were collected were clinically important for the management of the patient and are provided by treating physicians.

11.3. Interpretation

This final report summarizes safety and effectiveness data from patients with moderate-to-severe RA who were prescribed baricitinib across 31 sites in China, comprising a PMSS. This PMSS programme was able to provide information on safety, effectiveness, and utilisation of baricitinib in the real-world setting.

Analysis of results from this study indicated that the safety profile of baricitinib in clinical settings was generally consistent with the safety profile observed in the clinical trial (RA-BALANCE [a Phase 3 RCT containing 80% Chinese population]), global RA integrated safety analysis (including long-term data from nine Phase 3, Phase 2, and Phase 1b clinical trials, and 1 completed long-term extension study), and Japan all-case PMS study involving all patients with RA who started baricitinib treatment (Li Z et al. 2020, Genovese et al. 2020, Takagi et al. 2022, Taylor et al. 2021).

There were dose regimen differences between this China PMSS and clinical trials or the Japan all-case PMS study. In the clinical trial, Chinese patients were all started with 4 mg QD (Li Z et al. 2020). In the Japan PMS study, approximately two-thirds of patients received 4-mg baricitinib as their initial dose (Takagi et al. 2022). In this PMSS, dose regimen was as follows: 2 mg/day, n = 580 (87.0%); 4 mg/day, n = 53 (8.0%); 2/4 mg, n = 34 (5.1%). As this PMSS was an observational study conducted from 2020 onwards, prescribing physicians followed Chinese recommendations for dosage (2 mg QD as the only approved dosage). The protocol was amended in March 2021 to reflect the approval of the 4-mg dose in China: 2 mg QD is the recommended dose and 4 mg QD can be used in patients who have inadequately responded to baricitinib 2 mg QD (for 3 months) or inadequate responders to TNFis. Because the majority patients in this study did not have bDMARDs as previous treatment, it might result in the different dosage in prescription in this study.

Around 29.5% of patients discontinued the study mainly for patient's decision (n=101) and lost to follow-up (n=47), which was higher than observed in the clinical trial RA-BALANCE study (<10%) (Li Z et al. 2020), but comparable to the Japan noninterventional, observational PMS study (24.8% discontinued up to Week 24) (Takagi et al. 2022).

The proportion of patients reporting AEs over 24 weeks in this PMSS (37.5%) was lower than in the RA-BALANCE study (74.5%) and similar to the incidence in Japan PMS study (26.9%) (Takagi et al. 2022). The incidence of SAEs over 24 weeks in this study (4.2%, EAIR: 10.9) was similar to that in the Japan PMS study (4.3%, IR: 13.4) and global RA integrated safety analysis 0-to-24–week placebo-controlled dataset (EAIR 9.7 for baricitinib 2 mg/ EAIR 12.3 for baricitinib 4 mg) (Genovese et al. 2020, Takagi et al. 2022). Incidence of AEs leading to drug permanent discontinuation over 24 weeks in this study (EAIR 9.2) was similar to that in the global RA integrated safety analysis 0-to-24–week data (EAIR 10.8 for baricitinib 2 mg/EAIR 10.6 for baricitinib 4 mg) (Genovese et al. 2020).

Deaths reported in this study (2 patients [0.3%], IR – 0.7) occurred in patients >65 years with multiple concomitant diseases. The IR of death was similar to the IR in the global RA integrated safety analysis treated with baricitinib 4 mg for 24 weeks (0.6) (Genovese et al. 2020) and the IR

in the Japan PMS (0.4%, IR:0.85) (Takagi et al. 2022); it was within the reported IR of 1.5 to 2.4/100 patient-years in epidemiological studies of RA (Taylor et al. 2021).

The most common AEs in this study (for 24 weeks) were hepatic function abnormal (3.3%), upper respiratory tract infection (2.7%), and platelet count increased (2.4%). The common AEs (≥1% of population) reported were in line with the safety profile of baricitinib as presented in the current label in China. Terms from Adverse Reactions in Table 1 of current Chinese label observed in this study were also within the corresponding frequency range mentioned in the label.

A total of 8 patients (1.2%) reported SAEs within the infections and infestations SOC, similar with the proportion reported in the Japan PMSS or clinical trial (Li Z et al. 2020, Takagi et al. 2022). However, only 4 of these were reported by the investigator as an AESI (serious events of Influenza, otitis media and tonsillitis, and 1 pneumonia were not reported as AESIs).

Incidence of hepatotoxicity (3.4%, IR 8.5) was similar with the Japan PMS study (2.8%, IR 7.2). Postbaseline ALT/AST change to ≥3 × ULN (1.2% and 0.9%, respectively) was similar to the result observed in clinical trials (1.5% for ALT ≥3 × ULN) (Smolen et al 2019) and the Japan PMS study result (0.8% and 0.7%, respectively) over 24 weeks (Taylor et al. 2021). Though 2 AEs with reported term as DILI observed in the study, no one met potential Hy's law criteria (ALT/AST ≥3 × ULN and TBIL ≥2 × ULN) and or reported symptoms/signs in association with the event.

No VTE or MACE (including myocardial infarction, cardiovascular death, and stroke) occurred in this study. Only 1 malignancy of thyroid cancer (53-year-old female with medical history of thyroid nodules, not related to baricitinib as judged by the investigator) occurred in the study. However, these findings should be interpreted with caution given that exposure (24-week observation period) and sample size of this study (N=667) is limited to observe these AEs with a long latency time. VTE is an uncommon ADR of baricitinib. Malignancy and MACE are considered potential safety concerns with JAK inhibitors. In the global integrated safety analysis data, 139 patients (IR 0.9) reported malignancy excluding nonmelanoma skin cancer and 50 patients (IR 0.3) reported nonmelanoma skin cancer. A total of 73 patients (IR 0.5) reported MACE, and 73 patients (IR 0.5) reported deep vein thrombosis events of special interest in the all-Bari-RA dataset for a median of 4.6 years, up to 9.3 years (Taylor et al. 2021). Whereas, in the Japan PMS study, malignancy (including lymphoma) was reported in 17 patients (0.4%, IR 0.91), MACE was reported by 7 patients (0.1%, IR 0.38), and VTE was reported by 7 patients (0.1%, IR 0.38) who had received baricitinib 2 mg or 4 mg (Takagi et al. 2022).

In the previous integrated post-hoc subpopulation analysis, a total of 269 Chinese patients from two Phase 3 studies, RA-BEAM (NCT01710358) and RA-BALANCE (NCT02265705), and 1 long-term extension study RA-BEYOND (NCT01885078) were exposed to baricitinib, with a total of 921 PYE. The mean age of Chinese patients was 48.0 years, all patients were started with 4 mg QD. The majority of PYE (86.7%) were baricitinib 4 mg, while 13.7% of PYE were baricitinib 2 mg. None of the Chinese patients were more than 75 years old, only 11 patients were 65 to <75 years old (Yan et al. 2022). In this PMSS, 580 (87.0%) were treated with

2 mg/day and 34 (5.1%) with 2/4 mg; 106 (15.9%) were ≥65 and <75 years old and 19 (2.8%) were ≥75 years old, providing additional data in these subpopulations.

Safety subgroup analysis for this study suggested that safety profile of baricitinib 2 mg was generally similar to 4 mg. Incidence of AEs leading to permanent drug discontinuation was higher in the 4-mg–only group compared to 2-mg–only, but as these dose groups were not randomized and may differ in disease severity and risk factors, one cannot interpret this comparison.

Safety observations were generally similar between different age subgroups at 12 and 24 weeks, although patients from the ≥65 years group showed numerical differences with some events.

These findings should be interpreted with caution given that most of patients were from the <65 years group (81.3%) and treated with the 2-mg–only group (87.0%); sample size of other groups was limited and imbalanced. In summary, no clinically meaningful differences were noted in AEs by age and dosage.

Given the broad inclusion criteria of the present study, these real-world findings support the safety profile of baricitinib reported in the randomized Phase 3 trials. No new safety signals were observed, and no additional risk minimization activities are required for Chinese patients.

In this study, patients showed improvements in disease activity and PROs from baseline to Week 24 during baricitinib treatment. Similar to the observations from the BALANCE study and the Japan PMS study, with baricitinib treatment, in this study, DAS28-CRP scores kept reducing from baseline to Week 24. The proportion of patients with a SDAI score ≤11 at Week 24 in the BALANCE study was 27.6% (Li Z et al. 2020), and in the current study it was 64.6%. The proportion of patients with a CDAI score ≤10 in the BALANCE study at Week 24 was 26.9% (Li Z et al. 2020), and in the current study it was 63.5%. However, these findings should be interpreted with caution given that almost 30% of all patients discontinued the study, mainly for patient's decision and lost to follow-up. Some of these patients may have stopped because of lack of effectiveness. Similar improvements in achieving remission/low disease activity were also observed in the Japan PMS study with a discontinuation around 25% (Takagi et al. 2022).

Subgroup analysis for effectiveness suggested that baseline characteristics did not substantially affect treatment response. Significant differences were observed in the following: age subgroup for DAS28-CRP scores at baseline and change at 24 weeks, SDAI score at baseline and change at 24 weeks and CDAI score at baseline; baseline SDAI subgroup for DAS28-CRP, SDAI score and CDAI score at baseline and change at 24 weeks, and TNFi-IR for DAS28-CRP score at baseline. All other effectiveness results across patients with different gender, age, disease durations, dosage, and previous TNFi use, were similar.

11.4. Generalisability

This is a single-country, single arm, prospective, noninterventional study designed to collect all AEs and SAEs, including the incidence of AE/SAE related to baricitinib as assessed by investigator, and monitor the effectiveness and PROs of baricitinib at Weeks 12 and 24. The study results may not be generalizable to patients receiving baricitinib for more than 24 weeks.

The demographic characteristics of this study are In agreement with the clinical trial in China (RA-BALANCE) (Li Z et al. 2020), as well as with other global clinical trials (RA-BEAM [Taylor et al. 2017], RA-BEACON [Genovese et al. 2016], RA-BUILD [Dougados et al. 2017], RA-BEGIN [Fleischmann et al. 2017]). No restrictions regarding demographic characteristics were applied, and the observed characteristics of the study population were reflective of the epidemiology of moderate-to-severe active RA.

The patients enrolled from the 31 study sites in 17 provinces of China. These study sites are distributed in different regions of China, which have different natural geographical environments and economic development levels, and people living in these regions have different living habits. The selected study sites included general and local hospitals. Although the choice of study site to participate in the survey was limited by product access challenges and market uptake, results of this PMSS program can be considered generalizable to the populations of Chinese patients with moderate-to-severe active RA.

12. Other information

Not applicable.

13. Conclusions

This observational study was conducted to investigate and describe the incidence of AEs and SAEs and to monitor effectiveness among adult Chinese patients with moderate to severe active RA after receiving baricitinib for a period of 12 and 24 weeks.

The study results did not identify any new safety concern or signal. Baricitinib was effective at reducing disease activity and improving PROs in the real world.

The real-world usage of baricitinib confirmed both safety and effectiveness of baricitinib when used up to 24 weeks in Chinese patients with moderate to severe active RA.

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Annex 1. List of standalone documents

Not applicable.

Annex 2. Tables and figures

Participants

Table ANN. 1. Disposition of Patients - Screened Patients

	N(%)
Number of screened patients	699
Number of enrolled patients	667 (95.42%)
Number of screen failure patients	32 (4.58%)
Doesn't match the inclusion criteria	15 (46.88%)
The patient withdraws informed consent	9 (28.13%)
Other reasons	8 (25.00%)
Days from first study drug to completion or early termination of the study	
n (nmiss)	666 (33)
Mean (Std)	149.35 (54.18)
Median	169.00
Q1, Q3	138.00, 181.00
Min, Max	1, 314
Number of patients completed the study	470 (70.46%)
Number of patients prematurely withdraw from the study	197 (29.54%)
The patient's decision	101 (51.27%)
Lost follow-up	47 (23.86%)
Other reasons	23 (11.68%)
AE	12 (6.09%)
The investigator's decision	12 (6.09%)
Death	2 (1.02%)

Footnote: The percentage denominator of enrolled patients is the number of screening patients. The percentage denominator of patients completed the study is the number of enrolled patients. The percentage denominator of reason for screening failure is the number of screen failure patients. The percentage denominator of reason for prematurely withdraw is the number of patients prematurely withdraw from the study.
Days from first study drug to completion or early termination of the study = completion or early termination date in study termination page – the date of first study drug + 1.

Table ANN. 2. Analyses Population - Enrolled Patients

	Enrolled patients (N=667)
Number of patients in safety analyses population	667 (100.00%)
Number of patients excluded from safety analyses population	0
Number of patients in effectiveness analyses population	514 (77.06%)
Number of patients excluded from effectiveness analyses population, based on safety analyses population	153 (22.94%)
Lack of effectiveness outcomes after study treatment	113 (73.86%)
Study treatment was less than 10 weeks	101 (66.01%)

Footnote: N, number of patients in population.
For number of patients included in or excluded from safety analyses population, the denominator of percentage is the number of enrolled patients.
For number of patients included in or excluded from effectiveness analyses population, the denominator of percentage is the number of patients in safety analyses population.
The denominator of percentage for reason of exclusion is the number of patients excluded from the corresponding analyses population.

Table ANN. 3. **Protocol Deviations - Enrolled Patients**

	Enrolled patients (N=667)
Number of patients with at least one protocol deviation	29 (4.35%)
A2 Informed Consent Problem:The updated Informed Consent Form was not to be signed in time	17 (58.62%)
A3 Informed Consent Problem:The version of Informed Consent Form was to be signed is incorrect, and not be corrected	1 (3.45%)
D3 Visit Schedule:The visit was missing	9 (31.03%)
E1 Safety Reporting:Serious adverse events (SAEs) were reported late, or not reported.	1 (3.45%)
F1 Others:Any other protocol deviation	1 (3.45%)

Footnote: N, number of patients in population.
For number of patients with at least one protocol deviation, the denominator of percentage is the number of enrolled patients.
The denominator of percentage for each protocol deviation category is the number of patients with at least one protocol deviation.

Table ANN. 4. Demographics – Safety Analyses Population

		Safety Analyses Population (N=667)
Age (years)	n (nmiss)	667 (0)
	Mean (Std)	53.25 (12.51)
	Median	54.00
	Q1, Q3	46.00, 62.00
	Min, Max	20, 85
	18-34	61 (9.15%)
	35-44	92 (13.79%)
	45-64	389 (58.32%)
	65-74	106 (15.89%)
	>=75	19 (2.85%)
	Total	667 (100.00%)
Sex	Male	118 (17.69%)
	Female	549 (82.31%)
	Total	667 (100.00%)
Height (cm)	n (nmiss)	666 (1)
	Mean (Std)	160.33 (6.83)
	Median	160.00
	Q1, Q3	156.00, 164.00
	Min, Max	142, 198
Weight (kg)	n (nmiss)	666 (1)
	Mean (Std)	57.48 (10.08)
	Median	56.00
	Q1, Q3	50.00, 64.00
	Min, Max	27.0, 101.0
BMI (kg/m^2)	n (nmiss)	666 (1)
	Mean (Std)	22.32 (3.42)
	Median	21.84
	Q1, Q3	19.84, 24.24
	Min, Max	12.84, 39.45
	<18.5	76 (11.41%)
	>=18.5-<24	399 (59.91%)
	>=24-<28	151 (22.67%)
	>=28	40 (6.01%)
	Total	666 (100.00%)
	Missing	1
Smoking history	Never smoking	585 (87.71%)
	Used to smoke, given up now	29 (4.35%)
	Still smoking	53 (7.95%)
	Total	667 (100.00%)

Footnote: The smoking history information were from 'Life History' page in CRF.
N, number of patients in population; nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.
The percentage denominator is the number of patients with non-missing value.

Table ANN. 5 Demographics – Effectiveness Analyses Population

		Effectiveness Analyses Population (N=514)
Age (years)	n (nmiss)	514 (0)
	Mean (Std)	52.86 (12.61)
	Median	54.00
	Q1, Q3	46.00, 61.00
	Min, Max	20, 85
	18-34	49 (9.53%)
	35-44	73 (14.20%)
	45-64	300 (58.37%)
	65-74	78 (15.18%)
	>=75	14 (2.72%)
	Total	514 (%)
Sex	Male	86 (16.73%)
	Female	428 (83.27%)
	Total	514 (100.00%)
Height (cm)	n (nmiss)	514 (0)
	Mean (Std)	160.45 (6.75)
	Median	160.00
	Q1, Q3	156.00, 165.00
	Min, Max	144, 198
Weight (kg)	n (nmiss)	514 (0)
	Mean (Std)	57.51 (9.97)
	Median	56.00
	Q1, Q3	50.00, 64.00
	Min, Max	27.0, 100.0
BMI (kg/m^2)	n (nmiss)	514 (0)
	Mean (Std)	22.29 (3.34)
	Median	21.76
	Q1, Q3	19.97, 24.24
	Min, Max	12.84, 36.73
	<18.5	56 (10.89%)
	>=18.5-<24	314 (61.09%)
	>=24-<28	113 (21.98%)
	>=28	31 (6.03%)
	Total	514 (100.00%)
Smoking history	Never smoking	455 (88.52%)
	Used to smoke, given up now	21 (4.09%)
	Still smoking	38 (7.39%)
	Total	514 (100.00%)

Footnote: The smoking history information were from 'Life History' page in CRF.
N, number of patients in population; nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.
The percentage denominator is the number of patients with non-missing value.

Table ANN. 6 Prespecified Medical History – Safety Analyses Population

	Safety Analyses Population (N=667)
Number of patients with at least one prespecified medical history	29 (4.35%)
Cardiovascular disease	7 (1.05%)
Hepatic impairment	7 (1.05%)
Fragility fracture	5 (0.75%)
Recent or active infection	4 (0.60%)
Malignancy	4 (0.60%)
Allergy	2 (0.30%)
Venous thromboembolism (VTE)	1 (0.15%)
Renal impairment	0
Severity of hepatic impairment	
Mild	7 (100.00%)
Total	7 (100.00%)

Footnote: N, number of patients in population.
The percentage denominator of patients with at least one prespecified medical history is the number of analyses population.
The percentage denominator of renal impairment severity is the number of patients with renal impairment and non-missing severity.
The percentage denominator of hepatic impairment severity is the number of patients with hepatic impairment and non-missing severity.
Prespecified conditions ended before the first dose of study drug are prespecified medical histories.

Table ANN. 7 Prespecified Medical History – Effectiveness Analyses Population

	Effectiveness Analyses Population (N=514)
Number of patients with at least one prespecified medical history	24 (4.67%)
Hepatic impairment	6 (1.17%)
Cardiovascular disease	5 (0.97%)
Fragility fracture	4 (0.78%)
Malignancy	4 (0.78%)
Recent or active infection	3 (0.58%)
Allergy	2 (0.39%)
Venous thromboembolism (VTE)	1 (0.19%)
Renal impairment	0
Severity of hepatic impairment	
Mild	6 (100.00%)
Total	6 (100.00%)

Footnote: N, number of patients in population.
The percentage denominator of patients with at least one prespecified concomitant disease is the number of analyses population.
The percentage denominator of renal impairment severity is the number of patients with renal impairment and non-missing severity.
The percentage denominator of hepatic impairment severity is the number of patients with hepatic impairment and non-missing severity.
Prespecified conditions ended before the first dose of study drug are prespecified medical histories.

Table ANN. 8 Prespecified Concomitant Disease – Safety Analyses Population

	Safety Analyses Population (N=667)
Number of patients with at least one prespecified concomitant disease	275 (41.23%)
Cardiovascular disease	163 (24.44%)
Allergy	72 (10.79%)
Recent or active infection	54 (8.10%)
Hepatic impairment	45 (6.75%)
Renal impairment	14 (2.10%)
Fragility fracture	13 (1.95%)
Malignancy	3 (0.45%)
Venous thromboembolism (VTE)	3 (0.45%)
Severity of renal impairment	
Mild	12 (85.71%)
Moderate	1 (7.14%)
Severe	1 (7.14%)
Total	14 (0.00%)
Severity of hepatic impairment	
Mild	35 (81.40%)
Moderate	8 (18.60%)
Total	43 (100.00%)
Missing	2

Footnote: N, number of patients in population.
The percentage denominator of patients with at least one prespecified concomitant disease is the number of analyses population.
The percentage denominator of renal impairment severity is the number of patients with renal impairment and non-missing severity.
The percentage denominator of hepatic impairment severity is the number of patients with hepatic impairment and non-missing severity.
Prespecified conditions ended on or after the first dose of study drug or are still ongoing, are prespecified concomitant disease.

Table ANN. 9 **Prespecified Concomitant Disease – Effectiveness Analyses Population**

	Effectiveness Analyses Population (N=514)
Number of patients with at least one prespecified concomitant disease	205 (39.88%)
Cardiovascular disease	119 (23.15%)
Allergy	59 (11.48%)
Recent or active infection	38 (7.39%)
Hepatic impairment	32 (6.23%)
Renal impairment	13 (2.53%)
Fragility fracture	9 (1.75%)
Venous thromboembolism (VTE)	3 (0.58%)
Malignancy	2 (0.39%)
Severity of renal impairment	
Mild	12 (92.31%)
Severe	1 (7.69%)
Total	13 (100.00%)
Severity of hepatic impairment	
Mild	23 (76.67%)
Moderate	7 (23.33%)
Total	30 (100.00%)
Missing	2

Footnote: N, number of patients in population.
The percentage denominator of patients with at least one prespecified concomitant disease is the number of analyses population.
The percentage denominator of renal impairment severity is the number of patients with renal impairment and non-missing severity.
The percentage denominator of hepatic impairment severity is the number of patients with hepatic impairment and non-missing severity.
Prespecified conditions ended on or after the first dose of study drug or are still ongoing, are prespecified concomitant disease.

Table ANN. 10 **Prespecified Medical History and Prespecified Concomitant Disease – Safety Analyses Population**

	Safety Analyses Population (N=667)
Number of patients with at least one prespecified medical history or prespecified concomitant disease	290 (43.48%)
Cardiovascular disease	168 (25.19%)
Allergy	74 (11.09%)
Recent or active infection	58 (8.70%)
Hepatic impairment	52 (7.80%)
Fragility fracture	18 (2.70%)
Renal impairment	14 (2.10%)
Malignancy	7 (1.05%)
Venous thromboembolism (VTE)	4 (0.60%)
Severity of renal impairment	
Mild	12 (85.71%)
Moderate	1 (7.14%)
Severe	1 (7.14%)
Total	14 (0.00%)
Severity of hepatic impairment	
Mild	42 (84.00%)
Moderate	8 (16.00%)
Total	50 (100.00%)
Missing	2

Footnote: N, number of patients in population.
The percentage denominator of patients with at least one prespecified medical history or prespecified concomitant disease is the number of analyses population.
The percentage denominator of renal impairment severity is the number of patients with renal impairment and non-missing severity.
The percentage denominator of hepatic impairment severity is the number of patients with hepatic impairment and non-missing severity.
Prespecified conditions ended before the first dose of study drug are prespecified medical histories.
Prespecified conditions ended on or after the first dose of study drug or are still ongoing, are prespecified concomitant disease.

Table ANN. 11 Prespecified Medical History and Prespecified Concomitant Disease – Effectiveness Analyses Population

	Effectiveness Analyses Population (N=514)
Number of patients with at least one prespecified medical history or prespecified concomitant disease	218 (42.41%)
Cardiovascular disease	122 (23.74%)
Allergy	61 (11.87%)
Recent or active infection	41 (7.98%)
Hepatic impairment	38 (7.39%)
Fragility fracture	13 (2.53%)
Renal impairment	13 (2.53%)
Malignancy	6 (1.17%)
Venous thromboembolism (VTE)	4 (0.78%)
Severity of renal impairment	
Mild	12 (92.31%)
Severe	1 (7.69%)
Total	13 (100.00%)
Severity of hepatic impairment	
Mild	29 (80.56%)
Moderate	7 (19.44%)
Total	36 (100.00%)
Missing	2

Footnote: N, number of patients in population.
The percentage denominator of patients with at least one prespecified medical history or prespecified concomitant disease is the number of analyses population.
The percentage denominator of renal impairment severity is the number of patients with renal impairment and non-missing severity.
The percentage denominator of hepatic impairment severity is the number of patients with hepatic impairment and non-missing severity.
Prespecified conditions ended before the first dose of study drug are prespecified medical histories.
Prespecified conditions ended on or after the first dose of study drug or are still ongoing, are prespecified concomitant disease.

Table ANN. 12 Other Pre-existing Conditions/Medical History – Safety Analyses Population

SOC *PT*	*Safety Analyses Population (N=667)*
Number of patients have an allergy history	74 (11.09%)
Number of patients have a family history	32 (4.80%)
Number of patients experienced any historical illnesses, pre-existing conditions, or past surgeries other than prespecified medical history	91 (13.64%)
Surgical and medical procedures	60 (9.00%)
Knee arthroplasty	10 (1.50%)
Hip arthroplasty	6 (0.90%)
Hysterectomy	6 (0.90%)
Appendicectomy	4 (0.60%)
Cataract operation	3 (0.45%)
Joint arthroplasty	3 (0.45%)
Myomectomy	3 (0.45%)
Cholecystectomy	2 (0.30%)
Intervertebral disc operation	2 (0.30%)
Lithotripsy	2 (0.30%)
Mass excision	2 (0.30%)
Meniscus operation	2 (0.30%)
Spinal fusion surgery	2 (0.30%)
Spinal operation	2 (0.30%)
Thyroidectomy	2 (0.30%)
Arterial stent insertion	1 (0.15%)
Arthrodesis	1 (0.15%)
Breast operation	1 (0.15%)
Bunion operation	1 (0.15%)
Cervical conisation	1 (0.15%)
Fracture treatment	1 (0.15%)
Gastric polypectomy	1 (0.15%)
Gastrorrhaphy	1 (0.15%)
Knee operation	1 (0.15%)
Limb operation	1 (0.15%)
Lung neoplasm surgery	1 (0.15%)
Meningioma surgery	1 (0.15%)
Open reduction of fracture	1 (0.15%)
Osteotomy	1 (0.15%)
Ovarian operation	1 (0.15%)
Pituitary tumour removal	1 (0.15%)
Plastic surgery	1 (0.15%)
Pulmonary bullectomy	1 (0.15%)
Salpingo-oophorectomy bilateral	1 (0.15%)
Sinus operation	1 (0.15%)
Synovectomy	1 (0.15%)
Synovial cyst removal	1 (0.15%)
Thyroid adenoma removal	1 (0.15%)
Ureteric operation	1 (0.15%)
Uterine dilation and curettage	1 (0.15%)
Varicose vein operation	1 (0.15%)

Footnote: N, number of patients in population; PT, preferred term; SOC, system organ class.
Allergy history and family history information were from 'Life History' page in CRF.
The percentage denominator is the number of analyses population.
Other pre-existing conditions and medical histories are those ended before the first dose of study drug.
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SOC *PT*	*Safety Analyses Population* *(N=667)*
Infections and infestations	9 (1.35%)
Pulmonary tuberculosis	3 (0.45%)
Pneumonia	2 (0.30%)
Tuberculosis	2 (0.30%)
Bronchitis	1 (0.15%)
Herpes zoster	1 (0.15%)
Injury, poisoning and procedural complications	5 (0.75%)
Back injury	1 (0.15%)
Hand fracture	1 (0.15%)
Lower limb fracture	1 (0.15%)
Rib fracture	1 (0.15%)
Soft tissue injury	1 (0.15%)
Endocrine disorders	4 (0.60%)
Euthyroid sick syndrome	1 (0.15%)
Goitre	1 (0.15%)
Hyperthyroidism	1 (0.15%)
Thyroid mass	1 (0.15%)
Gastrointestinal disorders	4 (0.60%)
Duodenal ulcer	2 (0.30%)
Diarrhoea	1 (0.15%)
Pancreatitis acute	1 (0.15%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (0.60%)
Uterine leiomyoma	3 (0.45%)
Thyroid neoplasm	1 (0.15%)
Reproductive system and breast disorders	4 (0.60%)
Cervical dysplasia	1 (0.15%)
Endometriosis	1 (0.15%)
Ovarian cyst	1 (0.15%)
Uterine polyp	1 (0.15%)
Blood and lymphatic system disorders	3 (0.45%)
Leukopenia	3 (0.45%)
Musculoskeletal and connective tissue disorders	3 (0.45%)
Intervertebral disc protrusion	1 (0.15%)
Osteonecrosis	1 (0.15%)
Spinal osteoarthritis	1 (0.15%)
Respiratory, thoracic and mediastinal disorders	3 (0.45%)
Cough	1 (0.15%)
Interstitial lung disease	1 (0.15%)
Paranasal sinus inflammation	1 (0.15%)
Metabolism and nutrition disorders	2 (0.30%)

Footnote: N, number of patients in population; PT, preferred term; SOC, system organ class.
Allergy history and family history information were from 'Life History' page in CRF.
The percentage denominator is the number of analyses population.
Other pre-existing conditions and medical histories are those ended before the first dose of study drug.

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SOC *PT*	*Safety Analyses Population* *(N=667)*
Hyperuricaemia	1 (0.15%)
Hypokalaemia	1 (0.15%)
Renal and urinary disorders	2 (0.30%)
Nephrolithiasis	1 (0.15%)
Renal hydrocele	1 (0.15%)
Stress urinary incontinence	1 (0.15%)
Ureterolithiasis	1 (0.15%)
Skin and subcutaneous tissue disorders	2 (0.30%)
Pruritus	1 (0.15%)
Psoriasis	1 (0.15%)
Hepatobiliary disorders	1 (0.15%)
Cholecystitis acute	1 (0.15%)
Investigations	1 (0.15%)
Hysteroscopy	1 (0.15%)
Nervous system disorders	1 (0.15%)
Head discomfort	1 (0.15%)

Footnote: N, number of patients in population; PT, preferred term; SOC, system organ class.
Allergy history and family history information were from 'Life History' page in CRF.
The percentage denominator is the number of analyses population.
Other pre-existing conditions and medical histories are those ended before the first dose of study drug.
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Table ANN. 13 Other Pre-existing Conditions/Medical History – Effectiveness Analyses Population

SOC PT	*Effectiveness Analyses Population (N=514)*
Number of patients have an allergy history	61 (11.87%)
Number of patients have a family history	26 (5.06%)
Number of patients experienced any historical illnesses, pre-existing conditions, or past surgeries other than prespecified medical history	71 (13.81%)
Surgical and medical procedures	47 (9.14%)
Knee arthroplasty	6 (1.17%)
Hip arthroplasty	5 (0.97%)
Hysterectomy	5 (0.97%)
Cataract operation	3 (0.58%)
Myomectomy	3 (0.58%)
Appendicectomy	2 (0.39%)
Cholecystectomy	2 (0.39%)
Intervertebral disc operation	2 (0.39%)
Joint arthroplasty	2 (0.39%)
Lithotripsy	2 (0.39%)
Mass excision	2 (0.39%)
Spinal fusion surgery	2 (0.39%)
Thyroidectomy	2 (0.39%)
Arterial stent insertion	1 (0.19%)
Bunion operation	1 (0.19%)
Cervical conisation	1 (0.19%)
Gastric polypectomy	1 (0.19%)
Gastrorrhaphy	1 (0.19%)
Knee operation	1 (0.19%)
Limb operation	1 (0.19%)
Lung neoplasm surgery	1 (0.19%)
Meningioma surgery	1 (0.19%)
Meniscus operation	1 (0.19%)
Osteotomy	1 (0.19%)
Ovarian operation	1 (0.19%)
Pituitary tumour removal	1 (0.19%)
Plastic surgery	1 (0.19%)
Pulmonary bullectomy	1 (0.19%)
Salpingo-oophorectomy bilateral	1 (0.19%)
Sinus operation	1 (0.19%)
Spinal operation	1 (0.19%)
Synovectomy	1 (0.19%)
Synovial cyst removal	1 (0.19%)
Thyroid adenoma removal	1 (0.19%)
Ureteric operation	1 (0.19%)
Uterine dilation and curettage	1 (0.19%)
Varicose vein operation	1 (0.19%)
Infections and infestations	6 (1.17%)
Pulmonary tuberculosis	3 (0.58%)
Herpes zoster	1 (0.19%)
Pneumonia	1 (0.19%)

Footnote: N, number of patients in population; PT, preferred term; SOC, system organ class.
Allergy history and family history information were from ‘Life History’ page in CRF.
The percentage denominator is the number of analyses population.
Other pre-existing conditions and medical histories are those ended before the first dose of study drug.
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SOC *PT*	*Effectiveness Analyses Population (N=514)*
Tuberculosis	1 (0.19%)
Endocrine disorders	4 (0.78%)
Euthyroid sick syndrome	1 (0.19%)
Goitre	1 (0.19%)
Hyperthyroidism	1 (0.19%)
Thyroid mass	1 (0.19%)
Reproductive system and breast disorders	4 (0.78%)
Cervical dysplasia	1 (0.19%)
Endometriosis	1 (0.19%)
Ovarian cyst	1 (0.19%)
Uterine polyp	1 (0.19%)
Blood and lymphatic system disorders	3 (0.58%)
Leukopenia	3 (0.58%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (0.58%)
Uterine leiomyoma	2 (0.39%)
Thyroid neoplasm	1 (0.19%)
Respiratory, thoracic and mediastinal disorders	3 (0.58%)
Cough	1 (0.19%)
Interstitial lung disease	1 (0.19%)
Paranasal sinus inflammation	1 (0.19%)
Gastrointestinal disorders	2 (0.39%)
Diarrhoea	1 (0.19%)
Duodenal ulcer	1 (0.19%)
Injury, poisoning and procedural complications	2 (0.39%)
Hand fracture	1 (0.19%)
Rib fracture	1 (0.19%)
Metabolism and nutrition disorders	2 (0.39%)
Hyperuricaemia	1 (0.19%)
Hypokalaemia	1 (0.19%)
Musculoskeletal and connective tissue disorders	2 (0.39%)
Intervertebral disc protrusion	1 (0.19%)
Spinal osteoarthritis	1 (0.19%)
Renal and urinary disorders	2 (0.39%)
Nephrolithiasis	1 (0.19%)
Renal hydrocele	1 (0.19%)
Stress urinary incontinence	1 (0.19%)
Ureterolithiasis	1 (0.19%)
Hepatobiliary disorders	1 (0.19%)

Footnote: N, number of patients in population; PT, preferred term; SOC, system organ class.
Allergy history and family history information were from 'Life History' page in CRF.
The percentage denominator is the number of analyses population.
Other pre-existing conditions and medical histories are those ended before the first dose of study drug.

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SOC *PT*	*Effectiveness Analyses Population (N=514)*
Cholecystitis acute	1 (0.19%)
Investigations	1 (0.19%)
Hysteroscopy	1 (0.19%)
Nervous system disorders	1 (0.19%)
Head discomfort	1 (0.19%)
Skin and subcutaneous tissue disorders	1 (0.19%)
Psoriasis	1 (0.19%)

Footnote: N, number of patients in population; PT, preferred term; SOC, system organ class.
Allergy history and family history information were from 'Life History' page in CRF.
The percentage denominator is the number of analyses population.
Other pre-existing conditions and medical histories are those ended before the first dose of study drug.
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Table ANN. 14 Other Concomitant Disease – Safety Analyses Population

SOC *PT*	*Safety Analyses Population (N=667)*
Number of patients have any concomitant disease other than those prespecified	417 (62.52%)
Musculoskeletal and connective tissue disorders	193 (28.94%)
Osteoporosis	101 (15.14%)
Osteoarthritis	32 (4.80%)
Sjogren's syndrome	30 (4.50%)
Intervertebral disc protrusion	29 (4.35%)
Spinal osteoarthritis	22 (3.30%)
Connective tissue disorder	8 (1.20%)
Osteonecrosis	8 (1.20%)
Arthropathy	7 (1.05%)
Osteopenia	6 (0.90%)
Systemic lupus erythematosus	6 (0.90%)
Tenosynovitis	6 (0.90%)
Synovial cyst	4 (0.60%)
Synovitis	4 (0.60%)
Ankylosing spondylitis	3 (0.45%)
Lumbar spinal stenosis	3 (0.45%)
Periarthritis	3 (0.45%)
Rotator cuff syndrome	3 (0.45%)
Fasciitis	2 (0.30%)
Intervertebral disc degeneration	2 (0.30%)
Osteoarthropathy	2 (0.30%)
Palindromic rheumatism	2 (0.30%)
Sacroiliitis	2 (0.30%)
Tendon disorder	2 (0.30%)
Arthralgia	1 (0.15%)
Bone erosion	1 (0.15%)
Bone formation increased	1 (0.15%)
Bone hypertrophy	1 (0.15%)
Fibromyalgia	1 (0.15%)
Foot deformity	1 (0.15%)
Gouty arthritis	1 (0.15%)
Gouty tophus	1 (0.15%)
Haematoma muscle	1 (0.15%)
Intervertebral disc disorder	1 (0.15%)
Limb mass	1 (0.15%)
Myopathy	1 (0.15%)
Neck mass	1 (0.15%)
Neck pain	1 (0.15%)
Polymyositis	1 (0.15%)
Spondylolisthesis	1 (0.15%)
Synovial disorder	1 (0.15%)
Systemic scleroderma	1 (0.15%)
Temporomandibular joint syndrome	1 (0.15%)
Tendon calcification	1 (0.15%)
Tendonitis	1 (0.15%)
Tenosynovitis stenosans	1 (0.15%)
Undifferentiated connective tissue disease	1 (0.15%)
Vertebral osteophyte	1 (0.15%)

Footnote: PT, preferred term; SOC, system organ class.

The percentage denominator is the number of analyses population.
Other concomitant diseases are those ended on or after the first dose of study drug or are still ongoing.
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SOC *PT*	*Safety Analyses Population* *(N=667)*
Metabolism and nutrition disorders	136 (20.39%)
Hyperlipidaemia	52 (7.80%)
Diabetes mellitus	23 (3.45%)
Hypoproteinaemia	21 (3.15%)
Type 2 diabetes mellitus	17 (2.55%)
Hyperuricaemia	16 (2.40%)
Hypokalaemia	13 (1.95%)
Hypoalbuminaemia	9 (1.35%)
Vitamin D deficiency	7 (1.05%)
Hypercholesterolaemia	4 (0.60%)
Hyperglycaemia	4 (0.60%)
Dyslipidaemia	3 (0.45%)
Electrolyte imbalance	3 (0.45%)
Hypocalcaemia	3 (0.45%)
Glucose tolerance impaired	2 (0.30%)
Hypertriglyceridaemia	2 (0.30%)
Malnutrition	2 (0.30%)
Cachexia	1 (0.15%)
Gout	1 (0.15%)
Hyperkalaemia	1 (0.15%)
Impaired fasting glucose	1 (0.15%)
Lactose intolerance	1 (0.15%)
Obesity	1 (0.15%)
Steroid diabetes	1 (0.15%)
Respiratory, thoracic and mediastinal disorders	128 (19.19%)
Interstitial lung disease	50 (7.50%)
Pulmonary mass	50 (7.50%)
Bronchiectasis	10 (1.50%)
Emphysema	9 (1.35%)
Rheumatoid arthritis-associated interstitial lung disease	7 (1.05%)
Bronchitis chronic	6 (0.90%)
Asthma	5 (0.75%)
Chronic obstructive pulmonary disease	4 (0.60%)
Cough	2 (0.30%)
Cystic lung disease	2 (0.30%)
Pleural thickening	2 (0.30%)
Epiglottic cyst	1 (0.15%)
Laryngeal oedema	1 (0.15%)
Oropharyngeal pain	1 (0.15%)
Pleural disorder	1 (0.15%)
Pleural effusion	1 (0.15%)
Productive cough	1 (0.15%)
Pulmonary calcification	1 (0.15%)
Pulmonary fibrosis	1 (0.15%)
Pulmonary sarcoidosis	1 (0.15%)
Rhinitis allergic	1 (0.15%)
Sinus polyp degeneration	1 (0.15%)
Tracheal diverticulum	1 (0.15%)

Footnote: PT, preferred term; SOC, system organ class.
The percentage denominator is the number of analyses population.
Other concomitant diseases are those ended on or after the first dose of study drug or are still ongoing.
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SOC *PT*	*Safety Analyses Population* *(N=667)*
Blood and lymphatic system disorders	102 (15.29%)
Anaemia	73 (10.94%)
Iron deficiency anaemia	7 (1.05%)
Leukopenia	6 (0.90%)
Lymphadenopathy	6 (0.90%)
Thrombocytosis	5 (0.75%)
Anaemia of chronic disease	2 (0.30%)
Coagulopathy	2 (0.30%)
Hyperglobulinaemia	2 (0.30%)
Lymphopenia	2 (0.30%)
Secondary thrombocytosis	2 (0.30%)
Hypochromic anaemia	1 (0.15%)
Leukocytosis	1 (0.15%)
Lymphadenopathy mediastinal	1 (0.15%)
Neutropenia	1 (0.15%)
Spleen atrophy	1 (0.15%)
Splenomegaly	1 (0.15%)
White blood cell disorder	1 (0.15%)
Gastrointestinal disorders	93 (13.94%)
Chronic gastritis	32 (4.80%)
Gastritis erosive	30 (4.50%)
Gastritis	8 (1.20%)
Gastrooesophageal reflux disease	7 (1.05%)
Duodenal ulcer	5 (0.75%)
Gastric ulcer	5 (0.75%)
Diverticulum intestinal	3 (0.45%)
Gastric disorder	3 (0.45%)
Gastric polyps	3 (0.45%)
Haemorrhoids	2 (0.30%)
Large intestine polyp	2 (0.30%)
Abdominal pain	1 (0.15%)
Colitis	1 (0.15%)
Crohn's disease	1 (0.15%)
Diarrhoea	1 (0.15%)
Duodenal ulcer haemorrhage	1 (0.15%)
Dysbiosis	1 (0.15%)
Functional gastrointestinal disorder	1 (0.15%)
Gastric ulcer haemorrhage	1 (0.15%)
Gastroduodenal ulcer	1 (0.15%)
Gingival bleeding	1 (0.15%)
Intestinal polyp	1 (0.15%)
Parotid gland enlargement	1 (0.15%)
Salivary gland cyst	1 (0.15%)
Upper gastrointestinal perforation	1 (0.15%)
Hepatobiliary disorders	84 (12.59%)
Hepatic steatosis	37 (5.55%)
Cholelithiasis	20 (3.00%)

Footnote: PT, preferred term; SOC, system organ class.
The percentage denominator is the number of analyses population.
Other concomitant diseases are those ended on or after the first dose of study drug or are still ongoing.
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SOC *PT*	*Safety Analyses Population* *(N=667)*
Hepatic cyst	19 (2.85%)
Gallbladder polyp	8 (1.20%)
Bile duct stone	5 (0.75%)
Cholecystitis	2 (0.30%)
Cholecystitis chronic	2 (0.30%)
Hepatic calcification	2 (0.30%)
Hyperplastic cholecystopathy	2 (0.30%)
Biliary dilatation	1 (0.15%)
Cholecystitis acute	1 (0.15%)
Hepatic atrophy	1 (0.15%)
Hepatic function abnormal	1 (0.15%)
Post cholecystectomy syndrome	1 (0.15%)
Endocrine disorders	56 (8.40%)
Thyroid mass	28 (4.20%)
Hypothyroidism	16 (2.40%)
Autoimmune thyroiditis	3 (0.45%)
Goitre	3 (0.45%)
Thyroid disorder	3 (0.45%)
Euthyroid sick syndrome	2 (0.30%)
Hyperthyroidism	2 (0.30%)
Adrenal disorder	1 (0.15%)
Autoimmune thyroid disorder	1 (0.15%)
Glucocorticoid deficiency	1 (0.15%)
Thyroid cyst	1 (0.15%)
Renal and urinary disorders	44 (6.60%)
Nephrolithiasis	25 (3.75%)
Renal cyst	21 (3.15%)
Acquired cystic kidney disease	2 (0.30%)
Calculus urinary	1 (0.15%)
Chronic kidney disease	1 (0.15%)
Hydronephrosis	1 (0.15%)
Pyelocaliectasis	1 (0.15%)
Renal hydrocele	1 (0.15%)
Renal mass	1 (0.15%)
Ureterolithiasis	1 (0.15%)
Infections and infestations	41 (6.15%)
Latent tuberculosis	10 (1.50%)
Chronic hepatitis B	6 (0.90%)
Bronchitis	4 (0.60%)
Tuberculosis	3 (0.45%)
Chronic sinusitis	2 (0.30%)
Conjunctivitis	2 (0.30%)
Hepatitis B	2 (0.30%)
Laryngopharyngitis	2 (0.30%)
Pharyngitis	2 (0.30%)
Pulmonary tuberculosis	2 (0.30%)
Sinusitis	2 (0.30%)

Footnote: PT, preferred term; SOC, system organ class.
The percentage denominator is the number of analyses population.
Other concomitant diseases are those ended on or after the first dose of study drug or are still ongoing.
MedDRA English version 25.1

SOC *PT*	*Safety Analyses Population* *(N=667)*
Viral hepatitis carrier	2 (0.30%)
Bone tuberculosis	1 (0.15%)
Dermatophytosis of nail	1 (0.15%)
Lung abscess	1 (0.15%)
Onychomycosis	1 (0.15%)
Periodontitis	1 (0.15%)
Upper respiratory tract infection	1 (0.15%)
Urinary tract infection	1 (0.15%)
Vaginal infection	1 (0.15%)
Surgical and medical procedures	33 (4.95%)
Hip arthroplasty	4 (0.60%)
Knee arthroplasty	4 (0.60%)
Appendicectomy	3 (0.45%)
Cholecystectomy	3 (0.45%)
Hysterectomy	2 (0.30%)
Internal fixation of spine	2 (0.30%)
Thyroidectomy	2 (0.30%)
Ankle operation	1 (0.15%)
Arthroscopic surgery	1 (0.15%)
Bladder neoplasm surgery	1 (0.15%)
Breast operation	1 (0.15%)
Cholelithotomy	1 (0.15%)
Closed fracture manipulation	1 (0.15%)
Coronary arterial stent insertion	1 (0.15%)
Duodenal ulcer repair	1 (0.15%)
Eye operation	1 (0.15%)
Joint debridement	1 (0.15%)
Laparoscopic surgery	1 (0.15%)
Mitral valve replacement	1 (0.15%)
Myomectomy	1 (0.15%)
Renal stone removal	1 (0.15%)
Synovectomy	1 (0.15%)
Uterine polypectomy	1 (0.15%)
Vocal cord polypectomy	1 (0.15%)
Investigations	32 (4.80%)
Platelet count increased	4 (0.60%)
Blood glucose increased	3 (0.45%)
Cortisol abnormal	3 (0.45%)
Gamma-glutamyltransferase increased	3 (0.45%)
Lymphocyte count decreased	3 (0.45%)
Glucose tolerance decreased	2 (0.30%)
White blood cell count decreased	2 (0.30%)
White blood cells urine positive	2 (0.30%)
Arthroscopy	1 (0.15%)
Aspartate aminotransferase increased	1 (0.15%)
Blood glucose abnormal	1 (0.15%)
Blood methaemoglobin	1 (0.15%)
Blood uric acid increased	1 (0.15%)

Footnote: PT, preferred term; SOC, system organ class.
The percentage denominator is the number of analyses population.
Other concomitant diseases are those ended on or after the first dose of study drug or are still ongoing.
MedDRA English version 25.1

SOC *PT*	*Safety Analyses Population* *(N=667)*
Carbohydrate antigen 19-9 increased	1 (0.15%)
Coagulation test abnormal	1 (0.15%)
Glucose tolerance test abnormal	1 (0.15%)
Mycobacterium tuberculosis complex test positive	1 (0.15%)
Neurone-specific enolase increased	1 (0.15%)
Neutrophil count decreased	1 (0.15%)
Neutrophil count increased	1 (0.15%)
Serum ferritin increased	1 (0.15%)
Total bile acids increased	1 (0.15%)
Tumour marker increased	1 (0.15%)
Urinary occult blood positive	1 (0.15%)
Vitamin D decreased	1 (0.15%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	27 (4.05%)
Uterine leiomyoma	12 (1.80%)
Haemangioma of liver	6 (0.90%)
Renal hamartoma	3 (0.45%)
Benign ovarian tumour	1 (0.15%)
Fibroadenoma of breast	1 (0.15%)
Haemangioma	1 (0.15%)
Haemangioma of bone	1 (0.15%)
Meningioma	1 (0.15%)
Myelodysplastic syndrome	1 (0.15%)
Renal lipoma	1 (0.15%)
Skin papilloma	1 (0.15%)
Reproductive system and breast disorders	26 (3.90%)
Benign prostatic hyperplasia	6 (0.90%)
Breast mass	6 (0.90%)
Breast hyperplasia	2 (0.30%)
Prostatitis	2 (0.30%)
Adnexa uteri cyst	1 (0.15%)
Breast calcifications	1 (0.15%)
Endometriosis	1 (0.15%)
Galactocele	1 (0.15%)
Hydrometra	1 (0.15%)
Menopausal symptoms	1 (0.15%)
Menstruation irregular	1 (0.15%)
Ovarian cyst	1 (0.15%)
Prostatic calcification	1 (0.15%)
Uterine disorder	1 (0.15%)
Injury, poisoning and procedural complications	23 (3.45%)
Meniscus injury	6 (0.90%)
Pneumoconiosis	4 (0.60%)
Rib fracture	3 (0.45%)
Tendon injury	2 (0.30%)
Femur fracture	1 (0.15%)
Fibula fracture	1 (0.15%)
Ligament injury	1 (0.15%)

Footnote: PT, preferred term; SOC, system organ class.
The percentage denominator is the number of analyses population.
Other concomitant diseases are those ended on or after the first dose of study drug or are still ongoing.

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SOC *PT*	*Safety Analyses Population* *(N=667)*
Lumbar vertebral fracture	1 (0.15%)
Open globe injury	1 (0.15%)
Pelvic bone injury	1 (0.15%)
Radius fracture	1 (0.15%)
Silicosis	1 (0.15%)
Thermal burn	1 (0.15%)
Eye disorders	19 (2.85%)
Cataract	9 (1.35%)
Xerophthalmia	6 (0.90%)
Meibomian gland dysfunction	2 (0.30%)
Asthenopia	1 (0.15%)
Corneal exfoliation	1 (0.15%)
Dry eye	1 (0.15%)
Eyelid oedema	1 (0.15%)
Pterygium	1 (0.15%)
Trichiasis	1 (0.15%)
Vitreous floaters	1 (0.15%)
Psychiatric disorders	17 (2.55%)
Sleep disorder	10 (1.50%)
Insomnia	3 (0.45%)
Anxiety	2 (0.30%)
Anxiety disorder	2 (0.30%)
Depression	1 (0.15%)
Schizophrenia	1 (0.15%)
Nervous system disorders	16 (2.40%)
Neuropathy peripheral	3 (0.45%)
Carpal tunnel syndrome	2 (0.30%)
Cerebral atrophy	2 (0.30%)
Cervical radiculopathy	2 (0.30%)
Autonomic nervous system imbalance	1 (0.15%)
Diabetic neuropathy	1 (0.15%)
Lumbar radiculopathy	1 (0.15%)
Myasthenia gravis	1 (0.15%)
Myelopathy	1 (0.15%)
Paralysis	1 (0.15%)
Parkinsonism	1 (0.15%)
Post herpetic neuralgia	1 (0.15%)
Sciatica	1 (0.15%)
Skin and subcutaneous tissue disorders	9 (1.35%)
Dermatitis	2 (0.30%)
Urticaria	2 (0.30%)
Alopecia areata	1 (0.15%)
Decubitus ulcer	1 (0.15%)
Dermal cyst	1 (0.15%)
Papule	1 (0.15%)
Rash maculo-papular	1 (0.15%)

Footnote: PT, preferred term; SOC, system organ class.
The percentage denominator is the number of analyses population.
Other concomitant diseases are those ended on or after the first dose of study drug or are still ongoing.
MedDRA English version 25.1

SOC *PT*	*Safety Analyses Population* *(N=667)*
Urticaria chronic	1 (0.15%)
Congenital, familial and genetic disorders	5 (0.75%)
Thalassaemia	2 (0.30%)
Kidney duplex	1 (0.15%)
Retinitis pigmentosa	1 (0.15%)
Thalassaemia alpha	1 (0.15%)
General disorders and administration site conditions	5 (0.75%)
Oedema peripheral	3 (0.45%)
Hernia	1 (0.15%)
Systemic inflammatory response syndrome	1 (0.15%)
Ear and labyrinth disorders	4 (0.60%)
Vertigo	2 (0.30%)
Ear pain	1 (0.15%)
Mixed deafness	1 (0.15%)
Immune system disorders	3 (0.45%)
Decreased immune responsiveness	2 (0.30%)
Immune system disorder	1 (0.15%)
Vascular disorders	2 (0.30%)
Rheumatoid vasculitis	1 (0.15%)
Vasculitis	1 (0.15%)

Footnote: PT, preferred term; SOC, system organ class.
The percentage denominator is the number of analyses population.
Other concomitant diseases are those ended on or after the first dose of study drug or are still ongoing.
MedDRA English version 25.1

Table ANN. 15 Other Concomitant Disease – Effectiveness Analyses Population

SOC *PT*	*Effectiveness Analyses Population (N=514)*
Number of patients have any concomitant disease other than those prespecified	322 (62.65%)
Musculoskeletal and connective tissue disorders	153 (29.77%)
Osteoporosis	80 (15.56%)
Sjogren's syndrome	27 (5.25%)
Intervertebral disc protrusion	26 (5.06%)
Osteoarthritis	24 (4.67%)
Spinal osteoarthritis	15 (2.92%)
Osteonecrosis	8 (1.56%)
Connective tissue disorder	7 (1.36%)
Systemic lupus erythematosus	6 (1.17%)
Arthropathy	4 (0.78%)
Osteopenia	4 (0.78%)
Ankylosing spondylitis	3 (0.58%)
Periarthritis	3 (0.58%)
Rotator cuff syndrome	3 (0.58%)
Tenosynovitis	3 (0.58%)
Fasciitis	2 (0.39%)
Lumbar spinal stenosis	2 (0.39%)
Osteoarthropathy	2 (0.39%)
Palindromic rheumatism	2 (0.39%)
Synovial cyst	2 (0.39%)
Arthralgia	1 (0.19%)
Bone formation increased	1 (0.19%)
Bone hypertrophy	1 (0.19%)
Fibromyalgia	1 (0.19%)
Foot deformity	1 (0.19%)
Gouty arthritis	1 (0.19%)
Gouty tophus	1 (0.19%)
Haematoma muscle	1 (0.19%)
Limb mass	1 (0.19%)
Myopathy	1 (0.19%)
Neck mass	1 (0.19%)
Neck pain	1 (0.19%)
Polymyositis	1 (0.19%)
Sacroiliitis	1 (0.19%)
Spondylolisthesis	1 (0.19%)
Synovial disorder	1 (0.19%)
Synovitis	1 (0.19%)
Systemic scleroderma	1 (0.19%)
Tendon disorder	1 (0.19%)
Tenosynovitis stenosans	1 (0.19%)
Vertebral osteophyte	1 (0.19%)
Respiratory, thoracic and mediastinal disorders	103 (20.04%)
Interstitial lung disease	45 (8.75%)
Pulmonary mass	39 (7.59%)
Bronchiectasis	9 (1.75%)
Emphysema	6 (1.17%)
Bronchitis chronic	5 (0.97%)

Footnote: PT, preferred term; SOC, system organ class.

The percentage denominator is the number of analyses population.
Other concomitant diseases are those ended on or after the first dose of study drug or are still ongoing.
MedDRA English version 25.1

SOC *PT*	*Effectiveness Analyses Population* *(N=514)*
Rheumatoid arthritis-associated interstitial lung disease	4 (0.78%)
Asthma	3 (0.58%)
Chronic obstructive pulmonary disease	3 (0.58%)
Cystic lung disease	2 (0.39%)
Pleural thickening	2 (0.39%)
Cough	1 (0.19%)
Laryngeal oedema	1 (0.19%)
Oropharyngeal pain	1 (0.19%)
Pleural disorder	1 (0.19%)
Productive cough	1 (0.19%)
Pulmonary calcification	1 (0.19%)
Tracheal diverticulum	1 (0.19%)
Metabolism and nutrition disorders	99 (19.26%)
Hyperlipidaemia	40 (7.78%)
Diabetes mellitus	17 (3.31%)
Hypoproteinaemia	14 (2.72%)
Hyperuricaemia	12 (2.33%)
Type 2 diabetes mellitus	10 (1.95%)
Hypokalaemia	7 (1.36%)
Hypoalbuminaemia	6 (1.17%)
Vitamin D deficiency	4 (0.78%)
Hypercholesterolaemia	3 (0.58%)
Hyperglycaemia	3 (0.58%)
Hypocalcaemia	3 (0.58%)
Dyslipidaemia	2 (0.39%)
Glucose tolerance impaired	1 (0.19%)
Gout	1 (0.19%)
Hyperkalaemia	1 (0.19%)
Hypertriglyceridaemia	1 (0.19%)
Impaired fasting glucose	1 (0.19%)
Steroid diabetes	1 (0.19%)
Gastrointestinal disorders	77 (14.98%)
Chronic gastritis	28 (5.45%)
Gastritis erosive	26 (5.06%)
Gastritis	6 (1.17%)
Gastrooesophageal reflux disease	6 (1.17%)
Duodenal ulcer	3 (0.58%)
Gastric disorder	3 (0.58%)
Diverticulum intestinal	2 (0.39%)
Gastric polyps	2 (0.39%)
Gastric ulcer	2 (0.39%)
Large intestine polyp	2 (0.39%)
Abdominal pain	1 (0.19%)
Crohn's disease	1 (0.19%)
Diarrhoea	1 (0.19%)
Dysbiosis	1 (0.19%)
Functional gastrointestinal disorder	1 (0.19%)
Gastroduodenal ulcer	1 (0.19%)

Footnote: PT, preferred term; SOC, system organ class.
The percentage denominator is the number of analyses population.
Other concomitant diseases are those ended on or after the first dose of study drug or are still ongoing.
MedDRA English version 25.1

SOC *PT*	*Effectiveness Analyses Population (N=514)*
Gingival bleeding	1 (0.19%)
Haemorrhoids	1 (0.19%)
Intestinal polyp	1 (0.19%)
Parotid gland enlargement	1 (0.19%)
Salivary gland cyst	1 (0.19%)
Blood and lymphatic system disorders	75 (14.59%)
Anaemia	54 (10.51%)
Leukopenia	5 (0.97%)
Iron deficiency anaemia	4 (0.78%)
Lymphadenopathy	3 (0.58%)
Thrombocytosis	3 (0.58%)
Anaemia of chronic disease	2 (0.39%)
Coagulopathy	2 (0.39%)
Lymphopenia	2 (0.39%)
Hyperglobulinaemia	1 (0.19%)
Leukocytosis	1 (0.19%)
Secondary thrombocytosis	1 (0.19%)
Spleen atrophy	1 (0.19%)
White blood cell disorder	1 (0.19%)
Hepatobiliary disorders	60 (11.67%)
Hepatic steatosis	27 (5.25%)
Cholelithiasis	15 (2.92%)
Hepatic cyst	15 (2.92%)
Gallbladder polyp	4 (0.78%)
Bile duct stone	3 (0.58%)
Biliary dilatation	1 (0.19%)
Cholecystitis	1 (0.19%)
Cholecystitis chronic	1 (0.19%)
Hepatic calcification	1 (0.19%)
Hepatic function abnormal	1 (0.19%)
Hyperplastic cholecystopathy	1 (0.19%)
Post cholecystectomy syndrome	1 (0.19%)
Endocrine disorders	46 (8.95%)
Thyroid mass	23 (4.47%)
Hypothyroidism	14 (2.72%)
Autoimmune thyroiditis	2 (0.39%)
Euthyroid sick syndrome	2 (0.39%)
Goitre	2 (0.39%)
Thyroid disorder	2 (0.39%)
Adrenal disorder	1 (0.19%)
Autoimmune thyroid disorder	1 (0.19%)
Glucocorticoid deficiency	1 (0.19%)
Hyperthyroidism	1 (0.19%)
Thyroid cyst	1 (0.19%)
Infections and infestations	31 (6.03%)
Latent tuberculosis	8 (1.56%)

Footnote: PT, preferred term; SOC, system organ class.
The percentage denominator is the number of analyses population.
Other concomitant diseases are those ended on or after the first dose of study drug or are still ongoing.
MedDRA English version 25.1

SOC *PT*	*Effectiveness Analyses Population* *(N=514)*
Chronic hepatitis B	4 (0.78%)
Tuberculosis	3 (0.58%)
Bronchitis	2 (0.39%)
Hepatitis B	2 (0.39%)
Pulmonary tuberculosis	2 (0.39%)
Viral hepatitis carrier	2 (0.39%)
Bone tuberculosis	1 (0.19%)
Chronic sinusitis	1 (0.19%)
Dermatophytosis of nail	1 (0.19%)
Lung abscess	1 (0.19%)
Periodontitis	1 (0.19%)
Sinusitis	1 (0.19%)
Upper respiratory tract infection	1 (0.19%)
Urinary tract infection	1 (0.19%)
Vaginal infection	1 (0.19%)
Renal and urinary disorders	31 (6.03%)
Nephrolithiasis	16 (3.11%)
Renal cyst	14 (2.72%)
Acquired cystic kidney disease	2 (0.39%)
Calculus urinary	1 (0.19%)
Chronic kidney disease	1 (0.19%)
Hydronephrosis	1 (0.19%)
Pyelocaliectasis	1 (0.19%)
Renal hydrocele	1 (0.19%)
Renal mass	1 (0.19%)
Ureterolithiasis	1 (0.19%)
Reproductive system and breast disorders	24 (4.67%)
Benign prostatic hyperplasia	6 (1.17%)
Breast mass	6 (1.17%)
Breast hyperplasia	2 (0.39%)
Adnexa uteri cyst	1 (0.19%)
Endometriosis	1 (0.19%)
Galactocele	1 (0.19%)
Hydrometra	1 (0.19%)
Menopausal symptoms	1 (0.19%)
Menstruation irregular	1 (0.19%)
Ovarian cyst	1 (0.19%)
Prostatic calcification	1 (0.19%)
Prostatitis	1 (0.19%)
Uterine disorder	1 (0.19%)
Surgical and medical procedures	24 (4.67%)
Hip arthroplasty	3 (0.58%)
Appendicectomy	2 (0.39%)
Cholecystectomy	2 (0.39%)
Internal fixation of spine	2 (0.39%)
Knee arthroplasty	2 (0.39%)
Thyroidectomy	2 (0.39%)

Footnote: PT, preferred term; SOC, system organ class.
The percentage denominator is the number of analyses population.
Other concomitant diseases are those ended on or after the first dose of study drug or are still ongoing.
MedDRA English version 25.1

SOC *PT*	*Effectiveness Analyses Population* *(N=514)*
Ankle operation	1 (0.19%)
Arthroscopic surgery	1 (0.19%)
Breast operation	1 (0.19%)
Closed fracture manipulation	1 (0.19%)
Coronary arterial stent insertion	1 (0.19%)
Eye operation	1 (0.19%)
Hysterectomy	1 (0.19%)
Joint debridement	1 (0.19%)
Laparoscopic surgery	1 (0.19%)
Mitral valve replacement	1 (0.19%)
Myomectomy	1 (0.19%)
Synovectomy	1 (0.19%)
Vocal cord polypectomy	1 (0.19%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	23 (4.47%)
Uterine leiomyoma	11 (2.14%)
Haemangioma of liver	5 (0.97%)
Renal hamartoma	2 (0.39%)
Benign ovarian tumour	1 (0.19%)
Fibroadenoma of breast	1 (0.19%)
Haemangioma of bone	1 (0.19%)
Meningioma	1 (0.19%)
Myelodysplastic syndrome	1 (0.19%)
Renal lipoma	1 (0.19%)
Skin papilloma	1 (0.19%)
Investigations	21 (4.09%)
Cortisol abnormal	3 (0.58%)
Platelet count increased	3 (0.58%)
Blood glucose increased	2 (0.39%)
Glucose tolerance decreased	2 (0.39%)
Lymphocyte count decreased	2 (0.39%)
Arthroscopy	1 (0.19%)
Blood glucose abnormal	1 (0.19%)
Blood uric acid increased	1 (0.19%)
Gamma-glutamyltransferase increased	1 (0.19%)
Glucose tolerance test abnormal	1 (0.19%)
Mycobacterium tuberculosis complex test positive	1 (0.19%)
Neutrophil count increased	1 (0.19%)
Serum ferritin increased	1 (0.19%)
Total bile acids increased	1 (0.19%)
Tumour marker increased	1 (0.19%)
Urinary occult blood positive	1 (0.19%)
Vitamin D decreased	1 (0.19%)
White blood cell count decreased	1 (0.19%)
White blood cells urine positive	1 (0.19%)
Psychiatric disorders	14 (2.72%)
Sleep disorder	9 (1.75%)
Anxiety	2 (0.39%)

Footnote: PT, preferred term; SOC, system organ class.
The percentage denominator is the number of analyses population.
Other concomitant diseases are those ended on or after the first dose of study drug or are still ongoing.

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SOC *PT*	*Effectiveness Analyses Population (N=514)*
Insomnia	2 (0.39%)
Anxiety disorder	1 (0.19%)
Depression	1 (0.19%)
Schizophrenia	1 (0.19%)
Injury, poisoning and procedural complications	13 (2.53%)
Meniscus injury	4 (0.78%)
Pneumoconiosis	3 (0.58%)
Rib fracture	2 (0.39%)
Ligament injury	1 (0.19%)
Open globe injury	1 (0.19%)
Pelvic bone injury	1 (0.19%)
Tendon injury	1 (0.19%)
Thermal burn	1 (0.19%)
Eye disorders	12 (2.33%)
Cataract	6 (1.17%)
Xerophthalmia	4 (0.78%)
Asthenopia	1 (0.19%)
Dry eye	1 (0.19%)
Eyelid oedema	1 (0.19%)
Meibomian gland dysfunction	1 (0.19%)
Pterygium	1 (0.19%)
Nervous system disorders	11 (2.14%)
Neuropathy peripheral	3 (0.58%)
Carpal tunnel syndrome	2 (0.39%)
Autonomic nervous system imbalance	1 (0.19%)
Cerebral atrophy	1 (0.19%)
Cervical radiculopathy	1 (0.19%)
Diabetic neuropathy	1 (0.19%)
Myasthenia gravis	1 (0.19%)
Myelopathy	1 (0.19%)
Paralysis	1 (0.19%)
Post herpetic neuralgia	1 (0.19%)
Skin and subcutaneous tissue disorders	7 (1.36%)
Dermatitis	2 (0.39%)
Urticaria	2 (0.39%)
Alopecia areata	1 (0.19%)
Papule	1 (0.19%)
Rash maculo-papular	1 (0.19%)
Urticaria chronic	1 (0.19%)
Congenital, familial and genetic disorders	5 (0.97%)
Thalassaemia	2 (0.39%)
Kidney duplex	1 (0.19%)
Retinitis pigmentosa	1 (0.19%)
Thalassaemia alpha	1 (0.19%)

Footnote: PT, preferred term; SOC, system organ class.
The percentage denominator is the number of analyses population.
Other concomitant diseases are those ended on or after the first dose of study drug or are still ongoing.
MedDRA English version 25.1

SOC *PT*	*Effectiveness Analyses Population (N=514)*
General disorders and administration site conditions	4 (0.78%)
Oedema peripheral	3 (0.58%)
Hernia	1 (0.19%)
Ear and labyrinth disorders	2 (0.39%)
Mixed deafness	1 (0.19%)
Vertigo	1 (0.19%)
Vascular disorders	2 (0.39%)
Rheumatoid vasculitis	1 (0.19%)
Vasculitis	1 (0.19%)
Immune system disorders	1 (0.19%)
Immune system disorder	1 (0.19%)

Footnote: PT, preferred term; SOC, system organ class.
The percentage denominator is the number of analyses population.
Other concomitant diseases are those ended on or after the first dose of study drug or are still ongoing.
MedDRA English version 25.1

Table ANN. 16 Other Pre-existing Conditions/Medical History and Other Concomitant Disease – Safety Analyses Population

SOC *PT*	*Safety Analyses Population* *(N=667)*
Number of patients with at least one pre-existing conditions/ medical history or other concomitant disease	436 (65.37%)
Musculoskeletal and connective tissue disorders	193 (28.94%)
Osteoporosis	101 (15.14%)
Osteoarthritis	32 (4.80%)
Intervertebral disc protrusion	30 (4.50%)
Sjogren's syndrome	30 (4.50%)
Spinal osteoarthritis	23 (3.45%)
Osteonecrosis	9 (1.35%)
Connective tissue disorder	8 (1.20%)
Arthropathy	7 (1.05%)
Osteopenia	6 (0.90%)
Systemic lupus erythematosus	6 (0.90%)
Tenosynovitis	6 (0.90%)
Synovial cyst	4 (0.60%)
Synovitis	4 (0.60%)
Ankylosing spondylitis	3 (0.45%)
Lumbar spinal stenosis	3 (0.45%)
Periarthritis	3 (0.45%)
Rotator cuff syndrome	3 (0.45%)
Fasciitis	2 (0.30%)
Intervertebral disc degeneration	2 (0.30%)
Osteoarthropathy	2 (0.30%)
Palindromic rheumatism	2 (0.30%)
Sacroiliitis	2 (0.30%)
Tendon disorder	2 (0.30%)
Arthralgia	1 (0.15%)
Bone erosion	1 (0.15%)
Bone formation increased	1 (0.15%)
Bone hypertrophy	1 (0.15%)
Fibromyalgia	1 (0.15%)
Foot deformity	1 (0.15%)
Gouty arthritis	1 (0.15%)
Gouty tophus	1 (0.15%)
Haematoma muscle	1 (0.15%)
Intervertebral disc disorder	1 (0.15%)
Limb mass	1 (0.15%)
Myopathy	1 (0.15%)
Neck mass	1 (0.15%)
Neck pain	1 (0.15%)
Polymyositis	1 (0.15%)
Spondylolisthesis	1 (0.15%)
Synovial disorder	1 (0.15%)
Systemic scleroderma	1 (0.15%)
Temporomandibular joint syndrome	1 (0.15%)
Tendon calcification	1 (0.15%)
Tendonitis	1 (0.15%)
Tenosynovitis stenosans	1 (0.15%)
Undifferentiated connective tissue disease	1 (0.15%)

Footnote: N, number of patients in population; PT, preferred term; SOC, system organ class.

The percentage denominator is the number of analyses population.
Other pre-existing conditions and medical histories are those ended before the first dose of study drug.
Other concomitant diseases are those ended on or after the first dose of study drug or are still ongoing.
MedDRA English version 25.1

SOC *PT*	*Safety Analyses Population* *(N=667)*
Vertebral osteophyte	1 (0.15%)
Metabolism and nutrition disorders	137 (20.54%)
Hyperlipidaemia	52 (7.80%)
Diabetes mellitus	23 (3.45%)
Hypoproteinaemia	21 (3.15%)
Hyperuricaemia	17 (2.55%)
Type 2 diabetes mellitus	17 (2.55%)
Hypokalaemia	14 (2.10%)
Hypoalbuminaemia	9 (1.35%)
Vitamin D deficiency	7 (1.05%)
Hypercholesterolaemia	4 (0.60%)
Hyperglycaemia	4 (0.60%)
Dyslipidaemia	3 (0.45%)
Electrolyte imbalance	3 (0.45%)
Hypocalcaemia	3 (0.45%)
Glucose tolerance impaired	2 (0.30%)
Hypertriglyceridaemia	2 (0.30%)
Malnutrition	2 (0.30%)
Cachexia	1 (0.15%)
Gout	1 (0.15%)
Hyperkalaemia	1 (0.15%)
Impaired fasting glucose	1 (0.15%)
Lactose intolerance	1 (0.15%)
Obesity	1 (0.15%)
Steroid diabetes	1 (0.15%)
Respiratory, thoracic and mediastinal disorders	130 (19.49%)
Interstitial lung disease	51 (7.65%)
Pulmonary mass	50 (7.50%)
Bronchiectasis	10 (1.50%)
Emphysema	9 (1.35%)
Rheumatoid arthritis-associated interstitial lung disease	7 (1.05%)
Bronchitis chronic	6 (0.90%)
Asthma	5 (0.75%)
Chronic obstructive pulmonary disease	4 (0.60%)
Cough	3 (0.45%)
Cystic lung disease	2 (0.30%)
Pleural thickening	2 (0.30%)
Epiglottic cyst	1 (0.15%)
Laryngeal oedema	1 (0.15%)
Oropharyngeal pain	1 (0.15%)
Paranasal sinus inflammation	1 (0.15%)
Pleural disorder	1 (0.15%)
Pleural effusion	1 (0.15%)
Productive cough	1 (0.15%)
Pulmonary calcification	1 (0.15%)
Pulmonary fibrosis	1 (0.15%)
Pulmonary sarcoidosis	1 (0.15%)

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MedDRA English version 25.1

SOC *PT*	*Safety Analyses Population* *(N=667)*
Rhinitis allergic	1 (0.15%)
Sinus polyp degeneration	1 (0.15%)
Tracheal diverticulum	1 (0.15%)
Blood and lymphatic system disorders	104 (15.59%)
Anaemia	73 (10.94%)
Leukopenia	9 (1.35%)
Iron deficiency anaemia	7 (1.05%)
Lymphadenopathy	6 (0.90%)
Thrombocytosis	5 (0.75%)
Anaemia of chronic disease	2 (0.30%)
Coagulopathy	2 (0.30%)
Hyperglobulinaemia	2 (0.30%)
Lymphopenia	2 (0.30%)
Secondary thrombocytosis	2 (0.30%)
Hypochromic anaemia	1 (0.15%)
Leukocytosis	1 (0.15%)
Lymphadenopathy mediastinal	1 (0.15%)
Neutropenia	1 (0.15%)
Spleen atrophy	1 (0.15%)
Splenomegaly	1 (0.15%)
White blood cell disorder	1 (0.15%)
Gastrointestinal disorders	96 (14.39%)
Chronic gastritis	32 (4.80%)
Gastritis erosive	30 (4.50%)
Gastritis	8 (1.20%)
Duodenal ulcer	7 (1.05%)
Gastrooesophageal reflux disease	7 (1.05%)
Gastric ulcer	5 (0.75%)
Diverticulum intestinal	3 (0.45%)
Gastric disorder	3 (0.45%)
Gastric polyps	3 (0.45%)
Diarrhoea	2 (0.30%)
Haemorrhoids	2 (0.30%)
Large intestine polyp	2 (0.30%)
Abdominal pain	1 (0.15%)
Colitis	1 (0.15%)
Crohn's disease	1 (0.15%)
Duodenal ulcer haemorrhage	1 (0.15%)
Dysbiosis	1 (0.15%)
Functional gastrointestinal disorder	1 (0.15%)
Gastric ulcer haemorrhage	1 (0.15%)
Gastroduodenal ulcer	1 (0.15%)
Gingival bleeding	1 (0.15%)
Intestinal polyp	1 (0.15%)
Pancreatitis acute	1 (0.15%)
Parotid gland enlargement	1 (0.15%)
Salivary gland cyst	1 (0.15%)

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MedDRA English version 25.1

SOC *PT*	*Safety Analyses Population* *(N=667)*
Upper gastrointestinal perforation	1 (0.15%)
Surgical and medical procedures	88 (13.19%)
Knee arthroplasty	14 (2.10%)
Hip arthroplasty	8 (1.20%)
Hysterectomy	8 (1.20%)
Appendicectomy	7 (1.05%)
Cholecystectomy	5 (0.75%)
Myomectomy	4 (0.60%)
Thyroidectomy	4 (0.60%)
Cataract operation	3 (0.45%)
Joint arthroplasty	3 (0.45%)
Breast operation	2 (0.30%)
Internal fixation of spine	2 (0.30%)
Intervertebral disc operation	2 (0.30%)
Lithotripsy	2 (0.30%)
Mass excision	2 (0.30%)
Meniscus operation	2 (0.30%)
Spinal fusion surgery	2 (0.30%)
Spinal operation	2 (0.30%)
Synovectomy	2 (0.30%)
Ankle operation	1 (0.15%)
Arterial stent insertion	1 (0.15%)
Arthrodesis	1 (0.15%)
Arthroscopic surgery	1 (0.15%)
Bladder neoplasm surgery	1 (0.15%)
Bunion operation	1 (0.15%)
Cervical conisation	1 (0.15%)
Cholelithotomy	1 (0.15%)
Closed fracture manipulation	1 (0.15%)
Coronary arterial stent insertion	1 (0.15%)
Duodenal ulcer repair	1 (0.15%)
Eye operation	1 (0.15%)
Fracture treatment	1 (0.15%)
Gastric polypectomy	1 (0.15%)
Gastrorrhaphy	1 (0.15%)
Joint debridement	1 (0.15%)
Knee operation	1 (0.15%)
Laparoscopic surgery	1 (0.15%)
Limb operation	1 (0.15%)
Lung neoplasm surgery	1 (0.15%)
Meningioma surgery	1 (0.15%)
Mitral valve replacement	1 (0.15%)
Open reduction of fracture	1 (0.15%)
Osteotomy	1 (0.15%)
Ovarian operation	1 (0.15%)
Pituitary tumour removal	1 (0.15%)
Plastic surgery	1 (0.15%)
Pulmonary bullectomy	1 (0.15%)

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MedDRA English version 25.1

SOC *PT*	*Safety Analyses Population* *(N=667)*
Renal stone removal	1 (0.15%)
Salpingo-oophorectomy bilateral	1 (0.15%)
Sinus operation	1 (0.15%)
Synovial cyst removal	1 (0.15%)
Thyroid adenoma removal	1 (0.15%)
Ureteric operation	1 (0.15%)
Uterine dilation and curettage	1 (0.15%)
Uterine polypectomy	1 (0.15%)
Varicose vein operation	1 (0.15%)
Vocal cord polypectomy	1 (0.15%)
Hepatobiliary disorders	85 (12.74%)
Hepatic steatosis	37 (5.55%)
Cholelithiasis	20 (3.00%)
Hepatic cyst	19 (2.85%)
Gallbladder polyp	8 (1.20%)
Bile duct stone	5 (0.75%)
Cholecystitis	2 (0.30%)
Cholecystitis acute	2 (0.30%)
Cholecystitis chronic	2 (0.30%)
Hepatic calcification	2 (0.30%)
Hyperplastic cholecystopathy	2 (0.30%)
Biliary dilatation	1 (0.15%)
Hepatic atrophy	1 (0.15%)
Hepatic function abnormal	1 (0.15%)
Post cholecystectomy syndrome	1 (0.15%)
Endocrine disorders	58 (8.70%)
Thyroid mass	29 (4.35%)
Hypothyroidism	16 (2.40%)
Goitre	4 (0.60%)
Autoimmune thyroiditis	3 (0.45%)
Euthyroid sick syndrome	3 (0.45%)
Hyperthyroidism	3 (0.45%)
Thyroid disorder	3 (0.45%)
Adrenal disorder	1 (0.15%)
Autoimmune thyroid disorder	1 (0.15%)
Glucocorticoid deficiency	1 (0.15%)
Thyroid cyst	1 (0.15%)
Infections and infestations	49 (7.35%)
Latent tuberculosis	10 (1.50%)
Chronic hepatitis B	6 (0.90%)
Bronchitis	5 (0.75%)
Pulmonary tuberculosis	5 (0.75%)
Tuberculosis	5 (0.75%)
Chronic sinusitis	2 (0.30%)
Conjunctivitis	2 (0.30%)
Hepatitis B	2 (0.30%)

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MedDRA English version 25.1

SOC *PT*	*Safety Analyses Population* *(N=667)*
Laryngopharyngitis	2 (0.30%)
Pharyngitis	2 (0.30%)
Pneumonia	2 (0.30%)
Sinusitis	2 (0.30%)
Viral hepatitis carrier	2 (0.30%)
Bone tuberculosis	1 (0.15%)
Dermatophytosis of nail	1 (0.15%)
Herpes zoster	1 (0.15%)
Lung abscess	1 (0.15%)
Onychomycosis	1 (0.15%)
Periodontitis	1 (0.15%)
Upper respiratory tract infection	1 (0.15%)
Urinary tract infection	1 (0.15%)
Vaginal infection	1 (0.15%)
Renal and urinary disorders	45 (6.75%)
Nephrolithiasis	25 (3.75%)
Renal cyst	21 (3.15%)
Acquired cystic kidney disease	2 (0.30%)
Renal hydrocele	2 (0.30%)
Ureterolithiasis	2 (0.30%)
Calculus urinary	1 (0.15%)
Chronic kidney disease	1 (0.15%)
Hydronephrosis	1 (0.15%)
Pyelocaliectasis	1 (0.15%)
Renal mass	1 (0.15%)
Stress urinary incontinence	1 (0.15%)
Investigations	33 (4.95%)
Platelet count increased	4 (0.60%)
Blood glucose increased	3 (0.45%)
Cortisol abnormal	3 (0.45%)
Gamma-glutamyltransferase increased	3 (0.45%)
Lymphocyte count decreased	3 (0.45%)
Glucose tolerance decreased	2 (0.30%)
White blood cell count decreased	2 (0.30%)
White blood cells urine positive	2 (0.30%)
Arthroscopy	1 (0.15%)
Aspartate aminotransferase increased	1 (0.15%)
Blood glucose abnormal	1 (0.15%)
Blood methaemoglobin	1 (0.15%)
Blood uric acid increased	1 (0.15%)
Carbohydrate antigen 19-9 increased	1 (0.15%)
Coagulation test abnormal	1 (0.15%)
Glucose tolerance test abnormal	1 (0.15%)
Hysteroscopy	1 (0.15%)
Mycobacterium tuberculosis complex test positive	1 (0.15%)
Neurone-specific enolase increased	1 (0.15%)
Neutrophil count decreased	1 (0.15%)

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SOC *PT*	*Safety Analyses Population* *(N=667)*
Neutrophil count increased	1 (0.15%)
Serum ferritin increased	1 (0.15%)
Total bile acids increased	1 (0.15%)
Tumour marker increased	1 (0.15%)
Urinary occult blood positive	1 (0.15%)
Vitamin D decreased	1 (0.15%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	31 (4.65%)
Uterine leiomyoma	15 (2.25%)
Haemangioma of liver	6 (0.90%)
Renal hamartoma	3 (0.45%)
Benign ovarian tumour	1 (0.15%)
Fibroadenoma of breast	1 (0.15%)
Haemangioma	1 (0.15%)
Haemangioma of bone	1 (0.15%)
Meningioma	1 (0.15%)
Myelodysplastic syndrome	1 (0.15%)
Renal lipoma	1 (0.15%)
Skin papilloma	1 (0.15%)
Thyroid neoplasm	1 (0.15%)
Reproductive system and breast disorders	30 (4.50%)
Benign prostatic hyperplasia	6 (0.90%)
Breast mass	6 (0.90%)
Breast hyperplasia	2 (0.30%)
Endometriosis	2 (0.30%)
Ovarian cyst	2 (0.30%)
Prostatitis	2 (0.30%)
Adnexa uteri cyst	1 (0.15%)
Breast calcifications	1 (0.15%)
Cervical dysplasia	1 (0.15%)
Galactocele	1 (0.15%)
Hydrometra	1 (0.15%)
Menopausal symptoms	1 (0.15%)
Menstruation irregular	1 (0.15%)
Prostatic calcification	1 (0.15%)
Uterine disorder	1 (0.15%)
Uterine polyp	1 (0.15%)
Injury, poisoning and procedural complications	26 (3.90%)
Meniscus injury	6 (0.90%)
Pneumoconiosis	4 (0.60%)
Rib fracture	4 (0.60%)
Tendon injury	2 (0.30%)
Back injury	1 (0.15%)
Femur fracture	1 (0.15%)
Fibula fracture	1 (0.15%)
Hand fracture	1 (0.15%)
Ligament injury	1 (0.15%)

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MedDRA English version 25.1

SOC *PT*	*Safety Analyses Population* *(N=667)*
Lower limb fracture	1 (0.15%)
Lumbar vertebral fracture	1 (0.15%)
Open globe injury	1 (0.15%)
Pelvic bone injury	1 (0.15%)
Radius fracture	1 (0.15%)
Silicosis	1 (0.15%)
Soft tissue injury	1 (0.15%)
Thermal burn	1 (0.15%)
Eye disorders	19 (2.85%)
Cataract	9 (1.35%)
Xerophthalmia	6 (0.90%)
Meibomian gland dysfunction	2 (0.30%)
Asthenopia	1 (0.15%)
Corneal exfoliation	1 (0.15%)
Dry eye	1 (0.15%)
Eyelid oedema	1 (0.15%)
Pterygium	1 (0.15%)
Trichiasis	1 (0.15%)
Vitreous floaters	1 (0.15%)
Nervous system disorders	17 (2.55%)
Neuropathy peripheral	3 (0.45%)
Carpal tunnel syndrome	2 (0.30%)
Cerebral atrophy	2 (0.30%)
Cervical radiculopathy	2 (0.30%)
Autonomic nervous system imbalance	1 (0.15%)
Diabetic neuropathy	1 (0.15%)
Head discomfort	1 (0.15%)
Lumbar radiculopathy	1 (0.15%)
Myasthenia gravis	1 (0.15%)
Myelopathy	1 (0.15%)
Paralysis	1 (0.15%)
Parkinsonism	1 (0.15%)
Post herpetic neuralgia	1 (0.15%)
Sciatica	1 (0.15%)
Psychiatric disorders	17 (2.55%)
Sleep disorder	10 (1.50%)
Insomnia	3 (0.45%)
Anxiety	2 (0.30%)
Anxiety disorder	2 (0.30%)
Depression	1 (0.15%)
Schizophrenia	1 (0.15%)
Skin and subcutaneous tissue disorders	11 (1.65%)
Dermatitis	2 (0.30%)
Urticaria	2 (0.30%)
Alopecia areata	1 (0.15%)

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SOC *PT*	*Safety Analyses Population* *(N=667)*
Decubitus ulcer	1 (0.15%)
Dermal cyst	1 (0.15%)
Papule	1 (0.15%)
Pruritus	1 (0.15%)
Psoriasis	1 (0.15%)
Rash maculo-papular	1 (0.15%)
Urticaria chronic	1 (0.15%)
Congenital, familial and genetic disorders	5 (0.75%)
Thalassaemia	2 (0.30%)
Kidney duplex	1 (0.15%)
Retinitis pigmentosa	1 (0.15%)
Thalassaemia alpha	1 (0.15%)
General disorders and administration site conditions	5 (0.75%)
Oedema peripheral	3 (0.45%)
Hernia	1 (0.15%)
Systemic inflammatory response syndrome	1 (0.15%)
Ear and labyrinth disorders	4 (0.60%)
Vertigo	2 (0.30%)
Ear pain	1 (0.15%)
Mixed deafness	1 (0.15%)
Immune system disorders	3 (0.45%)
Decreased immune responsiveness	2 (0.30%)
Immune system disorder	1 (0.15%)
Vascular disorders	2 (0.30%)
Rheumatoid vasculitis	1 (0.15%)
Vasculitis	1 (0.15%)

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MedDRA English version 25.1

Table ANN. 17 Other Pre-existing Conditions/Medical History and Other Concomitant Disease – Effectiveness Analyses Population

SOC *PT*	*Effectiveness Analyses Population (N=514)*
Number of patients with at least one pre-existing conditions/ medical history or other concomitant disease	336 (65.37%)
Musculoskeletal and connective tissue disorders	153 (29.77%)
Osteoporosis	80 (15.56%)
Intervertebral disc protrusion	27 (5.25%)
Sjogren's syndrome	27 (5.25%)
Osteoarthritis	24 (4.67%)
Spinal osteoarthritis	16 (3.11%)
Osteonecrosis	8 (1.56%)
Connective tissue disorder	7 (1.36%)
Systemic lupus erythematosus	6 (1.17%)
Arthropathy	4 (0.78%)
Osteopenia	4 (0.78%)
Ankylosing spondylitis	3 (0.58%)
Periarthritis	3 (0.58%)
Rotator cuff syndrome	3 (0.58%)
Tenosynovitis	3 (0.58%)
Fasciitis	2 (0.39%)
Lumbar spinal stenosis	2 (0.39%)
Osteoarthropathy	2 (0.39%)
Palindromic rheumatism	2 (0.39%)
Synovial cyst	2 (0.39%)
Arthralgia	1 (0.19%)
Bone formation increased	1 (0.19%)
Bone hypertrophy	1 (0.19%)
Fibromyalgia	1 (0.19%)
Foot deformity	1 (0.19%)
Gouty arthritis	1 (0.19%)
Gouty tophus	1 (0.19%)
Haematoma muscle	1 (0.19%)
Limb mass	1 (0.19%)
Myopathy	1 (0.19%)
Neck mass	1 (0.19%)
Neck pain	1 (0.19%)
Polymyositis	1 (0.19%)
Sacroiliitis	1 (0.19%)
Spondylolisthesis	1 (0.19%)
Synovial disorder	1 (0.19%)
Synovitis	1 (0.19%)
Systemic scleroderma	1 (0.19%)
Tendon disorder	1 (0.19%)
Tenosynovitis stenosans	1 (0.19%)
Vertebral osteophyte	1 (0.19%)
Respiratory, thoracic and mediastinal disorders	105 (20.43%)
Interstitial lung disease	46 (8.95%)
Pulmonary mass	39 (7.59%)
Bronchiectasis	9 (1.75%)
Emphysema	6 (1.17%)

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SOC *PT*	*Effectiveness Analyses Population* *(N=514)*
Bronchitis chronic	5 (0.97%)
Rheumatoid arthritis-associated interstitial lung disease	4 (0.78%)
Asthma	3 (0.58%)
Chronic obstructive pulmonary disease	3 (0.58%)
Cough	2 (0.39%)
Cystic lung disease	2 (0.39%)
Pleural thickening	2 (0.39%)
Laryngeal oedema	1 (0.19%)
Oropharyngeal pain	1 (0.19%)
Paranasal sinus inflammation	1 (0.19%)
Pleural disorder	1 (0.19%)
Productive cough	1 (0.19%)
Pulmonary calcification	1 (0.19%)
Tracheal diverticulum	1 (0.19%)
Metabolism and nutrition disorders	100 (19.46%)
Hyperlipidaemia	40 (7.78%)
Diabetes mellitus	17 (3.31%)
Hypoproteinaemia	14 (2.72%)
Hyperuricaemia	13 (2.53%)
Type 2 diabetes mellitus	10 (1.95%)
Hypokalaemia	8 (1.56%)
Hypoalbuminaemia	6 (1.17%)
Vitamin D deficiency	4 (0.78%)
Hypercholesterolaemia	3 (0.58%)
Hyperglycaemia	3 (0.58%)
Hypocalcaemia	3 (0.58%)
Dyslipidaemia	2 (0.39%)
Glucose tolerance impaired	1 (0.19%)
Gout	1 (0.19%)
Hyperkalaemia	1 (0.19%)
Hypertriglyceridaemia	1 (0.19%)
Impaired fasting glucose	1 (0.19%)
Steroid diabetes	1 (0.19%)
Gastrointestinal disorders	78 (15.18%)
Chronic gastritis	28 (5.45%)
Gastritis erosive	26 (5.06%)
Gastritis	6 (1.17%)
Gastrooesophageal reflux disease	6 (1.17%)
Duodenal ulcer	4 (0.78%)
Gastric disorder	3 (0.58%)
Diarrhoea	2 (0.39%)
Diverticulum intestinal	2 (0.39%)
Gastric polyps	2 (0.39%)
Gastric ulcer	2 (0.39%)
Large intestine polyp	2 (0.39%)
Abdominal pain	1 (0.19%)
Crohn's disease	1 (0.19%)

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SOC *PT*	*Effectiveness Analyses Population* *(N=514)*
Dysbiosis	1 (0.19%)
Functional gastrointestinal disorder	1 (0.19%)
Gastroduodenal ulcer	1 (0.19%)
Gingival bleeding	1 (0.19%)
Haemorrhoids	1 (0.19%)
Intestinal polyp	1 (0.19%)
Parotid gland enlargement	1 (0.19%)
Salivary gland cyst	1 (0.19%)
Blood and lymphatic system disorders	77 (14.98%)
Anaemia	54 (10.51%)
Leukopenia	8 (1.56%)
Iron deficiency anaemia	4 (0.78%)
Lymphadenopathy	3 (0.58%)
Thrombocytosis	3 (0.58%)
Anaemia of chronic disease	2 (0.39%)
Coagulopathy	2 (0.39%)
Lymphopenia	2 (0.39%)
Hyperglobulinaemia	1 (0.19%)
Leukocytosis	1 (0.19%)
Secondary thrombocytosis	1 (0.19%)
Spleen atrophy	1 (0.19%)
White blood cell disorder	1 (0.19%)
Surgical and medical procedures	68 (13.23%)
Knee arthroplasty	8 (1.56%)
Hip arthroplasty	7 (1.36%)
Hysterectomy	6 (1.17%)
Appendicectomy	4 (0.78%)
Cholecystectomy	4 (0.78%)
Myomectomy	4 (0.78%)
Thyroidectomy	4 (0.78%)
Cataract operation	3 (0.58%)
Internal fixation of spine	2 (0.39%)
Intervertebral disc operation	2 (0.39%)
Joint arthroplasty	2 (0.39%)
Lithotripsy	2 (0.39%)
Mass excision	2 (0.39%)
Spinal fusion surgery	2 (0.39%)
Synovectomy	2 (0.39%)
Ankle operation	1 (0.19%)
Arterial stent insertion	1 (0.19%)
Arthroscopic surgery	1 (0.19%)
Breast operation	1 (0.19%)
Bunion operation	1 (0.19%)
Cervical conisation	1 (0.19%)
Closed fracture manipulation	1 (0.19%)
Coronary arterial stent insertion	1 (0.19%)
Eye operation	1 (0.19%)

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SOC *PT*	*Effectiveness Analyses Population* *(N=514)*
Gastric polypectomy	1 (0.19%)
Gastrorrhaphy	1 (0.19%)
Joint debridement	1 (0.19%)
Knee operation	1 (0.19%)
Laparoscopic surgery	1 (0.19%)
Limb operation	1 (0.19%)
Lung neoplasm surgery	1 (0.19%)
Meningioma surgery	1 (0.19%)
Meniscus operation	1 (0.19%)
Mitral valve replacement	1 (0.19%)
Osteotomy	1 (0.19%)
Ovarian operation	1 (0.19%)
Pituitary tumour removal	1 (0.19%)
Plastic surgery	1 (0.19%)
Pulmonary bullectomy	1 (0.19%)
Salpingo-oophorectomy bilateral	1 (0.19%)
Sinus operation	1 (0.19%)
Spinal operation	1 (0.19%)
Synovial cyst removal	1 (0.19%)
Thyroid adenoma removal	1 (0.19%)
Ureteric operation	1 (0.19%)
Uterine dilation and curettage	1 (0.19%)
Varicose vein operation	1 (0.19%)
Vocal cord polypectomy	1 (0.19%)
Hepatobiliary disorders	61 (11.87%)
Hepatic steatosis	27 (5.25%)
Cholelithiasis	15 (2.92%)
Hepatic cyst	15 (2.92%)
Gallbladder polyp	4 (0.78%)
Bile duct stone	3 (0.58%)
Biliary dilatation	1 (0.19%)
Cholecystitis	1 (0.19%)
Cholecystitis acute	1 (0.19%)
Cholecystitis chronic	1 (0.19%)
Hepatic calcification	1 (0.19%)
Hepatic function abnormal	1 (0.19%)
Hyperplastic cholecystopathy	1 (0.19%)
Post cholecystectomy syndrome	1 (0.19%)
Endocrine disorders	48 (9.34%)
Thyroid mass	24 (4.67%)
Hypothyroidism	14 (2.72%)
Euthyroid sick syndrome	3 (0.58%)
Goitre	3 (0.58%)
Autoimmune thyroiditis	2 (0.39%)
Hyperthyroidism	2 (0.39%)
Thyroid disorder	2 (0.39%)
Adrenal disorder	1 (0.19%)

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Other concomitant diseases are those ended on or after the first dose of study drug or are still ongoing.
MedDRA English version 25.1

SOC *PT*	*Effectiveness Analyses Population (N=514)*
Autoimmune thyroid disorder	1 (0.19%)
Glucocorticoid deficiency	1 (0.19%)
Thyroid cyst	1 (0.19%)
Infections and infestations	36 (7.00%)
Latent tuberculosis	8 (1.56%)
Pulmonary tuberculosis	5 (0.97%)
Chronic hepatitis B	4 (0.78%)
Tuberculosis	4 (0.78%)
Bronchitis	2 (0.39%)
Hepatitis B	2 (0.39%)
Viral hepatitis carrier	2 (0.39%)
Bone tuberculosis	1 (0.19%)
Chronic sinusitis	1 (0.19%)
Dermatophytosis of nail	1 (0.19%)
Herpes zoster	1 (0.19%)
Lung abscess	1 (0.19%)
Periodontitis	1 (0.19%)
Pneumonia	1 (0.19%)
Sinusitis	1 (0.19%)
Upper respiratory tract infection	1 (0.19%)
Urinary tract infection	1 (0.19%)
Vaginal infection	1 (0.19%)
Renal and urinary disorders	32 (6.23%)
Nephrolithiasis	16 (3.11%)
Renal cyst	14 (2.72%)
Acquired cystic kidney disease	2 (0.39%)
Renal hydrocele	2 (0.39%)
Ureterolithiasis	2 (0.39%)
Calculus urinary	1 (0.19%)
Chronic kidney disease	1 (0.19%)
Hydronephrosis	1 (0.19%)
Pyelocaliectasis	1 (0.19%)
Renal mass	1 (0.19%)
Stress urinary incontinence	1 (0.19%)
Reproductive system and breast disorders	28 (5.45%)
Benign prostatic hyperplasia	6 (1.17%)
Breast mass	6 (1.17%)
Breast hyperplasia	2 (0.39%)
Endometriosis	2 (0.39%)
Ovarian cyst	2 (0.39%)
Adnexa uteri cyst	1 (0.19%)
Cervical dysplasia	1 (0.19%)
Galactocele	1 (0.19%)
Hydrometra	1 (0.19%)
Menopausal symptoms	1 (0.19%)
Menstruation irregular	1 (0.19%)

Footnote: N, number of patients in population; PT, preferred term; SOC, system organ class.
The percentage denominator is the number of analyses population.
Other pre-existing conditions and medical histories are those ended before the first dose of study drug.
Other concomitant diseases are those ended on or after the first dose of study drug or are still ongoing.
MedDRA English version 25.1

SOC *PT*	*Effectiveness Analyses Population (N=514)*
Prostatic calcification	1 (0.19%)
Prostatitis	1 (0.19%)
Uterine disorder	1 (0.19%)
Uterine polyp	1 (0.19%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	26 (5.06%)
Uterine leiomyoma	13 (2.53%)
Haemangioma of liver	5 (0.97%)
Renal hamartoma	2 (0.39%)
Benign ovarian tumour	1 (0.19%)
Fibroadenoma of breast	1 (0.19%)
Haemangioma of bone	1 (0.19%)
Meningioma	1 (0.19%)
Myelodysplastic syndrome	1 (0.19%)
Renal lipoma	1 (0.19%)
Skin papilloma	1 (0.19%)
Thyroid neoplasm	1 (0.19%)
Investigations	22 (4.28%)
Cortisol abnormal	3 (0.58%)
Platelet count increased	3 (0.58%)
Blood glucose increased	2 (0.39%)
Glucose tolerance decreased	2 (0.39%)
Lymphocyte count decreased	2 (0.39%)
Arthroscopy	1 (0.19%)
Blood glucose abnormal	1 (0.19%)
Blood uric acid increased	1 (0.19%)
Gamma-glutamyltransferase increased	1 (0.19%)
Glucose tolerance test abnormal	1 (0.19%)
Hysteroscopy	1 (0.19%)
Mycobacterium tuberculosis complex test positive	1 (0.19%)
Neutrophil count increased	1 (0.19%)
Serum ferritin increased	1 (0.19%)
Total bile acids increased	1 (0.19%)
Tumour marker increased	1 (0.19%)
Urinary occult blood positive	1 (0.19%)
Vitamin D decreased	1 (0.19%)
White blood cell count decreased	1 (0.19%)
White blood cells urine positive	1 (0.19%)
Injury, poisoning and procedural complications	15 (2.92%)
Meniscus injury	4 (0.78%)
Pneumoconiosis	3 (0.58%)
Rib fracture	3 (0.58%)
Hand fracture	1 (0.19%)
Ligament injury	1 (0.19%)
Open globe injury	1 (0.19%)
Pelvic bone injury	1 (0.19%)
Tendon injury	1 (0.19%)

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The percentage denominator is the number of analyses population.
Other pre-existing conditions and medical histories are those ended before the first dose of study drug.
Other concomitant diseases are those ended on or after the first dose of study drug or are still ongoing.

MedDRA English version 25.1

SOC *PT*	*Effectiveness Analyses Population (N=514)*
Thermal burn	1 (0.19%)
Psychiatric disorders	14 (2.72%)
Sleep disorder	9 (1.75%)
Anxiety	2 (0.39%)
Insomnia	2 (0.39%)
Anxiety disorder	1 (0.19%)
Depression	1 (0.19%)
Schizophrenia	1 (0.19%)
Eye disorders	12 (2.33%)
Cataract	6 (1.17%)
Xerophthalmia	4 (0.78%)
Asthenopia	1 (0.19%)
Dry eye	1 (0.19%)
Eyelid oedema	1 (0.19%)
Meibomian gland dysfunction	1 (0.19%)
Pterygium	1 (0.19%)
Nervous system disorders	12 (2.33%)
Neuropathy peripheral	3 (0.58%)
Carpal tunnel syndrome	2 (0.39%)
Autonomic nervous system imbalance	1 (0.19%)
Cerebral atrophy	1 (0.19%)
Cervical radiculopathy	1 (0.19%)
Diabetic neuropathy	1 (0.19%)
Head discomfort	1 (0.19%)
Myasthenia gravis	1 (0.19%)
Myelopathy	1 (0.19%)
Paralysis	1 (0.19%)
Post herpetic neuralgia	1 (0.19%)
Skin and subcutaneous tissue disorders	8 (1.56%)
Dermatitis	2 (0.39%)
Urticaria	2 (0.39%)
Alopecia areata	1 (0.19%)
Papule	1 (0.19%)
Psoriasis	1 (0.19%)
Rash maculo-papular	1 (0.19%)
Urticaria chronic	1 (0.19%)
Congenital, familial and genetic disorders	5 (0.97%)
Thalassaemia	2 (0.39%)
Kidney duplex	1 (0.19%)
Retinitis pigmentosa	1 (0.19%)
Thalassaemia alpha	1 (0.19%)
General disorders and administration site conditions	4 (0.78%)
Oedema peripheral	3 (0.58%)

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The percentage denominator is the number of analyses population.
Other pre-existing conditions and medical histories are those ended before the first dose of study drug.
Other concomitant diseases are those ended on or after the first dose of study drug or are still ongoing.
MedDRA English version 25.1

SOC *PT*	*Effectiveness Analyses Population (N=514)*
Hernia	1 (0.19%)
Ear and labyrinth disorders	2 (0.39%)
Mixed deafness	1 (0.19%)
Vertigo	1 (0.19%)
Vascular disorders	2 (0.39%)
Rheumatoid vasculitis	1 (0.19%)
Vasculitis	1 (0.19%)
Immune system disorders	1 (0.19%)
Immune system disorder	1 (0.19%)

Footnote: N, number of patients in population; PT, preferred term; SOC, system organ class.
The percentage denominator is the number of analyses population.
Other pre-existing conditions and medical histories are those ended before the first dose of study drug.
Other concomitant diseases are those ended on or after the first dose of study drug or are still ongoing.
MedDRA English version 25.1

Table ANN. 18 Prior Medication – Safety Analyses Population

Anatomy group *Treatment subgroup* *Drug name*	*Safety Analyses Population* *(N=667)*
With at least one prior medication	535 (80.21%)
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	484 (72.56%)
IMMUNOSUPPRESSANTS	484 (72.56%)
Methotrexate	278 (41.68%)
Leflunomide	209 (31.33%)
Iguratimod	83 (12.44%)
Hydroxychloroquine sulfate	80 (11.99%)
Hydroxychloroquine	55 (8.25%)
Lei gong teng duo gan	55 (8.25%)
Tofacitinib citrate	31 (4.65%)
Adalimumab	13 (1.95%)
Tumor necrosis factor receptor 2 - igg	7 (1.05%)
Etanercept	6 (0.90%)
Tofacitinib	4 (0.60%)
Azathioprine	2 (0.30%)
Cyclosporine	2 (0.30%)
Tocilizumab	2 (0.30%)
Abatacept	1 (0.15%)
Cyclosporin	1 (0.15%)
Infliximab	1 (0.15%)
Tumor necrosis factor alpha (tnf-) inhibitors	1 (0.15%)
IMMUNOSTIMULANTS	2 (0.30%)
Di yu sheng bai	2 (0.30%)
ENDOCRINE THERAPY	1 (0.15%)
Hormones	1 (0.15%)
ALIMENTARY TRACT AND METABOLISM	298 (44.68%)
VITAMINS	207 (31.03%)
Alfacalcidol	101 (15.14%)
Calcitriol	88 (13.19%)
Vd	8 (1.20%)
Puria vitamin d drops	4 (0.60%)
Rocaltrol	2 (0.30%)
Vitamin d and analogues	2 (0.30%)
Calcitriol;calcium carbimide citrate;zinc	1 (0.15%)
Vitamin b complex	1 (0.15%)
Vitamin b1 nos	1 (0.15%)
Vitamin d [vitamin d nos]	1 (0.15%)
Vitamin-c	1 (0.15%)
MINERAL SUPPLEMENTS	183 (27.44%)
Calcium carbonate and vitamin d3	47 (7.05%)
Calci d	29 (4.35%)
Calcium carbonate	29 (4.35%)
D-cal	15 (2.25%)

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The percentage denominator is the number of analyses population.
Prior medication is defined as medication started before the date of first dose of study drug.
WHODrug Global (B3) English [V2022SEP]

Anatomy group *Treatment subgroup* *Drug name*	*Safety Analyses Population* *(N=667)*
Calcium carbonate;colecalciferol	10 (1.50%)
Calcium gluconate	10 (1.50%)
Calcium carbonate and vitamin d3 tablets (ii)	8 (1.20%)
Calcium malate	8 (1.20%)
Calcium citrate malate	7 (1.05%)
Potassium chloride	6 (0.90%)
Calcium carbonate/vitamin d3	5 (0.75%)
Calcium	2 (0.30%)
Calcium supplement with vitamin d chewable tablets children's formula	2 (0.30%)
Calcium vitamin d	2 (0.30%)
Cal mag [bambusa bambos;boron glycinate;calcium citrate;calcium lactate gluconate;colecalciferol;lithothamnium calcareum;lysine;magnesium citrate;minerals nos]	1 (0.15%)
Calcium acetate	1 (0.15%)
Calcium aspartate	1 (0.15%)
Calcium d [ascorbic acid;calcium gluconate;calcium lactate;calcium phosphate dibasic;ergocalciferol]	1 (0.15%)
Calcium d [calcium;colecalciferol]	1 (0.15%)
Calfor d	1 (0.15%)
Caltrate d [calcium;colecalciferol]	1 (0.15%)
Caltrate with vitamin d	1 (0.15%)
Gai er qi d	1 (0.15%)
DRUGS FOR ACID RELATED DISORDERS	84 (12.59%)
Pantoprazole sodium [pantoprazole sodium sesquihydrate]	26 (3.90%)
Omeprazole	9 (1.35%)
Rabeprazole sodium	9 (1.35%)
Teprenone	8 (1.20%)
Esomeprazole magnesium	7 (1.05%)
Hydrotalcite	7 (1.05%)
Rebamipide	6 (0.90%)
Sodium rabeprazole	5 (0.75%)
Lansoprazole	3 (0.45%)
Sucralfate	3 (0.45%)
Esomeprazole	2 (0.30%)
Omeprazole sodium	2 (0.30%)
Rabeprazole	2 (0.30%)
Famotidine	1 (0.15%)
Le mei ting	1 (0.15%)
Nexium [esomeprazole magnesium trihydrate]	1 (0.15%)
Pantoprazole	1 (0.15%)
Pantoprazole [pantoprazole sodium sesquihydrate]	1 (0.15%)
Pantoprazole sodium sesquihydrate	1 (0.15%)
Ranitidine hydrochloride	1 (0.15%)
Sofalcone	1 (0.15%)
DRUGS USED IN DIABETES	19 (2.85%)
Metformin hydrochloride	8 (1.20%)
Acarbose	6 (0.90%)
Dapagliflozin	1 (0.15%)

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WHODrug Global (B3) English [V2022SEP]

Anatomy group *Treatment subgroup* *Drug name*	*Safety Analyses Population* *(N=667)*
Empagliflozin	1 (0.15%)
Gliclazide (ii)	1 (0.15%)
Glimepiride	1 (0.15%)
Glipizide	1 (0.15%)
Glucophage	1 (0.15%)
Insulin	1 (0.15%)
Insulin aspart 30	1 (0.15%)
Insulin detemir	1 (0.15%)
Insulin injection	1 (0.15%)
Metformin	1 (0.15%)
Recombinant human insulin	1 (0.15%)
Saxagliptin	1 (0.15%)
Sitagliptin phosphate	1 (0.15%)
OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS	9 (1.35%)
Glucurolactone	5 (0.75%)
Glucuronolactone	4 (0.60%)
BILE AND LIVER THERAPY	6 (0.90%)
Polyene phosphatidylcholine	3 (0.45%)
Compound glycyrrhizin [dl-methionine;glycine;glycyrrhizic acid, ammonium salt]	1 (0.15%)
Silibinin	1 (0.15%)
Ursodeoxycholic acid	1 (0.15%)
DIGESTIVES, INCL. ENZYMES	3 (0.45%)
Pancreatin	2 (0.30%)
Compound digestive enzyme capsules (ii)	1 (0.15%)
DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	3 (0.45%)
Mosapride citrate	2 (0.30%)
Mo luo	1 (0.15%)
DRUGS FOR CONSTIPATION	2 (0.30%)
Lactulose	1 (0.15%)
Tong bian pian	1 (0.15%)
ANTIDIARRHEALS, INTESTINAL ANTIINFLAMMATORY/ANTIINFECTIVE AGENTS	1 (0.15%)
Live combined bifidobacterium and lactobacillus	1 (0.15%)
MUSCULO-SKELETAL SYSTEM	294 (44.08%)
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	245 (36.73%)
Total glucosides of white paeony	69 (10.34%)
Celecoxib	45 (6.75%)
Meloxicam	24 (3.60%)
Etoricoxib	23 (3.45%)
Loxoprofen sodium	23 (3.45%)
Imrecoxib	18 (2.70%)
Zheng qing feng tong ning	17 (2.55%)
Sulfasalazine	15 (2.25%)
Diclofenac sodium	14 (2.10%)
Loxoprofen	11 (1.65%)

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WHODrug Global (B3) English [V2022SEP]

Anatomy group *Treatment subgroup* *Drug name*	*Safety Analyses Population* *(N=667)*
Oxaprozin	11 (1.65%)
Celebrex	8 (1.20%)
Kun xian	8 (1.20%)
Diclofenac diethylamine	6 (0.90%)
Aceclofenac	5 (0.75%)
Glucosamine hydrochloride	4 (0.60%)
Nabumetone	4 (0.60%)
Bi qi [achyranthes bidentata root;atractylodes macrocephala, rhizoma;codonopsis spp. root;glycyrrhiza spp. root with rhizome;ligusticum chuanxiong rhizome;panax notoginseng root;pheretima spp.;poria c	2 (0.30%)
Naproxen sodium	2 (0.30%)
Acemetacin	1 (0.15%)
Chondroitin sulfate;glucosamine	1 (0.15%)
Dexibuprofen	1 (0.15%)
Dexketoprofen	1 (0.15%)
Glucosamine	1 (0.15%)
Glucosamine chondroitin calcium	1 (0.15%)
Glucosamine sulfate	1 (0.15%)
Herbal antiinflammatory and antirheumatic remedies	1 (0.15%)
Hua mo yan	1 (0.15%)
Huo xue zhi tong [angelica sinensis root;borneol;boswellia sacra bark resin;eupolyphaga sinensis;panax notoginseng root with rhizome;pyrite]	1 (0.15%)
Ketoprofen	1 (0.15%)
Lornoxicam	1 (0.15%)
Naproxen	1 (0.15%)
Nimesulide	1 (0.15%)
Other antiinflammatory and antirheumatic agents, non-steroids	1 (0.15%)
Other specific antirheumatic agents	1 (0.15%)
Paeonia lactiflora total glycoside extract	1 (0.15%)
Parecoxib	1 (0.15%)
Qiang gu	1 (0.15%)
Salazosulfapyridine	1 (0.15%)
Tong luo kai bi	1 (0.15%)
Trankal	1 (0.15%)
Wan tong jin gu [achyranthes bidentata root;aconitum carmichaelii root;aconitum kusnezoffii root tuber;asarum spp. root with rhizome;carthamus tinctorius flower;cinnamomum cassia twig;commiphora myrrh	1 (0.15%)
Wang bi	1 (0.15%)
Xue shan jin luo han zhi tong	1 (0.15%)
DRUGS FOR TREATMENT OF BONE DISEASES	109 (16.34%)
Methylene diphosphonate	83 (12.44%)
Risedronate sodium	11 (1.65%)
Alendronate sodium	10 (1.50%)
Alendronate	2 (0.30%)
Qiang gu	2 (0.30%)
Cervus and cucumis polypeptide	1 (0.15%)
Fosamax	1 (0.15%)
Ossotide	1 (0.15%)
Zoledronic acid	1 (0.15%)

TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN	22 (3.30%)

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WHODrug Global (B3) English [V2022SEP]

Anatomy group *Treatment subgroup* *Drug name*	*Safety Analyses Population* *(N=667)*
Flurbiprofen	7 (1.05%)
Diclofenac sodium	4 (0.60%)
Tong luo qu tong	3 (0.45%)
Xiao tong	3 (0.45%)
Aspirin (e.c.)	1 (0.15%)
Folate	1 (0.15%)
Loxonin [loxoprofen sodium]	1 (0.15%)
Loxoprofen	1 (0.15%)
Qing peng	1 (0.15%)
ANTIGOUT PREPARATIONS	2 (0.30%)
Allopurinol	1 (0.15%)
Febuxostat	1 (0.15%)
MUSCLE RELAXANTS	1 (0.15%)
Diazepam	1 (0.15%)
OTHER DRUGS FOR DISORDERS OF THE MUSCULO-SKELETAL SYSTEM	1 (0.15%)
Sodium hyaluronate	1 (0.15%)
SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	204 (30.58%)
CORTICOSTEROIDS FOR SYSTEMIC USE	198 (29.69%)
Methylprednisolone	90 (13.49%)
Prednisone acetate	74 (11.09%)
Prednisone	15 (2.25%)
Betamethasone	9 (1.35%)
Dexamethasone	5 (0.75%)
Compound betamethasone	4 (0.60%)
Betamethasone sodium phosphate	3 (0.45%)
Medrol [methylprednisolone]	3 (0.45%)
Methylprednisolone sodium succinate	3 (0.45%)
Dexamethasone acetate	2 (0.30%)
Dexamethasone sodium phosphate	2 (0.30%)
Hydroprednisone	2 (0.30%)
Triamcinolone acetonide	2 (0.30%)
Triamcinolone acetonide acetate	2 (0.30%)
Dexamethasone palmitate	1 (0.15%)
Meprednisone	1 (0.15%)
Prednisolone	1 (0.15%)
Prednisolone acetate	1 (0.15%)
Prednison	1 (0.15%)
Triamcinolone	1 (0.15%)
THYROID THERAPY	8 (1.20%)
Levothyroxine sodium	4 (0.60%)
Euthyrox	3 (0.45%)
Levothyroxine	1 (0.15%)
BLOOD AND BLOOD FORMING ORGANS	170 (25.49%)

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WHODrug Global (B3) English [V2022SEP]

Anatomy group *Treatment subgroup* *Drug name*	*Safety Analyses Population* *(N=667)*
ANTIANEMIC PREPARATIONS	151 (22.64%)
Folic acid	135 (20.24%)
Mecobalamin	8 (1.20%)
Folate	5 (0.75%)
Folic acid;iron amino acid chelate	2 (0.30%)
Iron dextran	2 (0.30%)
Iron polysaccharide complex	1 (0.15%)
Iron proteinsuccinylate	1 (0.15%)
Jian pi sheng xue	1 (0.15%)
ANTITHROMBOTIC AGENTS	19 (2.85%)
Sodium ferulate	8 (1.20%)
Aspirin (e.c.)	5 (0.75%)
Rivaroxaban	2 (0.30%)
Clopidogrel	1 (0.15%)
Clopidogrel bisulfate	1 (0.15%)
Ginkgo leaf extract and dipyridamole	1 (0.15%)
Pradaxa	1 (0.15%)
ANTIHEMORRHAGICS	2 (0.30%)
Leucogen	1 (0.15%)
Menatetrenone	1 (0.15%)
BLOOD SUBSTITUTES AND PERFUSION SOLUTIONS	1 (0.15%)
Potassium chloride	1 (0.15%)
CARDIOVASCULAR SYSTEM	68 (10.19%)
CALCIUM CHANNEL BLOCKERS	34 (5.10%)
Nifedipine	12 (1.80%)
Amlodipine besylate	7 (1.05%)
Amlodipine	5 (0.75%)
Felodipine	3 (0.45%)
Levamlodipine	3 (0.45%)
Levamlodipine besylate	3 (0.45%)
Levoamlodipine maleate	1 (0.15%)
Nifedipine sustained release tablets (ii)	1 (0.15%)
Nimodipine	1 (0.15%)
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	19 (2.85%)
Irbesartan	11 (1.65%)
Valsartan	3 (0.45%)
Losartan potassium and hydrochlorothiazide	2 (0.30%)
Allisartan isoproxil	1 (0.15%)
Irbesartan and hydrochlorothiazide	1 (0.15%)
Valsartan and amlodipine [amlodipine;valsartan]	1 (0.15%)
LIPID MODIFYING AGENTS	17 (2.55%)
Atorvastatin calcium	9 (1.35%)
Rosuvastatin calcium	3 (0.45%)
Atorvastatin	2 (0.30%)

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WHODrug Global (B3) English [V2022SEP]

Anatomy group *Treatment subgroup* *Drug name*	*Safety Analyses Population* *(N=667)*
Amlodipine besylate and atorvastatin calcium	1 (0.15%)
Fenofibrate	1 (0.15%)
Pravastatin sodium	1 (0.15%)
BETA BLOCKING AGENTS	13 (1.95%)
Betaloc zok	4 (0.60%)
Bisoprolol fumarate	3 (0.45%)
Metoprolol tartrate	2 (0.30%)
Carvedilol	1 (0.15%)
Metoprolol	1 (0.15%)
Metoprolol [metoprolol tartrate]	1 (0.15%)
Metoprolol succinate	1 (0.15%)
CARDIAC THERAPY	6 (0.90%)
She xiang bao xin	3 (0.45%)
Fu fang dan shen	1 (0.15%)
Hong hua huang se su lv hua na	1 (0.15%)
Isosorbide mononitrate	1 (0.15%)
Quick acting heart reliever	1 (0.15%)
Trimetazidine hydrochloride	1 (0.15%)
Yi xin shu	1 (0.15%)
DIURETICS	6 (0.90%)
Spironolactone	5 (0.75%)
Torasemide	3 (0.45%)
Furosemide	1 (0.15%)
VASOPROTECTIVES	2 (0.30%)
Titanoreine [chondrus crispus;titanium dioxide;zinc oxide]	2 (0.30%)
PERIPHERAL VASODILATORS	1 (0.15%)
Yin xing tong zhi	1 (0.15%)
ANTIINFECTIVES FOR SYSTEMIC USE	37 (5.55%)
ANTIMYCOBACTERIALS	20 (3.00%)
Isoniazid	19 (2.85%)
Rifampicin	4 (0.60%)
Ethambutol hydrochloride	1 (0.15%)
Isoniazide	1 (0.15%)
ANTIBACTERIALS FOR SYSTEMIC USE	8 (1.20%)
Amoxicillin and clavulanate potassium er	1 (0.15%)
Avelox	1 (0.15%)
Ceftizoxime	1 (0.15%)
Ceftriaxone sodium;tazobactam sodium	1 (0.15%)
Levofloxacin hydrochloride and sodium chloride	1 (0.15%)
Piperacillin sodium and tazobactam sodium	1 (0.15%)
Rifampicin	1 (0.15%)
Sulfadiazine	1 (0.15%)
ANTIVIRALS FOR SYSTEMIC USE	8 (1.20%)
Entecavir	7 (1.05%)

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WHODrug Global (B3) English [V2022SEP]

Anatomy group *Treatment subgroup* *Drug name*	*Safety Analyses Population* *(N=667)*
Lian hua qing wen	1 (0.15%)
ANTIMYCOTICS FOR SYSTEMIC USE	3 (0.45%)
Itraconazole	2 (0.30%)
Fluconazole	1 (0.15%)
IMMUNE SERA AND IMMUNOGLOBULINS	1 (0.15%)
Human immunoglobulin	1 (0.15%)
VARIOUS	32 (4.80%)
UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	25 (3.75%)
Feng shi gu tong	4 (0.60%)
Gu long jiao nang	3 (0.45%)
Unspecified herbal and traditional medicine	3 (0.45%)
Jin gu lian	2 (0.30%)
Traditional chinese medicine (tcm) decoction	2 (0.30%)
Aescuven forte [aesculus hippocastanum extract]	1 (0.15%)
Du yi wei	1 (0.15%)
Gan de zhi pian	1 (0.15%)
Gu kang	1 (0.15%)
Jiang tang	1 (0.15%)
Kang fu xin	1 (0.15%)
Qiang gan	1 (0.15%)
Rou kou wu wei	1 (0.15%)
Shang shi zhi tong gao	1 (0.15%)
Traditional medicine	1 (0.15%)
Wang bi	1 (0.15%)
Xia ku cao	1 (0.15%)
Xian ling gu bao	1 (0.15%)
Yu ping feng	1 (0.15%)
Zhen yuan	1 (0.15%)
ALL OTHER THERAPEUTIC PRODUCTS	5 (0.75%)
Glutathione	4 (0.60%)
Compound glycyrrhizin [dl-methionine;glycine;glycyrrhizic acid, ammonium salt]	1 (0.15%)
DIAGNOSTIC AGENTS	1 (0.15%)
Purified protein derivative of bcc (bcg-ppd)	1 (0.15%)
GENERAL NUTRIENTS	1 (0.15%)
Compound alpha ketoacid	1 (0.15%)
UNCODE	1 (0.15%)
Biologicals	1 (0.15%)
NERVOUS SYSTEM	20 (3.00%)
ANALGESICS	9 (1.35%)
Bulleyaconitine a	4 (0.60%)
Aspirin [acetylsalicylic acid]	2 (0.30%)
Duloxetine hydrochloride	1 (0.15%)
Propacetamol hydrochloride	1 (0.15%)

Footnote: N, number of patients in population.
The percentage denominator is the number of analyses population.
Prior medication is defined as medication started before the date of first dose of study drug.
WHODrug Global (B3) English [V2022SEP]

Anatomy group *Treatment subgroup* *Drug name*	*Safety Analyses Population* *(N=667)*
Tramadol hydrochloride	1 (0.15%)
PSYCHOLEPTICS	9 (1.35%)
Estazolam	5 (0.75%)
Oryzanol	2 (0.30%)
Olanzapine	1 (0.15%)
Remimazolam	1 (0.15%)
Risperidone	1 (0.15%)
Zopiclone	1 (0.15%)
PSYCHOANALEPTICS	2 (0.30%)
Flupentixol and melitracen	1 (0.15%)
Piracetam	1 (0.15%)
OTHER NERVOUS SYSTEM DRUGS	1 (0.15%)
Mecobalamin	1 (0.15%)
RESPIRATORY SYSTEM	8 (1.20%)
COUGH AND COLD PREPARATIONS	5 (0.75%)
Ambroxol hydrochloride	3 (0.45%)
Cydiodine	1 (0.15%)
Qie nuo	1 (0.15%)
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	4 (0.60%)
Bai ling [cordyceps sinensis mycelium]	2 (0.30%)
Compound methoxyphenamine	1 (0.15%)
Doxofylline	1 (0.15%)
Methoxyphenamine hydrochloride	1 (0.15%)
Montelukast sodium	1 (0.15%)
ANTIHISTAMINES FOR SYSTEMIC USE	1 (0.15%)
Levocetirizine hydrochloride	1 (0.15%)
SENSORY ORGANS	2 (0.30%)
OPHTHALMOLOGICALS	2 (0.30%)
Azelastine hydrochloride	1 (0.15%)
Sodium hyaluronate	1 (0.15%)
ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS	1 (0.15%)
ANTIPROTOZOALS	1 (0.15%)
Chloroquine sulfate	1 (0.15%)
DERMATOLOGICALS	1 (0.15%)
MEDICATED DRESSINGS	1 (0.15%)
Fusidic acid	1 (0.15%)
GENITO URINARY SYSTEM AND SEX HORMONES	1 (0.15%)
UROLOGICALS	1 (0.15%)
Niao du qing	1 (0.15%)

Footnote: N, number of patients in population.
The percentage denominator is the number of analyses population.
Prior medication is defined as medication started before the date of first dose of study drug.
WHODrug Global (B3) English [V2022SEP]

Table ANN. 19 Prior Medication – Effectiveness Analyses Population

Anatomy group *Treatment subgroup* *Drug name*	*Effectiveness Analyses Population (N=514)*
With at least one prior medication	418 (81.32%)
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	377 (73.35%)
IMMUNOSUPPRESSANTS	377 (73.35%)
Methotrexate	219 (42.61%)
Leflunomide	159 (30.93%)
Hydroxychloroquine sulfate	59 (11.48%)
Iguratimod	55 (10.70%)
Hydroxychloroquine	45 (8.75%)
Lei gong teng duo gan	40 (7.78%)
Tofacitinib citrate	21 (4.09%)
Adalimumab	12 (2.33%)
Etanercept	6 (1.17%)
Tumor necrosis factor receptor 2 - igg	5 (0.97%)
Tofacitinib	3 (0.58%)
Azathioprine	2 (0.39%)
Cyclosporine	2 (0.39%)
Abatacept	1 (0.19%)
Cyclosporin	1 (0.19%)
Infliximab	1 (0.19%)
Tocilizumab	1 (0.19%)
Tumor necrosis factor alpha (tnf-) inhibitors	1 (0.19%)
IMMUNOSTIMULANTS	2 (0.39%)
Di yu sheng bai	2 (0.39%)
ENDOCRINE THERAPY	1 (0.19%)
Hormones	1 (0.19%)
ALIMENTARY TRACT AND METABOLISM	238 (46.30%)
VITAMINS	164 (31.91%)
Alfacalcidol	85 (16.54%)
Calcitriol	66 (12.84%)
Vd	6 (1.17%)
Puria vitamin d drops	3 (0.58%)
Rocaltrol	2 (0.39%)
Vitamin d and analogues	2 (0.39%)
Calcitriol;calcium carbimide citrate;zinc	1 (0.19%)
Vitamin b complex	1 (0.19%)
Vitamin-c	1 (0.19%)
MINERAL SUPPLEMENTS	144 (28.02%)
Calcium carbonate and vitamin d3	34 (6.61%)
Calci d	24 (4.67%)
Calcium carbonate	24 (4.67%)
Calcium gluconate	9 (1.75%)
D-cal	9 (1.75%)
Calcium carbonate;colecalciferol	8 (1.56%)

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The percentage denominator is the number of analyses population.
Prior medication is defined as medication started before the date of first dose of study drug.
WHODrug Global (B3) English [V2022SEP]

Anatomy group *Treatment subgroup* *Drug name*	*Effectiveness Analyses Population (N=514)*
Calcium malate	8 (1.56%)
Calcium carbonate and vitamin d3 tablets (ii)	7 (1.36%)
Calcium citrate malate	7 (1.36%)
Calcium carbonate/vitamin d3	4 (0.78%)
Potassium chloride	3 (0.58%)
Calcium	2 (0.39%)
Calcium vitamin d	2 (0.39%)
Calcium acetate	1 (0.19%)
Calcium d [ascorbic acid;calcium gluconate;calcium lactate;calcium phosphate dibasic;ergocalciferol]	1 (0.19%)
Calcium supplement with vitamin d chewable tablets children's formula	1 (0.19%)
Calfor d	1 (0.19%)
Caltrate with vitamin d	1 (0.19%)
Gai er qi d	1 (0.19%)
DRUGS FOR ACID RELATED DISORDERS	68 (13.23%)
Pantoprazole sodium [pantoprazole sodium sesquihydrate]	22 (4.28%)
Omeprazole	7 (1.36%)
Rabeprazole sodium	7 (1.36%)
Hydrotalcite	6 (1.17%)
Sodium rabeprazole	5 (0.97%)
Teprenone	5 (0.97%)
Rebamipide	4 (0.78%)
Esomeprazole magnesium	3 (0.58%)
Lansoprazole	3 (0.58%)
Rabeprazole	2 (0.39%)
Sucralfate	2 (0.39%)
Esomeprazole	1 (0.19%)
Famotidine	1 (0.19%)
Le mei ting	1 (0.19%)
Nexium [esomeprazole magnesium trihydrate]	1 (0.19%)
Omeprazole sodium	1 (0.19%)
Pantoprazole	1 (0.19%)
Pantoprazole [pantoprazole sodium sesquihydrate]	1 (0.19%)
Pantoprazole sodium sesquihydrate	1 (0.19%)
Ranitidine hydrochloride	1 (0.19%)
Sofalcone	1 (0.19%)
DRUGS USED IN DIABETES	13 (2.53%)
Metformin hydrochloride	5 (0.97%)
Acarbose	4 (0.78%)
Dapagliflozin	1 (0.19%)
Empagliflozin	1 (0.19%)
Gliclazide (ii)	1 (0.19%)
Glipizide	1 (0.19%)
Insulin aspart 30	1 (0.19%)
Insulin detemir	1 (0.19%)
Metformin	1 (0.19%)

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Prior medication is defined as medication started before the date of first dose of study drug.
WHODrug Global (B3) English [V2022SEP]

Anatomy group *Treatment subgroup* *Drug name*	*Effectiveness Analyses Population (N=514)*
Recombinant human insulin	1 (0.19%)
Saxagliptin	1 (0.19%)
OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS	9 (1.75%)
Glucurolactone	5 (0.97%)
Glucuronolactone	4 (0.78%)
BILE AND LIVER THERAPY	5 (0.97%)
Polyene phosphatidylcholine	2 (0.39%)
Compound glycyrrhizin [dl-methionine;glycine;glycyrrhizic acid, ammonium salt]	1 (0.19%)
Silibinin	1 (0.19%)
Ursodeoxycholic acid	1 (0.19%)
DIGESTIVES, INCL. ENZYMES	3 (0.58%)
Pancreatin	2 (0.39%)
Compound digestive enzyme capsules (ii)	1 (0.19%)
DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	3 (0.58%)
Mosapride citrate	2 (0.39%)
Mo luo	1 (0.19%)
ANTIDIARRHEALS, INTESTINAL ANTIINFLAMMATORY/ANTIINFECTIVE AGENTS	1 (0.19%)
Live combined bifidobacterium and lactobacillus	1 (0.19%)
DRUGS FOR CONSTIPATION	1 (0.19%)
Tong bian pian	1 (0.19%)
MUSCULO-SKELETAL SYSTEM	220 (42.80%)
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	176 (34.24%)
Total glucosides of white paeony	60 (11.67%)
Celecoxib	29 (5.64%)
Loxoprofen sodium	17 (3.31%)
Zheng qing feng tong ning	16 (3.11%)
Etoricoxib	15 (2.92%)
Diclofenac sodium	13 (2.53%)
Meloxicam	11 (2.14%)
Oxaprozin	10 (1.95%)
Imrecoxib	9 (1.75%)
Loxoprofen	9 (1.75%)
Sulfasalazine	9 (1.75%)
Celebrex	6 (1.17%)
Diclofenac diethylamine	6 (1.17%)
Kun xian	4 (0.78%)
Nabumetone	4 (0.78%)
Aceclofenac	3 (0.58%)
Bi qi [achyranthes bidentata root;atractylodes macrocephala, rhizoma;codonopsis spp. root;glycyrrhiza spp. root with rhizome;ligusticum chuanxiong rhizome;panax notoginseng root;pheretima spp.;poria c	2 (0.39%)
Glucosamine hydrochloride	2 (0.39%)
Chondroitin sulfate;glucosamine	1 (0.19%)
Dexibuprofen	1 (0.19%)
Dexketoprofen	1 (0.19%)
Glucosamine	1 (0.19%)

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WHODrug Global (B3) English [V2022SEP]

Anatomy group *Treatment subgroup* *Drug name*	*Effectiveness Analyses Population (N=514)*
Glucosamine chondroitin calcium	1 (0.19%)
Herbal antiinflammatory and antirheumatic remedies	1 (0.19%)
Huo xue zhi tong [angelica sinensis root;borneol;boswellia sacra bark resin;eupolyphaga sinensis;panax notoginseng root with rhizome;pyrite]	1 (0.19%)
Ketoprofen	1 (0.19%)
Nimesulide	1 (0.19%)
Other specific antirheumatic agents	1 (0.19%)
Paeonia lactiflora total glycoside extract	1 (0.19%)
Parecoxib	1 (0.19%)
Salazosulfapyridine	1 (0.19%)
Tong luo kai bi	1 (0.19%)
Trankal	1 (0.19%)
Wan tong jin gu [achyranthes bidentata root;aconitum carmichaelii root;aconitum kusnezoffii root tuber;asarum spp. root with rhizome;carthamus tinctorius flower;cinnamomum cassia twig;commiphora myrrh	1 (0.19%)
Xue shan jin luo han zhi tong	1 (0.19%)
DRUGS FOR TREATMENT OF BONE DISEASES	90 (17.51%)
Methylene diphosphonate	69 (13.42%)
Risedronate sodium	11 (2.14%)
Alendronate sodium	6 (1.17%)
Alendronate	2 (0.39%)
Qiang gu	2 (0.39%)
Fosamax	1 (0.19%)
Ossotide	1 (0.19%)
TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN	18 (3.50%)
Flurbiprofen	5 (0.97%)
Diclofenac sodium	3 (0.58%)
Tong luo qu tong	3 (0.58%)
Xiao tong	3 (0.58%)
Aspirin (e.c.)	1 (0.19%)
Folate	1 (0.19%)
Loxonin [loxoprofen sodium]	1 (0.19%)
Qing peng	1 (0.19%)
ANTIGOUT PREPARATIONS	2 (0.39%)
Allopurinol	1 (0.19%)
Febuxostat	1 (0.19%)
MUSCLE RELAXANTS	1 (0.19%)
Diazepam	1 (0.19%)
OTHER DRUGS FOR DISORDERS OF THE MUSCULO-SKELETAL SYSTEM	1 (0.19%)
Sodium hyaluronate	1 (0.19%)
SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	155 (30.16%)
CORTICOSTEROIDS FOR SYSTEMIC USE	150 (29.18%)
Methylprednisolone	70 (13.62%)
Prednisone acetate	54 (10.51%)
Prednisone	14 (2.72%)
Betamethasone	8 (1.56%)
Betamethasone sodium phosphate	3 (0.58%)

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WHODrug Global (B3) English [V2022SEP]

Anatomy group *Treatment subgroup* *Drug name*	*Effectiveness Analyses Population (N=514)*
Compound betamethasone	3 (0.58%)
Dexamethasone	2 (0.39%)
Dexamethasone sodium phosphate	2 (0.39%)
Medrol [methylprednisolone]	2 (0.39%)
Methylprednisolone sodium succinate	2 (0.39%)
Triamcinolone acetonide	2 (0.39%)
Triamcinolone acetonide acetate	2 (0.39%)
Dexamethasone acetate	1 (0.19%)
Dexamethasone palmitate	1 (0.19%)
Hydroprednisone	1 (0.19%)
Meprednisone	1 (0.19%)
Prednisolone	1 (0.19%)
Prednisolone acetate	1 (0.19%)
Prednison	1 (0.19%)
THYROID THERAPY	7 (1.36%)
Levothyroxine sodium	4 (0.78%)
Euthyrox	3 (0.58%)
BLOOD AND BLOOD FORMING ORGANS	141 (27.43%)
ANTIANEMIC PREPARATIONS	126 (24.51%)
Folic acid	113 (21.98%)
Mecobalamin	7 (1.36%)
Folate	4 (0.78%)
Folic acid;iron amino acid chelate	2 (0.39%)
Iron dextran	1 (0.19%)
Iron polysaccharide complex	1 (0.19%)
Iron proteinsuccinylate	1 (0.19%)
ANTITHROMBOTIC AGENTS	16 (3.11%)
Sodium ferulate	6 (1.17%)
Aspirin (e.c.)	4 (0.78%)
Rivaroxaban	2 (0.39%)
Clopidogrel	1 (0.19%)
Clopidogrel bisulfate	1 (0.19%)
Ginkgo leaf extract and dipyridamole	1 (0.19%)
Pradaxa	1 (0.19%)
ANTIHEMORRHAGICS	2 (0.39%)
Leucogen	1 (0.19%)
Menatetrenone	1 (0.19%)
CARDIOVASCULAR SYSTEM	53 (10.31%)
CALCIUM CHANNEL BLOCKERS	27 (5.25%)
Nifedipine	9 (1.75%)
Amlodipine besylate	5 (0.97%)
Amlodipine	3 (0.58%)
Felodipine	3 (0.58%)

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WHODrug Global (B3) English [V2022SEP]

Anatomy group *Treatment subgroup* *Drug name*	*Effectiveness Analyses Population (N=514)*
Levamlodipine	3 (0.58%)
Levamlodipine besylate	3 (0.58%)
Levoamlodipine maleate	1 (0.19%)
Nifedipine sustained release tablets (ii)	1 (0.19%)
Nimodipine	1 (0.19%)
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	14 (2.72%)
Irbesartan	8 (1.56%)
Valsartan	3 (0.58%)
Allisartan isoproxil	1 (0.19%)
Irbesartan and hydrochlorothiazide	1 (0.19%)
Valsartan and amlodipine [amlodipine;valsartan]	1 (0.19%)
LIPID MODIFYING AGENTS	13 (2.53%)
Atorvastatin calcium	7 (1.36%)
Rosuvastatin calcium	3 (0.58%)
Amlodipine besylate and atorvastatin calcium	1 (0.19%)
Fenofibrate	1 (0.19%)
Pravastatin sodium	1 (0.19%)
BETA BLOCKING AGENTS	12 (2.33%)
Betaloc zok	4 (0.78%)
Bisoprolol fumarate	3 (0.58%)
Metoprolol tartrate	2 (0.39%)
Carvedilol	1 (0.19%)
Metoprolol [metoprolol tartrate]	1 (0.19%)
Metoprolol succinate	1 (0.19%)
CARDIAC THERAPY	5 (0.97%)
She xiang bao xin	2 (0.39%)
Fu fang dan shen	1 (0.19%)
Hong hua huang se su lv hua na	1 (0.19%)
Isosorbide mononitrate	1 (0.19%)
Quick acting heart reliever	1 (0.19%)
Trimetazidine hydrochloride	1 (0.19%)
Yi xin shu	1 (0.19%)
DIURETICS	5 (0.97%)
Spironolactone	5 (0.97%)
Torasemide	2 (0.39%)
Furosemide	1 (0.19%)
PERIPHERAL VASODILATORS	1 (0.19%)
Yin xing tong zhi	1 (0.19%)
VASOPROTECTIVES	1 (0.19%)
Titanoreine [chondrus crispus;titanium dioxide;zinc oxide]	1 (0.19%)
ANTIINFECTIVES FOR SYSTEMIC USE	27 (5.25%)
ANTIMYCOBACTERIALS	15 (2.92%)
Isoniazid	14 (2.72%)
Rifampicin	2 (0.39%)

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WHODrug Global (B3) English [V2022SEP]

Anatomy group *Treatment subgroup* *Drug name*	*Effectiveness Analyses Population (N=514)*
Isoniazide	1 (0.19%)
ANTIBACTERIALS FOR SYSTEMIC USE	7 (1.36%)
Amoxicillin and clavulanate potassium er	1 (0.19%)
Avelox	1 (0.19%)
Ceftizoxime	1 (0.19%)
Levofloxacin hydrochloride and sodium chloride	1 (0.19%)
Piperacillin sodium and tazobactam sodium	1 (0.19%)
Rifampicin	1 (0.19%)
Sulfadiazine	1 (0.19%)
ANTIVIRALS FOR SYSTEMIC USE	6 (1.17%)
Entecavir	5 (0.97%)
Lian hua qing wen	1 (0.19%)
ANTIMYCOTICS FOR SYSTEMIC USE	1 (0.19%)
Itraconazole	1 (0.19%)
IMMUNE SERA AND IMMUNOGLOBULINS	1 (0.19%)
Human immunoglobulin	1 (0.19%)
VARIOUS	22 (4.28%)
UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	17 (3.31%)
Gu long jiao nang	3 (0.58%)
Feng shi gu tong	2 (0.39%)
Jin gu lian	2 (0.39%)
Unspecified herbal and traditional medicine	2 (0.39%)
Aescuven forte [aesculus hippocastanum extract]	1 (0.19%)
Du yi wei	1 (0.19%)
Kang fu xin	1 (0.19%)
Rou kou wu wei	1 (0.19%)
Traditional chinese medicine (tcm) decoction	1 (0.19%)
Traditional medicine	1 (0.19%)
Wang bi	1 (0.19%)
Xia ku cao	1 (0.19%)
Xian ling gu bao	1 (0.19%)
Yu ping feng	1 (0.19%)
Zhen yuan	1 (0.19%)
ALL OTHER THERAPEUTIC PRODUCTS	4 (0.78%)
Glutathione	4 (0.78%)
UNCODE	1 (0.19%)
Biologicals	1 (0.19%)
NERVOUS SYSTEM	17 (3.31%)
PSYCHOLEPTICS	9 (1.75%)
Estazolam	5 (0.97%)
Oryzanol	2 (0.39%)
Olanzapine	1 (0.19%)
Remimazolam	1 (0.19%)

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Prior medication is defined as medication started before the date of first dose of study drug.
WHODrug Global (B3) English [V2022SEP]

Anatomy group *Treatment subgroup* *Drug name*	*Effectiveness Analyses Population (N=514)*
Risperidone	1 (0.19%)
Zopiclone	1 (0.19%)
ANALGESICS	7 (1.36%)
Bulleyaconitine a	4 (0.78%)
Aspirin [acetylsalicylic acid]	1 (0.19%)
Duloxetine hydrochloride	1 (0.19%)
Propacetamol hydrochloride	1 (0.19%)
OTHER NERVOUS SYSTEM DRUGS	1 (0.19%)
Mecobalamin	1 (0.19%)
PSYCHOANALEPTICS	1 (0.19%)
Piracetam	1 (0.19%)
RESPIRATORY SYSTEM	5 (0.97%)
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	3 (0.58%)
Bai ling [cordyceps sinensis mycelium]	2 (0.39%)
Doxofylline	1 (0.19%)
Methoxyphenamine hydrochloride	1 (0.19%)
Montelukast sodium	1 (0.19%)
COUGH AND COLD PREPARATIONS	2 (0.39%)
Ambroxol hydrochloride	1 (0.19%)
Cydiodine	1 (0.19%)
ANTIHISTAMINES FOR SYSTEMIC USE	1 (0.19%)
Levocetirizine hydrochloride	1 (0.19%)
SENSORY ORGANS	2 (0.39%)
OPHTHALMOLOGICALS	2 (0.39%)
Azelastine hydrochloride	1 (0.19%)
Sodium hyaluronate	1 (0.19%)
ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS	1 (0.19%)
ANTIPROTOZOALS	1 (0.19%)
Chloroquine sulfate	1 (0.19%)
DERMATOLOGICALS	1 (0.19%)
MEDICATED DRESSINGS	1 (0.19%)
Fusidic acid	1 (0.19%)
GENITO URINARY SYSTEM AND SEX HORMONES	1 (0.19%)
UROLOGICALS	1 (0.19%)
Niao du qing	1 (0.19%)

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Prior medication is defined as medication started before the date of first dose of study drug.
WHODrug Global (B3) English [V2022SEP]

Table ANN. 20 Concomitant Medication – Safety Analyses Population

Anatomy group *Treatment subgroup* *Drug name*	*Safety Analyses Population* *(N=667)*
With at least one concomitant medication	632 (94.75%)
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	582 (87.26%)
IMMUNOSUPPRESSANTS	582 (87.26%)
Methotrexate	362 (54.27%)
Leflunomide	237 (35.53%)
Hydroxychloroquine sulfate	97 (14.54%)
Iguratimod	96 (14.39%)
Lei gong teng duo gan	72 (10.79%)
Hydroxychloroquine	70 (10.49%)
Azathioprine	2 (0.30%)
Cyclosporine	2 (0.30%)
Cyclosporin	1 (0.15%)
Tocilizumab	1 (0.15%)
IMMUNOSTIMULANTS	13 (1.95%)
Recombinant human interleukin-2	4 (0.60%)
Thymopeptide	4 (0.60%)
Di yu sheng bai	3 (0.45%)
Glutathione	1 (0.15%)
Interleukin-2	1 (0.15%)
ANTINEOPLASTIC AGENTS	1 (0.15%)
Cyclophosphamide	1 (0.15%)
ENDOCRINE THERAPY	1 (0.15%)
Hormones	1 (0.15%)
ALIMENTARY TRACT AND METABOLISM	461 (69.12%)
VITAMINS	331 (49.63%)
Calcitriol	156 (23.39%)
Alfacalcidol	151 (22.64%)
Vd	13 (1.95%)
Puria vitamin d drops	6 (0.90%)
Vitamin b1 nos	3 (0.45%)
Vitamin-c	3 (0.45%)
Calcitriol injection	2 (0.30%)
Rocaltrol	2 (0.30%)
Vitamin b complex	2 (0.30%)
Vitamin d and analogues	2 (0.30%)
Calcitriol;calcium carbimide citrate;zinc	1 (0.15%)
Compound vitamin b [calcium pantothenate;nicotinamide;pyridoxine hydrochloride;riboflavin;thiamine hydrochloride]	1 (0.15%)
Pyridoxine hydrochloride	1 (0.15%)
Riboflavin	1 (0.15%)
Vitamin b1	1 (0.15%)
Vitamin b6	1 (0.15%)

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WHODrug Global (B3) English [V2022SEP]

Anatomy group *Treatment subgroup* *Drug name*	*Safety Analyses Population* *(N=667)*
Vitamin d [vitamin d nos]	1 (0.15%)
Vitamin d nos	1 (0.15%)
Vitamin d2	1 (0.15%)
MINERAL SUPPLEMENTS	317 (47.53%)
Calcium carbonate and vitamin d3	94 (14.09%)
Calci d	56 (8.40%)
Calcium carbonate	51 (7.65%)
Calcium carbonate;colecalciferol	21 (3.15%)
Calcium gluconate	19 (2.85%)
D-cal	19 (2.85%)
Potassium chloride	14 (2.10%)
Calcium malate	11 (1.65%)
Calcium carbonate and vitamin d3 tablets (ii)	10 (1.50%)
Calcium citrate malate	8 (1.20%)
Calcium carbonate/vitamin d3	5 (0.75%)
Calcium supplement with vitamin d chewable tablets children's formula	5 (0.75%)
Calcium vitamin d	4 (0.60%)
Calcium aspartate	2 (0.30%)
Calcium supplement with vitamin d	2 (0.30%)
Caltrate d [calcium;colecalciferol]	2 (0.30%)
Cal mag [bambusa bambos;boron glycinate;calcium citrate;calcium lactate gluconate;colecalciferol;lithothamnium calcareum;lysine;magnesium citrate;minerals nos]	1 (0.15%)
Calcium	1 (0.15%)
Calcium acetate	1 (0.15%)
Calcium and vitamin d	1 (0.15%)
Calcium carbonate;calcium lactobionate;colecalciferol	1 (0.15%)
Calcium d [ascorbic acid;calcium gluconate;calcium lactate;calcium phosphate dibasic;ergocalciferol]	1 (0.15%)
Calcium d [calcium;colecalciferol]	1 (0.15%)
Calfor d	1 (0.15%)
Caltrate d [calcium carbonate;colecalciferol]	1 (0.15%)
Caltrate with vitamin d	1 (0.15%)
Gai er qi d	1 (0.15%)
Potassium citrate	1 (0.15%)
Wei d2 lin pu gai	1 (0.15%)
DRUGS FOR ACID RELATED DISORDERS	171 (25.64%)
Pantoprazole sodium [pantoprazole sodium sesquihydrate]	53 (7.95%)
Teprenone	34 (5.10%)
Omeprazole	19 (2.85%)
Rebamipide	18 (2.70%)
Esomeprazole magnesium	13 (1.95%)
Rabeprazole sodium	13 (1.95%)
Sodium rabeprazole	11 (1.65%)
Lansoprazole	9 (1.35%)
Hydrotalcite	8 (1.20%)

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WHODrug Global (B3) English [V2022SEP]

Anatomy group *Treatment subgroup* *Drug name*	*Safety Analyses Population* *(N=667)*
Rabeprazole	5 (0.75%)
Sucralfate	5 (0.75%)
Omeprazole sodium	3 (0.45%)
Pantoprazole	3 (0.45%)
Esomeprazole	2 (0.30%)
Ilaprazole	2 (0.30%)
Nexium [esomeprazole magnesium trihydrate]	2 (0.30%)
Pantoprazole sodium sesquihydrate	2 (0.30%)
Sofalcone	2 (0.30%)
Almagate	1 (0.15%)
Cimetidine	1 (0.15%)
Compound magnesium trisilicate and sodium bicarbonate	1 (0.15%)
Esomeprazole magnesium trihydrate	1 (0.15%)
Famotidine	1 (0.15%)
Ilaprazole sodium	1 (0.15%)
Lafutidine	1 (0.15%)
Le mei ting	1 (0.15%)
Omeprazole magnesium	1 (0.15%)
Pantoprazole [pantoprazole sodium sesquihydrate]	1 (0.15%)
Ranitidine hydrochloride	1 (0.15%)
Sodium bicarbonate	1 (0.15%)
Sulpiride	1 (0.15%)
DRUGS USED IN DIABETES	30 (4.50%)
Metformin hydrochloride	10 (1.50%)
Acarbose	9 (1.35%)
Insulin injection	3 (0.45%)
Metformin	3 (0.45%)
Dapagliflozin	2 (0.30%)
Glimepiride	2 (0.30%)
Sitagliptin phosphate	2 (0.30%)
Voglibose	2 (0.30%)
Empagliflozin	1 (0.15%)
Gliclazide	1 (0.15%)
Gliclazide (ii)	1 (0.15%)
Glipizide	1 (0.15%)
Glucophage	1 (0.15%)
Insulin	1 (0.15%)
Insulin aspart 30	1 (0.15%)
Insulin detemir	1 (0.15%)
Recombinant human insulin	1 (0.15%)
Repaglinide	1 (0.15%)
Saxagliptin	1 (0.15%)
OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS	22 (3.30%)

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WHODrug Global (B3) English [V2022SEP]

Anatomy group *Treatment subgroup* *Drug name*	*Safety Analyses Population* *(N=667)*
Glucurolactone	12 (1.80%)
Glucuronolactone	10 (1.50%)
Acetylcysteine	1 (0.15%)
BILE AND LIVER THERAPY	20 (3.00%)
Bicyclol	5 (0.75%)
Polyene phosphatidylcholine	5 (0.75%)
Ursodeoxycholic acid	3 (0.45%)
Diammonium glycyrrhizinate	2 (0.30%)
Magnesium isoglycyrrhizinate	2 (0.30%)
Wu zhi	2 (0.30%)
Compound diisopropylamine dichloroacetate [diisopropylamine dichloroacetate;gluconate sodium]	1 (0.15%)
Compound glycyrrhizin [dl-methionine;glycine;glycyrrhizic acid, ammonium salt]	1 (0.15%)
Silibinin	1 (0.15%)
Tauroursodeoxycholic acid	1 (0.15%)
DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	9 (1.35%)
Itopride hydrochloride	2 (0.30%)
Mosapride citrate	2 (0.30%)
Domperidone	1 (0.15%)
Mo luo	1 (0.15%)
Pinaverium bromide	1 (0.15%)
Simethicone	1 (0.15%)
Trimebutine	1 (0.15%)
Trimebutine maleate	1 (0.15%)
ANTIDIARRHEALS, INTESTINAL ANTIINFLAMMATORY/ANTIINFECTIVE AGENTS	6 (0.90%)
Montmorillonite	3 (0.45%)
Live combined bifidobacterium and lactobacillus	2 (0.30%)
Bifid.triple viable	1 (0.15%)
Compound berberine hydrochloride	1 (0.15%)
Lactobacillus complex [lactobacillus acidophilus;lactobacillus lactis;streptococcus lactis]	1 (0.15%)
DIGESTIVES, INCL. ENZYMES	6 (0.90%)
Compound digestive enzyme capsules (ii)	3 (0.45%)
Pancreatin	2 (0.30%)
Glutamine and guaiazulene sulfonate sodium	1 (0.15%)
Oryz-aspergillus enzyme and pancreatin	1 (0.15%)
DRUGS FOR CONSTIPATION	5 (0.75%)
Lactulose	2 (0.30%)
Duphalac [galactose;lactose;lactulose]	1 (0.15%)
Kai sai lu	1 (0.15%)
Purge	1 (0.15%)
Tong bian pian	1 (0.15%)
ANTIEMETICS AND ANTINAUSEANTS	2 (0.30%)
Metoclopramide hydrochloride	1 (0.15%)
Palonosetron hydrochloride	1 (0.15%)

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WHODrug Global (B3) English [V2022SEP]

Anatomy group *Treatment subgroup* *Drug name*	*Safety Analyses Population* *(N=667)*
STOMATOLOGICAL PREPARATIONS	2 (0.30%)
Compound chlorhexidine gargle	1 (0.15%)
Metronidazole	1 (0.15%)
Xi pa yi gu yin	1 (0.15%)
TONICS	1 (0.15%)
Huai qi huang	1 (0.15%)
MUSCULO-SKELETAL SYSTEM	381 (57.12%)
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	328 (49.18%)
Total glucosides of white paeony	88 (13.19%)
Celecoxib	52 (7.80%)
Meloxicam	35 (5.25%)
Etoricoxib	29 (4.35%)
Imrecoxib	28 (4.20%)
Loxoprofen sodium	28 (4.20%)
Diclofenac sodium	27 (4.05%)
Sulfasalazine	25 (3.75%)
Zheng qing feng tong ning	20 (3.00%)
Loxoprofen	17 (2.55%)
Oxaprozin	13 (1.95%)
Celebrex	11 (1.65%)
Kun xian	10 (1.50%)
Aceclofenac	9 (1.35%)
Diclofenac diethylamine	9 (1.35%)
Glucosamine hydrochloride	6 (0.90%)
Nabumetone	5 (0.75%)
Diacerein	3 (0.45%)
Hua mo yan	3 (0.45%)
Wang bi	3 (0.45%)
Acemetacin	2 (0.30%)
Glucosamine sulfate	2 (0.30%)
Huo xue zhi tong [angelica sinensis root;borneol;boswellia sacra bark resin;eupolyphaga sinensis;panax notoginseng root with rhizome;pyrite]	2 (0.30%)
Naproxen sodium	2 (0.30%)
Xue shan jin luo han zhi tong	2 (0.30%)
Bi qi [achyranthes bidentata root;atractylodes macrocephala, rhizoma;codonopsis spp. root;glycyrrhiza spp. root with rhizome;ligusticum chuanxiong rhizome;panax notoginseng root;pheretima spp.;poria c	1 (0.15%)
Dexibuprofen	1 (0.15%)
Glucosamine	1 (0.15%)
Glucosamine chondroitin calcium	1 (0.15%)
Gu gua ti qu wu	1 (0.15%)
Ibuprofen	1 (0.15%)
Ketorolac tromethamine	1 (0.15%)
Lornoxicam	1 (0.15%)
Naproxen	1 (0.15%)

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WHODrug Global (B3) English [V2022SEP]

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Nimesulide	1 (0.15%)
Other antiinflammatory and antirheumatic agents, non-steroids	1 (0.15%)
Other specific antirheumatic agents	1 (0.15%)
Paeonia lactiflora total glycoside extract	1 (0.15%)
Pan long qi	1 (0.15%)
Parecoxib	1 (0.15%)
Pu di lan xiao yan	1 (0.15%)
Qiang gu	1 (0.15%)
Salazosulfapyridine	1 (0.15%)
Salicylazosulfapyridine	1 (0.15%)
Trankal	1 (0.15%)
Trast	1 (0.15%)
Xafon	1 (0.15%)
Xi huang	1 (0.15%)
DRUGS FOR TREATMENT OF BONE DISEASES	121 (18.14%)
Methylene diphosphonate	69 (10.34%)
Risedronate sodium	20 (3.00%)
Alendronate sodium	15 (2.25%)
Qiang gu	8 (1.20%)
Alendronate	3 (0.45%)
Alendronate sodium and vitamin d3	3 (0.45%)
Denosumab	3 (0.45%)
Alendronate sodium;colecalciferol	2 (0.30%)
Fosamax	2 (0.30%)
Zoledronic acid	2 (0.30%)
Cervus and cucumis polypeptide	1 (0.15%)
Sodium risedronate	1 (0.15%)
TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN	30 (4.50%)
Flurbiprofen	11 (1.65%)
Diclofenac sodium	5 (0.75%)
Tong luo qu tong	5 (0.75%)
Folic acid	3 (0.45%)
Xiao tong	3 (0.45%)
Aceclofenac	1 (0.15%)
Aspirin (e.c.)	1 (0.15%)
Folate	1 (0.15%)
Loxonin [loxoprofen sodium]	1 (0.15%)
Loxoprofen	1 (0.15%)
Qing peng	1 (0.15%)
Yun nan bai yao [aconitum kusnezoffii root tuber;aconitum spp. root tuber;herbal nos]	1 (0.15%)
ANTIGOUT PREPARATIONS	4 (0.60%)
Febuxostat	2 (0.30%)
Allopurinol	1 (0.15%)

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WHODrug Global (B3) English [V2022SEP]

Anatomy group *Treatment subgroup* *Drug name*	*Safety Analyses Population* *(N=667)*
Colchicin	1 (0.15%)
MUSCLE RELAXANTS	4 (0.60%)
Tizanidine	2 (0.30%)
Cisatracurium besilate	1 (0.15%)
Diazepam	1 (0.15%)
OTHER DRUGS FOR DISORDERS OF THE MUSCULO-SKELETAL SYSTEM	4 (0.60%)
Sodium hyaluronate	4 (0.60%)
BLOOD AND BLOOD FORMING ORGANS	274 (41.08%)
ANTIANEMIC PREPARATIONS	250 (37.48%)
Folic acid	218 (32.68%)
Mecobalamin	24 (3.60%)
Folate	7 (1.05%)
Iron polysaccharide complex	6 (0.90%)
Folic acid;iron amino acid chelate	3 (0.45%)
Iron dextran	3 (0.45%)
Compound ferrous sulfate and folic acid	1 (0.15%)
Cyanocobalamin	1 (0.15%)
Folic acid;vitamin b nos	1 (0.15%)
Iron proteinsuccinylate	1 (0.15%)
Jian pi sheng xue	1 (0.15%)
Vitamin b 12 [vitamin b12 nos]	1 (0.15%)
ANTITHROMBOTIC AGENTS	27 (4.05%)
Aspirin (e.c.)	9 (1.35%)
Ginkgo leaf extract and dipyridamole	5 (0.75%)
Beraprost sodium	4 (0.60%)
Rivaroxaban	3 (0.45%)
Alprostadil	2 (0.30%)
Clopidogrel	2 (0.30%)
Clopidogrel bisulfate	2 (0.30%)
Clopidogrel hydrogen sulphate	2 (0.30%)
Heparin sodium	2 (0.30%)
Pradaxa	1 (0.15%)
BLOOD SUBSTITUTES AND PERFUSION SOLUTIONS	7 (1.05%)
Potassium chloride	4 (0.60%)
Sodium chloride	2 (0.30%)
Compound amino acid injection (18aa-ii)	1 (0.15%)
Mannitol	1 (0.15%)
ANTIHEMORRHAGICS	5 (0.75%)
Leucogen	2 (0.30%)
Menatetrenone	2 (0.30%)
Tranexamic acid	1 (0.15%)

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WHODrug Global (B3) English [V2022SEP]

Anatomy group *Treatment subgroup* *Drug name*	*Safety Analyses Population* *(N=667)*
SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	270 (40.48%)
CORTICOSTEROIDS FOR SYSTEMIC USE	263 (39.43%)
Methylprednisolone	129 (19.34%)
Prednisone acetate	100 (14.99%)
Prednisone	22 (3.30%)
Betamethasone	9 (1.35%)
Compound betamethasone	5 (0.75%)
Triamcinolone acetonide acetate	5 (0.75%)
Methylprednisolone sodium succinate	4 (0.60%)
Dexamethasone sodium phosphate	3 (0.45%)
Prednisolone acetate	3 (0.45%)
Betamethasone sodium phosphate	2 (0.30%)
Dexamethasone palmitate	2 (0.30%)
Medrol [methylprednisolone]	2 (0.30%)
Triamcinolone acetonide	2 (0.30%)
Dexamethasone	1 (0.15%)
Dexamethasone acetate	1 (0.15%)
Diprospan [betamethasone dipropionate;betamethasone sodium phosphate]	1 (0.15%)
Hydroprednisone	1 (0.15%)
Meprednisone	1 (0.15%)
Prednisolone	1 (0.15%)
Prednison	1 (0.15%)
Triamcinolone	1 (0.15%)
THYROID THERAPY	12 (1.80%)
Levothyroxine sodium	6 (0.90%)
Euthyrox	5 (0.75%)
Levothyroxine	1 (0.15%)
CALCIUM HOMEOSTASIS	1 (0.15%)
Salcatonin	1 (0.15%)
CARDIOVASCULAR SYSTEM	102 (15.29%)
CALCIUM CHANNEL BLOCKERS	48 (7.20%)
Nifedipine	17 (2.55%)
Amlodipine besylate	9 (1.35%)
Amlodipine	7 (1.05%)
Felodipine	6 (0.90%)
Levamlodipine	5 (0.75%)
Levamlodipine besylate	4 (0.60%)
Lacidipine	1 (0.15%)
Levoamlodipine maleate	1 (0.15%)
Nifedipine sustained release tablets (ii)	1 (0.15%)
Nimodipine	1 (0.15%)
LIPID MODIFYING AGENTS	35 (5.25%)

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WHODrug Global (B3) English [V2022SEP]

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Atorvastatin calcium	16 (2.40%)
Atorvastatin	6 (0.90%)
Rosuvastatin calcium	5 (0.75%)
Fenofibrate	3 (0.45%)
Amlodipine besylate and atorvastatin calcium	1 (0.15%)
Bezafibrate	1 (0.15%)
Polyene phosphatidylcholine	1 (0.15%)
Pravastatin sodium	1 (0.15%)
Rosuvastatin zinc	1 (0.15%)
Simvastatin	1 (0.15%)
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	27 (4.05%)
Irbesartan	14 (2.10%)
Valsartan	3 (0.45%)
Irbesartan and hydrochlorothiazide	2 (0.30%)
Losartan potassium and hydrochlorothiazide	2 (0.30%)
Valsartan and hydrochlorothiazide	2 (0.30%)
Allisartan isoproxil	1 (0.15%)
Losartan potassium	1 (0.15%)
Perindopril tert-butylamine	1 (0.15%)
Valsartan and amlodipine [amlodipine;valsartan]	1 (0.15%)
BETA BLOCKING AGENTS	15 (2.25%)
Betaloc zok	4 (0.60%)
Bisoprolol fumarate	3 (0.45%)
Metoprolol tartrate	3 (0.45%)
Metoprolol succinate	2 (0.30%)
Bisoprolol	1 (0.15%)
Carvedilol	1 (0.15%)
Metoprolol	1 (0.15%)
Metoprolol [metoprolol tartrate]	1 (0.15%)
CARDIAC THERAPY	12 (1.80%)
She xiang bao xin	4 (0.60%)
Isosorbide mononitrate	2 (0.30%)
Su xiao jiu xin	2 (0.30%)
Amiodarone hydrochloride	1 (0.15%)
Ephedrine	1 (0.15%)
Fu fang dan shen	1 (0.15%)
Hong hua huang se su lv hua na	1 (0.15%)
Isoprenaline [isoprenaline hydrochloride]	1 (0.15%)
Metaraminol bitartrate	1 (0.15%)
Nao xin tong	1 (0.15%)
Nitroglycerin	1 (0.15%)
Quick acting heart reliever	1 (0.15%)
Trimetazidine hydrochloride	1 (0.15%)

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Yi xin shu	1 (0.15%)
DIURETICS	9 (1.35%)
Spironolactone	7 (1.05%)
Furosemide	3 (0.45%)
Torasemide	3 (0.45%)
VASOPROTECTIVES	4 (0.60%)
Titanoreine [chondrus crispus;titanium dioxide;zinc oxide]	2 (0.30%)
Escin	1 (0.15%)
Mai zhi ling	1 (0.15%)
PERIPHERAL VASODILATORS	1 (0.15%)
Yin xing tong zhi	1 (0.15%)
ANTIINFECTIVES FOR SYSTEMIC USE	88 (13.19%)
ANTIBACTERIALS FOR SYSTEMIC USE	34 (5.10%)
Cefixime	3 (0.45%)
Levofloxacin	3 (0.45%)
Levofloxacin lactate and sodium chloride	3 (0.45%)
Ceftazidime	2 (0.30%)
Levofloxacin hydrochloride	2 (0.30%)
Levofloxacin lactate	2 (0.30%)
Amoxicillin	1 (0.15%)
Amoxicillin and clavulanate potassium er	1 (0.15%)
Avelox	1 (0.15%)
Azithromycin	1 (0.15%)
Benzylpenicillin sodium	1 (0.15%)
Cefalexin	1 (0.15%)
Cefazolin sodium	1 (0.15%)
Cefminox	1 (0.15%)
Cefprozil	1 (0.15%)
Cefradine	1 (0.15%)
Ceftizoxime	1 (0.15%)
Ceftriaxone sodium;tazobactam sodium	1 (0.15%)
Clarithromycin	1 (0.15%)
Clindamycin	1 (0.15%)
Etimicin	1 (0.15%)
Fosfomycin trometamol	1 (0.15%)
Galculus bovis and metronidazole	1 (0.15%)
Ganmao tuire	1 (0.15%)
Levofloxacin and sodium chloride	1 (0.15%)
Levofloxacin hydrochloride and sodium chloride	1 (0.15%)
Meropenem	1 (0.15%)
Moxifloxacin hydrochloride	1 (0.15%)
Piperacillin sodium and tazobactam sodium	1 (0.15%)

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WHODrug Global (B3) English [V2022SEP]

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Rifampicin	1 (0.15%)
Roxithromycin	1 (0.15%)
Sulfadiazine	1 (0.15%)
Wu lin hua shi	1 (0.15%)
ANTIMYCOBACTERIALS	28 (4.20%)
Isoniazid	25 (3.75%)
Rifampicin	6 (0.90%)
Isoniazide	3 (0.45%)
Ethambutol hydrochloride	1 (0.15%)
ANTIVIRALS FOR SYSTEMIC USE	28 (4.20%)
Entecavir	18 (2.70%)
Lian hua qing wen	5 (0.75%)
Aciclovir	3 (0.45%)
Valaciclovir hydrochloride	2 (0.30%)
Antivirals	1 (0.15%)
Brivudine	1 (0.15%)
Valaciclovir	1 (0.15%)
Valacyclovir hydrochloride	1 (0.15%)
ANTIMYCOTICS FOR SYSTEMIC USE	4 (0.60%)
Itraconazole	3 (0.45%)
Fluconazole	1 (0.15%)
IMMUNE SERA AND IMMUNOGLOBULINS	3 (0.45%)
Human immunoglobulin	2 (0.30%)
Tetanus antitoxin	1 (0.15%)
VACCINES	3 (0.45%)
Covid-19 vaccine	3 (0.45%)
NERVOUS SYSTEM	68 (10.19%)
ANALGESICS	32 (4.80%)
Bulleyaconitine a	6 (0.90%)
Pregabalin	6 (0.90%)
Lyrica	3 (0.45%)
Aspirin [acetylsalicylic acid]	2 (0.30%)
Dezocine	2 (0.30%)
Gan mao ling [bidens biternata;caffeine;chlorphenamine maleate;chrysanthemum indicum flower;ilex asprella root;melicope pteleifolia;mentha canadensis oil;paracetamol]	2 (0.30%)
Paracetamol	2 (0.30%)
Propacetamol hydrochloride	2 (0.30%)
Tramadol hydrochloride	2 (0.30%)
999 ganmaoling	1 (0.15%)
Aminophenazone	1 (0.15%)
Bucinnazine hydrochloride	1 (0.15%)
Carbamazepine	1 (0.15%)
Compound paracetamol and sulfogaiacol	1 (0.15%)

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Duloxetine hydrochloride	1 (0.15%)
Hydromorphone hydrochloride	1 (0.15%)
Nalbuphine hydrochloride	1 (0.15%)
Oxycodone and acetaminophen	1 (0.15%)
Paracetamol and caffeine	1 (0.15%)
Xiao yan zhi tong	1 (0.15%)
PSYCHOLEPTICS	17 (2.55%)
Estazolam	7 (1.05%)
Alprazolam	5 (0.75%)
Dexzopiclone	2 (0.30%)
Oryzanol	2 (0.30%)
Dexmedetomidine hydrochloride for injection	1 (0.15%)
Duloxetine hydrochloride	1 (0.15%)
Melatonin;zolpidem tartrate	1 (0.15%)
Midazolam	1 (0.15%)
Olanzapine	1 (0.15%)
Remimazolam	1 (0.15%)
Risperidone	1 (0.15%)
Zopiclone	1 (0.15%)
ANESTHETICS	13 (1.95%)
Lidocaine hydrochloride	11 (1.65%)
Sufentanil citrate	2 (0.30%)
Diprivan	1 (0.15%)
Dyclonine hydrochloride	1 (0.15%)
Naropin [ropivacaine hydrochloride]	1 (0.15%)
Propofol	1 (0.15%)
Propofol medium and long chain fat emulsion	1 (0.15%)
Sevoflurane	1 (0.15%)
PSYCHOANALEPTICS	10 (1.50%)
Flupentixol and melitracen	4 (0.60%)
Duloxetine hydrochloride	2 (0.30%)
Trazodone hydrochloride	2 (0.30%)
Aceglutamide	1 (0.15%)
Piracetam	1 (0.15%)
OTHER NERVOUS SYSTEM DRUGS	7 (1.05%)
Mecobalamin	2 (0.30%)
Betahistine mesilate	1 (0.15%)
Gastrodin	1 (0.15%)
Mecobalamine	1 (0.15%)
Nerve growth factor, mouse	1 (0.15%)
Qiang li ding xuan	1 (0.15%)
VARIOUS	64 (9.60%)

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WHODrug Global (B3) English [V2022SEP]

Anatomy group *Treatment subgroup* *Drug name*	*Safety Analyses Population* *(N=667)*
UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	50 (7.50%)
Xian ling gu bao	7 (1.05%)
Shang shi zhi tong gao	5 (0.75%)
Traditional chinese medicine (tcm) decoction	5 (0.75%)
Jin gu lian	4 (0.60%)
Gu long jiao nang	3 (0.45%)
Co. danshen [salvia miltiorrhiza]	2 (0.30%)
Zao ren an shen	2 (0.30%)
Aescuven forte [aesculus hippocastanum extract]	1 (0.15%)
Bai ling [cordyceps sinensis mycelium]	1 (0.15%)
Dan shen tong	1 (0.15%)
Du yi wei	1 (0.15%)
Epimedium brevicornu	1 (0.15%)
Feng shi gu tong	1 (0.15%)
Fu fang dan shen	1 (0.15%)
Fu fang yi mu	1 (0.15%)
Gan de zhi pian	1 (0.15%)
Gu kang	1 (0.15%)
Hei gu teng zhui feng huo luo jiao nang	1 (0.15%)
Jiang huang xiao cuo cha ji	1 (0.15%)
Jiang tang	1 (0.15%)
Jin yin hua [lonicera japonica flower bud;lonicera japonica stem]	1 (0.15%)
Kang fu xin	1 (0.15%)
Lian hua qing wen	1 (0.15%)
Qiang gan	1 (0.15%)
Rou kou wu wei	1 (0.15%)
Si mo tang	1 (0.15%)
Tian dan tong luo	1 (0.15%)
Tian ma shou wu	1 (0.15%)
Traditional medicine	1 (0.15%)
Unspecified herbal and traditional medicine	1 (0.15%)
Wang bi	1 (0.15%)
Xia ku cao	1 (0.15%)
Xuan yun ning	1 (0.15%)
Yang xue sheng fa jiao nang	1 (0.15%)
Yu ping feng	1 (0.15%)
Yun nan bai yao [aconitum kusnezoffii root;herbal nos]	1 (0.15%)
Zhen yuan	1 (0.15%)
ALL OTHER THERAPEUTIC PRODUCTS	12 (1.80%)
Glutathione	11 (1.65%)
Compound glycyrrhizin [dl-methionine;glycine;glycyrrhizic acid, ammonium salt]	1 (0.15%)
GENERAL NUTRIENTS	2 (0.30%)
Compound alpha ketoacid	2 (0.30%)

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WHODrug Global (B3) English [V2022SEP]

Anatomy group *Treatment subgroup* *Drug name*	*Safety Analyses Population* *(N=667)*
CONTRAST MEDIA	1 (0.15%)
Iodixanol	1 (0.15%)
DIAGNOSTIC AGENTS	1 (0.15%)
Purified protein derivative of bcc (bcg-ppd)	1 (0.15%)
RESPIRATORY SYSTEM	28 (4.20%)
COUGH AND COLD PREPARATIONS	21 (3.15%)
Ambroxol hydrochloride	8 (1.20%)
Fu fang gan cao	4 (0.60%)
Acetylcysteine	3 (0.45%)
Compound dextromethorphan hydrobromide [dextromethorphan hydrobromide;guaifenesin]	2 (0.30%)
Cydiodine	2 (0.30%)
Ke te ling	2 (0.30%)
Codeine phosphate and platycodon tablets	1 (0.15%)
Fei li ke	1 (0.15%)
Qie nuo	1 (0.15%)
Qing fei yi huo [anemarrhena asphodeloides rhizome;gardenia jasminoides fruit;peucedanum praeruptorum root;phellodendron chinense bark;platycodon grandiflorus root;rheum spp. root with rhizome;scutell	1 (0.15%)
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	8 (1.20%)
Bai ling [cordyceps sinensis mycelium]	4 (0.60%)
Compound methoxyphenamine	2 (0.30%)
Methoxyphenamine hydrochloride	2 (0.30%)
Compound ipratropium bromide	1 (0.15%)
Doxofylline	1 (0.15%)
Montelukast sodium	1 (0.15%)
Salbutamol sulphate	1 (0.15%)
Salmeterol xinafoate and fluticasone propionate	1 (0.15%)
ANTIHISTAMINES FOR SYSTEMIC USE	5 (0.75%)
Levocetirizine hydrochloride	2 (0.30%)
Chlorphenamine	1 (0.15%)
Ketotifen fumarate	1 (0.15%)
Loratadine	1 (0.15%)
THROAT PREPARATIONS	3 (0.45%)
Gan ju bing mei	1 (0.15%)
Ibuprofen	1 (0.15%)
Kai hou jian pen wu ji (er tong xing)	1 (0.15%)
Yan li shuang kou han	1 (0.15%)
NASAL PREPARATIONS	1 (0.15%)
Budesonide	1 (0.15%)
OTHER RESPIRATORY SYSTEM PRODUCTS	1 (0.15%)
Caffeine	1 (0.15%)
SENSORY ORGANS	9 (1.35%)
OPHTHALMOLOGICALS	9 (1.35%)

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WHODrug Global (B3) English [V2022SEP]

Anatomy group *Treatment subgroup* *Drug name*	*Safety Analyses Population* *(N=667)*
Sodium hyaluronate	3 (0.45%)
Azelastine hydrochloride	1 (0.15%)
Compound tropicamide	1 (0.15%)
Deproteinized calf blood extract	1 (0.15%)
Dextran 70;glycerol;hypromellose	1 (0.15%)
Fluorescein sodium	1 (0.15%)
Fu fang xue shuan tong	1 (0.15%)
Pranopulin	1 (0.15%)
Retinol palmitate	1 (0.15%)
Tobramycin	1 (0.15%)
Tobramycin and dexamethasone	1 (0.15%)
DERMATOLOGICALS	6 (0.90%)
ANTIBIOTICS AND CHEMOTHERAPEUTICS FOR DERMATOLOGICAL USE	2 (0.30%)
Fusidic acid	1 (0.15%)
Interferon alfa-2b	1 (0.15%)
ANTIPRURITICS, INCL. ANTIHISTAMINES, ANESTHETICS, ETC.	2 (0.30%)
Calamine lotion phenolated	1 (0.15%)
Compound lidocaine	1 (0.15%)
Lidocaine	1 (0.15%)
Loratadine	1 (0.15%)
ANTIFUNGALS FOR DERMATOLOGICAL USE	1 (0.15%)
Butenafine hydrochloride	1 (0.15%)
ANTISEPTICS AND DISINFECTANTS	1 (0.15%)
Iodine	1 (0.15%)
EMOLLIENTS AND PROTECTIVES	1 (0.15%)
Zinc oxide	1 (0.15%)
MEDICATED DRESSINGS	1 (0.15%)
Fusidic acid	1 (0.15%)
PREPARATIONS FOR TREATMENT OF WOUNDS AND ULCERS	1 (0.15%)
Kang fu xin	1 (0.15%)
GENITO URINARY SYSTEM AND SEX HORMONES	3 (0.45%)
UROLOGICALS	2 (0.30%)
Niao du qing	1 (0.15%)
Potassium sodium hydrogen citrate	1 (0.15%)
OTHER GYNECOLOGICALS	1 (0.15%)
An kun	1 (0.15%)
ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS	2 (0.30%)
ANTIPROTOZOALS	1 (0.15%)
Chloroquine sulfate	1 (0.15%)
ECTOPARASITICIDES, INCL. SCABICIDES, INSECTICIDES AND REPELLENTS	1 (0.15%)

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WHODrug Global (B3) English [V2022SEP]

Anatomy group *Treatment subgroup* *Drug name*	*Safety Analyses Population (N=667)*
Acetic acid	1 (0.15%)

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WHODrug Global (B3) English [V2022SEP]

Table ANN. 21 Concomitant Medication – Effectiveness Analyses Population

Anatomy group *Treatment subgroup* *Drug name*	*Effectiveness Analyses Population (N=514)*
With at least one concomitant medication	489 (95.14%)
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	459 (89.30%)
IMMUNOSUPPRESSANTS	459 (89.30%)
Methotrexate	292 (56.81%)
Leflunomide	182 (35.41%)
Hydroxychloroquine sulfate	73 (14.20%)
Iguratimod	62 (12.06%)
Hydroxychloroquine	59 (11.48%)
Lei gong teng duo gan	50 (9.73%)
Azathioprine	2 (0.39%)
Cyclosporine	2 (0.39%)
Cyclosporin	1 (0.19%)
IMMUNOSTIMULANTS	8 (1.56%)
Thymopeptide	3 (0.58%)
Di yu sheng bai	2 (0.39%)
Recombinant human interleukin-2	2 (0.39%)
Glutathione	1 (0.19%)
ANTINEOPLASTIC AGENTS	1 (0.19%)
Cyclophosphamide	1 (0.19%)
ENDOCRINE THERAPY	1 (0.19%)
Hormones	1 (0.19%)
ALIMENTARY TRACT AND METABOLISM	357 (69.46%)
VITAMINS	261 (50.78%)
Alfacalcidol	129 (25.10%)
Calcitriol	114 (22.18%)
Vd	11 (2.14%)
Puria vitamin d drops	5 (0.97%)
Rocaltrol	2 (0.39%)
Vitamin b complex	2 (0.39%)
Vitamin b1 nos	2 (0.39%)
Vitamin d and analogues	2 (0.39%)
Calcitriol injection	1 (0.19%)
Calcitriol;calcium carbimide citrate;zinc	1 (0.19%)
Compound vitamin b [calcium pantothenate;nicotinamide;pyridoxine hydrochloride;riboflavin;thiamine hydrochloride]	1 (0.19%)
Pyridoxine hydrochloride	1 (0.19%)
Riboflavin	1 (0.19%)
Vitamin b1	1 (0.19%)
Vitamin b6	1 (0.19%)
Vitamin d nos	1 (0.19%)
Vitamin d2	1 (0.19%)
Vitamin-c	1 (0.19%)

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WHODrug Global (B3) English [V2022SEP]

Anatomy group *Treatment subgroup* *Drug name*	*Effectiveness Analyses Population (N=514)*
MINERAL SUPPLEMENTS	254 (49.42%)
Calcium carbonate and vitamin d3	73 (14.20%)
Calcium carbonate	45 (8.75%)
Calci d	44 (8.56%)
Calcium gluconate	18 (3.50%)
Calcium carbonate;colecalciferol	17 (3.31%)
Calcium malate	10 (1.95%)
D-cal	10 (1.95%)
Potassium chloride	10 (1.95%)
Calcium carbonate and vitamin d3 tablets (ii)	9 (1.75%)
Calcium citrate malate	8 (1.56%)
Calcium carbonate/vitamin d3	4 (0.78%)
Calcium supplement with vitamin d chewable tablets children's formula	4 (0.78%)
Calcium vitamin d	4 (0.78%)
Calcium	1 (0.19%)
Calcium acetate	1 (0.19%)
Calcium and vitamin d	1 (0.19%)
Calcium carbonate;calcium lactobionate;colecalciferol	1 (0.19%)
Calcium d [ascorbic acid;calcium gluconate;calcium lactate;calcium phosphate dibasic;ergocalciferol]	1 (0.19%)
Calcium supplement with vitamin d	1 (0.19%)
Calfor d	1 (0.19%)
Caltrate d [calcium carbonate;colecalciferol]	1 (0.19%)
Caltrate d [calcium;colecalciferol]	1 (0.19%)
Caltrate with vitamin d	1 (0.19%)
Gai er qi d	1 (0.19%)
Potassium citrate	1 (0.19%)
DRUGS FOR ACID RELATED DISORDERS	125 (24.32%)
Pantoprazole sodium [pantoprazole sodium sesquihydrate]	43 (8.37%)
Teprenone	19 (3.70%)
Rebamipide	14 (2.72%)
Omeprazole	13 (2.53%)
Sodium rabeprazole	11 (2.14%)
Rabeprazole sodium	9 (1.75%)
Esomeprazole magnesium	6 (1.17%)
Hydrotalcite	6 (1.17%)
Lansoprazole	6 (1.17%)
Rabeprazole	5 (0.97%)
Sucralfate	4 (0.78%)
Pantoprazole	3 (0.58%)
Omeprazole sodium	2 (0.39%)
Pantoprazole sodium sesquihydrate	2 (0.39%)
Sofalcone	2 (0.39%)
Almagate	1 (0.19%)

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WHODrug Global (B3) English [V2022SEP]

Anatomy group *Treatment subgroup* *Drug name*	*Effectiveness Analyses Population (N=514)*
Cimetidine	1 (0.19%)
Compound magnesium trisilicate and sodium bicarbonate	1 (0.19%)
Esomeprazole	1 (0.19%)
Esomeprazole magnesium trihydrate	1 (0.19%)
Famotidine	1 (0.19%)
Ilaprazole	1 (0.19%)
Ilaprazole sodium	1 (0.19%)
Lafutidine	1 (0.19%)
Le mei ting	1 (0.19%)
Nexium [esomeprazole magnesium trihydrate]	1 (0.19%)
Omeprazole magnesium	1 (0.19%)
Pantoprazole [pantoprazole sodium sesquihydrate]	1 (0.19%)
Ranitidine hydrochloride	1 (0.19%)
Sodium bicarbonate	1 (0.19%)
Sulpiride	1 (0.19%)
DRUGS USED IN DIABETES	22 (4.28%)
Metformin hydrochloride	7 (1.36%)
Acarbose	6 (1.17%)
Metformin	3 (0.58%)
Dapagliflozin	2 (0.39%)
Insulin injection	2 (0.39%)
Voglibose	2 (0.39%)
Empagliflozin	1 (0.19%)
Gliclazide (ii)	1 (0.19%)
Glimepiride	1 (0.19%)
Glipizide	1 (0.19%)
Insulin aspart 30	1 (0.19%)
Insulin detemir	1 (0.19%)
Recombinant human insulin	1 (0.19%)
Repaglinide	1 (0.19%)
Saxagliptin	1 (0.19%)
Sitagliptin phosphate	1 (0.19%)
OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS	19 (3.70%)
Glucurolactone	11 (2.14%)
Glucuronolactone	9 (1.75%)
BILE AND LIVER THERAPY	12 (2.33%)
Bicyclol	3 (0.58%)
Diammonium glycyrrhizinate	2 (0.39%)
Polyene phosphatidylcholine	2 (0.39%)
Ursodeoxycholic acid	2 (0.39%)
Wu zhi	2 (0.39%)
Compound glycyrrhizin [dl-methionine;glycine;glycyrrhizic acid, ammonium salt]	1 (0.19%)
Silibinin	1 (0.19%)

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WHODrug Global (B3) English [V2022SEP]

Anatomy group *Treatment subgroup* *Drug name*	*Effectiveness Analyses Population (N=514)*
DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	9 (1.75%)
Itopride hydrochloride	2 (0.39%)
Mosapride citrate	2 (0.39%)
Domperidone	1 (0.19%)
Mo luo	1 (0.19%)
Pinaverium bromide	1 (0.19%)
Simethicone	1 (0.19%)
Trimebutine	1 (0.19%)
Trimebutine maleate	1 (0.19%)
DIGESTIVES, INCL. ENZYMES	6 (1.17%)
Compound digestive enzyme capsules (ii)	3 (0.58%)
Pancreatin	2 (0.39%)
Glutamine and guaiazulene sulfonate sodium	1 (0.19%)
Oryz-aspergillus enzyme and pancreatin	1 (0.19%)
ANTIDIARRHEALS, INTESTINAL ANTIINFLAMMATORY/ANTIINFECTIVE AGENTS	5 (0.97%)
Live combined bifidobacterium and lactobacillus	2 (0.39%)
Montmorillonite	2 (0.39%)
Bifid.triple viable	1 (0.19%)
Lactobacillus complex [lactobacillus acidophilus;lactobacillus lactis;streptococcus lactis]	1 (0.19%)
DRUGS FOR CONSTIPATION	4 (0.78%)
Duphalac [galactose;lactose;lactulose]	1 (0.19%)
Kai sai lu	1 (0.19%)
Lactulose	1 (0.19%)
Purge	1 (0.19%)
Tong bian pian	1 (0.19%)
ANTIEMETICS AND ANTINAUSEANTS	2 (0.39%)
Metoclopramide hydrochloride	1 (0.19%)
Palonosetron hydrochloride	1 (0.19%)
STOMATOLOGICAL PREPARATIONS	2 (0.39%)
Compound chlorhexidine gargle	1 (0.19%)
Metronidazole	1 (0.19%)
Xi pa yi gu yin	1 (0.19%)
TONICS	1 (0.19%)
Huai qi huang	1 (0.19%)
MUSCULO-SKELETAL SYSTEM	286 (55.64%)
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	239 (46.50%)
Total glucosides of white paeony	74 (14.40%)
Celecoxib	34 (6.61%)
Diclofenac sodium	25 (4.86%)
Loxoprofen sodium	21 (4.09%)
Etoricoxib	20 (3.89%)
Meloxicam	20 (3.89%)

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WHODrug Global (B3) English [V2022SEP]

Anatomy group *Treatment subgroup* *Drug name*	*Effectiveness Analyses Population (N=514)*
Sulfasalazine	17 (3.31%)
Zheng qing feng tong ning	17 (3.31%)
Imrecoxib	16 (3.11%)
Loxoprofen	14 (2.72%)
Oxaprozin	11 (2.14%)
Diclofenac diethylamine	9 (1.75%)
Celebrex	8 (1.56%)
Glucosamine hydrochloride	5 (0.97%)
Kun xian	5 (0.97%)
Nabumetone	5 (0.97%)
Aceclofenac	4 (0.78%)
Diacerein	3 (0.58%)
Hua mo yan	2 (0.39%)
Huo xue zhi tong [angelica sinensis root;borneol;boswellia sacra bark resin;eupolyphaga sinensis;panax notoginseng root with rhizome;pyrite]	2 (0.39%)
Wang bi	2 (0.39%)
Xue shan jin luo han zhi tong	2 (0.39%)
Acemetacin	1 (0.19%)
Bi qi [achyranthes bidentata root;atractylodes macrocephala, rhizoma;codonopsis spp. root;glycyrrhiza spp. root with rhizome;ligusticum chuanxiong rhizome;panax notoginseng root;pheretima spp.;poria c	1 (0.19%)
Dexibuprofen	1 (0.19%)
Glucosamine	1 (0.19%)
Glucosamine chondroitin calcium	1 (0.19%)
Gu gua ti qu wu	1 (0.19%)
Ibuprofen	1 (0.19%)
Ketorolac tromethamine	1 (0.19%)
Nimesulide	1 (0.19%)
Other specific antirheumatic agents	1 (0.19%)
Paeonia lactiflora total glycoside extract	1 (0.19%)
Pan long qi	1 (0.19%)
Parecoxib	1 (0.19%)
Pu di lan xiao yan	1 (0.19%)
Salazosulfapyridine	1 (0.19%)
Salicylazosulfapyridine	1 (0.19%)
Trankal	1 (0.19%)
Trast	1 (0.19%)
Xafon	1 (0.19%)
Xi huang	1 (0.19%)
DRUGS FOR TREATMENT OF BONE DISEASES	97 (18.87%)
Methylene diphosphonate	56 (10.89%)
Risedronate sodium	20 (3.89%)
Alendronate sodium	9 (1.75%)
Qiang gu	7 (1.36%)
Alendronate	3 (0.58%)
Fosamax	2 (0.39%)

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WHODrug Global (B3) English [V2022SEP]

Anatomy group *Treatment subgroup* *Drug name*	*Effectiveness Analyses Population (N=514)*
Zoledronic acid	2 (0.39%)
Alendronate sodium and vitamin d3	1 (0.19%)
Alendronate sodium;colecalciferol	1 (0.19%)
Denosumab	1 (0.19%)
Sodium risedronate	1 (0.19%)
TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN	25 (4.86%)
Flurbiprofen	9 (1.75%)
Tong luo qu tong	5 (0.97%)
Diclofenac sodium	4 (0.78%)
Xiao tong	3 (0.58%)
Folic acid	2 (0.39%)
Aceclofenac	1 (0.19%)
Aspirin (e.c.)	1 (0.19%)
Folate	1 (0.19%)
Loxonin [loxoprofen sodium]	1 (0.19%)
Qing peng	1 (0.19%)
Yun nan bai yao [aconitum kusnezoffii root tuber;aconitum spp. root tuber;herbal nos]	1 (0.19%)
ANTIGOUT PREPARATIONS	4 (0.78%)
Febuxostat	2 (0.39%)
Allopurinol	1 (0.19%)
Colchicin	1 (0.19%)
MUSCLE RELAXANTS	4 (0.78%)
Tizanidine	2 (0.39%)
Cisatracurium besilate	1 (0.19%)
Diazepam	1 (0.19%)
OTHER DRUGS FOR DISORDERS OF THE MUSCULO-SKELETAL SYSTEM	4 (0.78%)
Sodium hyaluronate	4 (0.78%)
BLOOD AND BLOOD FORMING ORGANS	226 (43.97%)
ANTIANEMIC PREPARATIONS	210 (40.86%)
Folic acid	183 (35.60%)
Mecobalamin	22 (4.28%)
Folate	6 (1.17%)
Iron polysaccharide complex	4 (0.78%)
Folic acid;iron amino acid chelate	3 (0.58%)
Iron dextran	2 (0.39%)
Cyanocobalamin	1 (0.19%)
Folic acid;vitamin b nos	1 (0.19%)
Iron proteinsuccinylate	1 (0.19%)
Vitamin b 12 [vitamin b12 nos]	1 (0.19%)
ANTITHROMBOTIC AGENTS	22 (4.28%)
Aspirin (e.c.)	5 (0.97%)
Ginkgo leaf extract and dipyridamole	5 (0.97%)

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WHODrug Global (B3) English [V2022SEP]

Anatomy group *Treatment subgroup* *Drug name*	*Effectiveness Analyses Population (N=514)*
Beraprost sodium	3 (0.58%)
Clopidogrel	2 (0.39%)
Clopidogrel bisulfate	2 (0.39%)
Clopidogrel hydrogen sulphate	2 (0.39%)
Rivaroxaban	2 (0.39%)
Alprostadil	1 (0.19%)
Heparin sodium	1 (0.19%)
Pradaxa	1 (0.19%)
ANTIHEMORRHAGICS	4 (0.78%)
Leucogen	2 (0.39%)
Menatetrenone	1 (0.19%)
Tranexamic acid	1 (0.19%)
BLOOD SUBSTITUTES AND PERFUSION SOLUTIONS	4 (0.78%)
Potassium chloride	2 (0.39%)
Compound amino acid injection (18aa-ii)	1 (0.19%)
Mannitol	1 (0.19%)
Sodium chloride	1 (0.19%)
SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	203 (39.49%)
CORTICOSTEROIDS FOR SYSTEMIC USE	196 (38.13%)
Methylprednisolone	98 (19.07%)
Prednisone acetate	73 (14.20%)
Prednisone	19 (3.70%)
Betamethasone	8 (1.56%)
Triamcinolone acetonide acetate	5 (0.97%)
Compound betamethasone	4 (0.78%)
Dexamethasone sodium phosphate	3 (0.58%)
Methylprednisolone sodium succinate	3 (0.58%)
Betamethasone sodium phosphate	2 (0.39%)
Dexamethasone palmitate	2 (0.39%)
Prednisolone acetate	2 (0.39%)
Triamcinolone acetonide	2 (0.39%)
Dexamethasone	1 (0.19%)
Diprospan [betamethasone dipropionate;betamethasone sodium phosphate]	1 (0.19%)
Hydroprednisone	1 (0.19%)
Medrol [methylprednisolone]	1 (0.19%)
Meprednisone	1 (0.19%)
Prednisolone	1 (0.19%)
Prednison	1 (0.19%)
THYROID THERAPY	11 (2.14%)
Levothyroxine sodium	6 (1.17%)
Euthyrox	5 (0.97%)
CALCIUM HOMEOSTASIS	1 (0.19%)

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The percentage denominator is the number of analyses population.
Concomitant medication is defined as medication ended on or after the date of first dose of study drug or is still ongoing, which also started no later than the date of last dose of study drug.
WHODrug Global (B3) English [V2022SEP]

Anatomy group *Treatment subgroup* *Drug name*	*Effectiveness Analyses Population (N=514)*
Salcatonin	1 (0.19%)
CARDIOVASCULAR SYSTEM	80 (15.56%)
CALCIUM CHANNEL BLOCKERS	39 (7.59%)
Nifedipine	13 (2.53%)
Amlodipine besylate	7 (1.36%)
Felodipine	6 (1.17%)
Levamlodipine	5 (0.97%)
Amlodipine	4 (0.78%)
Levamlodipine besylate	4 (0.78%)
Lacidipine	1 (0.19%)
Levoamlodipine maleate	1 (0.19%)
Nifedipine sustained release tablets (ii)	1 (0.19%)
Nimodipine	1 (0.19%)
LIPID MODIFYING AGENTS	28 (5.45%)
Atorvastatin calcium	14 (2.72%)
Rosuvastatin calcium	5 (0.97%)
Atorvastatin	4 (0.78%)
Fenofibrate	2 (0.39%)
Amlodipine besylate and atorvastatin calcium	1 (0.19%)
Bezafibrate	1 (0.19%)
Pravastatin sodium	1 (0.19%)
Rosuvastatin zinc	1 (0.19%)
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	20 (3.89%)
Irbesartan	11 (2.14%)
Valsartan	3 (0.58%)
Allisartan isoproxil	1 (0.19%)
Irbesartan and hydrochlorothiazide	1 (0.19%)
Losartan potassium	1 (0.19%)
Perindopril tert-butylamine	1 (0.19%)
Valsartan and amlodipine [amlodipine;valsartan]	1 (0.19%)
Valsartan and hydrochlorothiazide	1 (0.19%)
BETA BLOCKING AGENTS	14 (2.72%)
Betaloc zok	4 (0.78%)
Bisoprolol fumarate	3 (0.58%)
Metoprolol tartrate	3 (0.58%)
Metoprolol succinate	2 (0.39%)
Bisoprolol	1 (0.19%)
Carvedilol	1 (0.19%)
Metoprolol [metoprolol tartrate]	1 (0.19%)
CARDIAC THERAPY	10 (1.95%)
She xiang bao xin	3 (0.58%)
Isosorbide mononitrate	2 (0.39%)

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WHODrug Global (B3) English [V2022SEP]

Anatomy group *Treatment subgroup* *Drug name*	*Effectiveness Analyses Population (N=514)*
Su xiao jiu xin	2 (0.39%)
Ephedrine	1 (0.19%)
Fu fang dan shen	1 (0.19%)
Hong hua huang se su lv hua na	1 (0.19%)
Metaraminol bitartrate	1 (0.19%)
Nao xin tong	1 (0.19%)
Nitroglycerin	1 (0.19%)
Quick acting heart reliever	1 (0.19%)
Trimetazidine hydrochloride	1 (0.19%)
Yi xin shu	1 (0.19%)
DIURETICS	7 (1.36%)
Spironolactone	7 (1.36%)
Furosemide	2 (0.39%)
Torasemide	2 (0.39%)
VASOPROTECTIVES	3 (0.58%)
Escin	1 (0.19%)
Mai zhi ling	1 (0.19%)
Titanoreine [chondrus crispus;titanium dioxide;zinc oxide]	1 (0.19%)
PERIPHERAL VASODILATORS	1 (0.19%)
Yin xing tong zhi	1 (0.19%)
ANTIINFECTIVES FOR SYSTEMIC USE	70 (13.62%)
ANTIBACTERIALS FOR SYSTEMIC USE	29 (5.64%)
Levofloxacin	3 (0.58%)
Levofloxacin lactate and sodium chloride	3 (0.58%)
Cefixime	2 (0.39%)
Ceftazidime	2 (0.39%)
Levofloxacin hydrochloride	2 (0.39%)
Levofloxacin lactate	2 (0.39%)
Amoxicillin	1 (0.19%)
Amoxicillin and clavulanate potassium er	1 (0.19%)
Avelox	1 (0.19%)
Azithromycin	1 (0.19%)
Benzylpenicillin sodium	1 (0.19%)
Cefalexin	1 (0.19%)
Cefazolin sodium	1 (0.19%)
Cefminox	1 (0.19%)
Cefprozil	1 (0.19%)
Cefradine	1 (0.19%)
Ceftizoxime	1 (0.19%)
Clarithromycin	1 (0.19%)
Clindamycin	1 (0.19%)
Ganmao tuire	1 (0.19%)

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WHODrug Global (B3) English [V2022SEP]

Anatomy group *Treatment subgroup* *Drug name*	*Effectiveness Analyses Population (N=514)*
Levofloxacin and sodium chloride	1 (0.19%)
Levofloxacin hydrochloride and sodium chloride	1 (0.19%)
Meropenem	1 (0.19%)
Moxifloxacin hydrochloride	1 (0.19%)
Piperacillin sodium and tazobactam sodium	1 (0.19%)
Rifampicin	1 (0.19%)
Roxithromycin	1 (0.19%)
Sulfadiazine	1 (0.19%)
Wu lin hua shi	1 (0.19%)
ANTIVIRALS FOR SYSTEMIC USE	23 (4.47%)
Entecavir	13 (2.53%)
Lian hua qing wen	5 (0.97%)
Aciclovir	3 (0.58%)
Valaciclovir hydrochloride	2 (0.39%)
Antivirals	1 (0.19%)
Brivudine	1 (0.19%)
Valaciclovir	1 (0.19%)
Valacyclovir hydrochloride	1 (0.19%)
ANTIMYCOBACTERIALS	22 (4.28%)
Isoniazid	19 (3.70%)
Isoniazide	3 (0.58%)
Rifampicin	3 (0.58%)
VACCINES	3 (0.58%)
Covid-19 vaccine	3 (0.58%)
ANTIMYCOTICS FOR SYSTEMIC USE	2 (0.39%)
Itraconazole	2 (0.39%)
IMMUNE SERA AND IMMUNOGLOBULINS	2 (0.39%)
Human immunoglobulin	1 (0.19%)
Tetanus antitoxin	1 (0.19%)
NERVOUS SYSTEM	57 (11.09%)
ANALGESICS	26 (5.06%)
Bulleyaconitine a	6 (1.17%)
Pregabalin	4 (0.78%)
Lyrica	3 (0.58%)
Dezocine	2 (0.39%)
Gan mao ling [bidens biternata;caffeine;chlorphenamine maleate;chrysanthemum indicum flower;ilex asprella root;melicope pteleifolia;mentha canadensis oil;paracetamol]	2 (0.39%)
Paracetamol	2 (0.39%)
999 ganmaoling	1 (0.19%)
Aminophenazone	1 (0.19%)
Aspirin [acetylsalicylic acid]	1 (0.19%)
Bucinnazine hydrochloride	1 (0.19%)
Compound paracetamol and sulfogaiacol	1 (0.19%)

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WHODrug Global (B3) English [V2022SEP]

Anatomy group *Treatment subgroup* *Drug name*	*Effectiveness Analyses Population (N=514)*
Duloxetine hydrochloride	1 (0.19%)
Hydromorphone hydrochloride	1 (0.19%)
Nalbuphine hydrochloride	1 (0.19%)
Oxycodone and acetaminophen	1 (0.19%)
Paracetamol and caffeine	1 (0.19%)
Propacetamol hydrochloride	1 (0.19%)
Tramadol hydrochloride	1 (0.19%)
Xiao yan zhi tong	1 (0.19%)
PSYCHOLEPTICS	15 (2.92%)
Estazolam	7 (1.36%)
Alprazolam	4 (0.78%)
Dexzopiclone	2 (0.39%)
Oryzanol	2 (0.39%)
Dexmedetomidine hydrochloride for injection	1 (0.19%)
Duloxetine hydrochloride	1 (0.19%)
Melatonin;zolpidem tartrate	1 (0.19%)
Olanzapine	1 (0.19%)
Remimazolam	1 (0.19%)
Risperidone	1 (0.19%)
Zopiclone	1 (0.19%)
ANESTHETICS	11 (2.14%)
Lidocaine hydrochloride	9 (1.75%)
Sufentanil citrate	2 (0.39%)
Diprivan	1 (0.19%)
Dyclonine hydrochloride	1 (0.19%)
Naropin [ropivacaine hydrochloride]	1 (0.19%)
Propofol	1 (0.19%)
Propofol medium and long chain fat emulsion	1 (0.19%)
Sevoflurane	1 (0.19%)
PSYCHOANALEPTICS	8 (1.56%)
Duloxetine hydrochloride	2 (0.39%)
Flupentixol and melitracen	2 (0.39%)
Trazodone hydrochloride	2 (0.39%)
Aceglutamide	1 (0.19%)
Piracetam	1 (0.19%)
OTHER NERVOUS SYSTEM DRUGS	7 (1.36%)
Mecobalamin	2 (0.39%)
Betahistine mesilate	1 (0.19%)
Gastrodin	1 (0.19%)
Mecobalamine	1 (0.19%)
Nerve growth factor, mouse	1 (0.19%)
Qiang li ding xuan	1 (0.19%)

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WHODrug Global (B3) English [V2022SEP]

Anatomy group *Treatment subgroup* *Drug name*	*Effectiveness Analyses Population (N=514)*
VARIOUS	51 (9.92%)
UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	41 (7.98%)
Traditional chinese medicine (tcm) decoction	5 (0.97%)
Xian ling gu bao	5 (0.97%)
Jin gu lian	4 (0.78%)
Shang shi zhi tong gao	4 (0.78%)
Gu long jiao nang	3 (0.58%)
Zao ren an shen	2 (0.39%)
Aescuven forte [aesculus hippocastanum extract]	1 (0.19%)
Bai ling [cordyceps sinensis mycelium]	1 (0.19%)
Co. danshen [salvia miltiorrhiza]	1 (0.19%)
Dan shen tong	1 (0.19%)
Du yi wei	1 (0.19%)
Epimedium brevicornu	1 (0.19%)
Fu fang dan shen	1 (0.19%)
Fu fang yi mu	1 (0.19%)
Hei gu teng zhui feng huo luo jiao nang	1 (0.19%)
Jiang huang xiao cuo cha ji	1 (0.19%)
Kang fu xin	1 (0.19%)
Lian hua qing wen	1 (0.19%)
Rou kou wu wei	1 (0.19%)
Si mo tang	1 (0.19%)
Tian dan tong luo	1 (0.19%)
Tian ma shou wu	1 (0.19%)
Traditional medicine	1 (0.19%)
Unspecified herbal and traditional medicine	1 (0.19%)
Wang bi	1 (0.19%)
Xia ku cao	1 (0.19%)
Xuan yun ning	1 (0.19%)
Yang xue sheng fa jiao nang	1 (0.19%)
Yu ping feng	1 (0.19%)
Yun nan bai yao [aconitum kusnezoffii root;herbal nos]	1 (0.19%)
Zhen yuan	1 (0.19%)
ALL OTHER THERAPEUTIC PRODUCTS	10 (1.95%)
Glutathione	10 (1.95%)
GENERAL NUTRIENTS	1 (0.19%)
Compound alpha ketoacid	1 (0.19%)
RESPIRATORY SYSTEM	21 (4.09%)
COUGH AND COLD PREPARATIONS	14 (2.72%)
Ambroxol hydrochloride	4 (0.78%)
Fu fang gan cao	4 (0.78%)
Acetylcysteine	2 (0.39%)

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WHODrug Global (B3) English [V2022SEP]

Anatomy group *Treatment subgroup* *Drug name*	*Effectiveness Analyses Population (N=514)*
Compound dextromethorphan hydrobromide [dextromethorphan hydrobromide;guaifenesin]	2 (0.39%)
Cydiodine	2 (0.39%)
Ke te ling	2 (0.39%)
Codeine phosphate and platycodon tablets	1 (0.19%)
Fei li ke	1 (0.19%)
ANTIHISTAMINES FOR SYSTEMIC USE	5 (0.97%)
Levocetirizine hydrochloride	2 (0.39%)
Chlorphenamine	1 (0.19%)
Ketotifen fumarate	1 (0.19%)
Loratadine	1 (0.19%)
DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	5 (0.97%)
Bai ling [cordyceps sinensis mycelium]	4 (0.78%)
Compound ipratropium bromide	1 (0.19%)
Doxofylline	1 (0.19%)
Methoxyphenamine hydrochloride	1 (0.19%)
Montelukast sodium	1 (0.19%)
Salbutamol sulphate	1 (0.19%)
Salmeterol xinafoate and fluticasone propionate	1 (0.19%)
THROAT PREPARATIONS	3 (0.58%)
Gan ju bing mei	1 (0.19%)
Ibuprofen	1 (0.19%)
Kai hou jian pen wu ji (er tong xing)	1 (0.19%)
Yan li shuang kou han	1 (0.19%)
NASAL PREPARATIONS	1 (0.19%)
Budesonide	1 (0.19%)
OTHER RESPIRATORY SYSTEM PRODUCTS	1 (0.19%)
Caffeine	1 (0.19%)
SENSORY ORGANS	9 (1.75%)
OPHTHALMOLOGICALS	9 (1.75%)
Sodium hyaluronate	3 (0.58%)
Azelastine hydrochloride	1 (0.19%)
Compound tropicamide	1 (0.19%)
Deproteinized calf blood extract	1 (0.19%)
Dextran 70;glycerol;hypromellose	1 (0.19%)
Fluorescein sodium	1 (0.19%)
Fu fang xue shuan tong	1 (0.19%)
Pranopulin	1 (0.19%)
Retinol palmitate	1 (0.19%)
Tobramycin	1 (0.19%)
Tobramycin and dexamethasone	1 (0.19%)
DERMATOLOGICALS	6 (1.17%)

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WHODrug Global (B3) English [V2022SEP]

Anatomy group *Treatment subgroup* *Drug name*	*Effectiveness Analyses Population (N=514)*
ANTIBIOTICS AND CHEMOTHERAPEUTICS FOR DERMATOLOGICAL USE	2 (0.39%)
Fusidic acid	1 (0.19%)
Interferon alfa-2b	1 (0.19%)
ANTIPRURITICS, INCL. ANTIHISTAMINES, ANESTHETICS, ETC.	2 (0.39%)
Calamine lotion phenolated	1 (0.19%)
Compound lidocaine	1 (0.19%)
Lidocaine	1 (0.19%)
Loratadine	1 (0.19%)
ANTIFUNGALS FOR DERMATOLOGICAL USE	1 (0.19%)
Butenafine hydrochloride	1 (0.19%)
ANTISEPTICS AND DISINFECTANTS	1 (0.19%)
Iodine	1 (0.19%)
EMOLLIENTS AND PROTECTIVES	1 (0.19%)
Zinc oxide	1 (0.19%)
MEDICATED DRESSINGS	1 (0.19%)
Fusidic acid	1 (0.19%)
PREPARATIONS FOR TREATMENT OF WOUNDS AND ULCERS	1 (0.19%)
Kang fu xin	1 (0.19%)
GENITO URINARY SYSTEM AND SEX HORMONES	3 (0.58%)
UROLOGICALS	2 (0.39%)
Niao du qing	1 (0.19%)
Potassium sodium hydrogen citrate	1 (0.19%)
OTHER GYNECOLOGICALS	1 (0.19%)
An kun	1 (0.19%)
ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS	2 (0.39%)
ANTIPROTOZOALS	1 (0.19%)
Chloroquine sulfate	1 (0.19%)
ECTOPARASITICIDES, INCL. SCABICIDES, INSECTICIDES AND REPELLENTS	1 (0.19%)
Acetic acid	1 (0.19%)

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WHODrug Global (B3) English [V2022SEP]

Table ANN. 22 **Specific Prior and Concomitant Medication – Safety Analyses Population**

Group *Drug name*	*Safety Analyses Population* *(N=667)*
Prior with specific RA medication	480 (71.96%)
csDMARDs	468 (70.16%)
Methotrexate	278 (41.68%)
Leflunomide	209 (31.33%)
Hydroxychloroquine (Hydroxychloroquine sulfate)	135 (20.24%)
Iguratimod	83 (12.44%)
Sulfasalazine	15 (2.25%)
Cyclosporine (Cyclosporin)	3 (0.45%)
Azathioprine (Azathioprin)	2 (0.30%)
bDMARDs	29 (4.35%)
TNF inhibitor	26 (3.90%)
Adalimumab (Humira)	13 (1.95%)
Tumor necrosis factor receptor 2 - igg	7 (1.05%)
Etanercept	6 (0.90%)
Infliximab	1 (0.15%)
Tumor necrosis factor alpha (tnf-) inhibitors	1 (0.15%)
Tocilizumab	2 (0.30%)
Abatacept	1 (0.15%)
tsDMARDs	35 (5.25%)
Tofacitinib, Tofacitinib citrate (Xeljanz)	35 (5.25%)
Concomitant with specific RA medication	579 (86.81%)
csDMARDs	579 (86.81%)
Methotrexate	362 (54.27%)
Leflunomide	237 (35.53%)
Hydroxychloroquine (Hydroxychloroquine sulfate)	166 (24.89%)
Iguratimod	96 (14.39%)
Sulfasalazine	25 (3.75%)
Cyclosporine (Cyclosporin)	3 (0.45%)
Azathioprine (Azathioprin)	2 (0.30%)
Cyclophosphamide	1 (0.15%)
bDMARDs	6 (0.90%)
Recombinant human interleukin-2	4 (0.60%)
Interleukin-2	1 (0.15%)
Tocilizumab	1 (0.15%)

Footnote: bDMARD, biological DMARD; csDMARD, conventional synthetic DMARD; DMARD, disease-modifying antirheumatic drug; N, number of patients in population; tsDMARD, targeted synthetic DMARD.
The percentage denominator is the number of analyses population.
Prior medication is defined as medication started before the date of first dose of study drug.
Concomitant medication is defined as medication ended on or after the date of first dose of study drug or is still ongoing, which also started no later than the date of last dose of study drug.
WHODrug Global (B3) English [V2022SEP]

Table ANN. 23 **Specific Prior and Concomitant Medication – Effectiveness Analyses Population**

Group *Drug name*	*Effectiveness Analyses Population (N=514)*
Prior with specific RA medication	374 (72.76%)
csDMARDs	365 (71.01%)
Methotrexate	219 (42.61%)
Leflunomide	159 (30.93%)
Hydroxychloroquine (Hydroxychloroquine sulfate)	104 (20.23%)
Iguratimod	55 (10.70%)
Sulfasalazine	9 (1.75%)
Cyclosporine (Cyclosporin)	3 (0.58%)
Azathioprine (Azathioprin)	2 (0.39%)
bDMARDs	25 (4.86%)
TNF inhibitor	23 (4.47%)
Adalimumab (Humira)	12 (2.33%)
Etanercept	6 (1.17%)
Tumor necrosis factor receptor 2 - igg	5 (0.97%)
Infliximab	1 (0.19%)
Tumor necrosis factor alpha (tnf-) inhibitors	1 (0.19%)
Abatacept	1 (0.19%)
Tocilizumab	1 (0.19%)
tsDMARDs	24 (4.67%)
Tofacitinib, Tofacitinib citrate (Xeljanz)	24 (4.67%)
Concomitant with specific RA medication	457 (88.91%)
csDMARDs	457 (88.91%)
Methotrexate	292 (56.81%)
Leflunomide	182 (35.41%)
Hydroxychloroquine (Hydroxychloroquine sulfate)	131 (25.49%)
Iguratimod	62 (12.06%)
Sulfasalazine	17 (3.31%)
Cyclosporine (Cyclosporin)	3 (0.58%)
Azathioprine (Azathioprin)	2 (0.39%)
Cyclophosphamide	1 (0.19%)
bDMARDs	2 (0.39%)
Recombinant human interleukin-2	2 (0.39%)

Footnote: bDMARD, biological DMARD; csDMARD, conventional synthetic DMARD; DMARD, disease-modifying antirheumatic drug; N, number of patients in population; tsDMARD, targeted synthetic DMARD.
The percentage denominator is the number of analyses population.
Prior medication is defined as medication started before the date of first dose of study drug.
Concomitant medication is defined as medication ended on or after the date of first dose of study drug or is still ongoing, which also started no later than the date of last dose of study drug.
WHODrug Global (B3) English [V2022SEP]

Table ANN. 24 Tuberculosis Test - Safety Analyses Population

		Safety Analyses Population (N=667)
Was PPD skin test performed	Yes	6 (0.90%)
	No	661 (99.10%)
	Total	667 (100.00%)
PPD skin test result	Negative	4 (66.67%)
	Positive	2 (33.33%)
	Total	6 (100.00%)
Was T-Spot TB test performed	Yes	81 (12.14%)
	No	586 (87.86%)
	Total	667 (100.00%)
T-Spot TB test result	Negative	71 (87.65%)
	Positive	10 (12.35%)
	Total	81 (100.00%)

Footnote: The percentage denominator is the number of patients with non-missing value.

Table ANN. 25 Tuberculosis Test - Effectiveness Analyses Population

		Effectiveness Analyses Population (N=514)
Was PPD skin test performed	Yes	4 (0.78%)
	No	510 (99.22%)
	Total	514 (100.00%)
PPD skin test result	Negative	3 (75.00%)
	Positive	1 (25.00%)
	Total	4 (100.00%)
Was T-Spot TB test performed	Yes	59 (11.48%)
	No	455 (88.52%)
	Total	514 (100.00%)
T-Spot TB test result	Negative	51 (86.44%)
	Positive	8 (13.56%)
	Total	59 (100.00%)

Footnote: The percentage denominator is the number of patients with non-missing value.

Table ANN. 26 Baseline DAS28/CDAI/SDAI – Safety Analyses Population

		Safety Analyses Population (N=667)
DAS28-CRP	n (nmiss)	647 (20)
	Mean (Std)	4.62 (1.86)
	Median	4.81
	Q1, Q3	3.70, 5.99
	Min, Max	0.25, 8.02
	<2.6	87 (13.45%)
	>=2.6 to <=3.2	27 (4.17%)
	>3.2 to <=5.1	269 (41.58%)
	>5.1	264 (40.80%)
	Total	647 (100.00%)
	Missing	20
	<=3.2	114 (17.62%)
	>3.2	533 (82.38%)
	Total	647 (100.00%)
	Missing	20
DAS28-ESR	n (nmiss)	632 (35)
	Mean (Std)	5.15 (2.00)
	Median	5.47
	Q1, Q3	4.23, 6.45
	Min, Max	0.22, 8.71
	<2.6	64 (10.13%)
	>=2.6 to <=3.2	23 (3.64%)
	>3.2 to <=5.1	175 (27.69%)
	>5.1	370 (58.54%)
	Total	632 (100.00%)
	Missing	35
	<=3.2	87 (13.77%)
	>3.2	545 (86.23%)
	Total	632 (100.00%)
	Missing	35
SDAI	n (nmiss)	647 (20)
	Mean (Std)	30.77 (18.36)
	Median	27.77
	Q1, Q3	17.41, 42.46
	Min, Max	1.23, 85.92
	<=3.3	33 (5.10%)
	>3.3 to <=11.0	59 (9.12%)
	>11.0 to <=26.0	193 (29.83%)
	>26.0	362 (55.95%)
	Total	647 (100.00%)
	Missing	20
	<=11.0	92 (14.22%)
	>11.0	555 (85.78%)

Footnote: CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; ESR, erythrocyte sedimentation rate; SDAI, Simplified Disease Activity Index
N, number of patients in population; nmiss, number of data missing patients; Q1 and Q3, interquartile range; Std, standard deviation
The percentage denominator is the number of patients with non-missing value.

		Safety Analyses Population (N=667)
	Total	647 (100.00%)
	Missing	20
CDAI	n (nmiss)	659 (8)
	Mean (Std)	28.66 (17.11)
	Median	26.20
	Q1, Q3	16.00, 39.30
	Min, Max	1.20, 74.00
	<=2.8	33 (5.01%)
	>2.8 to <=10.0	57 (8.65%)
	>10.0 to <=22.0	163 (24.73%)
	>22.0	406 (61.61%)
	Total	659 (100.00%)
	Missing	8
	<=10.0	90 (13.66%)
	>10.0	569 (86.34%)
	Total	659 (100.00%)
	Missing	8

Footnote: CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; ESR, erythrocyte sedimentation rate; SDAI, Simplified Disease Activity Index
N, number of patients in population; nmiss, number of data missing patients; Q1 and Q3, interquartile range; Std, standard deviation
The percentage denominator is the number of patients with non-missing value.

Table ANN. 27 Baseline DAS28/CDAI/SDAI – Effectiveness Analyses Population

		Effectiveness Analyses Population (N=514)
DAS28-CRP	n (nmiss)	502 (12)
	Mean (Std)	4.68 (1.84)
	Median	4.82
	Q1, Q3	3.73, 6.06
	Min, Max	0.25, 8.02
	<2.6	64 (12.75%)
	>=2.6 to <=3.2	20 (3.98%)
	>3.2 to <=5.1	206 (41.04%)
	>5.1	212 (42.23%)
	Total	502 (100.00%)
	Missing	12
	<=3.2	84 (16.73%)
	>3.2	418 (83.27%)
	Total	502 (100.00%)
	Missing	12
DAS28-ESR	n (nmiss)	490 (24)
	Mean (Std)	5.18 (1.99)
	Median	5.46
	Q1, Q3	4.23, 6.50
	Min, Max	0.22, 8.71
	<2.6	47 (9.59%)
	>=2.6 to <=3.2	17 (3.47%)
	>3.2 to <=5.1	140 (28.57%)
	>5.1	286 (58.37%)
	Total	490 (100.00%)
	Missing	24
	<=3.2	64 (13.06%)
	>3.2	426 (86.94%)
	Total	490 (100.00%)
	Missing	24
SDAI	n (nmiss)	502 (12)
	Mean (Std)	31.45 (18.43)
	Median	28.33
	Q1, Q3	18.86, 43.95
	Min, Max	1.23, 85.92
	<=3.3	24 (4.78%)
	>3.3 to <=11.0	39 (7.77%)
	>11.0 to <=26.0	157 (31.27%)
	>26.0	282 (56.18%)
	Total	502 (100.00%)
	Missing	12
	<=11.0	63 (12.55%)
	>11.0	439 (87.45%)

Footnote: CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; ESR, erythrocyte sedimentation rate; SDAI, Simplified Disease Activity Index
N, number of patients in population; nmiss, number of data missing patients; Q1 and Q3, interquartile range; Std, standard deviation
The percentage denominator is the number of patients with non-missing value.

		Effectiveness Analyses Population (N=514)
	Total	502 (100.00%)
	Missing	12
CDAI	n (nmiss)	508 (6)
	Mean (Std)	29.18 (17.26)
	Median	26.40
	Q1, Q3	17.00, 40.65
	Min, Max	1.20, 74.00
	<=2.8	24 (4.72%)
	>2.8 to <=10.0	37 (7.28%)
	>10.0 to <=22.0	132 (25.98%)
	>22.0	315 (62.01%)
	Total	508 (100.00%)
	Missing	6
	<=10.0	61 (12.01%)
	>10.0	447 (87.99%)
	Total	508 (100.00%)
	Missing	6

Footnote: CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; ESR, erythrocyte sedimentation rate; SDAI, Simplified Disease Activity Index
N, number of patients in population; nmiss, number of data missing patients; Q1 and Q3, interquartile range; Std, standard deviation
The percentage denominator is the number of patients with non-missing value.

Table ANN. 28 Baseline Key Indicator – Safety Analyses Population

Laboratory test (unit)		*Safety Analyses Population (N=667)*
ESR (mm/H)	n (nmiss)	598 (69)
	Mean (Std)	44.40 (29.87)
	Median	39.00
	Q1, Q3	21.00, 64.00
	Min, Max	2.00, 140.00
CRP (mg/L)	n (nmiss)	604 (63)
	Mean (Std)	23.40 (30.87)
	Median	10.41
	Q1, Q3	3.13, 30.25
	Min, Max	0.09, 241.00
RF (IU/mL)	n (nmiss)	496 (171)
	Mean (Std)	243.10 (400.21)
	Median	115.95
	Q1, Q3	34.30, 294.47
	Min, Max	1.00, 2980.00
	Negative	85 (17.14%)
	Positive	411 (82.86%)
	Total	496 (100.00%)
Anti-CCP (U/mL)	n (nmiss)	375 (292)
	Mean (Std)	308.05 (508.55)
	Median	192.00
	Q1, Q3	41.90, 345.98
	Min, Max	0.50, 4112.70
	Negative	53 (14.13%)
	Positive	322 (85.87%)
	Total	375 (100.00%)

Footnote: Anti-CCP, anti-cyclic peptide containing citrulline; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; N, number of patients in population; nmiss, number of data missing patients; Q1 and Q3, interquartile range; RF, rheumatoid factor; Std, standard deviation

Table ANN. 29 Baseline Key Indicator – Effectiveness Analyses Population

Laboratory test (unit)		*Effectiveness Analyses Population (N=514)*
ESR (mm/H)	n (nmiss)	462 (52)
	Mean (Std)	44.37 (30.70)
	Median	37.50
	Q1, Q3	21.00, 64.00
	Min, Max	2.00, 136.00
CRP (mg/L)	n (nmiss)	467 (47)
	Mean (Std)	23.91 (30.44)
	Median	11.05
	Q1, Q3	3.24, 33.30
	Min, Max	0.09, 178.20
RF (IU/mL)	n (nmiss)	388 (126)
	Mean (Std)	244.44 (398.01)
	Median	113.80
	Q1, Q3	32.87, 296.50
	Min, Max	1.00, 2830.00
	Negative	67 (17.27%)
	Positive	321 (82.73%)
	Total	388 (100.00%)
Anti-CCP (U/mL)	n (nmiss)	283 (231)
	Mean (Std)	306.86 (504.71)
	Median	200.00
	Q1, Q3	43.20, 356.89
	Min, Max	0.50, 4112.70
	Negative	40 (14.13%)
	Positive	243 (85.87%)
	Total	283 (100.00%)

Footnote: Anti-CCP, anti-cyclic peptide containing citrulline; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; N, number of patients in population; nmiss, number of data missing patients; Q1 and Q3, interquartile range; RF, rheumatoid factor; Std, standard deviation

Main Results

Safety

Table ANN. 30 Drug Exposure – Safety Analyses Population

		Safety Analyses Population (N=667)
Overall Olumiant exposure (days)	n (nmiss)	665 (2)
	Mean (Std)	143.94 (56.56)
	Median	167.00
	Q1, Q3	126.00, 179.00
	Min, Max	1, 314
Olumiant exposure (days)	n (nmiss)	665 (2)
	Mean (Std)	142.18 (56.65)
	Median	165.00
	Q1, Q3	116.00, 177.00
	Min, Max	1, 314
Total patient year exposure		262.1
Number of patients administered only 2mg Olumiant	n (%)	580 (86.96%)
Number of patients administered only 4mg Olumiant	n (%)	53 (7.95%)
Number of patients administered mixed dosage of Olumiant	n (%)	34 (5.10%)
2mg to 4mg	n (%)	14 (2.10%)
Other mixed dosage	n (%)	20 (3.00%)

Footnote: N, number of patients in population; nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.
Overall Olumiant exposure (days) = Olumiant discontinue date in study termination page – the earliest start date of treatment in treatment information page +1.
Olumiant exposure (days) = sum of (end date of treatment - start date of treatment +1). The start and end date of treatment are from the same record in treatment information page.
The sum are based on all records in this page.
Total patient year exposure = sum of all patients' year exposure. Patient year exposure = overall Olumiant exposure in days for the patient / 365.25, keep 1 decimal place.
2mg to 4mg in mixed dosage referred to patients who initiated treatment with 2mg daily and then increased to 4mg daily without changing dosasge anymore.

Table ANN. 31 Drug Exposure – Effectiveness Analyses Population

		Effectiveness Analyses Population (N=514)
Overall Olumiant exposure (days)	n (nmiss)	513 (1)
	Mean (Std)	164.34 (32.54)
	Median	170.00
	Q1, Q3	156.00, 181.00
	Min, Max	1, 314
Olumiant exposure (days)	n (nmiss)	513 (1)
	Mean (Std)	162.42 (33.51)
	Median	169.00
	Q1, Q3	154.00, 180.00
	Min, Max	1, 314
Total patient year exposure		230.8
Number of patients administered only 2mg Olumiant	n (%)	458 (89.11%)
Number of patients administered only 4mg Olumiant	n (%)	28 (5.45%)
Number of patients administered mixed dosage of Olumiant	n (%)	28 (5.45%)
2mg to 4mg	n (%)	12 (2.33%)
Other mixed dosage	n (%)	16 (3.11%)

Footnote: N, number of patients in population; nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.
Overall Olumiant exposure (days) = Olumiant discontinue date in study termination page – the earliest start date of treatment in treatment information page +1.
Olumiant exposure (days) = sum of (end date of treatment - start date of treatment +1). The start and end date of treatment are from the same record in treatment information page.
The sum are based on all records in this page.
Total patient year exposure = sum of all patients' year exposure. Patient year exposure = overall Olumiant exposure in days for the patient / 365.25, keep 1 decimal place.
2mg to 4mg in mixed dosage referred to patients who initiated treatment with 2mg daily and then increased to 4mg daily without changing dosasge anymore.

Table ANN. 32 **AEs over a Period of 12 Weeks by Maximum Severity — MedDRA Preferred Term by Decreasing Frequency, within System Organ Class (Safety Analyses Population)**

	Safety Analyses Population (N=667)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
AE	329	214 (32.08%)	237	136 (20.39%)	70	58 (8.70%)	22	20 (3.00%)
Infections and infestations	57	49 (7.35%)	34	27 (4.05%)	19	18 (2.70%)	4	4 (0.60%)
Upper respiratory tract infection	18	17 (2.55%)	13	12 (1.80%)	5	5 (0.75%)	0	0
Urinary tract infection	11	11 (1.65%)	7	7 (1.05%)	4	4 (0.60%)	0	0
Pneumonia	7	6 (0.90%)	0	0	4	3 (0.45%)	3	3 (0.45%)
Herpes zoster	3	3 (0.45%)	0	0	3	3 (0.45%)	0	0
Pharyngitis	3	3 (0.45%)	1	1 (0.15%)	2	2 (0.30%)	0	0
Bronchitis	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Enterovirus infection	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Gingivitis	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Herpes ophthalmic	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Herpes simplex	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Herpes virus infection	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Otitis externa	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Otitis media	1	1 (0.15%)	0	0	0	0	1	1 (0.15%)
Periodontitis	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Pulmonary tuberculosis	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Pulpitis dental	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Streptococcal infection	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=667)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Tonsillitis	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Urethritis	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Vulvovaginal mycotic infection	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Investigations	67	49 (7.35%)	66	48 (7.20%)	1	1 (0.15%)	0	0
Platelet count increased	14	14 (2.10%)	14	14 (2.10%)	0	0	0	0
White blood cell count increased	9	9 (1.35%)	9	9 (1.35%)	0	0	0	0
Lymphocyte count decreased	7	7 (1.05%)	7	7 (1.05%)	0	0	0	0
Neutrophil count increased	7	7 (1.05%)	7	7 (1.05%)	0	0	0	0
Alanine aminotransferase increased	5	5 (0.75%)	5	5 (0.75%)	0	0	0	0
White blood cell count decreased	5	5 (0.75%)	5	5 (0.75%)	0	0	0	0
Neutrophil percentage increased	4	4 (0.60%)	4	4 (0.60%)	0	0	0	0
Aspartate aminotransferase increased	2	2 (0.30%)	2	2 (0.30%)	0	0	0	0
Blood pressure increased	2	2 (0.30%)	1	1 (0.15%)	1	1 (0.15%)	0	0
Fibrin D dimer increased	2	2 (0.30%)	2	2 (0.30%)	0	0	0	0
Blood albumin decreased	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Blood creatine phosphokinase increased	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Blood triglycerides increased	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Coagulation test abnormal	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Haemoglobin decreased	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=667)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Lipids increased	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Lymphocyte count increased	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Lymphocyte percentage increased	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Red blood cells urine positive	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Weight increased	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Gastrointestinal disorders	33	31 (4.65%)	27	25 (3.75%)	4	4 (0.60%)	2	2 (0.30%)
Diarrhoea	4	4 (0.60%)	4	4 (0.60%)	0	0	0	0
Gastrointestinal disorder	4	4 (0.60%)	4	4 (0.60%)	0	0	0	0
Abdominal pain upper	3	3 (0.45%)	2	2 (0.30%)	1	1 (0.15%)	0	0
Nausea	3	3 (0.45%)	3	3 (0.45%)	0	0	0	0
Abdominal discomfort	2	2 (0.30%)	2	2 (0.30%)	0	0	0	0
Mouth ulceration	3	2 (0.30%)	3	2 (0.30%)	0	0	0	0
Abdominal distension	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Aphthous ulcer	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Dry mouth	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Functional gastrointestinal disorder	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Gastritis	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Gastrooesophageal reflux disease	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Haemorrhagic erosive gastritis	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=667)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Ileus paralytic	1	1 (0.15%)	0	0	0	0	1	1 (0.15%)
Noninfective gingivitis	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Oral blood blister	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Pancreatitis acute	1	1 (0.15%)	0	0	0	0	1	1 (0.15%)
Periodontal disease	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Stomatitis	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Toothache	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Metabolism and nutrition disorders	33	29 (4.35%)	26	23 (3.45%)	6	5 (0.75%)	1	1 (0.15%)
Hyperlipidaemia	8	8 (1.20%)	6	6 (0.90%)	2	2 (0.30%)	0	0
Hyperuricaemia	5	5 (0.75%)	5	5 (0.75%)	0	0	0	0
Decreased appetite	4	4 (0.60%)	4	4 (0.60%)	0	0	0	0
Hypocalcaemia	3	3 (0.45%)	3	3 (0.45%)	0	0	0	0
Electrolyte imbalance	3	2 (0.30%)	2	1 (0.15%)	1	1 (0.15%)	0	0
Hypokalaemia	2	2 (0.30%)	2	2 (0.30%)	0	0	0	0
Diabetes mellitus	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Dyslipidaemia	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Hypercholesterolaemia	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Hyperkalaemia	1	1 (0.15%)	0	0	0	0	1	1 (0.15%)
Hypertriglyceridaemia	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=667)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Hypoalbuminaemia	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Hypoglycaemia	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Vitamin D deficiency	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Blood and lymphatic system disorders	22	22 (3.30%)	19	19 (2.85%)	3	3 (0.45%)	0	0
Anaemia	10	10 (1.50%)	9	9 (1.35%)	1	1 (0.15%)	0	0
Thrombocytosis	4	4 (0.60%)	4	4 (0.60%)	0	0	0	0
Leukopenia	2	2 (0.30%)	2	2 (0.30%)	0	0	0	0
Myelosuppression	2	2 (0.30%)	0	0	2	2 (0.30%)	0	0
Coagulopathy	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Eosinophilia	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Monocytosis	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Thrombocytopenia	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Musculoskeletal and connective tissue disorders	25	21 (3.15%)	8	5 (0.75%)	10	9 (1.35%)	7	7 (1.05%)
Rheumatoid arthritis	8	8 (1.20%)	1	1 (0.15%)	3	3 (0.45%)	4	4 (0.60%)
Arthralgia	7	7 (1.05%)	2	2 (0.30%)	4	4 (0.60%)	1	1 (0.15%)
Intervertebral disc protrusion	3	3 (0.45%)	1	1 (0.15%)	1	1 (0.15%)	1	1 (0.15%)
Joint swelling	2	2 (0.30%)	1	1 (0.15%)	1	1 (0.15%)	0	0
Spinal osteoarthritis	2	2 (0.30%)	2	2 (0.30%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=667)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Back pain	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Lumbar spinal stenosis	1	1 (0.15%)	0	0	0	0	1	1 (0.15%)
Pain in extremity	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Hepatobiliary disorders	20	19 (2.85%)	12	12 (1.80%)	6	6 (0.90%)	2	1 (0.15%)
Hepatic function abnormal	18	18 (2.70%)	12	12 (1.80%)	6	6 (0.90%)	0	0
Drug-induced liver injury	2	1 (0.15%)	0	0	0	0	2	1 (0.15%)
Skin and subcutaneous tissue disorders	14	13 (1.95%)	10	9 (1.35%)	4	4 (0.60%)	0	0
Alopecia	4	4 (0.60%)	3	3 (0.45%)	1	1 (0.15%)	0	0
Acne	3	3 (0.45%)	2	2 (0.30%)	1	1 (0.15%)	0	0
Dermatitis	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Eczema	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Night sweats	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Pruritus	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Rash	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Skin erosion	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Skin ulcer	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
General disorders and administration site conditions	10	9 (1.35%)	7	6 (0.90%)	2	2 (0.30%)	1	1 (0.15%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=667)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Chest pain	2	2 (0.30%)	2	2 (0.30%)	0	0	0	0
Oedema peripheral	2	2 (0.30%)	1	1 (0.15%)	1	1 (0.15%)	0	0
Asthenia	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Chest discomfort	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Chills	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Death	1	1 (0.15%)	0	0	0	0	1	1 (0.15%)
Face oedema	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Peripheral swelling	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Respiratory, thoracic and mediastinal disorders	10	9 (1.35%)	5	4 (0.60%)	4	4 (0.60%)	1	1 (0.15%)
Cough	4	4 (0.60%)	2	2 (0.30%)	2	2 (0.30%)	0	0
Bronchiectasis	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Chronic obstructive pulmonary disease	1	1 (0.15%)	0	0	0	0	1	1 (0.15%)
Interstitial lung disease	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Laryngeal pain	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Oropharyngeal pain	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Productive cough	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Nervous system disorders	7	7 (1.05%)	4	4 (0.60%)	2	2 (0.30%)	1	1 (0.15%)
Headache	2	2 (0.30%)	2	2 (0.30%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=667)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Carotid artery aneurysm	1	1 (0.15%)	0	0	0	0	1	1 (0.15%)
Dizziness	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Neuropathy peripheral	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Optic neuritis	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Somnolence	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Vascular disorders	8	7 (1.05%)	5	4 (0.60%)	3	3 (0.45%)	0	0
Hypertension	7	6 (0.90%)	4	3 (0.45%)	3	3 (0.45%)	0	0
Arteriosclerosis	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Reproductive system and breast disorders	6	5 (0.75%)	5	4 (0.60%)	1	1 (0.15%)	0	0
Abnormal uterine bleeding	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Adenomyosis	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Dysmenorrhoea	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Ectropion of cervix	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Menstrual disorder	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Vaginal discharge	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Ear and labyrinth disorders	4	4 (0.60%)	1	1 (0.15%)	2	2 (0.30%)	1	1 (0.15%)
Vertigo	2	2 (0.30%)	0	0	2	2 (0.30%)	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=667)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Cerumen impaction	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Otolithiasis	1	1 (0.15%)	0	0	0	0	1	1 (0.15%)
Endocrine disorders	5	4 (0.60%)	3	2 (0.30%)	1	1 (0.15%)	1	1 (0.15%)
Hypothyroidism	2	2 (0.30%)	1	1 (0.15%)	1	1 (0.15%)	0	0
Thyroid mass	3	2 (0.30%)	2	1 (0.15%)	0	0	1	1 (0.15%)
Eye disorders	2	2 (0.30%)	2	2 (0.30%)	0	0	0	0
Cataract	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Eyelid oedema	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Renal and urinary disorders	2	2 (0.30%)	1	1 (0.15%)	1	1 (0.15%)	0	0
Renal failure	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Renal impairment	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Cardiac disorders	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Arteriosclerosis coronary artery	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Injury, poisoning and procedural complications	1	1 (0.15%)	0	0	0	0	1	1 (0.15%)
Lumbar vertebral fracture	1	1 (0.15%)	0	0	0	0	1	1 (0.15%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=667)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Thyroid cancer	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Psychiatric disorders	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Sleep disorder	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

Table ANN. 33 AEs over a Period of 12 Weeks — MedDRA Preferred Term by Decreasing Frequency (Safety Analyses Population)

	Safety Analyses Population (N=667)	
PT	*Event*	*n (%)*
AE	329	214 (32.08%)
Hepatic function abnormal	18	18 (2.70%)
Upper respiratory tract infection	18	17 (2.55%)
Platelet count increased	14	14 (2.10%)
Urinary tract infection	11	11 (1.65%)
Anaemia	10	10 (1.50%)
White blood cell count increased	9	9 (1.35%)
Hyperlipidaemia	8	8 (1.20%)
Rheumatoid arthritis	8	8 (1.20%)
Arthralgia	7	7 (1.05%)
Lymphocyte count decreased	7	7 (1.05%)
Neutrophil count increased	7	7 (1.05%)
Hypertension	7	6 (0.90%)
Pneumonia	7	6 (0.90%)
Alanine aminotransferase increased	5	5 (0.75%)
Hyperuricaemia	5	5 (0.75%)
White blood cell count decreased	5	5 (0.75%)
Alopecia	4	4 (0.60%)
Cough	4	4 (0.60%)
Decreased appetite	4	4 (0.60%)
Diarrhoea	4	4 (0.60%)
Gastrointestinal disorder	4	4 (0.60%)
Neutrophil percentage increased	4	4 (0.60%)
Thrombocytosis	4	4 (0.60%)
Abdominal pain upper	3	3 (0.45%)
Acne	3	3 (0.45%)
Herpes zoster	3	3 (0.45%)
Hypocalcaemia	3	3 (0.45%)
Intervertebral disc protrusion	3	3 (0.45%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

	Safety Analyses Population (N=667)	
PT	*Event*	*n (%)*
Nausea	3	3 (0.45%)
Pharyngitis	3	3 (0.45%)
Abdominal discomfort	2	2 (0.30%)
Aspartate aminotransferase increased	2	2 (0.30%)
Blood pressure increased	2	2 (0.30%)
Chest pain	2	2 (0.30%)
Electrolyte imbalance	3	2 (0.30%)
Fibrin D dimer increased	2	2 (0.30%)
Headache	2	2 (0.30%)
Hypokalaemia	2	2 (0.30%)
Hypothyroidism	2	2 (0.30%)
Joint swelling	2	2 (0.30%)
Leukopenia	2	2 (0.30%)
Mouth ulceration	3	2 (0.30%)
Myelosuppression	2	2 (0.30%)
Oedema peripheral	2	2 (0.30%)
Spinal osteoarthritis	2	2 (0.30%)
Thyroid mass	3	2 (0.30%)
Vertigo	2	2 (0.30%)
Abdominal distension	1	1 (0.15%)
Abnormal uterine bleeding	1	1 (0.15%)
Adenomyosis	1	1 (0.15%)
Aphthous ulcer	1	1 (0.15%)
Arteriosclerosis	1	1 (0.15%)
Arteriosclerosis coronary artery	1	1 (0.15%)
Asthenia	1	1 (0.15%)
Back pain	1	1 (0.15%)
Blood albumin decreased	1	1 (0.15%)
Blood creatine phosphokinase increased	1	1 (0.15%)
Blood triglycerides increased	1	1 (0.15%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

	Safety Analyses Population (N=667)	
PT	*Event*	*n (%)*
Bronchiectasis	1	1 (0.15%)
Bronchitis	1	1 (0.15%)
Carotid artery aneurysm	1	1 (0.15%)
Cataract	1	1 (0.15%)
Cerumen impaction	1	1 (0.15%)
Chest discomfort	1	1 (0.15%)
Chills	1	1 (0.15%)
Chronic obstructive pulmonary disease	1	1 (0.15%)
Coagulation test abnormal	1	1 (0.15%)
Coagulopathy	1	1 (0.15%)
Death	1	1 (0.15%)
Dermatitis	1	1 (0.15%)
Diabetes mellitus	1	1 (0.15%)
Dizziness	1	1 (0.15%)
Drug-induced liver injury	2	1 (0.15%)
Dry mouth	1	1 (0.15%)
Dyslipidaemia	1	1 (0.15%)
Dysmenorrhoea	1	1 (0.15%)
Ectropion of cervix	1	1 (0.15%)
Eczema	1	1 (0.15%)
Enterovirus infection	1	1 (0.15%)
Eosinophilia	1	1 (0.15%)
Eyelid oedema	1	1 (0.15%)
Face oedema	1	1 (0.15%)
Functional gastrointestinal disorder	1	1 (0.15%)
Gastritis	1	1 (0.15%)
Gastrooesophageal reflux disease	1	1 (0.15%)
Gingivitis	1	1 (0.15%)
Haemoglobin decreased	1	1 (0.15%)
Haemorrhagic erosive gastritis	1	1 (0.15%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

	Safety Analyses Population (N=667)	
PT	*Event*	*n (%)*
Herpes ophthalmic	1	1 (0.15%)
Herpes simplex	1	1 (0.15%)
Herpes virus infection	1	1 (0.15%)
Hypercholesterolaemia	1	1 (0.15%)
Hyperkalaemia	1	1 (0.15%)
Hypertriglyceridaemia	1	1 (0.15%)
Hypoalbuminaemia	1	1 (0.15%)
Hypoglycaemia	1	1 (0.15%)
Ileus paralytic	1	1 (0.15%)
Interstitial lung disease	1	1 (0.15%)
Laryngeal pain	1	1 (0.15%)
Lipids increased	1	1 (0.15%)
Lumbar spinal stenosis	1	1 (0.15%)
Lumbar vertebral fracture	1	1 (0.15%)
Lymphocyte count increased	1	1 (0.15%)
Lymphocyte percentage increased	1	1 (0.15%)
Menstrual disorder	1	1 (0.15%)
Monocytosis	1	1 (0.15%)
Neuropathy peripheral	1	1 (0.15%)
Night sweats	1	1 (0.15%)
Noninfective gingivitis	1	1 (0.15%)
Optic neuritis	1	1 (0.15%)
Oral blood blister	1	1 (0.15%)
Oropharyngeal pain	1	1 (0.15%)
Otitis externa	1	1 (0.15%)
Otitis media	1	1 (0.15%)
Otolithiasis	1	1 (0.15%)
Pain in extremity	1	1 (0.15%)
Pancreatitis acute	1	1 (0.15%)
Periodontal disease	1	1 (0.15%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

	Safety Analyses Population (N=667)	
PT	*Event*	*n (%)*
Periodontitis	1	1 (0.15%)
Peripheral swelling	1	1 (0.15%)
Productive cough	1	1 (0.15%)
Pruritus	1	1 (0.15%)
Pulmonary tuberculosis	1	1 (0.15%)
Pulpitis dental	1	1 (0.15%)
Rash	1	1 (0.15%)
Red blood cells urine positive	1	1 (0.15%)
Renal failure	1	1 (0.15%)
Renal impairment	1	1 (0.15%)
Skin erosion	1	1 (0.15%)
Skin ulcer	1	1 (0.15%)
Sleep disorder	1	1 (0.15%)
Somnolence	1	1 (0.15%)
Stomatitis	1	1 (0.15%)
Streptococcal infection	1	1 (0.15%)
Thrombocytopenia	1	1 (0.15%)
Thyroid cancer	1	1 (0.15%)
Tonsillitis	1	1 (0.15%)
Toothache	1	1 (0.15%)
Urethritis	1	1 (0.15%)
Vaginal discharge	1	1 (0.15%)
Vitamin D deficiency	1	1 (0.15%)
Vulvovaginal mycotic infection	1	1 (0.15%)
Weight increased	1	1 (0.15%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

Table ANN. 34 **AEs over a Period of 24 Weeks by Maximum Severity — MedDRA Preferred Term by Decreasing Frequency, within System Organ Class (Safety Analyses Population)**

	Safety Analyses Population (N=667)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
AE	428	250 (37.48%)	305	158 (23.69%)	94	67 (10.04%)	29	25 (3.75%)
Infections and infestations	74	64 (9.60%)	43	35 (5.25%)	25	23 (3.45%)	6	6 (0.90%)
Upper respiratory tract infection	21	18 (2.70%)	15	13 (1.95%)	6	5 (0.75%)	0	0
Urinary tract infection	15	15 (2.25%)	11	11 (1.65%)	4	4 (0.60%)	0	0
Pneumonia	10	9 (1.35%)	1	1 (0.15%)	6	5 (0.75%)	3	3 (0.45%)
Herpes zoster	7	7 (1.05%)	2	2 (0.30%)	5	5 (0.75%)	0	0
Pharyngitis	3	3 (0.45%)	1	1 (0.15%)	2	2 (0.30%)	0	0
Appendicitis	1	1 (0.15%)	0	0	0	0	1	1 (0.15%)
Bronchitis	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Enterovirus infection	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Gingivitis	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Herpes ophthalmic	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Herpes simplex	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Herpes virus infection	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Influenza	1	1 (0.15%)	0	0	0	0	1	1 (0.15%)
Laryngopharyngitis	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Otitis externa	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Otitis media	1	1 (0.15%)	0	0	0	0	1	1 (0.15%)
Periodontitis	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=667)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Pulmonary tuberculosis	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Pulpitis dental	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Streptococcal infection	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Tonsillitis	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Urethritis	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Vulvovaginal mycotic infection	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Investigations	86	62 (9.30%)	84	60 (9.00%)	2	2 (0.30%)	0	0
Platelet count increased	16	16 (2.40%)	16	16 (2.40%)	0	0	0	0
Lymphocyte count decreased	10	10 (1.50%)	9	9 (1.35%)	1	1 (0.15%)	0	0
White blood cell count increased	12	10 (1.50%)	12	10 (1.50%)	0	0	0	0
Neutrophil count increased	8	7 (1.05%)	8	7 (1.05%)	0	0	0	0
White blood cell count decreased	6	6 (0.90%)	6	6 (0.90%)	0	0	0	0
Alanine aminotransferase increased	5	5 (0.75%)	5	5 (0.75%)	0	0	0	0
Neutrophil percentage increased	4	4 (0.60%)	4	4 (0.60%)	0	0	0	0
Aspartate aminotransferase increased	3	3 (0.45%)	3	3 (0.45%)	0	0	0	0
Blood bilirubin increased	2	2 (0.30%)	2	2 (0.30%)	0	0	0	0
Blood pressure increased	2	2 (0.30%)	1	1 (0.15%)	1	1 (0.15%)	0	0
Fibrin D dimer increased	2	2 (0.30%)	2	2 (0.30%)	0	0	0	0
Blood albumin decreased	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=667)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Blood creatine phosphokinase increased	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Blood triglycerides increased	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Coagulation test abnormal	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Haemoglobin decreased	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Lipids increased	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Liver function test abnormal	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Lymphocyte count increased	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Lymphocyte percentage increased	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Neutrophil count decreased	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Platelet count decreased	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Protein urine present	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Red blood cells urine positive	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Rheumatoid factor increased	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Weight decreased	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Weight increased	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Metabolism and nutrition disorders	40	35 (5.25%)	33	29 (4.35%)	6	5 (0.75%)	1	1 (0.15%)
Hyperlipidaemia	11	11 (1.65%)	9	9 (1.35%)	2	2 (0.30%)	0	0
Hyperuricaemia	6	6 (0.90%)	6	6 (0.90%)	0	0	0	0
Decreased appetite	5	5 (0.75%)	5	5 (0.75%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=667)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Hypocalcaemia	3	3 (0.45%)	3	3 (0.45%)	0	0	0	0
Dyslipidaemia	2	2 (0.30%)	2	2 (0.30%)	0	0	0	0
Electrolyte imbalance	3	2 (0.30%)	2	1 (0.15%)	1	1 (0.15%)	0	0
Hypokalaemia	2	2 (0.30%)	2	2 (0.30%)	0	0	0	0
Diabetes mellitus	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Glucose tolerance impaired	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Hypercholesterolaemia	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Hyperkalaemia	1	1 (0.15%)	0	0	0	0	1	1 (0.15%)
Hypertriglyceridaemia	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Hypoalbuminaemia	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Hypoglycaemia	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Vitamin D deficiency	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Gastrointestinal disorders	38	33 (4.95%)	30	27 (4.05%)	6	4 (0.60%)	2	2 (0.30%)
Abdominal pain upper	4	4 (0.60%)	3	3 (0.45%)	1	1 (0.15%)	0	0
Diarrhoea	4	4 (0.60%)	4	4 (0.60%)	0	0	0	0
Gastrointestinal disorder	4	4 (0.60%)	4	4 (0.60%)	0	0	0	0
Abdominal discomfort	3	3 (0.45%)	3	3 (0.45%)	0	0	0	0
Nausea	3	3 (0.45%)	3	3 (0.45%)	0	0	0	0
Mouth ulceration	3	2 (0.30%)	3	2 (0.30%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
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	Safety Analyses Population (N=667)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Abdominal distension	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Aphthous ulcer	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Dry mouth	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Functional gastrointestinal disorder	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Gastritis	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Gastritis erosive	2	1 (0.15%)	0	0	2	1 (0.15%)	0	0
Gastrooesophageal reflux disease	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Haemorrhagic erosive gastritis	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Ileus paralytic	1	1 (0.15%)	0	0	0	0	1	1 (0.15%)
Noninfective gingivitis	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Oral blood blister	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Oral mucosal eruption	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Pancreatitis acute	1	1 (0.15%)	0	0	0	0	1	1 (0.15%)
Periodontal disease	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Stomatitis	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Toothache	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Musculoskeletal and connective tissue disorders	41	33 (4.95%)	14	10 (1.50%)	18	14 (2.10%)	9	9 (1.35%)
Rheumatoid arthritis	11	11 (1.65%)	3	3 (0.45%)	4	4 (0.60%)	4	4 (0.60%)
Arthralgia	12	10 (1.50%)	3	3 (0.45%)	7	5 (0.75%)	2	2 (0.30%)

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All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
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MedDRA English version 25.1

	Safety Analyses Population (N=667)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Intervertebral disc protrusion	3	3 (0.45%)	1	1 (0.15%)	1	1 (0.15%)	1	1 (0.15%)
Back pain	2	2 (0.30%)	1	1 (0.15%)	1	1 (0.15%)	0	0
Joint swelling	2	2 (0.30%)	1	1 (0.15%)	1	1 (0.15%)	0	0
Osteonecrosis	2	2 (0.30%)	1	1 (0.15%)	0	0	1	1 (0.15%)
Palindromic rheumatism	2	2 (0.30%)	0	0	2	2 (0.30%)	0	0
Spinal osteoarthritis	2	2 (0.30%)	2	2 (0.30%)	0	0	0	0
Synovial cyst	2	2 (0.30%)	1	1 (0.15%)	1	1 (0.15%)	0	0
Arthropathy	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Lumbar spinal stenosis	1	1 (0.15%)	0	0	0	0	1	1 (0.15%)
Pain in extremity	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Blood and lymphatic system disorders	28	27 (4.05%)	24	23 (3.45%)	4	4 (0.60%)	0	0
Anaemia	15	14 (2.10%)	13	12 (1.80%)	2	2 (0.30%)	0	0
Thrombocytosis	4	4 (0.60%)	4	4 (0.60%)	0	0	0	0
Coagulopathy	2	2 (0.30%)	2	2 (0.30%)	0	0	0	0
Leukopenia	2	2 (0.30%)	2	2 (0.30%)	0	0	0	0
Myelosuppression	2	2 (0.30%)	0	0	2	2 (0.30%)	0	0
Eosinophilia	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Monocytosis	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Thrombocytopenia	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0

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	Safety Analyses Population (N=667)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Hepatobiliary disorders	28	25 (3.75%)	17	16 (2.40%)	9	8 (1.20%)	2	1 (0.15%)
Hepatic function abnormal	24	22 (3.30%)	16	15 (2.25%)	8	7 (1.05%)	0	0
Drug-induced liver injury	3	2 (0.30%)	0	0	1	1 (0.15%)	2	1 (0.15%)
Liver injury	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Skin and subcutaneous tissue disorders	16	15 (2.25%)	11	10 (1.50%)	5	5 (0.75%)	0	0
Alopecia	5	5 (0.75%)	3	3 (0.45%)	2	2 (0.30%)	0	0
Acne	3	3 (0.45%)	2	2 (0.30%)	1	1 (0.15%)	0	0
Rash	2	2 (0.30%)	2	2 (0.30%)	0	0	0	0
Dermatitis	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Eczema	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Night sweats	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Pruritus	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Skin erosion	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Skin ulcer	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Respiratory, thoracic and mediastinal disorders	13	12 (1.80%)	8	7 (1.05%)	4	4 (0.60%)	1	1 (0.15%)
Cough	6	6 (0.90%)	4	4 (0.60%)	2	2 (0.30%)	0	0
Bronchiectasis	2	2 (0.30%)	1	1 (0.15%)	1	1 (0.15%)	0	0

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All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
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	Safety Analyses Population (N=667)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Chronic obstructive pulmonary disease	1	1 (0.15%)	0	0	0	0	1	1 (0.15%)
Interstitial lung disease	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Laryngeal pain	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Oropharyngeal pain	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Productive cough	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
General disorders and administration site conditions	12	11 (1.65%)	9	8 (1.20%)	2	2 (0.30%)	1	1 (0.15%)
Asthenia	2	2 (0.30%)	2	2 (0.30%)	0	0	0	0
Chest pain	2	2 (0.30%)	2	2 (0.30%)	0	0	0	0
Oedema peripheral	2	2 (0.30%)	1	1 (0.15%)	1	1 (0.15%)	0	0
Chest discomfort	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Chills	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Death	1	1 (0.15%)	0	0	0	0	1	1 (0.15%)
Face oedema	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Peripheral swelling	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Pyrexia	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Nervous system disorders	8	8 (1.20%)	4	4 (0.60%)	3	3 (0.45%)	1	1 (0.15%)
Headache	3	3 (0.45%)	2	2 (0.30%)	1	1 (0.15%)	0	0
Carotid artery aneurysm	1	1 (0.15%)	0	0	0	0	1	1 (0.15%)

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	Safety Analyses Population (N=667)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Dizziness	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Neuropathy peripheral	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Optic neuritis	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Somnolence	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Vascular disorders	8	7 (1.05%)	5	4 (0.60%)	3	3 (0.45%)	0	0
Hypertension	7	6 (0.90%)	4	3 (0.45%)	3	3 (0.45%)	0	0
Arteriosclerosis	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Reproductive system and breast disorders	7	6 (0.90%)	6	5 (0.75%)	1	1 (0.15%)	0	0
Abnormal uterine bleeding	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Adenomyosis	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Breast mass	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Dysmenorrhoea	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Ectropion of cervix	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Menstrual disorder	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Vaginal discharge	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Ear and labyrinth disorders	5	5 (0.75%)	2	2 (0.30%)	2	2 (0.30%)	1	1 (0.15%)
Vertigo	3	3 (0.45%)	1	1 (0.15%)	2	2 (0.30%)	0	0

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	Safety Analyses Population (N=667)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Cerumen impaction	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Otolithiasis	1	1 (0.15%)	0	0	0	0	1	1 (0.15%)
Eye disorders	6	5 (0.75%)	4	4 (0.60%)	0	0	2	1 (0.15%)
Cataract	3	2 (0.30%)	1	1 (0.15%)	0	0	2	1 (0.15%)
Dry eye	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Eyelid oedema	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Ocular discomfort	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Endocrine disorders	5	4 (0.60%)	3	2 (0.30%)	1	1 (0.15%)	1	1 (0.15%)
Hypothyroidism	2	2 (0.30%)	1	1 (0.15%)	1	1 (0.15%)	0	0
Thyroid mass	3	2 (0.30%)	2	1 (0.15%)	0	0	1	1 (0.15%)
Injury, poisoning and procedural complications	4	4 (0.60%)	2	2 (0.30%)	1	1 (0.15%)	1	1 (0.15%)
Limb injury	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Lumbar vertebral fracture	1	1 (0.15%)	0	0	0	0	1	1 (0.15%)
Nail injury	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Tendon injury	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Psychiatric disorders	4	4 (0.60%)	4	4 (0.60%)	0	0	0	0

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	Safety Analyses Population (N=667)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Sleep disorder	2	2 (0.30%)	2	2 (0.30%)	0	0	0	0
Anxiety disorder	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Insomnia	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Renal and urinary disorders	2	2 (0.30%)	1	1 (0.15%)	1	1 (0.15%)	0	0
Renal failure	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Renal impairment	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Cardiac disorders	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Arteriosclerosis coronary artery	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Thyroid cancer	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Pregnancy, puerperium and perinatal conditions	1	1 (0.15%)	0	0	0	0	1	1 (0.15%)
Abortion threatened	1	1 (0.15%)	0	0	0	0	1	1 (0.15%)

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Table ANN. 35 AEs over a Period of 24 Weeks — MedDRA Preferred Term by Decreasing Frequency (Safety Analyses Population)

	Safety Analyses Population (N=667)	
PT	*Event*	*n (%)*
AE	428	250 (37.48%)
Hepatic function abnormal	24	22 (3.30%)
Upper respiratory tract infection	21	18 (2.70%)
Platelet count increased	16	16 (2.40%)
Urinary tract infection	15	15 (2.25%)
Anaemia	15	14 (2.10%)
Hyperlipidaemia	11	11 (1.65%)
Rheumatoid arthritis	11	11 (1.65%)
Arthralgia	12	10 (1.50%)
Lymphocyte count decreased	10	10 (1.50%)
White blood cell count increased	12	10 (1.50%)
Pneumonia	10	9 (1.35%)
Herpes zoster	7	7 (1.05%)
Neutrophil count increased	8	7 (1.05%)
Cough	6	6 (0.90%)
Hypertension	7	6 (0.90%)
Hyperuricaemia	6	6 (0.90%)
White blood cell count decreased	6	6 (0.90%)
Alanine aminotransferase increased	5	5 (0.75%)
Alopecia	5	5 (0.75%)
Decreased appetite	5	5 (0.75%)
Abdominal pain upper	4	4 (0.60%)
Diarrhoea	4	4 (0.60%)
Gastrointestinal disorder	4	4 (0.60%)
Neutrophil percentage increased	4	4 (0.60%)
Thrombocytosis	4	4 (0.60%)
Abdominal discomfort	3	3 (0.45%)
Acne	3	3 (0.45%)
Aspartate aminotransferase increased	3	3 (0.45%)

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The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

	Safety Analyses Population (N=667)	
PT	*Event*	*n (%)*
Headache	3	3 (0.45%)
Hypocalcaemia	3	3 (0.45%)
Intervertebral disc protrusion	3	3 (0.45%)
Nausea	3	3 (0.45%)
Pharyngitis	3	3 (0.45%)
Vertigo	3	3 (0.45%)
Asthenia	2	2 (0.30%)
Back pain	2	2 (0.30%)
Blood bilirubin increased	2	2 (0.30%)
Blood pressure increased	2	2 (0.30%)
Bronchiectasis	2	2 (0.30%)
Cataract	3	2 (0.30%)
Chest pain	2	2 (0.30%)
Coagulopathy	2	2 (0.30%)
Drug-induced liver injury	3	2 (0.30%)
Dyslipidaemia	2	2 (0.30%)
Electrolyte imbalance	3	2 (0.30%)
Fibrin D dimer increased	2	2 (0.30%)
Hypokalaemia	2	2 (0.30%)
Hypothyroidism	2	2 (0.30%)
Joint swelling	2	2 (0.30%)
Leukopenia	2	2 (0.30%)
Mouth ulceration	3	2 (0.30%)
Myelosuppression	2	2 (0.30%)
Oedema peripheral	2	2 (0.30%)
Osteonecrosis	2	2 (0.30%)
Palindromic rheumatism	2	2 (0.30%)
Rash	2	2 (0.30%)
Sleep disorder	2	2 (0.30%)
Spinal osteoarthritis	2	2 (0.30%)

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n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
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	Safety Analyses Population (N=667)	
PT	*Event*	*n (%)*
Synovial cyst	2	2 (0.30%)
Thyroid mass	3	2 (0.30%)
Abdominal distension	1	1 (0.15%)
Abnormal uterine bleeding	1	1 (0.15%)
Abortion threatened	1	1 (0.15%)
Adenomyosis	1	1 (0.15%)
Anxiety disorder	1	1 (0.15%)
Aphthous ulcer	1	1 (0.15%)
Appendicitis	1	1 (0.15%)
Arteriosclerosis	1	1 (0.15%)
Arteriosclerosis coronary artery	1	1 (0.15%)
Arthropathy	1	1 (0.15%)
Blood albumin decreased	1	1 (0.15%)
Blood creatine phosphokinase increased	1	1 (0.15%)
Blood triglycerides increased	1	1 (0.15%)
Breast mass	1	1 (0.15%)
Bronchitis	1	1 (0.15%)
Carotid artery aneurysm	1	1 (0.15%)
Cerumen impaction	1	1 (0.15%)
Chest discomfort	1	1 (0.15%)
Chills	1	1 (0.15%)
Chronic obstructive pulmonary disease	1	1 (0.15%)
Coagulation test abnormal	1	1 (0.15%)
Death	1	1 (0.15%)
Dermatitis	1	1 (0.15%)
Diabetes mellitus	1	1 (0.15%)
Dizziness	1	1 (0.15%)
Dry eye	1	1 (0.15%)
Dry mouth	1	1 (0.15%)
Dysmenorrhoea	1	1 (0.15%)

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	Safety Analyses Population (N=667)	
PT	*Event*	*n (%)*
Ectropion of cervix	1	1 (0.15%)
Eczema	1	1 (0.15%)
Enterovirus infection	1	1 (0.15%)
Eosinophilia	1	1 (0.15%)
Eyelid oedema	1	1 (0.15%)
Face oedema	1	1 (0.15%)
Functional gastrointestinal disorder	1	1 (0.15%)
Gastritis	1	1 (0.15%)
Gastritis erosive	2	1 (0.15%)
Gastrooesophageal reflux disease	1	1 (0.15%)
Gingivitis	1	1 (0.15%)
Glucose tolerance impaired	1	1 (0.15%)
Haemoglobin decreased	1	1 (0.15%)
Haemorrhagic erosive gastritis	1	1 (0.15%)
Herpes ophthalmic	1	1 (0.15%)
Herpes simplex	1	1 (0.15%)
Herpes virus infection	1	1 (0.15%)
Hypercholesterolaemia	1	1 (0.15%)
Hyperkalaemia	1	1 (0.15%)
Hypertriglyceridaemia	1	1 (0.15%)
Hypoalbuminaemia	1	1 (0.15%)
Hypoglycaemia	1	1 (0.15%)
Ileus paralytic	1	1 (0.15%)
Influenza	1	1 (0.15%)
Insomnia	1	1 (0.15%)
Interstitial lung disease	1	1 (0.15%)
Laryngeal pain	1	1 (0.15%)
Laryngopharyngitis	1	1 (0.15%)
Limb injury	1	1 (0.15%)
Lipids increased	1	1 (0.15%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

	Safety Analyses Population (N=667)	
PT	*Event*	*n (%)*
Liver function test abnormal	1	1 (0.15%)
Liver injury	1	1 (0.15%)
Lumbar spinal stenosis	1	1 (0.15%)
Lumbar vertebral fracture	1	1 (0.15%)
Lymphocyte count increased	1	1 (0.15%)
Lymphocyte percentage increased	1	1 (0.15%)
Menstrual disorder	1	1 (0.15%)
Monocytosis	1	1 (0.15%)
Nail injury	1	1 (0.15%)
Neuropathy peripheral	1	1 (0.15%)
Neutrophil count decreased	1	1 (0.15%)
Night sweats	1	1 (0.15%)
Noninfective gingivitis	1	1 (0.15%)
Ocular discomfort	1	1 (0.15%)
Optic neuritis	1	1 (0.15%)
Oral blood blister	1	1 (0.15%)
Oral mucosal eruption	1	1 (0.15%)
Oropharyngeal pain	1	1 (0.15%)
Otitis externa	1	1 (0.15%)
Otitis media	1	1 (0.15%)
Otolithiasis	1	1 (0.15%)
Pain in extremity	1	1 (0.15%)
Pancreatitis acute	1	1 (0.15%)
Periodontal disease	1	1 (0.15%)
Periodontitis	1	1 (0.15%)
Peripheral swelling	1	1 (0.15%)
Platelet count decreased	1	1 (0.15%)
Productive cough	1	1 (0.15%)
Protein urine present	1	1 (0.15%)
Pruritus	1	1 (0.15%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

	Safety Analyses Population (N=667)	
PT	*Event*	*n (%)*
Pulmonary tuberculosis	1	1 (0.15%)
Pulpitis dental	1	1 (0.15%)
Pyrexia	1	1 (0.15%)
Red blood cells urine positive	1	1 (0.15%)
Renal failure	1	1 (0.15%)
Renal impairment	1	1 (0.15%)
Rheumatoid factor increased	1	1 (0.15%)
Skin erosion	1	1 (0.15%)
Skin ulcer	1	1 (0.15%)
Somnolence	1	1 (0.15%)
Stomatitis	1	1 (0.15%)
Streptococcal infection	1	1 (0.15%)
Tendon injury	1	1 (0.15%)
Thrombocytopenia	1	1 (0.15%)
Thyroid cancer	1	1 (0.15%)
Tonsillitis	1	1 (0.15%)
Toothache	1	1 (0.15%)
Urethritis	1	1 (0.15%)
Vaginal discharge	1	1 (0.15%)
Vitamin D deficiency	1	1 (0.15%)
Vulvovaginal mycotic infection	1	1 (0.15%)
Weight decreased	1	1 (0.15%)
Weight increased	1	1 (0.15%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

Table ANN. 36 **AEs Related to Study Treatment as Judged by the Investigator over a Period of 12 Weeks by Maximum Severity — MedDRA Preferred Term by Decreasing Frequency, within System Organ Class (Safety Analyses Population)**

	Safety Analyses Population (N=667)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
AEs Related to Study Treatment	111	95 (14.24%)	72	60 (9.00%)	32	29 (4.35%)	7	6 (0.90%)
Infections and infestations	36	33 (4.95%)	16	14 (2.10%)	16	15 (2.25%)	4	4 (0.60%)
Upper respiratory tract infection	9	9 (1.35%)	6	6 (0.90%)	3	3 (0.45%)	0	0
Urinary tract infection	8	8 (1.20%)	4	4 (0.60%)	4	4 (0.60%)	0	0
Pneumonia	7	6 (0.90%)	0	0	4	3 (0.45%)	3	3 (0.45%)
Herpes zoster	3	3 (0.45%)	0	0	3	3 (0.45%)	0	0
Bronchitis	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Gingivitis	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Herpes ophthalmic	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Herpes simplex	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Herpes virus infection	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Otitis media	1	1 (0.15%)	0	0	0	0	1	1 (0.15%)
Pharyngitis	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Pulmonary tuberculosis	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Tonsillitis	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Investigations	19	17 (2.55%)	19	17 (2.55%)	0	0	0	0
Platelet count increased	4	4 (0.60%)	4	4 (0.60%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
AEs related to study treatment were judged by the investigator.
MedDRA English version 25.1

	Safety Analyses Population (N=667)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Alanine aminotransferase increased	3	3 (0.45%)	3	3 (0.45%)	0	0	0	0
Lymphocyte count decreased	3	3 (0.45%)	3	3 (0.45%)	0	0	0	0
White blood cell count decreased	3	3 (0.45%)	3	3 (0.45%)	0	0	0	0
Blood triglycerides increased	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Haemoglobin decreased	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Lipids increased	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Lymphocyte count increased	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Lymphocyte percentage increased	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
White blood cell count increased	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Hepatobiliary disorders	14	13 (1.95%)	7	7 (1.05%)	5	5 (0.75%)	2	1 (0.15%)
Hepatic function abnormal	12	12 (1.80%)	7	7 (1.05%)	5	5 (0.75%)	0	0
Drug-induced liver injury	2	1 (0.15%)	0	0	0	0	2	1 (0.15%)
Gastrointestinal disorders	12	10 (1.50%)	10	8 (1.20%)	2	2 (0.30%)	0	0
Abdominal pain upper	2	2 (0.30%)	1	1 (0.15%)	1	1 (0.15%)	0	0
Gastrointestinal disorder	2	2 (0.30%)	2	2 (0.30%)	0	0	0	0
Abdominal discomfort	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Abdominal distension	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
AEs related to study treatment were judged by the investigator.
MedDRA English version 25.1

	Safety Analyses Population (N=667)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Dry mouth	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Mouth ulceration	2	1 (0.15%)	2	1 (0.15%)	0	0	0	0
Nausea	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Noninfective gingivitis	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Oral blood blister	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Blood and lymphatic system disorders	8	8 (1.20%)	6	6 (0.90%)	2	2 (0.30%)	0	0
Anaemia	5	5 (0.75%)	5	5 (0.75%)	0	0	0	0
Myelosuppression	2	2 (0.30%)	0	0	2	2 (0.30%)	0	0
Eosinophilia	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Metabolism and nutrition disorders	8	8 (1.20%)	7	7 (1.05%)	1	1 (0.15%)	0	0
Hyperlipidaemia	5	5 (0.75%)	4	4 (0.60%)	1	1 (0.15%)	0	0
Decreased appetite	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Dyslipidaemia	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Hypercholesterolaemia	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Nervous system disorders	3	3 (0.45%)	3	3 (0.45%)	0	0	0	0
Dizziness	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
AEs related to study treatment were judged by the investigator.
MedDRA English version 25.1

	Safety Analyses Population (N=667)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Headache	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Somnolence	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Respiratory, thoracic and mediastinal disorders	3	3 (0.45%)	1	1 (0.15%)	2	2 (0.30%)	0	0
Cough	2	2 (0.30%)	1	1 (0.15%)	1	1 (0.15%)	0	0
Laryngeal pain	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
General disorders and administration site conditions	2	2 (0.30%)	1	1 (0.15%)	1	1 (0.15%)	0	0
Asthenia	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Peripheral swelling	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Musculoskeletal and connective tissue disorders	2	2 (0.30%)	0	0	1	1 (0.15%)	1	1 (0.15%)
Arthralgia	1	1 (0.15%)	0	0	0	0	1	1 (0.15%)
Rheumatoid arthritis	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Skin and subcutaneous tissue disorders	2	2 (0.30%)	1	1 (0.15%)	1	1 (0.15%)	0	0
Acne	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Alopecia	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
AEs related to study treatment were judged by the investigator.
MedDRA English version 25.1

	Safety Analyses Population (N=667)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Renal and urinary disorders	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Renal impairment	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Vascular disorders	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Hypertension	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
AEs related to study treatment were judged by the investigator.
MedDRA English version 25.1

Table ANN. 37 AEs Related to Study Treatment as Judged by the Investigator over a Period of 12 Weeks — MedDRA Preferred Term by Decreasing Frequency (Safety Analyses Population)

	Safety Analyses Population (N=667)	
PT	*Event*	*n (%)*
AEs Related to Study Treatment	111	95 (14.24%)
Hepatic function abnormal	12	12 (1.80%)
Upper respiratory tract infection	9	9 (1.35%)
Urinary tract infection	8	8 (1.20%)
Pneumonia	7	6 (0.90%)
Anaemia	5	5 (0.75%)
Hyperlipidaemia	5	5 (0.75%)
Platelet count increased	4	4 (0.60%)
Alanine aminotransferase increased	3	3 (0.45%)
Herpes zoster	3	3 (0.45%)
Lymphocyte count decreased	3	3 (0.45%)
White blood cell count decreased	3	3 (0.45%)
Abdominal pain upper	2	2 (0.30%)
Cough	2	2 (0.30%)
Gastrointestinal disorder	2	2 (0.30%)
Myelosuppression	2	2 (0.30%)
Abdominal discomfort	1	1 (0.15%)
Abdominal distension	1	1 (0.15%)
Acne	1	1 (0.15%)
Alopecia	1	1 (0.15%)
Arthralgia	1	1 (0.15%)
Asthenia	1	1 (0.15%)
Blood triglycerides increased	1	1 (0.15%)
Bronchitis	1	1 (0.15%)
Decreased appetite	1	1 (0.15%)
Dizziness	1	1 (0.15%)
Drug-induced liver injury	2	1 (0.15%)
Dry mouth	1	1 (0.15%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
AEs related to study treatment were judged by the investigator.
MedDRA English version 25.1

	Safety Analyses Population (N=667)	
PT	*Event*	*n (%)*
Dyslipidaemia	1	1 (0.15%)
Eosinophilia	1	1 (0.15%)
Gingivitis	1	1 (0.15%)
Haemoglobin decreased	1	1 (0.15%)
Headache	1	1 (0.15%)
Herpes ophthalmic	1	1 (0.15%)
Herpes simplex	1	1 (0.15%)
Herpes virus infection	1	1 (0.15%)
Hypercholesterolaemia	1	1 (0.15%)
Hypertension	1	1 (0.15%)
Laryngeal pain	1	1 (0.15%)
Lipids increased	1	1 (0.15%)
Lymphocyte count increased	1	1 (0.15%)
Lymphocyte percentage increased	1	1 (0.15%)
Mouth ulceration	2	1 (0.15%)
Nausea	1	1 (0.15%)
Noninfective gingivitis	1	1 (0.15%)
Oral blood blister	1	1 (0.15%)
Otitis media	1	1 (0.15%)
Peripheral swelling	1	1 (0.15%)
Pharyngitis	1	1 (0.15%)
Pulmonary tuberculosis	1	1 (0.15%)
Renal impairment	1	1 (0.15%)
Rheumatoid arthritis	1	1 (0.15%)
Somnolence	1	1 (0.15%)
Tonsillitis	1	1 (0.15%)
White blood cell count increased	1	1 (0.15%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
AEs related to study treatment were judged by the investigator.
MedDRA English version 25.1

Table ANN. 38 **AEs Related to Study Treatment as Judged by the Investigator over a Period of 24 Weeks by Maximum Severity — MedDRA Preferred Term by Decreasing Frequency, within System Organ Class (Safety Analyses Population)**

	Safety Analyses Population (N=667)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
AEs Related to Study Treatment	147	120 (17.99%)	96	76 (11.39%)	42	36 (5.40%)	9	8 (1.20%)
Infections and infestations	49	46 (6.90%)	22	20 (3.00%)	21	20 (3.00%)	6	6 (0.90%)
Urinary tract infection	12	12 (1.80%)	8	8 (1.20%)	4	4 (0.60%)	0	0
Upper respiratory tract infection	9	9 (1.35%)	6	6 (0.90%)	3	3 (0.45%)	0	0
Pneumonia	9	8 (1.20%)	0	0	6	5 (0.75%)	3	3 (0.45%)
Herpes zoster	7	7 (1.05%)	2	2 (0.30%)	5	5 (0.75%)	0	0
Appendicitis	1	1 (0.15%)	0	0	0	0	1	1 (0.15%)
Bronchitis	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Gingivitis	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Herpes ophthalmic	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Herpes simplex	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Herpes virus infection	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Influenza	1	1 (0.15%)	0	0	0	0	1	1 (0.15%)
Laryngopharyngitis	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Otitis media	1	1 (0.15%)	0	0	0	0	1	1 (0.15%)
Pharyngitis	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Pulmonary tuberculosis	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Tonsillitis	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
AEs related to study treatment were judged by the investigator.
MedDRA English version 25.1

	Safety Analyses Population (N=667)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Investigations	25	22 (3.30%)	25	22 (3.30%)	0	0	0	0
Lymphocyte count decreased	5	5 (0.75%)	5	5 (0.75%)	0	0	0	0
Platelet count increased	4	4 (0.60%)	4	4 (0.60%)	0	0	0	0
Alanine aminotransferase increased	3	3 (0.45%)	3	3 (0.45%)	0	0	0	0
White blood cell count decreased	3	3 (0.45%)	3	3 (0.45%)	0	0	0	0
Blood bilirubin increased	2	2 (0.30%)	2	2 (0.30%)	0	0	0	0
Blood triglycerides increased	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Haemoglobin decreased	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Lipids increased	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Liver function test abnormal	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Lymphocyte count increased	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Lymphocyte percentage increased	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Platelet count decreased	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
White blood cell count increased	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Hepatobiliary disorders	20	18 (2.70%)	10	10 (1.50%)	8	7 (1.05%)	2	1 (0.15%)
Hepatic function abnormal	16	15 (2.25%)	9	9 (1.35%)	7	6 (0.90%)	0	0
Drug-induced liver injury	3	2 (0.30%)	0	0	1	1 (0.15%)	2	1 (0.15%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
AEs related to study treatment were judged by the investigator.
MedDRA English version 25.1

	Safety Analyses Population (N=667)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Liver injury	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Blood and lymphatic system disorders	12	11 (1.65%)	9	8 (1.20%)	3	3 (0.45%)	0	0
Anaemia	9	8 (1.20%)	8	7 (1.05%)	1	1 (0.15%)	0	0
Myelosuppression	2	2 (0.30%)	0	0	2	2 (0.30%)	0	0
Eosinophilia	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Gastrointestinal disorders	13	11 (1.65%)	11	9 (1.35%)	2	2 (0.30%)	0	0
Abdominal pain upper	2	2 (0.30%)	1	1 (0.15%)	1	1 (0.15%)	0	0
Gastrointestinal disorder	2	2 (0.30%)	2	2 (0.30%)	0	0	0	0
Abdominal discomfort	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Abdominal distension	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Dry mouth	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Mouth ulceration	2	1 (0.15%)	2	1 (0.15%)	0	0	0	0
Nausea	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Noninfective gingivitis	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Oral blood blister	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Oral mucosal eruption	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
AEs related to study treatment were judged by the investigator.
MedDRA English version 25.1

	Safety Analyses Population (N=667)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Metabolism and nutrition disorders	10	10 (1.50%)	9	9 (1.35%)	1	1 (0.15%)	0	0
Hyperlipidaemia	6	6 (0.90%)	5	5 (0.75%)	1	1 (0.15%)	0	0
Dyslipidaemia	2	2 (0.30%)	2	2 (0.30%)	0	0	0	0
Decreased appetite	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Hypercholesterolaemia	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Musculoskeletal and connective tissue disorders	5	5 (0.75%)	2	2 (0.30%)	2	2 (0.30%)	1	1 (0.15%)
Rheumatoid arthritis	3	3 (0.45%)	2	2 (0.30%)	1	1 (0.15%)	0	0
Arthralgia	1	1 (0.15%)	0	0	0	0	1	1 (0.15%)
Synovial cyst	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Nervous system disorders	3	3 (0.45%)	3	3 (0.45%)	0	0	0	0
Dizziness	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Headache	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Somnolence	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Respiratory, thoracic and mediastinal disorders	3	3 (0.45%)	1	1 (0.15%)	2	2 (0.30%)	0	0
Cough	2	2 (0.30%)	1	1 (0.15%)	1	1 (0.15%)	0	0
Laryngeal pain	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
AEs related to study treatment were judged by the investigator.
MedDRA English version 25.1

	Safety Analyses Population (N=667)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Skin and subcutaneous tissue disorders	3	3 (0.45%)	2	2 (0.30%)	1	1 (0.15%)	0	0
Acne	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Alopecia	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Rash	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
General disorders and administration site conditions	2	2 (0.30%)	1	1 (0.15%)	1	1 (0.15%)	0	0
Asthenia	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Peripheral swelling	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Renal and urinary disorders	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Renal impairment	1	1 (0.15%)	1	1 (0.15%)	0	0	0	0
Vascular disorders	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0
Hypertension	1	1 (0.15%)	0	0	1	1 (0.15%)	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
AEs related to study treatment were judged by the investigator.
MedDRA English version 25.1

Table ANN. 39 AEs Related to Study Treatment as Judged by the Investigator over a Period of 24 Weeks — MedDRA Preferred Term by Decreasing Frequency (Safety Analyses Population)

	Safety Analyses Population (N=667)	
PT	*Event*	*n (%)*
AEs Related to Study Treatment	147	120 (17.99%)
Hepatic function abnormal	16	15 (2.25%)
Urinary tract infection	12	12 (1.80%)
Upper respiratory tract infection	9	9 (1.35%)
Anaemia	9	8 (1.20%)
Pneumonia	9	8 (1.20%)
Herpes zoster	7	7 (1.05%)
Hyperlipidaemia	6	6 (0.90%)
Lymphocyte count decreased	5	5 (0.75%)
Platelet count increased	4	4 (0.60%)
Alanine aminotransferase increased	3	3 (0.45%)
Rheumatoid arthritis	3	3 (0.45%)
White blood cell count decreased	3	3 (0.45%)
Abdominal pain upper	2	2 (0.30%)
Blood bilirubin increased	2	2 (0.30%)
Cough	2	2 (0.30%)
Drug-induced liver injury	3	2 (0.30%)
Dyslipidaemia	2	2 (0.30%)
Gastrointestinal disorder	2	2 (0.30%)
Myelosuppression	2	2 (0.30%)
Abdominal discomfort	1	1 (0.15%)
Abdominal distension	1	1 (0.15%)
Acne	1	1 (0.15%)
Alopecia	1	1 (0.15%)
Appendicitis	1	1 (0.15%)
Arthralgia	1	1 (0.15%)
Asthenia	1	1 (0.15%)
Blood triglycerides increased	1	1 (0.15%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
AEs related to study treatment were judged by the investigator.
MedDRA English version 25.1

	Safety Analyses Population (N=667)	
PT	*Event*	*n (%)*
Bronchitis	1	1 (0.15%)
Decreased appetite	1	1 (0.15%)
Dizziness	1	1 (0.15%)
Dry mouth	1	1 (0.15%)
Eosinophilia	1	1 (0.15%)
Gingivitis	1	1 (0.15%)
Haemoglobin decreased	1	1 (0.15%)
Headache	1	1 (0.15%)
Herpes ophthalmic	1	1 (0.15%)
Herpes simplex	1	1 (0.15%)
Herpes virus infection	1	1 (0.15%)
Hypercholesterolaemia	1	1 (0.15%)
Hypertension	1	1 (0.15%)
Influenza	1	1 (0.15%)
Laryngeal pain	1	1 (0.15%)
Laryngopharyngitis	1	1 (0.15%)
Lipids increased	1	1 (0.15%)
Liver function test abnormal	1	1 (0.15%)
Liver injury	1	1 (0.15%)
Lymphocyte count increased	1	1 (0.15%)
Lymphocyte percentage increased	1	1 (0.15%)
Mouth ulceration	2	1 (0.15%)
Nausea	1	1 (0.15%)
Noninfective gingivitis	1	1 (0.15%)
Oral blood blister	1	1 (0.15%)
Oral mucosal eruption	1	1 (0.15%)
Otitis media	1	1 (0.15%)
Peripheral swelling	1	1 (0.15%)
Pharyngitis	1	1 (0.15%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
AEs related to study treatment were judged by the investigator.
MedDRA English version 25.1

	Safety Analyses Population (N=667)	
PT	*Event*	*n (%)*
Platelet count decreased	1	1 (0.15%)
Pulmonary tuberculosis	1	1 (0.15%)
Rash	1	1 (0.15%)
Renal impairment	1	1 (0.15%)
Somnolence	1	1 (0.15%)
Synovial cyst	1	1 (0.15%)
Tonsillitis	1	1 (0.15%)
White blood cell count increased	1	1 (0.15%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
AEs related to study treatment were judged by the investigator.
MedDRA English version 25.1

Table ANN. 40 **SAEs over a Period of 12 Weeks — MedDRA Preferred Term by Decreasing Frequency, within System Organ Class (Safety Analyses Population)**

SOC	*Safety Analyses Population (N=667)*		
PT	*Event*	*n (%)*	*EAIR and 95% CI*
SAE	23	22 (3.30%)	14.96 (9.38, 22.65)
Infections and infestations	6	6 (0.90%)	4.04 (1.48, 8.80)
Pneumonia	4	4 (0.60%)	2.69 (0.73, 6.90)
Otitis media	1	1 (0.15%)	0.67 (0.02, 3.75)
Tonsillitis	1	1 (0.15%)	0.67 (0.02, 3.75)
Musculoskeletal and connective tissue disorders	6	6 (0.90%)	4.05 (1.49, 8.81)
Rheumatoid arthritis	3	3 (0.45%)	2.02 (0.42, 5.91)
Arthralgia	1	1 (0.15%)	0.67 (0.02, 3.75)
Intervertebral disc protrusion	1	1 (0.15%)	0.67 (0.02, 3.75)
Lumbar spinal stenosis	1	1 (0.15%)	0.67 (0.02, 3.75)
Gastrointestinal disorders	2	2 (0.30%)	1.35 (0.16, 4.86)
Ileus paralytic	1	1 (0.15%)	0.67 (0.02, 3.75)

Footnote: N, number of patients in population; PT, preferred term; SAE, serious adverse event; SOC, system organ class
n is the number of patients and % is the percentage.
The SOCs are sorted by decreasing number of patients, while the PTs are sorted by decreasing number of patients within SOC.
MedDRA English version 25.1

SOC	*Safety Analyses Population (N=667)*		
PT	*Event*	*n (%)*	*EAIR and 95% CI*
Pancreatitis acute	1	1 (0.15%)	0.67 (0.02, 3.75)
Nervous system disorders	2	2 (0.30%)	1.35 (0.16, 4.87)
Carotid artery aneurysm	1	1 (0.15%)	0.67 (0.02, 3.75)
Optic neuritis	1	1 (0.15%)	0.67 (0.02, 3.76)
Ear and labyrinth disorders	1	1 (0.15%)	0.67 (0.02, 3.75)
Otolithiasis	1	1 (0.15%)	0.67 (0.02, 3.75)
Endocrine disorders	1	1 (0.15%)	0.67 (0.02, 3.75)
Thyroid mass	1	1 (0.15%)	0.67 (0.02, 3.75)
General disorders and administration site conditions	1	1 (0.15%)	0.67 (0.02, 3.75)
Death	1	1 (0.15%)	0.67 (0.02, 3.75)

Footnote: N, number of patients in population; PT, preferred term; SAE, serious adverse event; SOC, system organ class
n is the number of patients and % is the percentage.
The SOCs are sorted by decreasing number of patients, while the PTs are sorted by decreasing number of patients within SOC.
MedDRA English version 25.1

SOC	*Safety Analyses Population (N=667)*		
PT	*Event*	*n (%)*	*EAIR and 95% CI*
Hepatobiliary disorders	1	1 (0.15%)	0.67 (0.02, 3.75)
Drug-induced liver injury	1	1 (0.15%)	0.67 (0.02, 3.75)
Injury, poisoning and procedural complications	1	1 (0.15%)	0.67 (0.02, 3.75)
Lumbar vertebral fracture	1	1 (0.15%)	0.67 (0.02, 3.75)
Metabolism and nutrition disorders	1	1 (0.15%)	0.67 (0.02, 3.75)
Hyperkalaemia	1	1 (0.15%)	0.67 (0.02, 3.75)
Respiratory, thoracic and mediastinal disorders	1	1 (0.15%)	0.67 (0.02, 3.75)
Chronic obstructive pulmonary disease	1	1 (0.15%)	0.67 (0.02, 3.75)

Footnote: N, number of patients in population; PT, preferred term; SAE, serious adverse event; SOC, system organ class
n is the number of patients and % is the percentage.
The SOCs are sorted by decreasing number of patients, while the PTs are sorted by decreasing number of patients within SOC.
MedDRA English version 25.1

Table ANN. 41 **SAEs Related to Study Treatment as Judged by the Investigator over a Period of 12 Weeks — MedDRA Preferred Term by Decreasing Frequency, within System Organ Class (Safety Analyses Population)**

SOC	*Safety Analyses Population (N=667)*	
PT	*Event*	*n (%)*
SAEs Related to Study Treatment	8	8 (1.20%)
Infections and infestations	6	6 (0.90%)
Pneumonia	4	4 (0.60%)
Otitis media	1	1 (0.15%)
Tonsillitis	1	1 (0.15%)
Hepatobiliary disorders	1	1 (0.15%)
Drug-induced liver injury	1	1 (0.15%)
Musculoskeletal and connective tissue disorders	1	1 (0.15%)
Arthralgia	1	1 (0.15%)

Footnote: N, number of patients in population; PT, preferred term; SAE, serious adverse event; SOC, system organ class
n is the number of patients and % is the percentage.
The SOCs are sorted by decreasing number of patients, while the PTs are sorted by decreasing number of patients within SOC.
SAEs related to study treatment were judged by the investigator.
MedDRA English version 25.1

Table ANN. 42 SAEs over a Period of 12 Weeks — MedDRA Preferred Term by Decreasing Frequency (Safety Analyses Population)

	Safety Analyses Population (N=667)	
PT	*Event*	*n (%)*
SAE	23	22 (3.30%)
Pneumonia	4	4 (0.60%)
Rheumatoid arthritis	3	3 (0.45%)
Arthralgia	1	1 (0.15%)
Carotid artery aneurysm	1	1 (0.15%)
Chronic obstructive pulmonary disease	1	1 (0.15%)
Death	1	1 (0.15%)
Drug-induced liver injury	1	1 (0.15%)
Hyperkalaemia	1	1 (0.15%)
Ileus paralytic	1	1 (0.15%)
Intervertebral disc protrusion	1	1 (0.15%)
Lumbar spinal stenosis	1	1 (0.15%)
Lumbar vertebral fracture	1	1 (0.15%)
Optic neuritis	1	1 (0.15%)
Otitis media	1	1 (0.15%)
Otolithiasis	1	1 (0.15%)
Pancreatitis acute	1	1 (0.15%)
Thyroid mass	1	1 (0.15%)
Tonsillitis	1	1 (0.15%)

Footnote: N, number of patients in population; PT, preferred term; SAE, serious adverse event
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

Table ANN. 43 SAEs Related to Study Treatment as Judged by the Investigator over a Period of 12 Weeks — MedDRA Preferred Term by Decreasing Frequency (Safety Analyses Population)

	Safety Analyses Population (N=667)	
PT	*Event*	*n (%)*
SAEs Related to Study Treatment	8	8 (1.20%)
Pneumonia	4	4 (0.60%)
Arthralgia	1	1 (0.15%)
Drug-induced liver injury	1	1 (0.15%)
Otitis media	1	1 (0.15%)
Tonsillitis	1	1 (0.15%)

Footnote: N, number of patients in population; PT, preferred term; SAE, serious adverse event
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
SAEs related to study treatment were judged by the investigator.
MedDRA English version 25.1

Table ANN. 44 **SAEs over a Period of 24 Weeks — MedDRA Preferred Term by Decreasing Frequency, within System Organ Class (Safety Analyses Population)**

SOC	*Safety Analyses Population (N=667)*		
PT	*Event*	*n (%)*	*EAIR and 95% CI*
SAE	31	28 (4.20%)	10.91 (7.25, 15.76)
Infections and infestations	8	8 (1.20%)	3.07 (1.33, 6.05)
Pneumonia	4	4 (0.60%)	1.53 (0.42, 3.92)
Appendicitis	1	1 (0.15%)	0.38 (0.01, 2.13)
Influenza	1	1 (0.15%)	0.38 (0.01, 2.13)
Otitis media	1	1 (0.15%)	0.38 (0.01, 2.14)
Tonsillitis	1	1 (0.15%)	0.38 (0.01, 2.13)
Musculoskeletal and connective tissue disorders	8	8 (1.20%)	3.08 (1.33, 6.07)
Rheumatoid arthritis	3	3 (0.45%)	1.15 (0.24, 3.36)
Arthralgia	2	2 (0.30%)	0.77 (0.09, 2.76)
Intervertebral disc protrusion	1	1 (0.15%)	0.38 (0.01, 2.14)
Lumbar spinal stenosis	1	1 (0.15%)	0.38 (0.01, 2.14)
Osteonecrosis	1	1 (0.15%)	0.38 (0.01, 2.13)

Footnote: N, number of patients in population; PT, preferred term; SAE, serious adverse event; SOC, system organ class
n is the number of patients and % is the percentage.
The SOCs are sorted by decreasing number of patients, while the PTs are sorted by decreasing number of patients within SOC.
MedDRA English version 25.1

SOC	*Safety Analyses Population (N=667)*		
PT	*Event*	*n (%)*	*EAIR and 95% CI*
Gastrointestinal disorders	3	3 (0.45%)	1.15 (0.24, 3.36)
Gastritis erosive	1	1 (0.15%)	0.38 (0.01, 2.13)
Ileus paralytic	1	1 (0.15%)	0.38 (0.01, 2.13)
Pancreatitis acute	1	1 (0.15%)	0.38 (0.01, 2.13)
Nervous system disorders	2	2 (0.30%)	0.77 (0.09, 2.77)
Carotid artery aneurysm	1	1 (0.15%)	0.38 (0.01, 2.13)
Optic neuritis	1	1 (0.15%)	0.38 (0.01, 2.14)
Ear and labyrinth disorders	1	1 (0.15%)	0.38 (0.01, 2.13)
Otolithiasis	1	1 (0.15%)	0.38 (0.01, 2.13)
Endocrine disorders	1	1 (0.15%)	0.38 (0.01, 2.14)
Thyroid mass	1	1 (0.15%)	0.38 (0.01, 2.14)

Footnote: N, number of patients in population; PT, preferred term; SAE, serious adverse event; SOC, system organ class
n is the number of patients and % is the percentage.
The SOCs are sorted by decreasing number of patients, while the PTs are sorted by decreasing number of patients within SOC.
MedDRA English version 25.1

SOC / *PT*	*Safety Analyses Population (N=667)*		
	Event	*n (%)*	*EAIR and 95% CI*
Eye disorders	2	1 (0.15%)	0.38 (0.01, 2.14)
Cataract	2	1 (0.15%)	0.38 (0.01, 2.14)
General disorders and administration site conditions	1	1 (0.15%)	0.38 (0.01, 2.13)
Death	1	1 (0.15%)	0.38 (0.01, 2.13)
Hepatobiliary disorders	1	1 (0.15%)	0.38 (0.01, 2.13)
Drug-induced liver injury	1	1 (0.15%)	0.38 (0.01, 2.13)
Injury, poisoning and procedural complications	1	1 (0.15%)	0.38 (0.01, 2.13)
Lumbar vertebral fracture	1	1 (0.15%)	0.38 (0.01, 2.13)
Metabolism and nutrition disorders	1	1 (0.15%)	0.38 (0.01, 2.14)
Hyperkalaemia	1	1 (0.15%)	0.38 (0.01, 2.14)

Footnote: N, number of patients in population; PT, preferred term; SAE, serious adverse event; SOC, system organ class
n is the number of patients and % is the percentage.
The SOCs are sorted by decreasing number of patients, while the PTs are sorted by decreasing number of patients within SOC.
MedDRA English version 25.1

SOC / *PT*	*Safety Analyses Population (N=667)*		
	Event	*n (%)*	*EAIR and 95% CI*
Pregnancy, puerperium and perinatal conditions	1	1 (0.15%)	0.38 (0.01, 2.13)
Abortion threatened	1	1 (0.15%)	0.38 (0.01, 2.13)
Respiratory, thoracic and mediastinal disorders	1	1 (0.15%)	0.38 (0.01, 2.14)
Chronic obstructive pulmonary disease	1	1 (0.15%)	0.38 (0.01, 2.14)

Footnote: N, number of patients in population; PT, preferred term; SAE, serious adverse event; SOC, system organ class
n is the number of patients and % is the percentage.
The SOCs are sorted by decreasing number of patients, while the PTs are sorted by decreasing number of patients within SOC.
MedDRA English version 25.1

Table ANN. 45 **SAEs Related to Study Treatment as Judged by the Investigator over a Period of 24 Weeks — MedDRA Preferred Term by Decreasing Frequency, within System Organ Class (Safety Analyses Population)**

SOC	*Safety Analyses Population (N=667)*	
PT	*Event*	*n (%)*
SAEs Related to Study Treatment	10	10 (1.50%)
Infections and infestations	8	8 (1.20%)
Pneumonia	4	4 (0.60%)
Appendicitis	1	1 (0.15%)
Influenza	1	1 (0.15%)
Otitis media	1	1 (0.15%)
Tonsillitis	1	1 (0.15%)
Hepatobiliary disorders	1	1 (0.15%)
Drug-induced liver injury	1	1 (0.15%)
Musculoskeletal and connective tissue disorders	1	1 (0.15%)
Arthralgia	1	1 (0.15%)

Footnote: N, number of patients in population; PT, preferred term; SAE, serious adverse event; SOC, system organ class
n is the number of patients and % is the percentage.
The SOCs are sorted by decreasing number of patients, while the PTs are sorted by decreasing number of patients within SOC.
SAEs related to study treatment were judged by the investigator.
MedDRA English version 25.1

SOC	*Safety Analyses Population (N=667)*	
PT	*Event*	*n (%)*

Footnote: N, number of patients in population; PT, preferred term; SAE, serious adverse event; SOC, system organ class
n is the number of patients and % is the percentage.
The SOCs are sorted by decreasing number of patients, while the PTs are sorted by decreasing number of patients within SOC.
SAEs related to study treatment were judged by the investigator.
MedDRA English version 25.1

Table ANN. 46 **SAEs over a Period of 24 Weeks — MedDRA Preferred Term by Decreasing Frequency (Safety Analyses Population)**

	Safety Analyses Population (N=667)	
PT	*Event*	*n (%)*
SAE	31	28 (4.20%)
Pneumonia	4	4 (0.60%)
Rheumatoid arthritis	3	3 (0.45%)
Arthralgia	2	2 (0.30%)
Abortion threatened	1	1 (0.15%)
Appendicitis	1	1 (0.15%)
Carotid artery aneurysm	1	1 (0.15%)
Cataract	2	1 (0.15%)
Chronic obstructive pulmonary disease	1	1 (0.15%)
Death	1	1 (0.15%)
Drug-induced liver injury	1	1 (0.15%)
Gastritis erosive	1	1 (0.15%)
Hyperkalaemia	1	1 (0.15%)
Ileus paralytic	1	1 (0.15%)
Influenza	1	1 (0.15%)
Intervertebral disc protrusion	1	1 (0.15%)
Lumbar spinal stenosis	1	1 (0.15%)
Lumbar vertebral fracture	1	1 (0.15%)
Optic neuritis	1	1 (0.15%)
Osteonecrosis	1	1 (0.15%)
Otitis media	1	1 (0.15%)
Otolithiasis	1	1 (0.15%)
Pancreatitis acute	1	1 (0.15%)
Thyroid mass	1	1 (0.15%)
Tonsillitis	1	1 (0.15%)

Footnote: N, number of patients in population; PT, preferred term; SAE, serious adverse event
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

Table ANN. 47 SAEs Related to Study Treatment as Judged by the Investigator over a Period of 24 Weeks — MedDRA Preferred Term by Decreasing Frequency (Safety Analyses Population)

	Safety Analyses Population (N=667)	
PT	*Event*	*n (%)*
SAEs Related to Study Treatment	10	10 (1.50%)
Pneumonia	4	4 (0.60%)
Appendicitis	1	1 (0.15%)
Arthralgia	1	1 (0.15%)
Drug-induced liver injury	1	1 (0.15%)
Influenza	1	1 (0.15%)
Otitis media	1	1 (0.15%)
Tonsillitis	1	1 (0.15%)

Footnote: N, number of patients in population; PT, preferred term; SAE, serious adverse event
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
SAEs related to study treatment were judged by the investigator.
MedDRA English version 25.1

Table ANN. 48 AEs Leading to Drug Adjustment over a Period of 12 Weeks — MedDRA Preferred Term by Decreasing Frequency (Safety Analyses Population)

	Safety Analyses Population (N=667)	
PT	*Event*	*n (%)*
AEs Leading to Drug Adjustment	36	30 (4.50%)
Hepatic function abnormal	3	3 (0.45%)
Pneumonia	4	3 (0.45%)
Herpes zoster	2	2 (0.30%)
Upper respiratory tract infection	2	2 (0.30%)
Acne	1	1 (0.15%)
Arthralgia	1	1 (0.15%)
Blood pressure increased	1	1 (0.15%)
Cataract	1	1 (0.15%)
Chronic obstructive pulmonary disease	1	1 (0.15%)
Diarrhoea	1	1 (0.15%)
Drug-induced liver injury	2	1 (0.15%)
Face oedema	1	1 (0.15%)
Gastrointestinal disorder	1	1 (0.15%)
Herpes simplex	1	1 (0.15%)
Hypocalcaemia	1	1 (0.15%)
Joint swelling	1	1 (0.15%)
Lumbar vertebral fracture	1	1 (0.15%)
Mouth ulceration	1	1 (0.15%)
Oedema peripheral	1	1 (0.15%)
Otitis media	1	1 (0.15%)
Otolithiasis	1	1 (0.15%)
Peripheral swelling	1	1 (0.15%)
Rash	1	1 (0.15%)
Renal failure	1	1 (0.15%)
Renal impairment	1	1 (0.15%)
Thyroid mass	1	1 (0.15%)
Urinary tract infection	1	1 (0.15%)
Weight increased	1	1 (0.15%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

	Safety Analyses Population (N=667)	
PT	*Event*	*n (%)*

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

Table ANN. 49 **AEs Leading to Drug Permanent Discontinuation over a Period of 12 Weeks — MedDRA Preferred Term by Decreasing Frequency (Safety Analyses Population)**

	Safety Analyses Population (N=667)	
PT	*Event*	*n (%)*
AEs leading to drug permanent discontinuation	22	20 (3.00%)
Rheumatoid arthritis	3	3 (0.45%)
Arthralgia	2	2 (0.30%)
Abdominal discomfort	1	1 (0.15%)
Abdominal distension	1	1 (0.15%)
Abdominal pain upper	1	1 (0.15%)
Decreased appetite	1	1 (0.15%)
Dry mouth	1	1 (0.15%)
Haemorrhagic erosive gastritis	1	1 (0.15%)
Headache	1	1 (0.15%)
Hepatic function abnormal	1	1 (0.15%)
Herpes virus infection	1	1 (0.15%)
Joint swelling	1	1 (0.15%)
Mouth ulceration	1	1 (0.15%)
Oral blood blister	1	1 (0.15%)
Pancreatitis acute	1	1 (0.15%)
Pneumonia	1	1 (0.15%)
Pulmonary tuberculosis	1	1 (0.15%)
Tonsillitis	1	1 (0.15%)
Urinary tract infection	1	1 (0.15%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

Table ANN. 50 AEs Leading to Drug Adjustment over a Period of 24 Weeks — MedDRA Preferred Term by Decreasing Frequency (Safety Analyses Population)

	Safety Analyses Population (N=667)	
PT	*Event*	*n (%)*
AEs Leading to Drug Adjustment	45	39 (5.85%)
Herpes zoster	6	6 (0.90%)
Hepatic function abnormal	4	4 (0.60%)
Pneumonia	5	4 (0.60%)
Upper respiratory tract infection	3	3 (0.45%)
Acne	1	1 (0.15%)
Arthralgia	1	1 (0.15%)
Blood pressure increased	1	1 (0.15%)
Cataract	1	1 (0.15%)
Chronic obstructive pulmonary disease	1	1 (0.15%)
Diarrhoea	1	1 (0.15%)
Drug-induced liver injury	2	1 (0.15%)
Face oedema	1	1 (0.15%)
Gastrointestinal disorder	1	1 (0.15%)
Herpes simplex	1	1 (0.15%)
Hypocalcaemia	1	1 (0.15%)
Influenza	1	1 (0.15%)
Joint swelling	1	1 (0.15%)
Lumbar vertebral fracture	1	1 (0.15%)
Mouth ulceration	1	1 (0.15%)
Oedema peripheral	1	1 (0.15%)
Oral mucosal eruption	1	1 (0.15%)
Otitis media	1	1 (0.15%)
Otolithiasis	1	1 (0.15%)
Peripheral swelling	1	1 (0.15%)
Rash	1	1 (0.15%)
Renal failure	1	1 (0.15%)
Renal impairment	1	1 (0.15%)
Thyroid mass	1	1 (0.15%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

	Safety Analyses Population (N=667)	
PT	*Event*	*n (%)*
Urinary tract infection	1	1 (0.15%)
Weight increased	1	1 (0.15%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

Table ANN. 51 AEs Leading to Drug Permanent Discontinuation over a Period of 24 Weeks — MedDRA Preferred Term by Decreasing Frequency (Safety Analyses Population)

	Safety Analyses Population (N=667)	
PT	*Event*	*n (%)*
AEs leading to drug permanent discontinuation	26	24 (3.60%)
Rheumatoid arthritis	4	4 (0.60%)
Arthralgia	3	3 (0.45%)
Abdominal discomfort	1	1 (0.15%)
Abdominal distension	1	1 (0.15%)
Abdominal pain upper	1	1 (0.15%)
Alopecia	1	1 (0.15%)
Decreased appetite	1	1 (0.15%)
Dry mouth	1	1 (0.15%)
Haemorrhagic erosive gastritis	1	1 (0.15%)
Headache	1	1 (0.15%)
Hepatic function abnormal	1	1 (0.15%)
Herpes virus infection	1	1 (0.15%)
Joint swelling	1	1 (0.15%)
Mouth ulceration	1	1 (0.15%)
Oral blood blister	1	1 (0.15%)
Pancreatitis acute	1	1 (0.15%)
Pneumonia	1	1 (0.15%)
Pulmonary tuberculosis	1	1 (0.15%)
Rash	1	1 (0.15%)
Tonsillitis	1	1 (0.15%)
Urinary tract infection	1	1 (0.15%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

Table ANN. 52 AEs with Special Interest: Serious Infection over a Period of 12 Weeks — MedDRA Preferred Term by Decreasing Frequency (Safety Analyses Population)

	Safety Analyses Population (N=667)	
PT	*Event*	*n (%)*
AESI	4	3 (0.45%)
Pneumonia	4	3 (0.45%)

Footnote: AE, adverse event; AESI, AE with special interest; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage. AESI is based on the judgement of investigator recorded in EDC.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

Table ANN. 53 AEs with Special Interest Related to Study Treatment as Judged by the Investigator: Serious Infection over a Period of 12 Weeks — MedDRA Preferred Term by Decreasing Frequency (Safety Analyses Population)

	Safety Analyses Population (N=667)	
PT	*Event*	*n (%)*
AESI Related to Study Treatment	4	3 (0.45%)
Pneumonia	4	3 (0.45%)

Footnote: AE, adverse event; AESI, AE with special interest; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage. AESI is based on the judgement of investigator recorded in EDC.
The PTs are sorted by decreasing number of patients.
AEs related to study treatment were judged by the investigator.
MedDRA English version 25.1

Table ANN. 54 SAEs with Special Interest: Serious Infection over a Period of 12 Weeks — MedDRA Preferred Term by Decreasing Frequency (Safety Analyses Population)

	Safety Analyses Population (N=667)	
PT	*Event*	*n (%)*
SAEs with Special Interest	3	3 (0.45%)
Pneumonia	3	3 (0.45%)

Footnote: N, number of patients in population; PT, preferred term; SAE, serious adverse event
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
SAEs related to study treatment were judged by the investigator.
AE with special interest is based on the judgement of investigator recorded in EDC.
MedDRA English version 25.1

Table ANN. 55 AEs with Special Interest: Serious Infection over a Period of 24 Weeks — MedDRA Preferred Term by Decreasing Frequency (Safety Analyses Population)

	Safety Analyses Population (N=667)	
PT	*Event*	*n (%)*
AESI	5	4 (0.60%)
Pneumonia	4	3 (0.45%)
Appendicitis	1	1 (0.15%)

Footnote: AE, adverse event; AESI, AE with special interest; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage. AESI is based on the judgement of investigator recorded in EDC.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

Table ANN. 56 AEs with Special Interest Related to Study Treatment as Judged by the Investigator: Serious Infection over a Period of 24 Weeks — MedDRA Preferred Term by Decreasing Frequency (Safety Analyses Population)

	Safety Analyses Population (N=667)	
PT	*Event*	*n (%)*
AESI Related to Study Treatment	5	4 (0.60%)
Pneumonia	4	3 (0.45%)
Appendicitis	1	1 (0.15%)

Footnote: AE, adverse event; AESI, AE with special interest; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage. AESI is based on the judgement of investigator recorded in EDC.
The PTs are sorted by decreasing number of patients.
AEs related to study treatment were judged by the investigator.
MedDRA English version 25.1

Table ANN. 57 **SAEs with Special Interest: Serious Infection over a Period of 24 Weeks — MedDRA Preferred Term by Decreasing Frequency (Safety Analyses Population)**

	Safety Analyses Population (N=667)	
PT	*Event*	*n (%)*
SAEs with Special Interest	4	4 (0.60%)
Pneumonia	3	3 (0.45%)
Appendicitis	1	1 (0.15%)

Footnote: N, number of patients in population; PT, preferred term; SAE, serious adverse event
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
SAEs related to study treatment were judged by the investigator.
AE with special interest is based on the judgement of investigator recorded in EDC.
MedDRA English version 25.1

Table ANN. 58 AEs with Special Interest: Hepatotoxicity over a Period of 12 Weeks — MedDRA Preferred Term by Decreasing Frequency (Safety Analyses Population)

	Safety Analyses Population (N=667)	
PT	*Event*	*n (%)*
AESI	17	16 (2.40%)
Hepatic function abnormal	14	14 (2.10%)
Alanine aminotransferase increased	1	1 (0.15%)
Drug-induced liver injury	2	1 (0.15%)

Footnote: AE, adverse event; AESI, AE with special interest; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage. AESI is based on the judgement of investigator recorded in EDC.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

Table ANN. 59 AEs with Special Interest Related to Study Treatment as Judged by the Investigator: Hepatotoxicity over a Period of 12 Weeks — MedDRA Preferred Term by Decreasing Frequency (Safety Analyses Population)

	Safety Analyses Population (N=667)	
PT	*Event*	*n (%)*
AESI Related to Study Treatment	13	12 (1.80%)
Hepatic function abnormal	10	10 (1.50%)
Alanine aminotransferase increased	1	1 (0.15%)
Drug-induced liver injury	2	1 (0.15%)

Footnote: AE, adverse event; AESI, AE with special interest; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage. AESI is based on the judgement of investigator recorded in EDC.
The PTs are sorted by decreasing number of patients.
AEs related to study treatment were judged by the investigator.
MedDRA English version 25.1

Table ANN. 60 SAEs with Special Interest: Hepatotoxicity over a Period of 12 Weeks — MedDRA Preferred Term by Decreasing Frequency (Safety Analyses Population)

	Safety Analyses Population (N=667)	
PT	*Event*	*n (%)*
SAEs with Special Interest	1	1 (0.15%)
Drug-induced liver injury	1	1 (0.15%)

Footnote: N, number of patients in population; PT, preferred term; SAE, serious adverse event
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
SAEs related to study treatment were judged by the investigator.
AE with special interest is based on the judgement of investigator recorded in EDC.
MedDRA English version 25.1

Table ANN. 61 AEs with Special Interest: Hepatotoxicity over a Period of 24 Weeks — MedDRA Preferred Term by Decreasing Frequency (Safety Analyses Population)

	Safety Analyses Population (N=667)	
PT	*Event*	*n (%)*
AESI	26	23 (3.45%)
Hepatic function abnormal	19	17 (2.55%)
Drug-induced liver injury	3	2 (0.30%)
Alanine aminotransferase increased	1	1 (0.15%)
Aspartate aminotransferase increased	1	1 (0.15%)
Blood bilirubin increased	1	1 (0.15%)
Liver function test abnormal	1	1 (0.15%)

Footnote: AE, adverse event; AESI, AE with special interest; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage. AESI is based on the judgement of investigator recorded in EDC.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

Table ANN. 62 AEs with Special Interest Related to Study Treatment as Judged by the Investigator: Hepatotoxicity over a Period of 24 Weeks — MedDRA Preferred Term by Decreasing Frequency (Safety Analyses Population)

	Safety Analyses Population (N=667)	
PT	*Event*	*n (%)*
AESI Related to Study Treatment	20	18 (2.70%)
Hepatic function abnormal	14	13 (1.95%)
Drug-induced liver injury	3	2 (0.30%)
Alanine aminotransferase increased	1	1 (0.15%)
Blood bilirubin increased	1	1 (0.15%)
Liver function test abnormal	1	1 (0.15%)

Footnote: AE, adverse event; AESI, AE with special interest; N, number of patients in population; PT, preferred term

n is the number of patients and % is the percentage. AESI is based on the judgement of investigator recorded in EDC.

The PTs are sorted by decreasing number of patients.

AEs related to study treatment were judged by the investigator.

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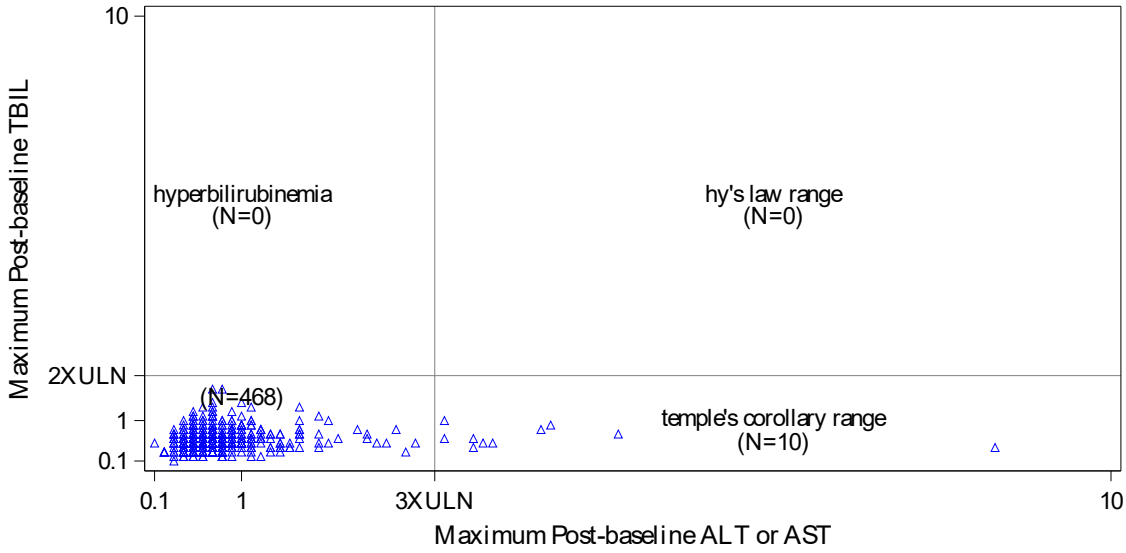
Table ANN. 63 SAEs with Special Interest: Hepatotoxicity over a Period of 24 Weeks — MedDRA Preferred Term by Decreasing Frequency (Safety Analyses Population)

	Safety Analyses Population (N=667)	
PT	*Event*	*n (%)*
SAEs with Special Interest	1	1 (0.15%)
Drug-induced liver injury	1	1 (0.15%)

Footnote: N, number of patients in population; PT, preferred term; SAE, serious adverse event
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
SAEs related to study treatment were judged by the investigator.
AE with special interest is based on the judgement of investigator recorded in EDC.
MedDRA English version 25.1

Table ANN. 64 **Graph of Maximum Post-baseline TBIL vs Maximum Post-baseline ALT or AST (Safety Analyses Population)**



Footnote: X axis: higher one of ALT/ULN and AST/ULN, a reference line at 3 times. Y axis: TBIL/ULN, a reference line at 2 times. One point for one patient.

Table ANN. 65 Summary for Haematology - Safety Analyses Population

Laboratory test (unit)	*visits*		*observed*	*change（post－baseline）*
WBC(10^9/L)	Baseline	n (nmiss)	615 (52)	
		Mean (Std)	6.97 (2.35)	
		Median	6.68	
		Q1, Q3	5.37, 8.12	
		Min, Max	2.10, 18.70	
	4-weeks	n (nmiss)	446 (221)	424 (243)
		Mean (Std)	6.72 (2.27)	-0.24 (2.01)
		Median	6.32	-0.28
		Q1, Q3	5.19, 7.87	-1.45, 1.03
		Min, Max	2.43, 16.93	-9.38, 7.68
	12-weeks	n (nmiss)	387 (280)	368 (299)
		Mean (Std)	6.42 (2.12)	-0.39 (2.07)
		Median	6.07	-0.35
		Q1, Q3	4.88, 7.63	-1.60, 0.77
		Min, Max	2.75, 15.55	-11.26, 7.83
	24-weeks	n (nmiss)	324 (343)	307 (360)
		Mean (Std)	6.17 (1.94)	-0.63 (2.03)
		Median	5.80	-0.60
		Q1, Q3	4.80, 7.17	-1.90, 0.62
		Min, Max	2.56, 14.10	-7.69, 4.83
HGB(g/L)	Baseline	n (nmiss)	613 (54)	
		Mean (Std)	119.86 (16.16)	
		Median	120.00	
		Q1, Q3	110.00, 130.00	
		Min, Max	68.00, 167.00	
	4-weeks	n (nmiss)	446 (221)	424 (243)
		Mean (Std)	121.40 (14.43)	3.05 (10.44)
		Median	122.00	2.00
		Q1, Q3	113.00, 131.00	-3.00, 8.00
		Min, Max	68.00, 169.00	-22.00, 54.00
	12-weeks	n (nmiss)	387 (280)	368 (299)
		Mean (Std)	122.21 (14.82)	2.93 (12.96)
		Median	123.00	3.00
		Q1, Q3	114.00, 131.00	-5.00, 10.00
		Min, Max	67.00, 169.00	-46.00, 56.00
	24-weeks	n (nmiss)	324 (343)	306 (361)
		Mean (Std)	123.84 (14.10)	3.05 (12.43)
		Median	124.00	2.00
		Q1, Q3	117.00, 131.00	-5.00, 11.00
		Min, Max	56.00, 161.00	-32.00, 59.00
PLT(10^9/L)	Baseline	n (nmiss)	615 (52)	
		Mean (Std)	279.72 (93.20)	
		Median	267.00	
		Q1, Q3	221.00, 326.00	

Footnote: nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.
HCT, hematocrit; HGB, hemoglobin; LYM, lymphocyte count; NEUT, neutrophilic granulocyte; PLT, platelet; RBC, red blood cell; WBC, white blood cell.

Laboratory test (unit)	*visits*		*observed*	*change（post－baseline）*
		Min, Max	78.00, 714.00	
	4-weeks	n (nmiss)	446 (221)	424 (243)
		Mean (Std)	277.18 (85.87)	-1.92 (63.67)
		Median	272.00	0.000
		Q1, Q3	217.00, 328.00	-33.00, 37.00
		Min, Max	79.00, 691.00	-311.00, 169.00
	12-weeks	n (nmiss)	387 (280)	368 (299)
		Mean (Std)	282.49 (91.56)	4.63 (72.96)
		Median	271.00	6.00
		Q1, Q3	223.00, 328.00	-33.50, 46.00
		Min, Max	73.00, 937.00	-313.00, 418.00
	24-weeks	n (nmiss)	324 (343)	307 (360)
		Mean (Std)	273.52 (82.16)	-1.20 (72.81)
		Median	265.50	8.00
		Q1, Q3	217.50, 321.00	-39.00, 41.00
		Min, Max	90.00, 735.00	-286.00, 192.00
NEUT(10^9/L)	Baseline	n (nmiss)	607 (60)	
		Mean (Std)	4.72 (2.09)	
		Median	4.34	
		Q1, Q3	3.28, 5.82	
		Min, Max	0.67, 13.52	
	4-weeks	n (nmiss)	446 (221)	421 (246)
		Mean (Std)	4.35 (1.97)	-0.35 (1.89)
		Median	3.87	-0.25
		Q1, Q3	3.07, 5.36	-1.41, 0.76
		Min, Max	0.77, 14.10	-7.13, 7.48
	12-weeks	n (nmiss)	386 (281)	366 (301)
		Mean (Std)	4.14 (1.83)	-0.45 (1.96)
		Median	3.86	-0.31
		Q1, Q3	2.85, 5.09	-1.42, 0.65
		Min, Max	0.82, 12.98	-8.71, 6.53
	24-weeks	n (nmiss)	323 (344)	305 (362)
		Mean (Std)	3.96 (1.65)	-0.59 (1.83)
		Median	3.64	-0.49
		Q1, Q3	2.86, 4.73	-1.60, 0.42
		Min, Max	0.79, 10.83	-7.71, 4.90
LYM(10^9/L)	Baseline	n (nmiss)	607 (60)	
		Mean (Std)	1.63 (0.65)	
		Median	1.56	
		Q1, Q3	1.18, 1.99	
		Min, Max	0.19, 6.43	
	4-weeks	n (nmiss)	446 (221)	421 (246)
		Mean (Std)	1.80 (0.74)	0.18 (0.61)

Footnote: nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.

HCT, hematocrit; HGB, hemoglobin; LYM, lymphocyte count; NEUT, neutrophilic granulocyte; PLT, platelet; RBC, red blood cell; WBC, white blood cell.

Laboratory test (unit)	*visits*		*observed*	*change（post－baseline）*
		Median	1.63	0.12
		Q1, Q3	1.27, 2.20	-0.18, 0.50
		Min, Max	0.45, 5.06	-3.53, 2.67
	12-weeks	n (nmiss)	385 (282)	365 (302)
		Mean (Std)	1.72 (0.65)	0.10 (0.63)
		Median	1.60	0.10
		Q1, Q3	1.29, 2.10	-0.22, 0.40
		Min, Max	0.25, 4.67	-3.19, 2.50
	24-weeks	n (nmiss)	323 (344)	305 (362)
		Mean (Std)	1.69 (0.67)	0.07 (0.68)
		Median	1.58	0.10
		Q1, Q3	1.24, 2.04	-0.27, 0.40
		Min, Max	0.20, 6.26	-2.82, 4.96
RBC(10^12/L)	Baseline	n (nmiss)	611 (56)	
		Mean (Std)	4.18 (0.53)	
		Median	4.17	
		Q1, Q3	3.81, 4.50	
		Min, Max	2.18, 6.28	
	4-weeks	n (nmiss)	446 (221)	422 (245)
		Mean (Std)	4.21 (0.49)	0.07 (0.37)
		Median	4.17	0.04
		Q1, Q3	3.89, 4.50	-0.15, 0.24
		Min, Max	2.76, 5.96	-0.98, 2.45
	12-weeks	n (nmiss)	386 (281)	367 (300)
		Mean (Std)	4.13 (0.52)	-0.03 (0.40)
		Median	4.12	-0.03
		Q1, Q3	3.80, 4.44	-0.30, 0.23
		Min, Max	2.40, 5.79	-1.44, 1.27
	24-weeks	n (nmiss)	324 (343)	307 (360)
		Mean (Std)	4.16 (0.49)	-0.06 (0.37)
		Median	4.11	-0.07
		Q1, Q3	3.86, 4.42	-0.31, 0.18
		Min, Max	2.70, 5.64	-1.23, 1.18
HCT(%)	Baseline	n (nmiss)	611 (56)	
		Mean (Std)	37.13 (4.48)	
		Median	37.10	
		Q1, Q3	34.30, 40.00	
		Min, Max	20.90, 50.90	
	4-weeks	n (nmiss)	445 (222)	421 (246)
		Mean (Std)	37.60 (3.98)	0.80 (3.35)
		Median	37.50	0.50
		Q1, Q3	35.00, 40.40	-1.40, 2.30
		Min, Max	24.50, 48.80	-8.70, 16.20

Footnote: nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.

HCT, hematocrit; HGB, hemoglobin; LYM, lymphocyte count; NEUT, neutrophilic granulocyte; PLT, platelet; RBC, red blood cell; WBC, white blood cell.

Laboratory test (unit)	*visits*		*observed*	*change（post－baseline）*
	12-weeks	n (nmiss)	385 (282)	366 (301)
		Mean (Std)	37.59 (4.02)	0.54 (3.86)
		Median	37.90	0.60
		Q1, Q3	35.20, 39.90	-1.80, 2.90
		Min, Max	25.50, 51.50	-14.40, 14.80
	24-weeks	n (nmiss)	323 (344)	306 (361)
		Mean (Std)	38.14 (3.95)	0.63 (3.70)
		Median	38.20	0.30
		Q1, Q3	35.90, 40.40	-1.90, 2.90
		Min, Max	21.00, 48.80	-11.20, 12.50

Footnote: nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.
HCT, hematocrit; HGB, hemoglobin; LYM, lymphocyte count; NEUT, neutrophilic granulocyte; PLT, platelet; RBC, red blood cell; WBC, white blood cell.

Table ANN. 66 **Summary for Coagulation - Safety Analyses Population**

Laboratory test (unit)	*visits*		*observed*	*change（post－baseline）*
D-Dimer(mg/L)	Baseline	n (nmiss)	116 (551)	
		Mean (Std)	2.28 (2.57)	
		Median	1.40	
		Q1, Q3	0.52, 3.00	
		Min, Max	0.11, 15.19	
	4-weeks	n (nmiss)	19 (648)	11 (656)
		Mean (Std)	1.41 (1.78)	-1.23 (2.30)
		Median	0.65	-1.40
		Q1, Q3	0.32, 1.56	-3.02, -0.03
		Min, Max	0.12, 7.41	-4.84, 3.84
	12-weeks	n (nmiss)	17 (650)	7 (660)
		Mean (Std)	1.48 (3.12)	-1.23 (1.36)
		Median	0.48	-1.28
		Q1, Q3	0.33, 0.97	-2.26, 0.08
		Min, Max	0.12, 13.30	-3.34, 0.33
	24-weeks	n (nmiss)	15 (652)	2 (665)
		Mean (Std)	1.34 (2.29)	-4.79 (2.06)
		Median	0.59	-4.79
		Q1, Q3	0.36, 1.45	-6.25, -3.33
		Min, Max	0.13, 9.31	-6.25, -3.33
PT(second)	Baseline	n (nmiss)	162 (505)	
		Mean (Std)	11.93 (1.57)	
		Median	11.70	
		Q1, Q3	10.90, 12.90	
		Min, Max	9.10, 18.10	
	4-weeks	n (nmiss)	18 (649)	15 (652)
		Mean (Std)	11.45 (1.87)	0.01 (2.79)
		Median	11.10	0.000
		Q1, Q3	10.40, 12.10	-0.70, 0.60
		Min, Max	9.50, 17.80	-5.50, 8.30
	12-weeks	n (nmiss)	15 (652)	9 (658)
		Mean (Std)	11.49 (1.24)	-1.10 (2.52)
		Median	11.60	-0.30
		Q1, Q3	10.50, 12.30	-1.40, 0.30
		Min, Max	9.70, 14.40	-5.50, 1.40
	24-weeks	n (nmiss)	9 (658)	5 (662)
		Mean (Std)	11.36 (1.87)	-0.24 (1.60)
		Median	11.00	-0.40
		Q1, Q3	10.80, 11.70	-1.40, 0.60
		Min, Max	8.80, 15.60	-2.00, 2.00
APTT(second)	Baseline	n (nmiss)	163 (504)	
		Mean (Std)	30.57 (7.29)	
		Median	28.60	
		Q1, Q3	25.90, 35.20	

Footnote: nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.
APTT, activated partial thromboplastin time; INR, international normalized ratio; PT, prothrombin time.

Laboratory test (unit)	*visits*		*observed*	*change（post－baseline）*
		Min, Max	17.60, 81.40	
	4-weeks	n (nmiss)	18 (649)	15 (652)
		Mean (Std)	31.56 (9.27)	1.61 (10.29)
		Median	28.20	1.50
		Q1, Q3	25.90, 36.10	-2.10, 4.00
		Min, Max	20.50, 57.00	-24.40, 25.40
	12-weeks	n (nmiss)	15 (652)	9 (658)
		Mean (Std)	28.41 (6.58)	-4.73 (14.52)
		Median	27.70	0.30
		Q1, Q3	23.70, 34.00	-2.50, 1.70
		Min, Max	18.70, 39.90	-41.50, 6.10
	24-weeks	n (nmiss)	8 (659)	5 (662)
		Mean (Std)	28.71 (6.10)	0.50 (3.58)
		Median	28.45	-1.10
		Q1, Q3	24.35, 33.00	-2.30, 4.00
		Min, Max	19.90, 38.20	-2.80, 4.70
PT INR(NA)	Baseline	n (nmiss)	163 (504)	
		Mean (Std)	0.99 (0.11)	
		Median	0.98	
		Q1, Q3	0.92, 1.05	
		Min, Max	0.78, 1.55	
	4-weeks	n (nmiss)	18 (649)	15 (652)
		Mean (Std)	0.97 (0.14)	-0.009 (0.22)
		Median	0.93	0.000
		Q1, Q3	0.89, 0.99	-0.06, 0.05
		Min, Max	0.82, 1.45	-0.48, 0.63
	12-weeks	n (nmiss)	15 (652)	9 (658)
		Mean (Std)	0.96 (0.07)	-0.04 (0.20)
		Median	0.97	0.02
		Q1, Q3	0.90, 1.03	-0.11, 0.09
		Min, Max	0.85, 1.07	-0.48, 0.17
	24-weeks	n (nmiss)	9 (658)	5 (662)
		Mean (Std)	0.95 (0.07)	0.008 (0.12)
		Median	0.96	0.01
		Q1, Q3	0.92, 1.00	-0.08, 0.05
		Min, Max	0.81, 1.04	-0.12, 0.18

Footnote: nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.
APTT, activated partial thromboplastin time; INR, international normalized ratio; PT, prothrombin time.

Table ANN. 67 Shift Table Between Baseline and Minimum Postbaseline Value: Haematology - Safety Analyses Population

		CTCAE grade of minimum post-baseline value n(%)					
	Baseline CTCAE grade	*0*	*1*	*2*	*3*	*4*	*Total*
WBC (Nx=506)	0	457 (90.32%)	21 (4.15%)	4 (0.79%)	0	0	482 (95.26%)
	1	11 (2.17%)	4 (0.79%)	1 (0.20%)	0	0	16 (3.16%)
	2	6 (1.19%)	2 (0.40%)	0	0	0	8 (1.58%)
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	474 (93.68%)	27 (5.34%)	5 (0.99%)	0	0	506 (100.00%)
HGB (Nx=505)	0	275 (54.46%)	51 (10.10%)	0	0	0	326 (64.55%)
	1	58 (11.49%)	121 (23.96%)	0	0	0	179 (35.45%)
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	333 (65.94%)	172 (34.06%)	0	0	0	505 (100.00%)
PLT (Nx=506)	0	494 (97.63%)	5 (0.99%)	0	0	0	499 (98.62%)
	1	4 (0.79%)	2 (0.40%)	1 (0.20%)	0	0	7 (1.38%)
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	498 (98.42%)	7 (1.38%)	1 (0.20%)	0	0	506 (100.00%)
NEUT (Nx=503)	0	446 (88.67%)	21 (4.17%)	9 (1.79%)	1 (0.20%)	0	477 (94.83%)
	1	12 (2.39%)	1 (0.20%)	2 (0.40%)	1 (0.20%)	0	16 (3.18%)
	2	4 (0.80%)	3 (0.60%)	0	0	0	7 (1.39%)
	3	3 (0.60%)	0	0	0	0	3 (0.60%)
	4	0	0	0	0	0	0
	Total	465 (92.45%)	25 (4.97%)	11 (2.19%)	2 (0.40%)	0	503 (100.00%)
LYM (Nx=503)	0	336 (66.80%)	49 (9.74%)	12 (2.39%)	0	0	397 (78.93%)
	1	31 (6.16%)	43 (8.55%)	6 (1.19%)	1 (0.20%)	0	81 (16.10%)
	2	6 (1.19%)	3 (0.60%)	11 (2.19%)	2 (0.40%)	0	22 (4.37%)
	3	0	1 (0.20%)	2 (0.40%)	0	0	3 (0.60%)
	4	0	0	0	0	0	0
	Total	373 (74.16%)	96 (19.09%)	31 (6.16%)	3 (0.60%)	0	503 (100.00%)

Footnote: CTCAE, common terminology criteria for adverse events; HGB, hemoglobin; LYM, lymphocyte count; NEUT, neutrophilic granulocyte; PLT, platelet; WBC, white blood cell.
The denominators are the number of patients in the cell of total row and column. The grade of minimum post-baseline value take the highest CTCAE grade of all visits, including unscheduled
visit. Patients with baseline and at least one post-baseline value for the variable are included in the analyses. CTCAE use version 5.0.

Table ANN. 68 **Treatment Emergent Abnormalities, Haematology - Safety Analyses Population**

Laboratory test	*Shift between baseline and minimum post-baseline category*	*Safety Analyses Population (N=667) n (%)*
WBC (Nx=506)	Decreased	19 (3.75%)
	Same	461 (91.11%)
	Increased	26 (5.14%)
	Change from < Grade 3 to >= Grade 3	0
HGB (Nx=505)	Decreased	58 (11.49%)
	Same	396 (78.42%)
	Increased	51 (10.10%)
	Change from < Grade 3 to >= Grade 3	0
NEUT (Nx=503)	Decreased	22 (4.37%)
	Same	447 (88.87%)
	Increased	34 (6.76%)
	Change from < Grade 3 to >= Grade 3	2 (0.40%)
LYM (Nx=503)	Decreased	43 (8.55%)
	Same	390 (77.53%)
	Increased	70 (13.92%)
	Change from < Grade 3 to >= Grade 3	3 (0.60%)
PLT (Nx=506)	Decreased	4 (0.79%)
	Same	496 (98.02%)
	Increased	6 (1.19%)
	Change from < Grade 3 to >= Grade 3	0
	Thrombocytosis: Change from <=600X 10^9/L to >600X 10^9/L	2 (0.40%)

Footnote: N, number of patients in the analysis population; n, number of patients in the specified category; Nx, number of patients with baseline and at least one post baseline value.
HGB, hemoglobin; LYM, lymphocyte count; NEUT, neutrophilic granulocyte; PLT, platelet; WBC, white blood cell.
Percentage is calculated by n/Nx*100%
Decreased: minimum post-baseline value category < baseline category.
Same: minimum post-baseline value category = baseline category.
Increased: minimum post-baseline value category > baseline category.

Table ANN. 69 **Summary for Chemistry - Safety Analyses Population**

Laboratory test (unit)	*visits*		*observed*	*change（post－baseline）*
ALT(U/L)	Baseline	n (nmiss)	595 (72)	
		Mean (Std)	20.46 (20.82)	
		Median	15.00	
		Q1, Q3	10.00, 22.00	
		Min, Max	4.00, 248.00	
	4-weeks	n (nmiss)	430 (237)	403 (264)
		Mean (Std)	21.57 (23.83)	0.95 (25.35)
		Median	16.00	1.00
		Q1, Q3	12.00, 23.30	-4.00, 5.00
		Min, Max	3.70, 351.00	-125.00, 334.00
	12-weeks	n (nmiss)	375 (292)	348 (319)
		Mean (Std)	20.08 (13.26)	0.16 (18.36)
		Median	16.00	1.00
		Q1, Q3	12.00, 24.00	-4.00, 6.00
		Min, Max	5.00, 100.00	-141.00, 88.00
	24-weeks	n (nmiss)	311 (356)	291 (376)
		Mean (Std)	22.20 (17.71)	1.26 (20.89)
		Median	18.00	2.00
		Q1, Q3	13.00, 25.00	-3.00, 7.00
		Min, Max	1.00, 149.10	-145.00, 119.00
AST(U/L)	Baseline	n (nmiss)	571 (96)	
		Mean (Std)	23.12 (14.25)	
		Median	19.60	
		Q1, Q3	15.70, 26.00	
		Min, Max	5.00, 145.00	
	4-weeks	n (nmiss)	413 (254)	380 (287)
		Mean (Std)	24.86 (14.68)	1.53 (14.89)
		Median	22.00	2.00
		Q1, Q3	17.00, 28.00	-2.00, 6.00
		Min, Max	7.00, 172.00	-96.00, 146.00
	12-weeks	n (nmiss)	355 (312)	323 (344)
		Mean (Std)	25.66 (11.87)	2.66 (14.18)
		Median	23.63	3.00
		Q1, Q3	18.70, 29.00	-2.00, 8.00
		Min, Max	5.70, 123.00	-97.00, 107.00
	24-weeks	n (nmiss)	300 (367)	276 (391)
		Mean (Std)	27.33 (15.70)	3.53 (14.85)
		Median	24.00	3.00
		Q1, Q3	19.20, 30.00	-1.00, 8.93
		Min, Max	10.00, 166.10	-96.00, 95.00
ALP(U/L)	Baseline	n (nmiss)	411 (256)	
		Mean (Std)	84.32 (28.27)	
		Median	80.00	

Footnote: nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.

A/G, albumin/ globulin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; Cr, creatinine; DBIL, direct bilirubin; GGT, gamma-glutamyl transpeptidase; LDH, lactate dehydrogenase; PA, pre-albumin; TBIL, total bilirubin; TP, total protein; UA, uric acid.

Laboratory test (unit)	*visits*		*observed*	*change（post－baseline）*
		Q1, Q3	65.00, 100.00	
		Min, Max	29.00, 265.00	
	4-weeks	n (nmiss)	271 (396)	234 (433)
		Mean (Std)	84.65 (32.88)	1.70 (22.19)
		Median	79.00	1.00
		Q1, Q3	65.00, 99.00	-9.70, 9.00
		Min, Max	31.00, 312.00	-75.00, 161.00
	12-weeks	n (nmiss)	247 (420)	210 (457)
		Mean (Std)	78.31 (25.75)	-4.42 (19.82)
		Median	76.00	-4.00
		Q1, Q3	60.00, 91.00	-15.00, 6.30
		Min, Max	14.00, 165.00	-71.00, 71.00
	24-weeks	n (nmiss)	198 (469)	171 (496)
		Mean (Std)	75.42 (23.39)	-6.43 (20.79)
		Median	72.40	-5.90
		Q1, Q3	62.00, 88.00	-18.00, 8.00
		Min, Max	13.00, 166.00	-88.20, 66.00
GGT(U/L)	Baseline	n (nmiss)	413 (254)	
		Mean (Std)	26.66 (29.47)	
		Median	18.36	
		Q1, Q3	13.00, 27.00	
		Min, Max	1.00, 333.00	
	4-weeks	n (nmiss)	256 (411)	224 (443)
		Mean (Std)	25.52 (27.35)	0.02 (19.18)
		Median	18.00	0.000
		Q1, Q3	13.00, 25.00	-3.00, 3.70
		Min, Max	6.00, 236.00	-98.00, 144.80
	12-weeks	n (nmiss)	240 (427)	204 (463)
		Mean (Std)	24.17 (20.58)	-0.29 (15.61)
		Median	17.95	0.000
		Q1, Q3	13.00, 25.25	-3.95, 2.95
		Min, Max	8.00, 128.10	-59.90, 86.10
	24-weeks	n (nmiss)	183 (484)	161 (506)
		Mean (Std)	21.95 (15.36)	-1.69 (13.02)
		Median	17.70	0.000
		Q1, Q3	13.00, 25.10	-5.00, 4.00
		Min, Max	2.00, 124.00	-63.60, 35.00
ALB(g/L)	Baseline	n (nmiss)	546 (121)	
		Mean (Std)	39.57 (5.12)	
		Median	40.20	
		Q1, Q3	36.40, 42.90	
		Min, Max	19.40, 69.40	

Footnote: nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.
A/G, albumin/ globulin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; Cr, creatinine; DBIL, direct bilirubin; GGT, gamma-glutamyl transpeptidase; LDH, lactate dehydrogenase;

PA, pre-albumin; TBIL, total bilirubin; TP, total protein; UA, uric acid.

Laboratory test (unit)	*visits*		*observed*	*change（post－baseline）*
	4-weeks	n (nmiss)	372 (295)	337 (330)
		Mean (Std)	41.74 (4.00)	2.37 (4.06)
		Median	42.00	2.30
		Q1, Q3	39.60, 44.40	0.000, 4.90
		Min, Max	21.60, 51.50	-25.60, 14.50
	12-weeks	n (nmiss)	328 (339)	295 (372)
		Mean (Std)	42.99 (3.76)	3.08 (4.52)
		Median	43.40	2.70
		Q1, Q3	40.60, 45.65	0.000, 5.80
		Min, Max	28.00, 50.80	-24.70, 16.00
	24-weeks	n (nmiss)	269 (398)	246 (421)
		Mean (Std)	43.20 (3.63)	3.14 (4.57)
		Median	43.50	2.80
		Q1, Q3	41.00, 45.50	0.000, 5.94
		Min, Max	23.40, 51.48	-14.90, 16.70
TBIL(μmol/L)	Baseline	n (nmiss)	532 (135)	
		Mean (Std)	10.30 (4.59)	
		Median	9.60	
		Q1, Q3	7.17, 12.55	
		Min, Max	2.00, 30.00	
	4-weeks	n (nmiss)	391 (276)	364 (303)
		Mean (Std)	10.48 (4.45)	0.38 (4.02)
		Median	9.74	0.20
		Q1, Q3	7.30, 12.80	-1.90, 2.62
		Min, Max	2.00, 26.00	-18.90, 13.90
	12-weeks	n (nmiss)	337 (330)	307 (360)
		Mean (Std)	11.41 (4.58)	1.15 (4.08)
		Median	10.72	1.12
		Q1, Q3	8.40, 13.90	-1.16, 3.20
		Min, Max	3.00, 38.23	-16.20, 17.50
	24-weeks	n (nmiss)	276 (391)	258 (409)
		Mean (Std)	11.58 (4.72)	1.16 (4.52)
		Median	10.70	1.06
		Q1, Q3	8.30, 13.90	-1.40, 4.10
		Min, Max	2.60, 36.00	-14.20, 22.40
DBIL(μmol/L)	Baseline	n (nmiss)	525 (142)	
		Mean (Std)	3.16 (1.65)	
		Median	2.88	
		Q1, Q3	2.00, 3.89	
		Min, Max	0.10, 11.40	
	4-weeks	n (nmiss)	379 (288)	351 (316)
		Mean (Std)	3.10 (1.48)	0.07 (1.47)
		Median	2.80	0.000

Footnote: nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.
A/G, albumin/ globulin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; Cr, creatinine; DBIL, direct bilirubin; GGT, gamma-glutamyl transpeptidase; LDH, lactate dehydrogenase;

PA, pre-albumin; TBIL, total bilirubin; TP, total protein; UA, uric acid.

Laboratory test (unit)	*visits*		*observed*	*change（post－baseline）*
		Q1, Q3	2.10, 3.98	-0.70, 0.78
		Min, Max	0.16, 8.20	-6.70, 5.20
	12-weeks	n (nmiss)	330 (337)	300 (367)
		Mean (Std)	3.26 (1.55)	0.07 (1.36)
		Median	3.00	0.10
		Q1, Q3	2.10, 4.00	-0.70, 0.72
		Min, Max	0.29, 9.20	-5.00, 4.60
	24-weeks	n (nmiss)	266 (401)	247 (420)
		Mean (Std)	3.28 (1.52)	0.08 (1.48)
		Median	2.94	0.20
		Q1, Q3	2.20, 4.10	-0.70, 0.80
		Min, Max	0.49, 9.20	-5.30, 4.40
Cr(μmol/L)	Baseline	n (nmiss)	526 (141)	
		Mean (Std)	59.65 (37.71)	
		Median	56.00	
		Q1, Q3	49.00, 65.00	
		Min, Max	23.00, 849.10	
	4-weeks	n (nmiss)	386 (281)	333 (334)
		Mean (Std)	60.04 (15.78)	2.89 (8.83)
		Median	57.90	3.00
		Q1, Q3	49.00, 69.00	-2.00, 7.30
		Min, Max	29.00, 169.00	-35.00, 34.00
	12-weeks	n (nmiss)	330 (337)	278 (389)
		Mean (Std)	61.71 (16.13)	3.46 (8.78)
		Median	60.55	3.00
		Q1, Q3	51.00, 69.30	-2.00, 9.00
		Min, Max	27.00, 186.00	-30.00, 29.00
	24-weeks	n (nmiss)	280 (387)	238 (429)
		Mean (Std)	62.40 (15.61)	4.75 (9.46)
		Median	60.00	3.84
		Q1, Q3	51.00, 69.95	-0.83, 10.00
		Min, Max	37.00, 159.00	-27.00, 32.00
Urea(mmol/L)	Baseline	n (nmiss)	395 (272)	
		Mean (Std)	5.06 (2.25)	
		Median	4.70	
		Q1, Q3	3.81, 5.95	
		Min, Max	1.59, 35.28	
	4-weeks	n (nmiss)	266 (401)	225 (442)
		Mean (Std)	5.06 (1.68)	0.13 (1.60)
		Median	4.88	0.14
		Q1, Q3	3.90, 5.90	-0.75, 1.00
		Min, Max	1.88, 11.60	-4.19, 7.03

Footnote: nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.
A/G, albumin/ globulin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; Cr, creatinine; DBIL, direct bilirubin; GGT, gamma-glutamyl transpeptidase; LDH, lactate dehydrogenase;

PA, pre-albumin; TBIL, total bilirubin; TP, total protein; UA, uric acid.

Laboratory test (unit)	*visits*		*observed*	*change（post－baseline）*
	12-weeks	n (nmiss)	220 (447)	188 (479)
		Mean (Std)	5.01 (1.53)	-0.06 (1.57)
		Median	4.86	-0.03
		Q1, Q3	3.90, 5.82	-0.91, 0.90
		Min, Max	1.65, 10.36	-4.70, 4.72
	24-weeks	n (nmiss)	188 (479)	165 (502)
		Mean (Std)	5.06 (1.67)	-0.11 (1.82)
		Median	4.93	-0.10
		Q1, Q3	3.87, 5.90	-1.02, 0.85
		Min, Max	1.90, 10.84	-6.51, 6.29
TP(g/L)	Baseline	n (nmiss)	502 (165)	
		Mean (Std)	69.98 (7.00)	
		Median	70.60	
		Q1, Q3	65.20, 75.00	
		Min, Max	42.70, 90.00	
	4-weeks	n (nmiss)	353 (314)	315 (352)
		Mean (Std)	71.60 (6.02)	1.55 (6.13)
		Median	71.90	1.20
		Q1, Q3	67.90, 75.40	-1.90, 4.40
		Min, Max	48.70, 89.70	-21.30, 36.20
	12-weeks	n (nmiss)	316 (351)	277 (390)
		Mean (Std)	72.10 (5.51)	1.56 (6.61)
		Median	72.15	1.00
		Q1, Q3	68.30, 76.00	-2.40, 5.00
		Min, Max	56.40, 88.50	-14.80, 38.10
	24-weeks	n (nmiss)	259 (408)	233 (434)
		Mean (Std)	73.19 (5.55)	2.17 (6.03)
		Median	73.00	1.60
		Q1, Q3	69.90, 76.30	-1.80, 5.50
		Min, Max	59.30, 92.90	-19.30, 23.00
A/G(NA)	Baseline	n (nmiss)	483 (184)	
		Mean (Std)	1.34 (0.29)	
		Median	1.30	
		Q1, Q3	1.12, 1.50	
		Min, Max	0.64, 2.46	
	4-weeks	n (nmiss)	337 (330)	300 (367)
		Mean (Std)	1.46 (0.29)	0.13 (0.21)
		Median	1.44	0.10
		Q1, Q3	1.25, 1.60	0.000, 0.25
		Min, Max	0.85, 2.60	-0.60, 0.90
	12-weeks	n (nmiss)	303 (364)	267 (400)
		Mean (Std)	1.54 (0.33)	0.20 (0.29)
		Median	1.50	0.20

Footnote: nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.
A/G, albumin/ globulin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; Cr, creatinine; DBIL, direct bilirubin; GGT, gamma-glutamyl transpeptidase; LDH, lactate dehydrogenase;

PA, pre-albumin; TBIL, total bilirubin; TP, total protein; UA, uric acid.

Laboratory test (unit)	*visits*		*observed*	*change（post－baseline）*
		Q1, Q3	1.35, 1.72	0.000, 0.38
		Min, Max	0.70, 3.00	-0.63, 1.25
	24-weeks	n (nmiss)	244 (423)	222 (445)
		Mean (Std)	1.50 (0.29)	0.16 (0.28)
		Median	1.50	0.13
		Q1, Q3	1.30, 1.67	0.000, 0.33
		Min, Max	0.61, 2.29	-0.72, 1.03
LDH(U/L)	Baseline	n (nmiss)	196 (471)	
		Mean (Std)	194.34 (43.66)	
		Median	189.70	
		Q1, Q3	163.50, 216.00	
		Min, Max	105.76, 348.00	
	4-weeks	n (nmiss)	47 (620)	25 (642)
		Mean (Std)	210.72 (68.11)	15.37 (58.19)
		Median	195.00	13.00
		Q1, Q3	170.84, 237.00	-2.00, 38.00
		Min, Max	134.00, 527.00	-193.00, 153.00
	12-weeks	n (nmiss)	40 (627)	24 (643)
		Mean (Std)	231.12 (58.48)	42.10 (52.24)
		Median	221.50	34.00
		Q1, Q3	187.00, 274.20	13.60, 71.50
		Min, Max	153.00, 373.00	-52.00, 147.00
	24-weeks	n (nmiss)	43 (624)	25 (642)
		Mean (Std)	208.92 (56.53)	28.43 (33.64)
		Median	211.00	25.00
		Q1, Q3	191.00, 249.00	6.87, 46.00
		Min, Max	2.90, 307.00	-54.44, 90.00
CK(U/L)	Baseline	n (nmiss)	168 (499)	
		Mean (Std)	52.65 (36.10)	
		Median	42.00	
		Q1, Q3	27.00, 71.14	
		Min, Max	5.68, 200.50	
	4-weeks	n (nmiss)	42 (625)	23 (644)
		Mean (Std)	79.31 (50.75)	28.44 (32.25)
		Median	64.50	18.00
		Q1, Q3	43.00, 99.00	2.30, 50.00
		Min, Max	18.00, 256.00	-6.00, 112.54
	12-weeks	n (nmiss)	30 (637)	18 (649)
		Mean (Std)	121.47 (92.29)	54.54 (62.55)
		Median	91.00	35.50
		Q1, Q3	54.00, 157.00	4.00, 81.00
		Min, Max	23.30, 447.00	-7.10, 215.85

Footnote: nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.
A/G, albumin/ globulin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; Cr, creatinine; DBIL, direct bilirubin; GGT, gamma-glutamyl transpeptidase; LDH, lactate dehydrogenase;

PA, pre-albumin; TBIL, total bilirubin; TP, total protein; UA, uric acid.

Laboratory test (unit)	*visits*		*observed*	*change（post－baseline）*
	24-weeks	n (nmiss)	31 (636)	20 (647)
		Mean (Std)	102.09 (55.49)	44.89 (47.80)
		Median	82.00	42.50
		Q1, Q3	60.00, 134.00	8.65, 71.50
		Min, Max	27.44, 237.00	-28.00, 150.00
UA(μmol/L)	Baseline	n (nmiss)	460 (207)	
		Mean (Std)	263.80 (85.33)	
		Median	259.50	
		Q1, Q3	202.75, 318.00	
		Min, Max	55.00, 720.00	
	4-weeks	n (nmiss)	326 (341)	278 (389)
		Mean (Std)	264.24 (87.49)	7.39 (60.14)
		Median	257.00	6.00
		Q1, Q3	204.00, 321.00	-26.00, 40.00
		Min, Max	79.00, 683.00	-167.00, 229.70
	12-weeks	n (nmiss)	279 (388)	236 (431)
		Mean (Std)	267.00 (82.49)	6.99 (58.40)
		Median	263.00	6.65
		Q1, Q3	207.00, 312.00	-30.00, 42.01
		Min, Max	94.00, 628.00	-153.00, 173.00
	24-weeks	n (nmiss)	241 (426)	205 (462)
		Mean (Std)	271.40 (79.10)	16.11 (59.60)
		Median	266.00	10.00
		Q1, Q3	222.00, 321.00	-19.00, 50.00
		Min, Max	80.00, 585.80	-138.00, 232.00
PA(mg/L)	Baseline	n (nmiss)	187 (480)	
		Mean (Std)	224.39 (69.17)	
		Median	215.80	
		Q1, Q3	177.00, 269.70	
		Min, Max	68.00, 432.00	
	4-weeks	n (nmiss)	86 (581)	65 (602)
		Mean (Std)	241.28 (61.78)	19.20 (52.47)
		Median	240.00	25.00
		Q1, Q3	197.80, 280.80	-15.00, 56.50
		Min, Max	123.00, 410.21	-106.00, 135.43
	12-weeks	n (nmiss)	88 (579)	60 (607)
		Mean (Std)	250.39 (59.13)	11.90 (69.34)
		Median	240.00	9.50
		Q1, Q3	207.15, 288.00	-28.30, 50.50
		Min, Max	115.50, 417.00	-159.80, 262.30
	24-weeks	n (nmiss)	69 (598)	51 (616)
		Mean (Std)	242.50 (49.15)	8.02 (50.88)
		Median	233.00	3.50

Footnote: nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.
A/G, albumin/ globulin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; Cr, creatinine; DBIL, direct bilirubin; GGT, gamma-glutamyl transpeptidase; LDH, lactate dehydrogenase;

PA, pre-albumin; TBIL, total bilirubin; TP, total protein; UA, uric acid.

Laboratory test (unit)	*visits*		*observed*	*change（post－baseline）*
		Q1, Q3	210.00, 290.00	-16.60, 43.00
		Min, Max	147.60, 361.00	-101.20, 114.00
Ca(mmol/L)	Baseline	n (nmiss)	290 (377)	
		Mean (Std)	2.25 (0.14)	
		Median	2.26	
		Q1, Q3	2.16, 2.35	
		Min, Max	1.61, 2.65	
	4-weeks	n (nmiss)	101 (566)	81 (586)
		Mean (Std)	2.29 (0.13)	0.006 (0.12)
		Median	2.29	0.000
		Q1, Q3	2.20, 2.37	-0.05, 0.06
		Min, Max	1.79, 2.65	-0.51, 0.26
	12-weeks	n (nmiss)	80 (587)	62 (605)
		Mean (Std)	2.31 (0.15)	0.04 (0.14)
		Median	2.30	0.02
		Q1, Q3	2.24, 2.39	-0.06, 0.13
		Min, Max	1.82, 2.77	-0.28, 0.39
	24-weeks	n (nmiss)	83 (584)	67 (600)
		Mean (Std)	2.33 (0.13)	0.03 (0.15)
		Median	2.33	0.03
		Q1, Q3	2.24, 2.43	-0.07, 0.13
		Min, Max	1.96, 2.67	-0.30, 0.39
P(mmol/L)	Baseline	n (nmiss)	180 (487)	
		Mean (Std)	1.16 (0.23)	
		Median	1.13	
		Q1, Q3	1.02, 1.27	
		Min, Max	0.75, 3.02	
	4-weeks	n (nmiss)	61 (606)	36 (631)
		Mean (Std)	1.12 (0.21)	-0.05 (0.23)
		Median	1.17	-0.07
		Q1, Q3	0.98, 1.26	-0.17, 0.09
		Min, Max	0.55, 1.59	-0.73, 0.45
	12-weeks	n (nmiss)	51 (616)	32 (635)
		Mean (Std)	1.14 (0.17)	-0.06 (0.22)
		Median	1.14	-0.08
		Q1, Q3	1.02, 1.27	-0.21, 0.09
		Min, Max	0.79, 1.66	-0.54, 0.58
	24-weeks	n (nmiss)	50 (617)	34 (633)
		Mean (Std)	1.15 (0.19)	-0.03 (0.19)
		Median	1.18	-0.05
		Q1, Q3	1.03, 1.31	-0.14, 0.12
		Min, Max	0.72, 1.48	-0.33, 0.36

Footnote: nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.
A/G, albumin/ globulin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; Cr, creatinine; DBIL, direct bilirubin; GGT, gamma-glutamyl transpeptidase; LDH, lactate dehydrogenase;

PA, pre-albumin; TBIL, total bilirubin; TP, total protein; UA, uric acid.

Table ANN. 70 **Shift Table Between Baseline and Maximum Postbaseline Value: ALT, AST, ALP and TBIL (Safety Analyses Population) — Parameter: ALT**

		Grade of maximum post-baseline value n (%)						
	Baseline grade	*<=ULN*	*>1 to <3X ULN*	*>=3 to <5X ULN*	*>=5 to <10X ULN*	*>=10 to <20X ULN*	*>=20X ULN*	*Total*
ALT (Nx=488)	<=ULN	416 (85.25%)	34 (6.97%)	4 (0.82%)	1 (0.20%)	0	0	455 (93.24%)
	>1 to <3X ULN	14 (2.87%)	13 (2.66%)	1 (0.20%)	0	0	0	28 (5.74%)
	>=3 to <5X ULN	1 (0.20%)	3 (0.61%)	1 (0.20%)	0	0	0	5 (1.02%)
	>=5 to <10X ULN	0	0	0	0	0	0	0
	>=10 to <20X ULN	0	0	0	0	0	0	0
	>=20X ULN	0	0	0	0	0	0	0
	Total	431 (88.32%)	50 (10.25%)	6 (1.23%)	1 (0.20%)	0	0	488 (100.00%)

Footnote: ALT, alanine aminotransferase; Nx, number of patients in denominator.
The denominators are the number of patients in the cell of total row and column. The grade of maximum post-baseline value take the highest grade of all visits, including unscheduled visit.
ULN is upper limit normal. Patients with baseline and at least one post-baseline value for the variable are included in the analyses.

Table ANN. 71 **Shift Table Between Baseline and Maximum Postbaseline Value: ALT, AST, ALP, and TBIL (Safety Analyses Population) — Parameter: AST**

		Grade of maximum post-baseline value n (%)						
	Baseline grade	*<=ULN*	*>1 to <3X ULN*	*>=3 to <5X ULN*	*>=5 to <10X ULN*	*>=10 to <20X ULN*	*>=20X ULN*	*Total*
AST (Nx=462)	<=ULN	369 (79.87%)	46 (9.96%)	3 (0.65%)	0	0	0	418 (90.48%)
	>1 to <3X ULN	19 (4.11%)	21 (4.55%)	1 (0.22%)	0	0	0	41 (8.87%)
	>=3 to <5X ULN	2 (0.43%)	0	1 (0.22%)	0	0	0	3 (0.65%)
	>=5 to <10X ULN	0	0	0	0	0	0	0
	>=10 to <20X ULN	0	0	0	0	0	0	0
	>=20X ULN	0	0	0	0	0	0	0
	Total	390 (84.42%)	67 (14.50%)	5 (1.08%)	0	0	0	462 (100.00%)

Footnote: AST, aspartate aminotransferase; Nx, number of patients in denominator.
The denominators are the number of patients in the cell of total row and column. The grade of maximum post-baseline value take the highest grade of all visits, including unscheduled visit.
ULN is upper limit normal. Patients with baseline and at least one post-baseline value for the variable are included in the analyses.

Table ANN. 72 **Shift Table Between Baseline and Maximum Postbaseline Value: ALT, AST, ALP, and TBIL (Safety Analyses Population) — Parameter: ALP**

		Grade of maximum post-baseline value n (%)			
	Baseline grade	*<=ULN*	*>1 to <1.5X ULN*	*>=1.5X ULN*	*Total*
ALP (Nx=313)	<=ULN	285 (91.05%)	12 (3.83%)	1 (0.32%)	298 (95.21%)
	>1 to <1.5X ULN	6 (1.92%)	6 (1.92%)	3 (0.96%)	15 (4.79%)
	>=1.5X ULN	0	0	0	0
	Total	291 (92.97%)	18 (5.75%)	4 (1.28%)	313 (100.00%)

Footnote: ALP, a lkaline phosphatase; Nx, number of patients in denominator.
The denominators are the number of patients in the cell of total row and column. The grade of maximum post-baseline value take the highest grade of all visits, including unscheduled visit.
ULN is upper limit normal. Patients with baseline and at least one post-baseline value for the variable are included in the analyses.

Table ANN. 73 Shift Table Between Baseline and Maximum Postbaseline Value: ALT, AST, ALP and TBIL (Safety Analyses Population) — Parameter: TBIL

		Grade of maximum post-baseline value n (%)			
	Baseline grade	*<=ULN*	*>1 to <2X ULN*	*>=2X ULN*	*Total*
TBIL (Nx=435)	<=ULN	398 (91.49%)	23 (5.29%)	0	421 (96.78%)
	>1 to <2X ULN	10 (2.30%)	4 (0.92%)	0	14 (3.22%)
	>=2X ULN	0	0	0	0
	Total	408 (93.79%)	27 (6.21%)	0	435 (100.00%)

Footnote: Nx, number of patients in denominator; TBIL, total bilirubin.
The denominators are the number of patients in the cell of total row and column. The grade of maximum post-baseline value take the highest grade of all visits, including unscheduled visit.
ULN is upper limit normal. Patients with baseline and at least one post-baseline value for the variable are included in the analyses.

Table ANN. 74 **Shift Table Between Baseline and Minimum Postbaseline Value: Cr (Safety Analyses Population)**

		CTCAE grade of maximum post-baseline value n (%)					
	Baseline CTCAE grade	*0*	*1*	*2*	*3*	*4*	*Total*
Cr (Nx=408)	0	382 (93.63%)	15 (3.68%)	0	0	0	397 (97.30%)
	1	3 (0.74%)	5 (1.23%)	2 (0.49%)	0	0	10 (2.45%)
	2	0	0	1 (0.25%)	0	0	1 (0.25%)
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	385 (94.36%)	20 (4.90%)	3 (0.74%)	0	0	408 (100.00%)

Footnote: Cr, creatinine; CTCAE, common terminology criteria for adverse events; Nx, number of patients in denominator.
The denominators are the number of patients in the cell of total row and column. The grade of minimum post-baseline value take the highest CTCAE grade of all visits, including unscheduled visit.
Patients with baseline and at least one post-baseline value for the variable are included in the analyses. CTCAE use version 5.0.

Table ANN. 75 **Shift Table Between Baseline and Minimum Postbaseline Value: CPK (Safety Analyses Population)**

		CTCAE grade of maximum post-baseline value n (%)					
	Baseline CTCAE grade	*0*	*1*	*2*	*3*	*4*	*Total*
CPK (Nx=40)	0	36 (90.00%)	4 (10.00%)	0	0	0	40 (100.00%)
	1	0	0	0	0	0	0
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	Total	36 (90.00%)	4 (10.00%)	0	0	0	40 (100.00%)

Footnote: CPK, creatine phosphokinase; CTCAE, common terminology criteria for adverse events; Nx, number of patients in denominator.
The denominators are the number of patients in the cell of total row and column. The grade of minimum post-baseline value take the highest CTCAE grade of all visits, including unscheduled visit.
Patients with baseline and at least one post-baseline value for the variable are included in the analyses. CTCAE use version 5.0.

Table ANN. 76 **Treatment Emergent Abnormalities, Chemistry - Safety Analyses Population**

Laboratory test	*Shift between baseline and maximum post-baseline category*	*Safety Analyses Population (N=667) n (%)*
ALT (Nx=488)	Decreased	18 (3.69%)
	Same	430 (88.11%)
	Increased	40 (8.20%)
	Change from <3X ULN to >=3X ULN	6 (1.23%)
	Change from <5X ULN to >=5X ULN	1 (0.20%)
AST (Nx=462)	Decreased	21 (4.55%)
	Same	391 (84.63%)
	Increased	50 (10.82%)
	Change from <3X ULN to >=3X ULN	4 (0.87%)
	Change from <5X ULN to >=5X ULN	0
ALP (Nx=313)	Decreased	6 (1.92%)
	Same	291 (92.97%)
	Increased	16 (5.11%)
	Change from <1.5X ULN to >=1.5X ULN	4 (1.28%)
TBIL (Nx=435)	Decreased	10 (2.30%)
	Same	402 (92.41%)
	Increased	23 (5.29%)
	Change from <2X ULN to >=2X ULN	0
Cr (Nx=408)	Decreased	3 (0.74%)
	Same	388 (95.10%)
	Increased	17 (4.17%)
	Change from < Grade 3 to >= Grade 3	0
CK (Nx=40)	Decreased	0
	Same	36 (90.00%)
	Increased	4 (10.00%)
	Change from < Grade 3 to >= Grade 3	0

Footnote: N, number of patients in the analysis population; n, number of patients in the specified category; Nx, number of patients with baseline and at least one post baseline value.
ALP, a lkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; Cr, creatinine; TBIL, total bilirubin.
Percentage is calculated by n/Nx*100%
Decreased: maximum post-baseline value category < baseline category.
Same: maximum post-baseline value category = baseline category.
Increased: maximum post-baseline value category > baseline category.

Table ANN. 77 Treatment Emergent Abnormalities, Urinalysis - Safety Analyses Population

Laboratory test	*Shift between baseline and maximum post-baseline category*	*Safety Analyses Population (N=667) n (%)*
URBC (Nx=74)	Decreased	3 (4.05%)
	Same	58 (78.38%)
	Increased	13 (17.57%)
ULEU (Nx=65)	Decreased	8 (12.31%)
	Same	45 (69.23%)
	Increased	12 (18.46%)
PRO (Nx=1)	Decreased	0
	Same	1 (100.00%)
	Increased	0

Footnote: N, number of patients in the analysis population; n, number of patients in the specified category; Nx, number of patients with baseline and at least one post baseline value.
PRO, urine protein; ULEU, urine leukocytes; URBC, urine red blood cell.
Percentage is calculated by n/Nx*100%.
Decreased: maximum post-baseline value category < baseline category.
Same: maximum post-baseline value category = baseline category.
Increased: maximum post-baseline value category > baseline category.
The category order is abnormal and clinically significant > abnormal but no clinically significant > normal. Not done are not analyzed.

Effectiveness

Table ANN. 78 DAS28-CRP Score - Effectiveness Analyses Population

	visit		*observed*	*change（post－baseline）*
DAS28-CRP Score	Baseline	n (nmiss)	502 (12)	
		Mean (Std)	4.68 (1.84)	
		Median	4.82	
		Q1, Q3	3.73, 6.06	
		Min, Max	0.25, 8.02	
	12-weeks	n (nmiss)	417 (97)	413 (101)
		Mean (Std)	3.08 (1.67)	-1.55 (1.55)
		Median	3.00	-1.31
		Q1, Q3	1.86, 4.22	-2.68, -0.32
		Min, Max	0.11, 7.88	-5.71, 3.58
		P value		<.0001[b]
	24-weeks	n (nmiss)	353 (161)	350 (164)
		Mean (Std)	2.72 (1.51)	-1.96 (1.67)
		Median	2.54	-1.92
		Q1, Q3	1.65, 3.66	-3.18, -0.59
		Min, Max	0.11, 7.12	-6.01, 2.58
		P value		<.0001[b]

Footnote: CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.

Table ANN. 79 **DAS28-CRP Score Shift Table - Effectiveness Analyses Population**

Visit	*<2.6*	*>=2.6 to <=3.2*	*>3.2 to <=5.1*	*>5.1*	*<=3.2*	*>3.2*	*Non-missing Total*
Baseline	64 (12.75%)	20 (3.98%)	206 (41.04%)	212 (42.23%)	84 (16.73%)	418 (83.27%)	502 (100.00%)
12-weeks	174 (41.73%)	52 (12.47%)	135 (32.37%)	56 (13.43%)	226 (54.20%)	191 (45.80%)	417 (100.00%)
24-weeks	185 (52.41%)	50 (14.16%)	88 (24.93%)	30 (8.50%)	235 (66.57%)	118 (33.43%)	353 (100.00%)

Footnote: CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count.
Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 80 **DAS28-CRP Score Mixed-Effects Model Analysis - Effectiveness Analyses Population**

variable	*Effectiveness Analyses Population (N=514)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.56	0.036	<.0001	-0.6327,-0.4920
week 12	0.53	0.173	0.0023	0.1908,0.8694
week 24	0.68	0.179	0.0002	0.3274,1.0325
baseline*week 12	0.12	0.031	0.0001	0.0590,0.1813
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of DAS28-CRP at 12 weeks	-1.53	0.064	<.0001	-1.6569,-1.4049
the least-squares mean of the change of DAS28-CRP at 24 weeks	-1.94	0.065	<.0001	-2.0695,-1.8125

Footnote: CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; N, number of patients in population.
MMRM is applied by using the change of DAS28-CRP Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline DAS28 score and baseline DAS28 score-by-week-interaction.

Table ANN. 81 SDAI Score - Effectiveness Analyses Population

	visit		*observed*	*change（post－baseline）*
SDAI Score	Baseline	n (nmiss)	502 (12)	
		Mean (Std)	31.45 (18.43)	
		Median	28.33	
		Q1, Q3	18.86, 43.95	
		Min, Max	1.23, 85.92	
	12-weeks	n (nmiss)	417 (97)	413 (101)
		Mean (Std)	15.58 (15.19)	-15.61 (16.12)
		Median	10.43	-11.90
		Q1, Q3	4.63, 22.14	-24.50, -3.32
		Min, Max	0.01, 75.30	-83.51, 25.74
		P value		<.0001[b]
	24-weeks	n (nmiss)	353 (161)	350 (164)
		Mean (Std)	11.92 (13.46)	-19.37 (17.74)
		Median	6.75	-17.12
		Q1, Q3	2.93, 16.83	-30.64, -5.01
		Min, Max	0.02, 66.11	-83.91, 31.01
		P value		<.0001[b]

Footnote: SDAI, Simplified Disease Activity Index; nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.

Table ANN. 82 SDAI Score Shift Table Summary by Category and Visit - Effectiveness Analyses Population

Visit	*<=3.3*	*>3.3 to <=11.0*	*>11.0 to <=26.0*	*>26.0*	*<=11.0*	*>11.0*	*Non-missing Total*
Baseline	24 (4.78%)	39 (7.77%)	157 (31.27%)	282 (56.18%)	63 (12.55%)	439 (87.45%)	502 (100.00%)
12-weeks	83 (19.90%)	135 (32.37%)	119 (28.54%)	80 (19.18%)	218 (52.28%)	199 (47.72%)	417 (100.00%)
24-weeks	97 (27.48%)	131 (37.11%)	81 (22.95%)	44 (12.46%)	228 (64.59%)	125 (35.41%)	353 (100.00%)

Footnote: Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 83 **SDAI Score Mixed-Effects Model Analysis - Effectiveness Analyses Population**

variable	*Effectiveness Analyses Population (N=514)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.69	0.033	<.0001	-0.7531,-0.6227
week 12	1.32	1.213	0.2774	-1.0648,3.7032
week 24	2.21	1.202	0.0664	-0.1506,4.5744
baseline*week 12	0.15	0.029	<.0001	0.0955,0.2101
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of SDAI at 12 weeks	-15.39	0.620	<.0001	-16.6034,-14.1672
the least-squares mean of the change of SDAI at 24 weeks	-19.26	0.612	<.0001	-20.4666,-18.0603

Footnote: SDAI, Simplified Disease Activity Index; N, number of patients in population.
MMRM is applied by using the change of SDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline SDAI score and baseline SDAI score-by-week-interaction.

Table ANN. 84 CDAI Score - Effectiveness Analyses Population

	visit		*observed*	*change（post－baseline）*
CDAI Score	Baseline	n (nmiss)	508 (6)	
		Mean (Std)	29.18 (17.26)	
		Median	26.40	
		Q1, Q3	17.00, 40.65	
		Min, Max	1.20, 74.00	
	12-weeks	n (nmiss)	439 (75)	435 (79)
		Mean (Std)	15.21 (14.86)	-14.30 (14.92)
		Median	10.00	-11.00
		Q1, Q3	4.80, 22.00	-22.40, -2.90
		Min, Max	0.000, 71.60	-66.20, 25.90
		P value		<.0001[b]
	24-weeks	n (nmiss)	381 (133)	378 (136)
		Mean (Std)	11.98 (13.74)	-17.79 (16.15)
		Median	7.00	-16.30
		Q1, Q3	2.50, 16.00	-27.00, -4.60
		Min, Max	0.000, 66.00	-67.60, 32.50
		P value		<.0001[b]

Footnote: CDAI, Clinical Disease Activity Index; nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.

Table ANN. 85 CDAI Score Shift Table Summary by Category and Visit - Effectiveness Analyses Population

Visit	*<=2.8*	*>2.8 to <=10.0*	*>10.0 to <=22.0*	*>22.0*	*<=10.0*	*>10.0*	*Non-missing Total*
Baseline	24 (4.72%)	37 (7.28%)	132 (25.98%)	315 (62.01%)	61 (12.01%)	447 (87.99%)	508 (100.00%)
12-weeks	79 (18.00%)	142 (32.35%)	115 (26.20%)	103 (23.46%)	221 (50.34%)	218 (49.66%)	439 (100.00%)
24-weeks	105 (27.56%)	137 (35.96%)	78 (20.47%)	61 (16.01%)	242 (63.52%)	139 (36.48%)	381 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 86 **CDAI Score Mixed-Effects Model Analysis - Effectiveness Analyses Population**

variable	*Effectiveness Analyses Population (N=514)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.63	0.033	<.0001	-0.6967,-0.5653
week 12	0.79	1.107	0.4735	-1.3810,2.9691
week 24	0.93	1.145	0.4178	-1.3215,3.1786
baseline*week 12	0.12	0.028	<.0001	0.0682,0.1770
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of CDAI at 12 weeks	-14.24	0.566	<.0001	-15.3531,-13.1289
the least-squares mean of the change of CDAI at 24 weeks	-17.73	0.584	<.0001	-18.8786,-16.5834

Footnote: CDAI, Clinical Disease Activity Index; N, number of patients in population.
MMRM is applied by using the change of CDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline CDAI score and baseline CDAI score-by-week-interaction.

Table ANN. 87 MJS - Effectiveness Analyses Population

	visit		*observed*	*change（post－baseline）*
MJS(minutes)	Baseline	n (nmiss)	514 (0)	
		Mean (Std)	44.71 (52.29)	
		Median	30.00	
		Q1, Q3	10.00, 60.00	
		Min, Max	0.000, 420.00	
	12-weeks	n (nmiss)	452 (62)	452 (62)
		Mean (Std)	24.84 (74.22)	-20.60 (78.85)
		Median	10.00	-10.00
		Q1, Q3	0.000, 30.00	-30.00, 0.000
		Min, Max	0.000, 1440.00	-300.00, 1380.00
		P value		<.0001[b]
	24-weeks	n (nmiss)	403 (111)	403 (111)
		Mean (Std)	15.59 (29.87)	-28.27 (47.04)
		Median	5.00	-15.00
		Q1, Q3	0.000, 20.00	-30.00, 0.000
		Min, Max	0.000, 300.00	-360.00, 210.00
		P value		<.0001[b]
Tender joint count	Baseline	n (nmiss)	511 (3)	
		Mean (Std)	10.52 (8.16)	
		Median	8.00	
		Q1, Q3	4.00, 16.00	
		Min, Max	0.000, 28.00	
	12-weeks	n (nmiss)	451 (63)	450 (64)
		Mean (Std)	4.92 (6.74)	-5.59 (7.52)
		Median	2.00	-3.00
		Q1, Q3	0.000, 6.00	-9.00, 0.000
		Min, Max	0.000, 28.00	-28.00, 12.00
		P value		<.0001[b]
	24-weeks	n (nmiss)	403 (111)	403 (111)
		Mean (Std)	3.82 (6.20)	-6.61 (7.60)
		Median	1.00	-5.00
		Q1, Q3	0.000, 4.00	-11.00, 0.000
		Min, Max	0.000, 28.00	-28.00, 22.00
		P value		<.0001[b]
Swollen joint count	Baseline	n (nmiss)	514 (0)	
		Mean (Std)	9.47 (7.57)	
		Median	8.00	
		Q1, Q3	3.00, 14.00	
		Min, Max	0.000, 28.00	
	12-weeks	n (nmiss)	450 (64)	450 (64)
		Mean (Std)	4.46 (6.38)	-5.19 (6.73)
		Median	2.00	-3.00
		Q1, Q3	0.000, 6.00	-9.00, 0.000
		Min, Max	0.000, 28.00	-28.00, 22.00

P value	<.0001[b]

Footnote: MJS, Morning Joint Stiffness ; nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.

visit		*observed*	*change（post－baseline）*
24-weeks	n (nmiss)	403 (111)	403 (111)
	Mean (Std)	3.28 (5.59)	-6.39 (7.25)
	Median	1.00	-5.00
	Q1, Q3	0.000, 4.00	-11.00, 0.000
	Min, Max	0.000, 26.00	-28.00, 17.00
	P value		<.0001[b]

Footnote: MJS, Morning Joint Stiffness ; nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.

Table ANN. 88 VAS Score - Effectiveness Analyses Population

	visit		*observed*	*change（post－baseline）*
VAS score of patients' pain	Baseline	n (nmiss)	512 (2)	
		Mean (Std)	5.87 (2.03)	
		Median	6.00	
		Q1, Q3	4.20, 7.50	
		Min, Max	0.000, 10.00	
	12-weeks	n (nmiss)	448 (66)	446 (68)
		Mean (Std)	3.52 (2.06)	-2.44 (2.19)
		Median	3.15	-2.20
		Q1, Q3	2.00, 5.00	-3.70, -1.00
		Min, Max	0.000, 9.50	-10.00, 6.00
		P value		<.0001[b]
	24-weeks	n (nmiss)	402 (112)	400 (114)
		Mean (Std)	2.85 (2.12)	-3.00 (2.45)
		Median	2.10	-3.00
		Q1, Q3	1.00, 4.50	-4.50, -1.35
		Min, Max	0.000, 10.00	-10.00, 8.50
		P value		<.0001[b]
VAS score of overall disease status	Baseline	n (nmiss)	512 (2)	
		Mean (Std)	5.98 (1.98)	
		Median	6.00	
		Q1, Q3	4.90, 7.50	
		Min, Max	0.40, 10.00	
	12-weeks	n (nmiss)	448 (66)	446 (68)
		Mean (Std)	3.59 (2.04)	-2.42 (2.18)
		Median	3.50	-2.10
		Q1, Q3	2.00, 5.00	-3.80, -1.00
		Min, Max	0.000, 10.00	-9.50, 4.60
		P value		<.0001[b]
	24-weeks	n (nmiss)	402 (112)	400 (114)
		Mean (Std)	2.89 (2.06)	-3.05 (2.41)
		Median	2.50	-3.00
		Q1, Q3	1.10, 4.30	-4.50, -1.50
		Min, Max	0.000, 10.00	-10.00, 7.00
		P value		<.0001[b]
VAS score of overall disease status of doctors	Baseline	n (nmiss)	512 (2)	
		Mean (Std)	5.98 (1.94)	
		Median	6.00	
		Q1, Q3	4.80, 7.50	
		Min, Max	0.40, 10.00	
	12-weeks	n (nmiss)	448 (66)	446 (68)

	Mean (Std)	3.57 (2.05)	-2.43 (2.10)
	Median	3.30	-2.10
	Q1, Q3	2.00, 5.00	-3.60, -1.00
	Min, Max	0.000, 10.00	-9.00, 6.70
	P value		<.0001[b]

Footnote: VAS, Visual Analogue Scale; nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.

visit		*observed*	*change（post－baseline）*
24-weeks	n (nmiss)	401 (113)	399 (115)
	Mean (Std)	2.90 (2.16)	-3.00 (2.33)
	Median	2.50	-3.00
	Q1, Q3	1.00, 4.50	-4.70, -1.30
	Min, Max	0.000, 10.00	-9.00, 7.00
	P value		<.0001[b]

Footnote: VAS, Visual Analogue Scale; nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.

Table ANN. 89 DAS-ESR Score - Effectiveness Analyses Population

	visit		*observed*	*change（post－baseline）*
DAS28-ESR Score	Baseline	n (nmiss)	490 (24)	
		Mean (Std)	5.18 (1.99)	
		Median	5.46	
		Q1, Q3	4.23, 6.50	
		Min, Max	0.22, 8.71	
	12-weeks	n (nmiss)	414 (100)	401 (113)
		Mean (Std)	3.62 (1.82)	-1.50 (1.58)
		Median	3.55	-1.24
		Q1, Q3	2.37, 4.86	-2.72, -0.23
		Min, Max	0.12, 8.63	-6.22, 2.39
		P value		<.0001[b]
	24-weeks	n (nmiss)	346 (168)	333 (181)
		Mean (Std)	3.26 (1.70)	-1.88 (1.68)
		Median	3.05	-1.71
		Q1, Q3	2.16, 4.34	-3.09, -0.47
		Min, Max	0.11, 8.18	-6.23, 2.52
		P value		<.0001[b]

Footnote: DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; ESR, erythrocyte sedimentation rate; nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.

Table ANN. 90 **DAS28-ESR Score Shift Table Summary by Category and Visit - Effectiveness Analyses Population**

Visit	*<2.6*	*>=2.6 to <=3.2*	*>3.2 to <=5.1*	*>5.1*	*<=3.2*	*>3.2*	*Non-missing Total*
Baseline	47 (9.59%)	17 (3.47%)	140 (28.57%)	286 (58.37%)	64 (13.06%)	426 (86.94%)	490 (100.00%)
12-weeks	124 (29.95%)	50 (12.08%)	149 (35.99%)	91 (21.98%)	174 (42.03%)	240 (57.97%)	414 (100.00%)
24-weeks	129 (37.28%)	58 (16.76%)	113 (32.66%)	46 (13.29%)	187 (54.05%)	159 (45.95%)	346 (100.00%)

Footnote: DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; ESR, erythrocyte sedimentation rate.
Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 91 Key Indicator - Effectiveness Analyses Population

	visits		*observed*	*change（post－baseline）*
ESR(mm/H)	Baseline	n (nmiss)	462 (52)	
		Mean (Std)	44.37 (30.70)	
		Median	37.50	
		Q1, Q3	21.00, 64.00	
		Min, Max	2.00, 136.00	
	4-weeks	n (nmiss)	380 (134)	353 (161)
		Mean (Std)	32.21 (25.53)	-13.03 (24.97)
		Median	23.00	-10.00
		Q1, Q3	13.50, 47.50	-26.00, 1.00
		Min, Max	0.30, 140.00	-94.00, 117.00
	12-weeks	n (nmiss)	370 (144)	343 (171)
		Mean (Std)	30.29 (24.54)	-14.01 (28.43)
		Median	24.00	-9.00
		Q1, Q3	12.00, 43.00	-32.00, 2.00
		Min, Max	1.00, 120.00	-125.38, 90.00
	24-weeks	n (nmiss)	303 (211)	278 (236)
		Mean (Std)	28.81 (23.66)	-15.42 (28.11)
		Median	22.00	-12.00
		Q1, Q3	12.00, 41.00	-34.00, 1.00
		Min, Max	0.50, 120.00	-101.00, 82.00
CRP(mg/L)	Baseline	n (nmiss)	467 (47)	
		Mean (Std)	23.91 (30.44)	
		Median	11.05	
		Q1, Q3	3.24, 33.30	
		Min, Max	0.09, 178.20	
	4-weeks	n (nmiss)	385 (129)	364 (150)
		Mean (Std)	10.09 (18.99)	-14.92 (27.03)
		Median	3.90	-6.19
		Q1, Q3	1.60, 10.00	-25.42, 0.000
		Min, Max	0.01, 200.00	-123.10, 101.68
	12-weeks	n (nmiss)	363 (151)	338 (176)
		Mean (Std)	9.86 (18.74)	-15.37 (30.98)
		Median	3.81	-6.41
		Q1, Q3	1.43, 10.06	-26.20, 0.000
		Min, Max	0.03, 200.00	-178.10, 97.35
	24-weeks	n (nmiss)	304 (210)	283 (231)
		Mean (Std)	8.19 (13.51)	-16.32 (30.99)
		Median	3.33	-6.20
		Q1, Q3	1.31, 9.57	-27.30, 0.000
		Min, Max	0.000, 91.18	-151.21, 90.68
RF(IU/mL)	Baseline	n (nmiss)	388 (126)	
		Mean (Std)	244.44 (398.01)	
		Median	113.80	
		Q1, Q3	32.87, 296.50	

Footnote: Anti-CCP, anti-cyclic peptide containing citrulline; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; N, number of patients in population; nmiss, number of data missing patients; Q1 and Q3, interquartile range; RF, rheumatoid factor Std, standard deviation.

	visits		*observed*	*change（post－baseline）*
		Min, Max	1.00, 2830.00	
	4-weeks	n (nmiss)	178 (336)	164 (350)
		Mean (Std)	211.01 (350.55)	-45.48 (163.49)
		Median	101.56	-9.00
		Q1, Q3	29.70, 232.10	-78.70, 0.60
		Min, Max	1.50, 2440.00	-832.10, 710.00
	12-weeks	n (nmiss)	192 (322)	174 (340)
		Mean (Std)	165.27 (358.18)	-62.17 (292.20)
		Median	67.70	-15.85
		Q1, Q3	20.10, 181.50	-100.00, 2.00
		Min, Max	1.00, 4239.00	-1660.00, 1729.00
	24-weeks	n (nmiss)	161 (353)	140 (374)
		Mean (Std)	173.75 (357.36)	-64.73 (350.11)
		Median	64.10	-8.85
		Q1, Q3	23.00, 177.03	-70.20, 7.30
		Min, Max	0.09, 3720.00	-2143.00, 1210.00
Anti-CCP(U/mL)	Baseline	n (nmiss)	283 (231)	
		Mean (Std)	306.86 (504.71)	
		Median	200.00	
		Q1, Q3	43.20, 356.89	
		Min, Max	0.50, 4112.70	
	4-weeks	n (nmiss)	58 (456)	48 (466)
		Mean (Std)	322.21 (407.67)	18.02 (85.54)
		Median	204.50	0.000
		Q1, Q3	42.00, 452.00	-6.47, 17.05
		Min, Max	0.50, 2032.90	-151.00, 400.00
	12-weeks	n (nmiss)	69 (445)	60 (454)
		Mean (Std)	333.78 (448.75)	24.05 (155.12)
		Median	200.00	0.000
		Q1, Q3	43.67, 377.15	-15.00, 13.10
		Min, Max	0.50, 1997.24	-286.90, 543.01
	24-weeks	n (nmiss)	70 (444)	57 (457)
		Mean (Std)	428.98 (615.51)	-90.86 (300.38)
		Median	200.00	-1.60
		Q1, Q3	65.10, 474.10	-105.60, 46.40
		Min, Max	0.50, 3200.00	-1003.51, 398.70

Footnote: Anti-CCP, anti-cyclic peptide containing citrulline; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; N, number of patients in population; nmiss, number of data missing patients; Q1 and Q3, interquartile range; RF, rheumatoid factor Std, standard deviation.

Subgroup Analyses

Table ANN. 92 Demographics (Gender Subgroups, Effectiveness Analyses Population)

		Effectiveness Analyses Population		
		Male (N=86)	*Female (N=428)*	*P value*
Age (years)	n (nmiss)	86 (0)	428 (0)	0.0773
	Mean (Std)	55.31 (12.46)	52.36 (12.59)	
	Median	56.50	54.00	
	Q1, Q3	47.00, 63.00	44.50, 61.00	
	Min, Max	21, 85	20, 84	
	18-34	5 (5.81%)	44 (10.28%)	0.2390[b]
	35-44	10 (11.63%)	63 (14.72%)	
	45-64	53 (61.63%)	247 (57.71%)	
	65-74	13 (15.12%)	65 (15.19%)	
	>=75	5 (5.81%)	9 (2.10%)	
	Total	86 (100.00%)	428 (100.00%)	
Height (cm)	n (nmiss)	86 (0)	428 (0)	<.0001
	Mean (Std)	168.81 (7.15)	158.78 (5.26)	
	Median	168.00	159.00	
	Q1, Q3	165.00, 172.00	155.00, 162.00	
	Min, Max	154, 198	144, 174	
Weight (kg)	n (nmiss)	86 (0)	428 (0)	<.0001
	Mean (Std)	64.27 (10.74)	56.15 (9.24)	
	Median	62.75	55.00	
	Q1, Q3	58.00, 70.00	50.00, 61.50	
	Min, Max	46.0, 90.0	27.0, 100.0	
BMI (kg/m^2)	n (nmiss)	86 (0)	428 (0)	0.5640
	Mean (Std)	22.53 (3.38)	22.24 (3.33)	
	Median	21.67	21.77	
	Q1, Q3	19.96, 24.49	19.98, 24.23	
	Min, Max	16.49, 31.22	12.84, 36.73	
	<18.5	8 (9.30%)	48 (11.21%)	0.7333[b]
	>=18.5-<24	51 (59.30%)	263 (61.45%)	
	>=24-<28	20 (23.26%)	93 (21.73%)	
	>=28	7 (8.14%)	24 (5.61%)	
	Total	86 (100.00%)	428 (100.00%)	
Smoking history	Never smoking	31 (36.05%)	424 (99.07%)	<.0001[b]
	Used to smoke, given up now	19 (22.09%)	2 (0.47%)	
	Still smoking	36 (41.86%)	2 (0.47%)	
	Total	86 (100.00%)	428 (100.00%)	

Footnote: The smoking history information were from 'Life History' page in CRF.
N, number of patients in population; nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.
The percentage denominator is the number of patients with non-missing value.
P values for continuous values were from Wilcoxon rank sum test. b: P values for categorical values were from Fisher exact tests.

Table ANN. 93 Rheumatoid Arthritis Diagnosis (Gender Subgroups, Effectiveness Analyses Population)

		Effectiveness Analyses Population		
		Male (N=86)	*Female (N=428)*	*P value*
Months from the onset date of RA to ICF (months)	n (nmiss)	86 (0)	428 (0)	0.0005
	Mean (Std)	67.59 (79.07)	108.27 (107.82)	
	Median	34.55	71.43	
	Q1, Q3	13.57, 108.58	24.46, 154.18	
	Min, Max	1.68, 413.54	0, 623.67	
Duration of RA (months)	n (nmiss)	86 (0)	428 (0)	0.0009
	Mean (Std)	57.67 (77.54)	94.12 (104.08)	
	Median	24.74	57.24	
	Q1, Q3	8.02, 92.65	15.26, 140.25	
	Min, Max	0.07, 411.50	0, 623.67	
	<=1 year	27 (31.40%)	86 (20.09%)	0.0030[b]
	>1-<=3 years	23 (26.74%)	80 (18.69%)	
	>3-<=10 years	24 (27.91%)	135 (31.54%)	
	>10 years	12 (13.95%)	127 (29.67%)	
	Total	86 (100.00%)	428 (100.00%)	
Meet the ACR/EULAR 2010 criteria and number of points	Yes	86 (100.00%)	428 (100.00%)	NA[b]
	n (nmiss)	86 (0)	428 (0)	
	Mean (Std)	8.37 (1.59)	8.43 (1.45)	
	Median	8.00	8.00	
	Q1, Q3	7.00, 10.00	7.00, 10.00	
	Min, Max	6, 10	6, 10	
	Total	86 (100.00%)	428 (100.00%)	

Footnote: The duration of RA (months) = (Date of informed consent – date of diagnosis of RA) / 30.4375, round to 2 decimal place. Months from the onset date of RA to ICF (months) = (Date of informed consent – the onset date of RA) / 30.4375, round to 2 decimal place.
N, number of patients in population; nmiss, no. of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range. The percentage denominator is the number of patients with non-missing value.
P values for continuous values were from Wilcoxon rank sum test. b: P values for categorical values were from Fisher exact tests.

Table ANN. 94 **Drug Exposure (Gender Subgroups, Effectiveness Analyses Population)**

		Effectiveness Analyses Population		
		Male (N=86)	*Female (N=428)*	*P value*
Overall Olumiant exposure (days)	n (nmiss)	86 (0)	427 (1)	0.2228
	Mean (Std)	164.64 (35.12)	164.28 (32.04)	
	Median	173.00	169.00	
	Q1, Q3	159.00, 183.00	155.00, 179.00	
	Min, Max	55, 252	1, 314	
Olumiant exposure (days)	n (nmiss)	86 (0)	427 (1)	0.3060
	Mean (Std)	162.57 (35.41)	162.38 (33.16)	
	Median	172.50	169.00	
	Q1, Q3	156.00, 182.00	154.00, 178.00	
	Min, Max	55, 249	1, 314	
Total patient year exposure		38.8	192.1	
Number of patients administered only 2mg Olumiant	n (%)	74 (86.05%)	384 (89.72%)	0.3425
Number of patients administered only 4mg Olumiant	n (%)	8 (9.30%)	20 (4.67%)	0.1129
Number of patients administered mixed dosage of Olumiant	n (%)	4 (4.65%)	24 (5.61%)	>.9999

Footnote: N, number of patients in population; nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.
Overall Olumiant exposure (days) = Olumiant discontinue date in study termination page – the earliest start date of treatment in treatment information page +1.
Olumiant exposure (days) = sum of (end date of treatment - start date of treatment +1). The start and end date of treatment are from the same record in treatment information page.
The sum are based on all records in this page.
Total patient year exposure = sum of all patients' year exposure. Patient year exposure = overall Olumiant exposure in days for the patient / 365.25, keep 1 decimal place.
P values for continuous values were from Wilcoxon rank sum test. P values for categorical values were from Fisher exact tests.

Table ANN. 95 **DAS28-CRP Score (Gender Subgroups, Effectiveness Analyses Population)**

		observed			*change (post −baseline)*		
visit		*Male (N=86)*	*Female (N=428)*	*P value**	*Male (N=86)*	*Female (N=428)*	*P value**
Baseline	n (nmiss)	84 (2)	418 (10)	0.1764			
	Mean (Std)	4.92 (1.83)	4.63 (1.84)				
	Median	5.03	4.81				
	Q1, Q3	3.98, 6.16	3.70, 6.05				
	Min, Max	0.25, 8.02	0.30, 7.95				
12-weeks	n (nmiss)	67 (19)	350 (78)	0.3728	67 (19)	346 (82)	0.6713
	Mean (Std)	3.25 (1.70)	3.05 (1.66)		-1.63 (1.57)	-1.53 (1.55)	
	Median	3.18	2.91		-1.49	-1.29	
	Q1, Q3	2.06, 4.29	1.82, 4.18		-2.94, -0.30	-2.64, -0.32	
	Min, Max	0.19, 7.88	0.11, 7.56		-5.38, 1.91	-5.71, 3.58	
	P value				<.0001[a]	<.0001[b]	
24-weeks	n (nmiss)	54 (32)	299 (129)	0.1705	54 (32)	296 (132)	0.2242
	Mean (Std)	2.87 (1.35)	2.69 (1.54)		-2.19 (1.73)	-1.92 (1.65)	
	Median	2.68	2.45		-2.43	-1.78	
	Q1, Q3	2.03, 3.67	1.61, 3.66		-3.57, -0.68	-3.09, -0.56	
	Min, Max	0.17, 6.49	0.11, 7.12		-5.12, 1.93	-6.01, 2.58	
	P value				<.0001[a]	<.0001[b]	

Footnote: CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Wilcoxon rank sum tests.

Table ANN. 96 **DAS28-CRP Score (DAS28-CRP ≤3.2, Gender Subgroups, Effectiveness Analyses Population)**

		observed			*change (post −baseline)*		
visit		*Male (N=54)*	*Female (N=296)*	*P value**	*Male (N=54)*	*Female (N=296)*	*P value**
Baseline	n (nmiss)	11 (75)	73 (355)	0.9155			
	%	13.10%	17.46%				
	Mean (Std)	1.45 (1.12)	1.54 (1.11)				
	Median	0.70	1.53				
	Q1, Q3	0.40, 2.66	0.45, 2.56				
	Min, Max	0.25, 2.93	0.30, 3.15				
12-weeks	n (nmiss)	34 (52)	192 (236)	0.2989	34 (52)	189 (239)	0.7994
	%	50.75%	54.86%		50.75%	54.62%	
	Mean (Std)	1.95 (0.95)	1.82 (0.87)		-2.16 (1.57)	-2.09 (1.53)	
	Median	2.10	1.93		-1.97	-1.97	
	Q1, Q3	1.45, 2.72	1.37, 2.50		-3.57, -0.56	-3.32, -0.68	
	Min, Max	0.19, 3.18	0.11, 3.19		-5.38, 0.20	-5.71, 0.55	
	P value				<.0001[a]	<.0001[b]	
24-weeks	n (nmiss)	36 (50)	199 (229)	0.0109	36 (50)	197 (231)	0.0378
	%	66.67%	66.56%		66.67%	66.55%	
	Mean (Std)	2.12 (0.76)	1.80 (0.80)		-2.93 (1.37)	-2.39 (1.60)	
	Median	2.19	1.80		-3.26	-2.47	
	Q1, Q3	1.77, 2.68	1.41, 2.45		-3.91, -2.20	-3.52, -0.99	
	Min, Max	0.17, 3.14	0.11, 3.13		-5.12, 0.01	-6.01, 0.19	
	P value				<.0001[b]	<.0001[b]	

Footnote: CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
The numerator of percentage was n. The denominator of percentage for observed value was the number of patients with non-missing observed value at the visit in the subgroup. The denominator of
percentage for change from baseline was the number of patients with non-missing change at the visit in the subgroup.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Wilcoxon rank sum tests.

Table ANN. 97 DAS28-CRP Score Summary by Category and Visit (Male, Effectiveness Analyses Population)

Visit	*<2.6*	*>=2.6 to <=3.2*	*>3.2 to <=5.1*	*>5.1*	*<=3.2*	*>3.2*	*Non-missing Total*
Baseline	8 (9.52%)	3 (3.57%)	34 (40.48%)	39 (46.43%)	11 (13.10%)	73 (86.90%)	84 (100.00%)
12-weeks	23 (34.33%)	11 (16.42%)	23 (34.33%)	10 (14.93%)	34 (50.75%)	33 (49.25%)	67 (100.00%)
24-weeks	23 (42.59%)	13 (24.07%)	14 (25.93%)	4 (7.41%)	36 (66.67%)	18 (33.33%)	54 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 98 **DAS28-CRP Score Summary by Category and Visit (Female, Effectiveness Analyses Population)**

Visit	*<2.6*	*>=2.6 to <=3.2*	*>3.2 to <=5.1*	*>5.1*	*<=3.2*	*>3.2*	*Non-missing Total*
Baseline	56 (13.40%)	17 (4.07%)	172 (41.15%)	173 (41.39%)	73 (17.46%)	345 (82.54%)	418 (100.00%)
12-weeks	151 (43.14%)	41 (11.71%)	112 (32.00%)	46 (13.14%)	192 (54.86%)	158 (45.14%)	350 (100.00%)
24-weeks	162 (54.18%)	37 (12.37%)	74 (24.75%)	26 (8.70%)	199 (66.56%)	100 (33.44%)	299 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 99 **DAS28-CRP Score Mixed-Effects Model Analysis (Male, Effectiveness Analyses Population)**

variable	*Effectiveness Analyses Population (N=86)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.70	0.090	<.0001	-0.8780,-0.5187
week 12	0.56	0.469	0.2401	-0.3797,1.4907
week 24	1.31	0.477	0.0075	0.3627,2.2671
baseline*week 12	0.26	0.087	0.0043	0.0830,0.4285
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of DAS28-CRP at 12 weeks	-1.64	0.168	<.0001	-1.9754,-1.3062
the least-squares mean of the change of DAS28-CRP at 24 weeks	-2.15	0.155	<.0001	-2.4602,-1.8403

Footnote: CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; N, number of patients in Male population.
MMRM is applied by using the change of DAS28-CRP Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline DAS28 score and baseline DAS28 score-by-week-interaction.

Table ANN. 100 DAS28-CRP Score Mixed-Effects Model Analysis (Female, Effectiveness Analysis Population)

variable	*Effectiveness Analyses Population (N=428)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.54	0.039	<.0001	-0.6171,-0.4631
week 12	0.53	0.186	0.0047	0.1635,0.8948
week 24	0.59	0.194	0.0027	0.2053,0.9692
baseline*week 12	0.10	0.033	0.0038	0.0316,0.1623
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of DAS28-CRP at 12 weeks	-1.51	0.069	<.0001	-1.6475,-1.3743
the least-squares mean of the change of DAS28-CRP at 24 weeks	-1.90	0.072	<.0001	-2.0406,-1.7576

Footnote: CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; N, number of patients in Female population.
MMRM is applied by using the change of DAS28-CRP Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline DAS28 score and baseline DAS28 score-by-week-interaction.

Table ANN. 101 **SDAI Score (Gender Subgroups, Effectiveness Analyses Population)**

		observed			*change (post −baseline)*		
visit		*Male (N=86)*	*Female (N=428)*	*P value**	*Male (N=86)*	*Female (N=428)*	*P value**
Baseline	n (nmiss)	84 (2)	418 (10)	0.3001			
	Mean (Std)	33.40 (18.86)	31.06 (18.34)				
	Median	31.32	28.09				
	Q1, Q3	19.42, 43.62	18.22, 44.06				
	Min, Max	1.43, 77.80	1.23, 85.92				
12-weeks	n (nmiss)	67 (19)	350 (78)	0.7936	67 (19)	346 (82)	0.4457
	Mean (Std)	15.71 (15.68)	15.55 (15.12)		-16.99 (16.23)	-15.34 (16.11)	
	Median	10.42	10.54		-15.80	-11.67	
	Q1, Q3	5.77, 19.75	4.55, 22.50		-29.02, -3.28	-23.49, -3.32	
	Min, Max	0.63, 75.30	0.01, 72.19		-65.71, 11.45	-83.51, 25.74	
	P value				<.0001[b]	<.0001[b]	
24-weeks	n (nmiss)	54 (32)	299 (129)	0.4323	54 (32)	296 (132)	0.2133
	Mean (Std)	11.31 (10.41)	12.03 (13.95)		-22.22 (18.74)	-18.85 (17.54)	
	Median	9.24	6.57		-20.80	-16.46	
	Q1, Q3	3.92, 15.37	2.65, 17.06		-33.54, -6.94	-29.63, -4.65	
	Min, Max	0.53, 48.40	0.02, 66.11		-66.40, 8.45	-83.91, 31.01	
	P value				<.0001[a]	<.0001[b]	

Footnote: nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Wilcoxon rank sum tests.

Table ANN. 102 **SDAI Score (SDAI ≤11, Gender Subgroups, Effectiveness Analyses Population)**

		observed			*change (post −baseline)*		
visit		*Male (N=54)*	*Female (N=296)*	*P value**	*Male (N=54)*	*Female (N=296)*	*P value**
Baseline	n (nmiss)	7 (79)	56 (372)	0.7678			
	%	8.33%	13.40%				
	Mean (Std)	4.40 (3.28)	4.62 (2.80)				
	Median	3.32	3.98				
	Q1, Q3	1.72, 6.23	2.02, 6.10				
	Min, Max	1.43, 10.47	1.23, 10.92				
12-weeks	n (nmiss)	37 (49)	181 (247)	0.0965	37 (49)	179 (249)	0.2077
	%	55.22%	51.71%		55.22%	51.73%	
	Mean (Std)	5.91 (3.53)	4.93 (3.18)		-22.19 (16.31)	-19.36 (16.62)	
	Median	5.97	4.82		-21.09	-17.17	
	Q1, Q3	2.40, 8.76	2.05, 7.67		-32.00, -10.92	-26.84, -5.16	
	Min, Max	0.63, 10.90	0.01, 10.93		-65.71, 0.81	-83.51, 0.18	
	P value				<.0001[b]	<.0001[b]	
24-weeks	n (nmiss)	34 (52)	194 (234)	0.0922	34 (52)	192 (236)	0.0419
	%	62.96%	64.88%		62.96%	64.86%	
	Mean (Std)	5.19 (3.45)	4.08 (2.88)		-27.91 (17.09)	-22.15 (17.46)	
	Median	4.21	3.63		-26.76	-19.65	
	Q1, Q3	2.59, 8.60	1.55, 6.46		-35.75, -15.91	-32.14, -6.88	
	Min, Max	0.53, 10.70	0.02, 10.99		-66.40, -0.45	-83.91, 0.41	
	P value				<.0001[a]	<.0001[b]	

Footnote: nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
The numerator of percentage was n. The denominator of percentage for observed value was the number of patients with non-missing observed value at the visit in the subgroup. The denominator of
percentage for change from baseline was the number of patients with non-missing change at the visit in the subgroup.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Wilcoxon rank sum tests.

Table ANN. 103 **SDAI Score Summary by Category and Visit (Male, Effectiveness Analyses Population)**

Visit	*<=3.3*	*>3.3 to <=11.0*	*>11.0 to <=26.0*	*>26.0*	*<=11.0*	*>11.0*	*Non-missing Total*
Baseline	3 (3.57%)	4 (4.76%)	24 (28.57%)	53 (63.10%)	7 (8.33%)	77 (91.67%)	84 (100.00%)
12-weeks	13 (19.40%)	24 (35.82%)	18 (26.87%)	12 (17.91%)	37 (55.22%)	30 (44.78%)	67 (100.00%)
24-weeks	11 (20.37%)	23 (42.59%)	14 (25.93%)	6 (11.11%)	34 (62.96%)	20 (37.04%)	54 (100.00%)

Footnote: Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 104 SDAI Score Summary by Category and Visit (Female, Effectiveness Analyses Population)

Visit	*<=3.3*	*>3.3 to <=11.0*	*>11.0 to <=26.0*	*>26.0*	*<=11.0*	*>11.0*	*Non-missing Total*
Baseline	21 (5.02%)	35 (8.37%)	133 (31.82%)	229 (54.78%)	56 (13.40%)	362 (86.60%)	418 (100.00%)
12-weeks	70 (20.00%)	111 (31.71%)	101 (28.86%)	68 (19.43%)	181 (51.71%)	169 (48.29%)	350 (100.00%)
24-weeks	86 (28.76%)	108 (36.12%)	67 (22.41%)	38 (12.71%)	194 (64.88%)	105 (35.12%)	299 (100.00%)

Footnote: Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 105 SDAI Score Mixed-Effects Model Analysis (Male, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=86)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.87	0.068	<.0001	-1.0016,-0.7295
week 12	0.33	3.170	0.9175	-5.9942,6.6533
week 24	6.52	2.600	0.0145	1.3307,11.7050
baseline*week 12	0.34	0.075	<.0001	0.1920,0.4912
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of SDAI at 12 weeks	-17.00	1.589	<.0001	-20.1691,-13.8294
the least-squares mean of the change of SDAI at 24 weeks	-22.11	1.260	<.0001	-24.6208,-19.5941

Footnote: SDAI, Simplified Disease Activity Index; N, number of patients in Male population.
MMRM is applied by using the change of SDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline SDAI score and baseline SDAI score-by-week-interaction.

Table ANN. 106 **SDAI Score Mixed-Effects Model Analysis (Female, Effectiveness Analyses Population)**

variable	*Effectiveness Analyses Population (N=428)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.65	0.037	<.0001	-0.7254,-0.5800
week 12	1.52	1.313	0.2485	-1.0645,4.1002
week 24	1.44	1.328	0.2800	-1.1745,4.0473
baseline*week 12	0.12	0.031	0.0002	0.0539,0.1761
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of SDAI at 12 weeks	-15.08	0.674	<.0001	-16.4051,-13.7560
the least-squares mean of the change of SDAI at 24 weeks	-18.71	0.682	<.0001	-20.0537,-17.3711

Footnote: SDAI, Simplified Disease Activity Index; N, number of patients in Female population.
MMRM is applied by using the change of SDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline SDAI score and baseline SDAI score-by-week-interaction.

Table ANN. 107 **CDAI Score (Gender Subgroups, Effectiveness Analyses Population)**

		observed			*change (post −baseline)*		
visit		*Male (N=86)*	*Female (N=428)*	*P value**	*Male (N=86)*	*Female (N=428)*	*P value**
Baseline	n (nmiss)	84 (2)	424 (4)	0.5180			
	Mean (Std)	30.13 (17.14)	28.99 (17.30)				
	Median	28.25	26.00				
	Q1, Q3	17.00, 37.05	16.75, 41.05				
	Min, Max	1.40, 72.30	1.20, 74.00				
12-weeks	n (nmiss)	70 (16)	369 (59)	0.8048	70 (16)	365 (63)	0.6323
	Mean (Std)	14.42 (14.68)	15.36 (14.91)		-15.03 (14.02)	-14.16 (15.10)	
	Median	9.75	10.20		-15.00	-10.50	
	Q1, Q3	5.50, 17.20	4.70, 22.00		-24.78, -2.50	-22.00, -3.00	
	Min, Max	0.000, 71.60	0.000, 68.00		-55.00, 4.20	-66.20, 25.90	
	P value				<.0001[b]	<.0001[b]	
24-weeks	n (nmiss)	60 (26)	321 (107)	0.9247	60 (26)	318 (110)	0.2660
	Mean (Std)	10.47 (11.07)	12.27 (14.18)		-19.90 (16.06)	-17.40 (16.17)	
	Median	8.20	6.90		-18.85	-15.55	
	Q1, Q3	2.25, 12.75	2.50, 17.00		-27.30, -5.35	-26.90, -4.50	
	Min, Max	0.000, 47.30	0.000, 66.00		-64.00, 4.00	-67.60, 32.50	
	P value				<.0001[b]	<.0001[b]	

Footnote: nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Wilcoxon rank sum tests.

Table ANN. 108 **CDAI Score (CDAI ≤10, Gender Subgroups, Effectiveness Analyses Population)**

		observed			*change (post −baseline)*		
visit		*Male (N=60)*	*Female (N=318)*	*P value**	*Male (N=60)*	*Female (N=318)*	*P value**
Baseline	n (nmiss)	6 (80)	55 (373)	0.3202			
	%	7.14%	12.97%				
	Mean (Std)	3.23 (2.01)	4.25 (2.54)				
	Median	2.50	3.60				
	Q1, Q3	1.60, 5.20	1.90, 6.00				
	Min, Max	1.40, 6.20	1.20, 10.00				
12-weeks	n (nmiss)	38 (48)	183 (245)	0.1280	38 (48)	181 (247)	0.2056
	%	54.29%	49.59%		54.29%	49.59%	
	Mean (Std)	5.35 (3.24)	4.54 (2.94)		-19.56 (13.59)	-17.75 (15.57)	
	Median	5.70	4.50		-19.90	-15.50	
	Q1, Q3	2.00, 8.00	2.00, 7.00		-27.00, -9.00	-23.00, -4.60	
	Min, Max	0.000, 10.00	0.000, 10.00		-55.00, 0.80	-66.20, 1.60	
	P value				<.0001[a]	<.0001[b]	
24-weeks	n (nmiss)	39 (47)	203 (225)	0.2797	39 (47)	201 (227)	0.1132
	%	65.00%	63.24%		65.00%	63.21%	
	Mean (Std)	4.50 (3.41)	3.82 (2.87)		-23.90 (15.47)	-20.51 (15.79)	
	Median	3.70	3.40		-23.50	-18.70	
	Q1, Q3	1.50, 8.00	1.20, 6.10		-29.60, -12.90	-29.20, -7.50	
	Min, Max	0.000, 10.00	0.000, 10.00		-64.00, -0.60	-67.60, 0.50	
	P value				<.0001[b]	<.0001[b]	

Footnote: nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
The numerator of percentage was n. The denominator of percentage for observed value was the number of patients with non-missing observed value at the visit in the subgroup. The denominator of
percentage for change from baseline was the number of patients with non-missing change at the visit in the subgroup.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Wilcoxon rank sum tests.

Table ANN. 109 CDAI Score Summary by Category and Visit (Male, Effectiveness Analyses Population)

Visit	*<=2.8*	*>2.8 to <=10.0*	*>10.0 to <=22.0*	*>22.0*	*<=10.0*	*>10.0*	*Non-missing Total*
Baseline	3 (3.57%)	3 (3.57%)	22 (26.19%)	56 (66.67%)	6 (7.14%)	78 (92.86%)	84 (100.00%)
12-weeks	12 (17.14%)	26 (37.14%)	19 (27.14%)	13 (18.57%)	38 (54.29%)	32 (45.71%)	70 (100.00%)
24-weeks	17 (28.33%)	22 (36.67%)	13 (21.67%)	8 (13.33%)	39 (65.00%)	21 (35.00%)	60 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 110 CDAI Score Summary by Category and Visit (Female, Effectiveness Analyses Population)

Visit	*<=2.8*	*>2.8 to <=10.0*	*>10.0 to <=22.0*	*>22.0*	*<=10.0*	*>10.0*	*Non-missing Total*
Baseline	21 (4.95%)	34 (8.02%)	110 (25.94%)	259 (61.08%)	55 (12.97%)	369 (87.03%)	424 (100.00%)
12-weeks	67 (18.16%)	116 (31.44%)	96 (26.02%)	90 (24.39%)	183 (49.59%)	186 (50.41%)	369 (100.00%)
24-weeks	88 (27.41%)	115 (35.83%)	65 (20.25%)	53 (16.51%)	203 (63.24%)	118 (36.76%)	321 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 111 CDAI Score Mixed-Effects Model (Male, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=86)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.75	0.073	<.0001	-0.8986,-0.6095
week 12	-1.08	2.758	0.6954	-6.5819,4.4136
week 24	2.81	2.503	0.2654	-2.1800,7.8000
baseline*week 12	0.29	0.069	<.0001	0.1506,0.4243
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of CDAI at 12 weeks	-15.02	1.389	<.0001	-17.7921,-12.2557
the least-squares mean of the change of CDAI at 24 weeks	-19.72	1.233	<.0001	-22.1739,-17.2595

Footnote: CDAI, Clinical Disease Activity Index; N, number of patients in Male population.
MMRM is applied by using the change of CDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline CDAI score and baseline CDAI score-by-week-interaction.

Table ANN. 112 CDAI Score Mixed-Effects Model Analysis (Female, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=428)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.61	0.037	<.0001	-0.6816,-0.5361
week 12	1.16	1.210	0.3375	-1.2169,3.5410
week 24	0.61	1.265	0.6311	-1.8797,3.0958
baseline*week 12	0.09	0.030	0.0022	0.0332,0.1508
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of CDAI at 12 weeks	-14.09	0.621	<.0001	-15.3117,-12.8702
the least-squares mean of the change of CDAI at 24 weeks	-17.36	0.650	<.0001	-18.6385,-16.0821

Footnote: CDAI, Clinical Disease Activity Index; N, number of patients in Female population.
MMRM is applied by using the change of CDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline CDAI score and baseline CDAI score-by-week-interaction.

Table ANN. 113 Demographics (Age Subgroups, Effectiveness Analyses Population)

		Effectiveness Analyses Population			
		<65 years (N=422)	*>=65 and <75 years (N=78)*	*>=75 years (N=14)*	*P value*
Age (years)	n (nmiss)	422 (0)	78 (0)	14 (0)	<.0001
	Mean (Std)	49.09 (10.48)	68.63 (2.53)	78.57 (3.18)	
	Median	51.00	69.00	78.00	
	Q1, Q3	41.00, 57.00	66.00, 70.00	76.00, 80.00	
	Min, Max	20, 64	65, 74	75, 85	
	18-34	49 (11.61%)	0	0	<.0001[b]
	35-44	73 (17.30%)	0	0	
	45-64	300 (71.09%)	0	0	
	65-74	0	78 (100.00%)	0	
	>=75	0	0	14 (100.00%)	
	Total	422 (100.00%)	78 (100.00%)	14 (100.00%)	
Sex	Male	68 (16.11%)	13 (16.67%)	5 (35.71%)	0.1583[b]
	Female	354 (83.89%)	65 (83.33%)	9 (64.29%)	
	Total	422 (100.00%)	78 (100.00%)	14 (100.00%)	
Height (cm)	n (nmiss)	422 (0)	78 (0)	14 (0)	0.2093
	Mean (Std)	160.67 (6.77)	159.17 (6.59)	161.21 (6.74)	
	Median	160.00	160.00	161.00	
	Q1, Q3	157.00, 165.00	155.00, 165.00	158.00, 165.00	
	Min, Max	144, 198	146, 175	148, 172	
Weight (kg)	n (nmiss)	422 (0)	78 (0)	14 (0)	0.0229
	Mean (Std)	57.68 (9.87)	55.56 (9.90)	63.04 (11.28)	
	Median	56.25	54.50	61.75	
	Q1, Q3	50.00, 64.00	50.00, 60.00	56.00, 69.00	
	Min, Max	27.0, 90.0	34.0, 100.0	45.0, 90.0	
BMI (kg/m^2)	n (nmiss)	422 (0)	78 (0)	14 (0)	0.0443
	Mean (Std)	22.31 (3.34)	21.87 (3.26)	24.15 (3.24)	
	Median	21.79	21.37	23.88	
	Q1, Q3	19.83, 24.41	19.98, 23.44	21.51, 25.71	
	Min, Max	12.84, 34.63	15.95, 36.73	18.37, 30.42	
	<18.5	48 (11.37%)	7 (8.97%)	1 (7.14%)	0.5286[b]
	>=18.5-<24	253 (59.95%)	54 (69.23%)	7 (50.00%)	
	>=24-<28	95 (22.51%)	14 (17.95%)	4 (28.57%)	
	>=28	26 (6.16%)	3 (3.85%)	2 (14.29%)	
	Total	422 (100.00%)	78 (100.00%)	14 (100.00%)	
Smoking history	Never smoking	374 (88.63%)	69 (88.46%)	12 (85.71%)	0.7621[b]
	Used to smoke, given up now	16 (3.79%)	4 (5.13%)	1 (7.14%)	
	Still smoking	32 (7.58%)	5 (6.41%)	1 (7.14%)	
	Total	422 (100.00%)	78 (100.00%)	14 (100.00%)	

Footnote: The smoking history information were from 'Life History' page in CRF.

N, number of patients in population; nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.
The percentage denominator is the number of patients with non-missing value.
P values for continuous values were from Wilcoxon rank sum test. b: P values for categorical values were from Fisher exact tests.

Table ANN. 114 Rheumatoid Arthritis Diagnosis (Age Subgroups, Effectiveness Analyses Population)

		Effectiveness Analyses Population			
		<65 years (N=422)	*>=65 and <75 years (N=78)*	*>=75 years (N=14)*	*P value*
Months from the onset date of RA to ICF (months)	n (nmiss)	422 (0)	78 (0)	14 (0)	0.6230
	Mean (Std)	96.28 (95.06)	126.84 (144.38)	116.53 (103.70)	
	Median	61.31	65.73	97.40	
	Q1, Q3	23.43, 141.34	16.95, 176.23	30.00, 152.84	
	Min, Max	0, 492.02	0.23, 623.67	6.34, 360.61	
Duration of RA (months)	n (nmiss)	422 (0)	78 (0)	14 (0)	0.8402
	Mean (Std)	84.87 (92.77)	104.73 (136.73)	90.01 (104.82)	
	Median	50.60	48.37	56.71	
	Q1, Q3	14.72, 125.93	8.41, 139.63	18.37, 108.78	
	Min, Max	0, 489.99	0, 623.67	5.36, 360.61	
	<=1 year	88 (20.85%)	24 (30.77%)	1 (7.14%)	0.0653[a]
	>1-<=3 years	85 (20.14%)	13 (16.67%)	5 (35.71%)	
	>3-<=10 years	137 (32.46%)	16 (20.51%)	6 (42.86%)	
	>10 years	112 (26.54%)	25 (32.05%)	2 (14.29%)	
	Total	422 (100.00%)	78 (100.00%)	14 (100.00%)	
Meet the ACR/EULAR 2010 criteria and number of points	Yes	422 (100.00%)	78 (100.00%)	14 (100.00%)	NA[b]
	n (nmiss)	422 (0)	78 (0)	14 (0)	
	Mean (Std)	8.32 (1.50)	8.83 (1.23)	9.29 (1.07)	
	Median	8.00	9.00	10.00	
	Q1, Q3	7.00, 10.00	8.00, 10.00	8.00, 10.00	
	Min, Max	6, 10	6, 10	7, 10	
	Total	422 (100.00%)	78 (100.00%)	14 (100.00%)	

Footnote: The duration of RA (months) = (Date of informed consent – date of diagnosis of RA) / 30.4375, round to 2 decimal place. Months from the onset date of RA to ICF (months) = (Date of informed consent – the onset date of RA) / 30.4375, round to 2 decimal place.
N, number of patients in population; nmiss, no. of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range. The percentage denominator is the number of patients with non-missing value.
P values for continuous values were from Wilcoxon rank sum test.
a:P values for categorical values were from Chi-squared test. b:P values for categorical values were from Fisher exact tests.

Table ANN. 115 **Drug Exposure (Age Subgroups, Effectiveness Analyses Population)**

		Effectiveness Analyses Population			
		<65 years (N=422)	*≥65 and <75 years (N=78)*	*≥75 years (N=14)*	*P value*
Overall Olumiant exposure (days)	n (nmiss)	421 (1)	78 (0)	14 (0)	0.6916
	Mean (Std)	164.11 (32.10)	166.31 (36.61)	160.21 (20.71)	
	Median	170.00	169.00	171.00	
	Q1, Q3	155.00, 181.00	159.00, 181.00	136.00, 174.00	
	Min, Max	1, 285	65, 314	127, 185	
Olumiant exposure (days)	n (nmiss)	421 (1)	78 (0)	14 (0)	0.7299
	Mean (Std)	162.19 (32.62)	164.73 (38.94)	156.36 (28.23)	
	Median	169.00	169.00	171.50	
	Q1, Q3	154.00, 180.00	158.00, 180.00	136.00, 174.00	
	Min, Max	1, 285	46, 314	98, 185	
Total patient year exposure		189.2	35.5	6.1	
Number of patients administered only 2mg Olumiant	n (%)	375 (88.86%)	70 (89.74%)	13 (92.86%)	>.9999
Number of patients administered only 4mg Olumiant	n (%)	25 (5.92%)	3 (3.85%)	0	0.8187
Number of patients administered mixed dosage of Olumiant	n (%)	22 (5.21%)	5 (6.41%)	1 (7.14%)	0.5848

Footnote: N, number of patients in population; nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.
Overall Olumiant exposure (days) = Olumiant discontinue date in study termination page – the earliest start date of treatment in treatment information page +1.
Olumiant exposure (days) = sum of (end date of treatment - start date of treatment +1). The start and end date of treatment are from the same record in treatment information page.
The sum are based on all records in this page.
Total patient year exposure = sum of all patients' year exposure. Patient year exposure = overall Olumiant exposure in days for the patient / 365.25, keep 1 decimal place.
P values for continuous values were from Wilcoxon rank sum test. P values for categorical values were from Fisher exact tests.

Table ANN. 116 **DAS28-CRP Score (Age Subgroups, Effectiveness Analyses Population)**

visit		*observed*				*change (post −baseline)*			
		<65 years (N=422)	*>=65 and <75 years (N=78)*	*>=75 years (N=14)*	*P value**	*<65 years (N=422)*	*>=65 and <75 years (N=78)*	*>=75 years (N=14)*	*P value**
Baseline	n (nmiss)	413 (9)	75 (3)	14 (0)	0.0015				
	Mean	4.55	5.16	5.93					
	(Std)	(1.88)	(1.53)	(1.31)					
	Median	4.77	5.21	6.08					
	Q1, Q3	3.57, 5.95	4.33, 6.32	4.90, 7.03					
	Min, Max	0.25, 7.96	0.45, 7.95	3.50, 8.02					
12-weeks	n (nmiss)	345 (77)	60 (18)	12 (2)	0.0045	342 (80)	59 (19)	12 (2)	0.2623
	Mean	2.99	3.31	4.56		-1.50	-1.85	-1.42	
	(Std)	(1.69)	(1.42)	(1.55)		(1.54)	(1.65)	(1.31)	
	Median	2.82	3.37	4.33		-1.29	-1.76	-1.23	
	Q1, Q3	1.72, 4.14	2.17, 4.31	3.42, 5.52		-2.55, -0.30	-3.02, 0.68	-1.96, 0.62	
	Min, Max	0.11, 7.88	0.21, 7.12	2.33, 7.72		-5.71, 3.58	-5.52, 2.12	-4.26, 0.63	
	P value					<.0001[b]	<.0001[a]	0.0031[a]	
24-weeks	n (nmiss)	291 (131)	52 (26)	10 (4)	0.1571	289 (133)	51 (27)	10 (4)	0.0288
	Mean	2.70	2.70	3.39		-1.86	-2.39	-2.74	
	(Std)	(1.59)	(1.03)	(1.30)		(1.64)	(1.66)	(2.03)	
	Median	2.43	2.66	3.11		-1.75	-2.55	-2.88	
	Q1, Q3	1.63, 3.66	1.87, 3.59	2.71, 3.77		-3.06, -0.47	-3.56, 1.01	-4.55, 0.79	
	Min, Max	0.11, 7.12	0.19, 4.48	1.95, 6.60		-6.01, 2.58	-5.46, 1.98	-5.12, 0.41	
	P value					<.0001[b]	<.0001[a]	0.0021[a]	

Footnote: CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Kruskal-Wallis tests.

Table ANN. 117 **DAS28-CRP Score (DAS28-CRP ≤3.2, Age Subgroups, Effectiveness Analyses Population)**

		observed				*change (post −baseline)*			
visit		*<65 years (N=422)*	*>=65 and <75 years (N=78)*	*>=75 years (N=14)*	*P value**	*<65 years (N=422)*	*>=65 and <75 years (N=78)*	*>=75 years (N=14)*	*P value**
Baseline	n (nmiss)	77 (345)	7 (71)	0 (14)	0.1302				
	%	18.64%	9.33%	0					
	Mean	1.47	2.09	NA (NA)					
	(Std)	(1.09)	(1.15)						
	Median	0.70	2.45	NA					
	Q1, Q3	0.43, 2.55	0.53, 3.12	NA					
	Min, Max	0.25, 3.13	0.45, 3.15	NA					
12-weeks	n (nmiss)	196 (226)	27 (51)	3 (11)	0.0441	194 (228)	26 (52)	3 (11)	0.0109
	%	56.81%	45.00%	25.00%		56.73%	44.07%	25.00%	
	Mean	1.79	2.07	2.85		-1.99	-2.91	-2.24	
	(Std)	(0.90)	(0.66)	(0.45)		(1.54)	(1.24)	(1.75)	
	Median	1.92	2.06	3.09		-1.83	-3.00	-1.28	
	Q1, Q3	1.33, 2.51	1.54, 2.69	2.33, 3.13		-3.20, -0.60	-3.57, -2.21	-4.26, -1.17	
	Min, Max	0.11, 3.19	0.21, 3.07	2.33, 3.13		-5.71, 0.55	-5.52, -0.32	-4.26, -1.17	
	P value					<.0001[b]	<.0001[a]	0.1577[a]	
24-weeks	n (nmiss)	195 (227)	34 (44)	6 (8)	0.0030	194 (228)	33 (45)	6 (8)	0.0533
	%	67.01%	65.38%	60.00%		67.13%	64.71%	60.00%	
	Mean	1.78	2.10	2.66		-2.37	-2.88	-3.45	
	(Std)	(0.80)	(0.70)	(0.47)		(1.57)	(1.48)	(1.74)	
	Median	1.80	2.28	2.78		-2.49	-3.07	-4.22	
	Q1, Q3	1.41, 2.44	1.47, 2.61	2.27, 3.09		-3.51, -0.95	-3.77, -1.73	-4.55, -1.78	
	Min, Max	0.11, 3.14	0.19, 3.13	1.95, 3.12		-6.01, 0.19	-5.46, 0.000	-5.12, -0.79	
	P value					<.0001[b]	<.0001[a]	0.0047[a]	

Footnote: CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
The numerator of percentage was n. The denominator of percentage for observed value was the number of patients with non-missing observed value at the visit in the subgroup. The denominator of
percentage for change from baseline was the number of patients with non-missing change at the visit in the subgroup.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Kruskal-Wallis tests.

Table ANN. 118 **DAS28-CRP Score Summary by Category and Visit (<65 Years, Effectiveness Analyses Population)**

Visit	*<2.6*	*>=2.6 to <=3.2*	*>3.2 to <=5.1*	*>5.1*	*<=3.2*	*>3.2*	*Non-missing Total*
Baseline	60 (14.53%)	17 (4.12%)	174 (42.13%)	162 (39.23%)	77 (18.64%)	336 (81.36%)	413 (100.00%)
12-weeks	154 (44.64%)	42 (12.17%)	103 (29.86%)	46 (13.33%)	196 (56.81%)	149 (43.19%)	345 (100.00%)
24-weeks	160 (54.98%)	35 (12.03%)	67 (23.02%)	29 (9.97%)	195 (67.01%)	96 (32.99%)	291 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 119 DAS28-CRP Score Summary by Category and Visit (≥65 and <75 Years, Effectiveness Analyses Population)

Visit	*<2.6*	*>=2.6 to <=3.2*	*>3.2 to <=5.1*	*>5.1*	*<=3.2*	*>3.2*	*Non-missing Total*
Baseline	4 (5.33%)	3 (4.00%)	27 (36.00%)	41 (54.67%)	7 (9.33%)	68 (90.67%)	75 (100.00%)
12-weeks	19 (31.67%)	8 (13.33%)	27 (45.00%)	6 (10.00%)	27 (45.00%)	33 (55.00%)	60 (100.00%)
24-weeks	23 (44.23%)	11 (21.15%)	18 (34.62%)	0	34 (65.38%)	18 (34.62%)	52 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 120 DAS28-CRP Score Summary by Category and Visit (≥75 Years, Effectiveness Analyses Population)

Visit	*<2.6*	*>=2.6 to <=3.2*	*>3.2 to <=5.1*	*>5.1*	*<=3.2*	*>3.2*	*Non-missing Total*
Baseline	0	0	5 (35.71%)	9 (64.29%)	0	14 (100.00%)	14 (100.00%)
12-weeks	1 (8.33%)	2 (16.67%)	5 (41.67%)	4 (33.33%)	3 (25.00%)	9 (75.00%)	12 (100.00%)
24-weeks	2 (20.00%)	4 (40.00%)	3 (30.00%)	1 (10.00%)	6 (60.00%)	4 (40.00%)	10 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 121 DAS28-CRP Score Mixed-Effects Model Analysis (<65 Years, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=422)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.51	0.039	<.0001	-0.5855,-0.4329
week 12	0.46	0.180	0.0104	0.1097,0.8182
week 24	0.49	0.190	0.0111	0.1114,0.8596
baseline*week 12	0.08	0.031	0.0113	0.0180,0.1403
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of DAS28-CRP at 12 weeks	-1.48	0.070	<.0001	-1.6203,-1.3458
the least-squares mean of the change of DAS28-CRP at 24 weeks	-1.82	0.072	<.0001	-1.9617,-1.6779

Footnote: CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; N, number of patients in Age<65 years population.
MMRM is applied by using the change of DAS28-CRP Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline DAS28 score and baseline DAS28 score-by-week-interaction.

Table ANN. 122 DAS28-CRP Score Mixed-Effects Model Analysis (≥65 and <75 Years, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=78)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.85	0.094	<.0001	-1.0388,-0.6625
week 12	1.56	0.628	0.0158	0.3040,2.8154
week 24	1.91	0.503	0.0003	0.9015,2.9123
baseline*week 12	0.20	0.111	0.0846	-0.0275,0.4184
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of DAS28-CRP at 12 weeks	-1.81	0.171	<.0001	-2.1548,-1.4704
the least-squares mean of the change of DAS28-CRP at 24 weeks	-2.47	0.143	<.0001	-2.7572,-2.1854

Footnote: CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; N, number of patients in Age>=65 and <75 years population.
MMRM is applied by using the change of DAS28-CRP Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline DAS28 score and baseline DAS28 score-by-week-interaction.

Table ANN. 123 DAS28-CRP Score Mixed-Effects Model Analysis (≥75 Years, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=14)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-1.08	0.316	0.0055	-1.7794,-0.3905
week 12	0.46	1.753	0.7964	-3.3947,4.3212
week 24	3.92	1.980	0.0733	-0.4382,8.2788
baseline*week 12	0.77	0.401	0.0813	-0.1132,1.6528
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of DAS28-CRP at 12 weeks	-1.44	0.374	0.0027	-2.2657,-0.6197
the least-squares mean of the change of DAS28-CRP at 24 weeks	-2.64	0.435	<.0001	-3.6001,-1.6832

Footnote: CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; N, number of patients in Age>=75 years population.
MMRM is applied by using the change of DAS28-CRP Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline DAS28 score and baseline DAS28 score-by-week-interaction.

Table ANN. 124 SDAI Score (Age Subgroups, Effectiveness Analyses Population)

		observed				*change (post −baseline)*			
visit		*<65 years (N=422)*	*>=65 and <75 years (N=78)*	*>=75 years (N=14)*	*P value**	*<65 years (N=422)*	*>=65 and <75 years (N=78)*	*>=75 years (N=14)*	*P value**
Baseline	n (nmiss)	413 (9)	75 (3)	14 (0)	0.0028				
	Mean	30.45	34.20	46.39					
	(Std)	(18.47)	(16.99)	(17.74)					
	Median	27.77	30.88	49.92					
	Q1, Q3	17.05, 42.46	22.40, 44.20	30.11, 59.45					
	Min, Max	1.23, 85.92	2.73, 76.88	22.08, 77.80					
12-weeks	n (nmiss)	345 (77)	60 (18)	12 (2)	0.0030	342 (80)	59 (19)	12 (2)	0.3443
	Mean	14.97	16.03	30.80		-15.19	-17.80	-16.67	
	(Std)	(14.98)	(14.20)	(18.98)		(15.84)	(17.73)	(16.29)	
	Median	10.00	11.88	26.28		-11.67	-16.54	-15.50	
	Q1, Q3	4.10, 20.81	5.84, 20.96	17.74, 43.26		-23.60, 3.00	-28.94, 4.08	-22.74, 7.61	
	Min, Max	0.01, 75.30	0.42, 66.31	5.65, 70.53		-83.51, 25.74	-66.20, 20.44	-51.12, 12.08	
	P value					<.0001[b]	<.0001[a]	0.0046[a]	
24-weeks	n (nmiss)	291 (131)	52 (26)	10 (4)	0.0675	289 (133)	51 (27)	10 (4)	0.0400
	Mean	11.98	10.32	18.57		-18.29	-23.08	-31.36	
	(Std)	(14.08)	(7.38)	(18.09)		(17.07)	(18.74)	(25.63)	
	Median	6.30	8.90	15.89		-16.42	-20.77	-36.09	
	Q1, Q3	2.55, 17.06	4.51, 14.59	6.46, 18.09		-28.25, 4.55	-34.92, 10.92	-52.07, 11.31	
	Min, Max	0.02, 63.58	0.02, 28.55	4.81, 66.11		-83.91, 31.01	-69.88, 18.44	-64.00, 13.75	
	P value					<.0001[b]	<.0001[a]	0.0038[a]	

Footnote: nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Kruskal-Wallis tests.

Table ANN. 125 **SDAI Score (SDAI ≤11, Age Subgroups, Effectiveness Analyses Population)**

		observed				*change (post −baseline)*			
visit		*<65 years (N=422)*	*>=65 and <75 years (N=78)*	*>=75 years (N=14)*	*P value**	*<65 years (N=422)*	*>=65 and <75 years (N=78)*	*>=75 years (N=14)*	*P value**
Baseline	n (nmiss)	59 (363)	4 (74)	0 (14)	0.3170				
	%	14.29%	5.33%	0					
	Mean	4.53	5.65	NA (NA)					
	(Std)	(2.85)	(2.69)						
	Median	3.83	5.82	NA					
	Q1, Q3	1.94, 6.08	3.38, 7.92	NA					
	Min, Max	1.23, 10.92	2.73, 8.23	NA					
12-weeks	n (nmiss)	187 (235)	29 (49)	2 (12)	0.2125	186 (236)	28 (50)	2 (12)	0.0026
	%	54.20%	48.33%	16.67%		54.39%	47.46%	16.67%	
	Mean	4.97	5.71	8.27		-18.49	-27.82	-34.19	
	(Std)	(3.27)	(3.07)	(3.70)		(16.32)	(15.64)	(23.95)	
	Median	4.55	5.77	8.27		-16.10	-25.97	-34.19	
	Q1, Q3	1.97, 8.05	2.74, 7.82	5.65, 10.88		-25.35, -4.71	-32.41, -18.64	-51.12, -17.25	
	Min, Max	0.01, 10.93	0.42, 10.90	5.65, 10.88		-83.51, 0.81	-66.20, -3.32	-51.12, -17.25	
	P value					<.0001[b]	<.0001[a]	0.2928[a]	
24-weeks	n (nmiss)	192 (230)	32 (46)	4 (10)	0.0098	191 (231)	31 (47)	4 (10)	0.0210
	%	65.98%	61.54%	40.00%		66.09%	60.78%	40.00%	
	Mean	3.99	5.49	6.57		-21.74	-28.14	-44.44	
	(Std)	(2.91)	(3.17)	(2.36)		(17.00)	(17.98)	(20.21)	
	Median	3.53	5.21	5.77		-19.26	-24.37	-48.65	
	Q1, Q3	1.54, 6.24	3.63, 7.67	4.94, 8.20		-31.87, -6.65	-42.58, -12.48	-58.04, -30.84	
	Min, Max	0.02, 10.99	0.02, 10.70	4.81, 9.93		-83.91, 0.41	-69.88, 0.000	-64.00, -16.44	
	P value					<.0001[b]	<.0001[a]	0.0218[a]	

Footnote: nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
The numerator of percentage was n. The denominator of percentage for observed value was the number of patients with non-missing observed value at the visit in the subgroup. The denominator of
percentage for change from baseline was the number of patients with non-missing change at the visit in the subgroup.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Wilcoxon rank sum tests or Kruskal-Wallis tests.

Table ANN. 126 SDAI Score Summary by Category and Visit (<65 Years, Effectiveness Analyses Population)

Visit	*<=3.3*	*>3.3 to <=11.0*	*>11.0 to <=26.0*	*>26.0*	*<=11.0*	*>11.0*	*Non-missing Total*
Baseline	23 (5.57%)	36 (8.72%)	130 (31.48%)	224 (54.24%)	59 (14.29%)	354 (85.71%)	413 (100.00%)
12-weeks	75 (21.74%)	112 (32.46%)	96 (27.83%)	62 (17.97%)	187 (54.20%)	158 (45.80%)	345 (100.00%)
24-weeks	90 (30.93%)	102 (35.05%)	60 (20.62%)	39 (13.40%)	192 (65.98%)	99 (34.02%)	291 (100.00%)

Footnote: Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 127 SDAI Score Summary by Category and Visit (≥65 and <75 Years, Effectiveness Analyses Population)

Visit	*<=3.3*	*>3.3 to <=11.0*	*>11.0 to <=26.0*	*>26.0*	*<=11.0*	*>11.0*	*Non-missing Total*
Baseline	1 (1.33%)	3 (4.00%)	25 (33.33%)	46 (61.33%)	4 (5.33%)	71 (94.67%)	75 (100.00%)
12-weeks	8 (13.33%)	21 (35.00%)	19 (31.67%)	12 (20.00%)	29 (48.33%)	31 (51.67%)	60 (100.00%)
24-weeks	7 (13.46%)	25 (48.08%)	17 (32.69%)	3 (5.77%)	32 (61.54%)	20 (38.46%)	52 (100.00%)

Footnote: Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 128 SDAI Score Summary by Category and Visit (≥75 Years, Effectiveness Analyses Population)

Visit	*<=3.3*	*>3.3 to <=11.0*	*>11.0 to <=26.0*	*>26.0*	*<=11.0*	*>11.0*	*Non-missing Total*
Baseline	0	0	2 (14.29%)	12 (85.71%)	0	14 (100.00%)	14 (100.00%)
12-weeks	0	2 (16.67%)	4 (33.33%)	6 (50.00%)	2 (16.67%)	10 (83.33%)	12 (100.00%)
24-weeks	0	4 (40.00%)	4 (40.00%)	2 (20.00%)	4 (40.00%)	6 (60.00%)	10 (100.00%)

Footnote: Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 129 SDAI Score Mixed-Effects Model Analysis (<65 Years, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=422)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.63	0.036	<.0001	-0.7002,-0.5568
week 12	1.02	1.260	0.4178	-1.4556,3.4992
week 24	0.85	1.287	0.5093	-1.6805,3.3804
baseline*week 12	0.10	0.028	0.0003	0.0460,0.1548
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of SDAI at 12 weeks	-14.91	0.661	<.0001	-16.2136,-13.6140
the least-squares mean of the change of SDAI at 24 weeks	-18.11	0.671	<.0001	-19.4340,-16.7952

Footnote: SDAI, Simplified Disease Activity Index; N, number of patients in Age<65 years population.
MMRM is applied by using the change of SDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline SDAI score and baseline SDAI score-by-week-interaction.

Table ANN. 130 SDAI Score Mixed-Effects Model Analysis (≥65 and <75 Years, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=78)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.99	0.060	<.0001	-1.1154,-0.8736
week 12	6.20	4.009	0.1273	-1.8193,14.2133
week 24	9.91	2.275	<.0001	5.3600,14.4578
baseline*week 12	0.29	0.101	0.0054	0.0894,0.4916
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of SDAI at 12 weeks	-17.57	1.741	<.0001	-21.0475,-14.0858
the least-squares mean of the change of SDAI at 24 weeks	-23.66	1.016	<.0001	-25.6911,-21.6276

Footnote: SDAI, Simplified Disease Activity Index; N, number of patients in Age>=65 and <75 years population.
MMRM is applied by using the change of SDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline SDAI score and baseline SDAI score-by-week-interaction.

Table ANN. 131 SDAI Score Mixed-Effects Model Analysis (≥75 years, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=14)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.95	0.327	0.0139	-1.6722,-0.2348
week 12	0.56	12.785	0.9658	-27.5787,28.6998
week 24	16.71	17.377	0.3568	-21.5326,54.9622
baseline*week 12	0.59	0.386	0.1541	-0.2587,1.4397
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of SDAI at 12 weeks	-17.07	4.498	0.0030	-26.9746,-7.1753
the least-squares mean of the change of SDAI at 24 weeks	-29.61	6.064	0.0005	-42.9559,-16.2627

Footnote: SDAI, Simplified Disease Activity Index; N, number of patients in Age>=75 years population.
MMRM is applied by using the change of SDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline SDAI score and baseline SDAI score-by-week-interaction.

Table ANN. 132 CDAI Score (Age Subgroups, Effectiveness Analyses Population)

		observed				*change (post −baseline)*			
visit		*<65 years (N=422)*	*>=65 and <75 years (N=78)*	*>=75 years (N=14)*	*P value**	*<65 years (N=422)*	*>=65 and <75 years (N=78)*	*>=75 years (N=14)*	*P value**
Baseline	n (nmiss)	417 (5)	77 (1)	14 (0)	0.0071				
	Mean	28.39	30.93	43.02					
	(Std)	(17.27)	(16.24)	(17.04)					
	Median	26.00	26.80	48.20					
	Q1, Q3	16.00, 38.60	20.00, 40.60	29.00, 56.00					
	Min, Max	1.20, 72.30	2.70, 74.00	12.70, 67.30					
12-weeks	n (nmiss)	363 (59)	63 (15)	13 (1)	0.0028	360 (62)	62 (16)	13 (1)	0.6168
	Mean	14.61	15.74	29.51		-14.08	-15.53	-14.52	
	(Std)	(14.57)	(14.71)	(17.51)		(14.68)	(16.36)	(15.21)	
	Median	9.60	12.00	24.20		-11.00	-12.15	-13.30	
	Q1, Q3	4.00, 20.80	5.60, 19.70	15.70, 40.00		-22.00, 2.65	-25.10, 3.30	-20.00, 7.20	
	Min, Max	0.000, 71.60	0.000, 65.30	5.50, 63.00		-64.10, 25.90	-66.20, 21.00	-45.40, 12.20	
	P value					<.0001[b]	<.0001[a]	0.0049[a]	
24-weeks	n (nmiss)	312 (110)	57 (21)	12 (2)	0.0197	310 (112)	56 (22)	12 (2)	0.2454
	Mean	11.77	11.04	21.96		-17.13	-20.27	-23.32	
	(Std)	(13.98)	(10.06)	(19.22)		(15.49)	(17.23)	(25.34)	
	Median	6.40	9.20	15.15		-16.15	-19.65	-19.95	
	Q1, Q3	2.00, 16.00	4.00, 15.00	7.90, 33.00		-26.00, 4.40	-29.15, 9.60	-44.85, 6.95	
	Min, Max	0.000, 62.00	0.000, 49.40	3.30, 66.00		-60.20, 32.50	-67.60, 19.00	-64.00, 14.00	
	P value					<.0001[b]	<.0001[a]	0.0087[a]	

Footnote: nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Kruskal-Wallis tests.

Table ANN. 133 **CDAI Score (CDAI ≤10, Age Subgroups, Effectiveness Analyses Population)**

		observed				*change (post −baseline)*			
visit		*<65 years (N=422)*	*>=65 and <75 years (N=78)*	*>=75 years (N=14)*	*P value**	*<65 years (N=422)*	*>=65 and <75 years (N=78)*	*>=75 years (N=14)*	*P value**
Baseline	n (nmiss)	56 (366)	5 (73)	0 (14)	0.1405				
	%	13.43%	6.49%	0					
	Mean	4.05	5.30	NA (NA)					
	(Std)	(2.53)	(1.90)						
	Median	3.40	5.80	NA					
	Q1, Q3	1.90, 5.65	4.00, 7.00	NA					
	Min, Max	1.20, 10.00	2.70, 7.00	NA					
12-weeks	n (nmiss)	190 (232)	30 (48)	1 (13)	0.8313	189 (233)	29 (49)	1 (13)	0.0181
	%	52.34%	47.62%	7.69%		52.50%	46.77%	7.69%	
	Mean	4.63	4.98	5.50 (NA)		-17.19	-24.16	-7.20	
	(Std)	(3.06)	(2.69)			(15.11)	(15.00)	(NA)	
	Median	4.30	5.55	5.50		-15.20	-22.00	-7.20	
	Q1, Q3	2.00, 7.40	2.60, 7.00	5.50, 5.50		-23.00, -4.30	-28.40, -15.30	-7.20, -7.20	
	Min, Max	0.000, 10.00	0.000, 9.00	5.50, 5.50		-64.10, 1.60	-66.20, -1.60	-7.20, -7.20	
	P value					<.0001[b]	<.0001[a]	1.0000[b]	
24-weeks	n (nmiss)	206 (216)	32 (46)	4 (10)	0.1393	205 (217)	31 (47)	4 (10)	0.0484
	%	66.03%	56.14%	33.33%		66.13%	55.36%	33.33%	
	Mean	3.79	4.59	5.83		-20.03	-25.40	-40.28	
	(Std)	(2.94)	(3.02)	(2.88)		(15.14)	(16.91)	(24.09)	
	Median	3.08	4.20	5.10		-18.50	-23.00	-45.20	
	Q1, Q3	1.30, 6.20	2.00, 6.55	3.75, 7.90		-27.10, -7.00	-37.60, -13.20	-55.10, -25.45	
	Min, Max	0.000, 10.00	0.000, 10.00	3.30, 9.80		-60.20, 0.50	-67.60, 0.000	-64.00, -6.70	
	P value					<.0001[b]	<.0001[a]	0.0443[a]	

Footnote: nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
The numerator of percentage was n. The denominator of percentage for observed value was the number of patients with non-missing observed value at the visit in the subgroup. The denominator of
percentage for change from baseline was the number of patients with non-missing change at the visit in the subgroup.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Wilcoxon rank sum tests or Kruskal-Wallis tests.

Table ANN. 134 CDAI Score Summary by Category and Visit (<65 Years, Effectiveness Analyses Population)

Visit	*<=2.8*	*>2.8 to <=10.0*	*>10.0 to <=22.0*	*>22.0*	*<=10.0*	*>10.0*	*Non-missing Total*
Baseline	23 (5.52%)	33 (7.91%)	108 (25.90%)	253 (60.67%)	56 (13.43%)	361 (86.57%)	417 (100.00%)
12-weeks	70 (19.28%)	120 (33.06%)	91 (25.07%)	82 (22.59%)	190 (52.34%)	173 (47.66%)	363 (100.00%)
24-weeks	96 (30.77%)	110 (35.26%)	56 (17.95%)	50 (16.03%)	206 (66.03%)	106 (33.97%)	312 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 135 CDAI Score Summary by Category and Visit (≥65 and <75 Years, Effectiveness Analyses Population)

Visit	*<=2.8*	*>2.8 to <=10.0*	*>10.0 to <=22.0*	*>22.0*	*<=10.0*	*>10.0*	*Non-missing Total*
Baseline	1 (1.30%)	4 (5.19%)	22 (28.57%)	50 (64.94%)	5 (6.49%)	72 (93.51%)	77 (100.00%)
12-weeks	9 (14.29%)	21 (33.33%)	19 (30.16%)	14 (22.22%)	30 (47.62%)	33 (52.38%)	63 (100.00%)
24-weeks	9 (15.79%)	23 (40.35%)	18 (31.58%)	7 (12.28%)	32 (56.14%)	25 (43.86%)	57 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 136 CDAI Score Summary by Category and Visit (≥75 years, Effectiveness Analyses Population)

Visit	*<=2.8*	*>2.8 to <=10.0*	*>10.0 to <=22.0*	*>22.0*	*<=10.0*	*>10.0*	*Non-missing Total*
Baseline	0	0	2 (14.29%)	12 (85.71%)	0	14 (100.00%)	14 (100.00%)
12-weeks	0	1 (7.69%)	5 (38.46%)	7 (53.85%)	1 (7.69%)	12 (92.31%)	13 (100.00%)
24-weeks	0	4 (33.33%)	4 (33.33%)	4 (33.33%)	4 (33.33%)	8 (66.67%)	12 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 137 CDAI Score Mixed-Effects Model Analysis (<65 Years, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=422)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.59	0.036	<.0001	-0.6612,-0.5188
week 12	0.70	1.152	0.5459	-1.5687,2.9616
week 24	-0.08	1.207	0.9496	-2.4503,2.2975
baseline*week 12	0.08	0.026	0.0035	0.0255,0.1290
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of CDAI at 12 weeks	-14.01	0.601	<.0001	-15.1920,-12.8295
the least-squares mean of the change of CDAI at 24 weeks	-17.00	0.627	<.0001	-18.2319,-15.7659

Footnote: CDAI, Clinical Disease Activity Index; N, number of patients in Age<65 years population.
MMRM is applied by using the change of CDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline CDAI score and baseline CDAI score-by-week-interaction.

Table ANN. 138 CDAI Score Mixed-Effects Model Analysis (≥65 and <75 Years, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=78)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.83	0.075	<.0001	-0.9849,-0.6835
week 12	3.28	3.641	0.3713	-3.9974,10.5557
week 24	5.60	2.696	0.0420	0.2102,10.9853
baseline*week 12	0.24	0.093	0.0124	0.0537,0.4254
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of CDAI at 12 weeks	-15.40	1.682	<.0001	-18.7656,-12.0435
the least-squares mean of the change of CDAI at 24 weeks	-20.61	1.266	<.0001	-23.1438,-18.0849

Footnote: CDAI, Clinical Disease Activity Index; N, number of patients in Age>=65 and <75 years population.
MMRM is applied by using the change of CDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline CDAI score and baseline CDAI score-by-week-interaction.

Table ANN. 139 CDAI Score Mixed-Effects Model Analysis (≥75 Years, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=14)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.94	0.345	0.0186	-1.6908,-0.1871
week 12	1.98	11.287	0.8640	-22.6156,26.5673
week 24	19.03	16.611	0.2743	-17.1648,55.2188
baseline*week 12	0.56	0.353	0.1355	-0.2041,1.3328
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of CDAI at 12 weeks	-14.74	3.990	0.0031	-23.4331,-6.0479
the least-squares mean of the change of CDAI at 24 weeks	-22.87	5.765	0.0019	-35.4327,-10.3118

Footnote: CDAI, Clinical Disease Activity Index; N, number of patients in Age>=75 years population.
MMRM is applied by using the change of CDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline CDAI score and baseline CDAI score-by-week-interaction.

Table ANN. 140 Demographics (Baseline SDAI subgroups, Effectiveness Analyses Population)

		Effectiveness Analyses Population			
		<Q1 (N=125)	*>=Q1 and <Q3 (N=251)*	*>=Q3 (N=126)*	*P value*
Age (years)	n (nmiss)	125 (0)	251 (0)	126 (0)	<.0001
	Mean (Std)	48.22 (12.27)	53.73 (12.61)	55.62 (11.96)	
	Median	51.00	55.00	56.00	
	Q1, Q3	36.00, 58.00	46.00, 63.00	49.00, 63.00	
	Min, Max	20, 71	21, 84	20, 85	
	18-34	19 (15.20%)	23 (9.16%)	7 (5.56%)	<.0001[a]
	35-44	29 (23.20%)	33 (13.15%)	9 (7.14%)	
	45-64	65 (52.00%)	145 (57.77%)	83 (65.87%)	
	65-74	12 (9.60%)	44 (17.53%)	19 (15.08%)	
	>=75	0	6 (2.39%)	8 (6.35%)	
	Total	125 (100.00%)	251 (100.00%)	126 (100.00%)	
Sex	Male	20 (16.00%)	44 (17.53%)	20 (15.87%)	0.9143[b]
	Female	105 (84.00%)	207 (82.47%)	106 (84.13%)	
	Total	125 (100.00%)	251 (100.00%)	126 (100.00%)	
Height (cm)	n (nmiss)	125 (0)	251 (0)	126 (0)	0.0038
	Mean (Std)	162.34 (7.17)	159.87 (6.64)	159.92 (6.40)	
	Median	160.00	160.00	160.00	
	Q1, Q3	158.00, 166.00	155.00, 165.00	156.00, 165.00	
	Min, Max	150, 198	145, 180	144, 179	
Weight (kg)	n (nmiss)	125 (0)	251 (0)	126 (0)	0.8654
	Mean (Std)	57.31 (9.92)	57.61 (10.09)	57.37 (10.14)	
	Median	55.00	57.00	56.00	
	Q1, Q3	50.00, 62.00	50.00, 64.00	50.00, 64.00	
	Min, Max	40.0, 89.0	27.0, 90.0	34.0, 100.0	
BMI (kg/m^2)	n (nmiss)	125 (0)	251 (0)	126 (0)	0.0348
	Mean (Std)	21.69 (3.13)	22.49 (3.44)	22.37 (3.36)	
	Median	21.05	22.22	21.76	
	Q1, Q3	19.53, 23.42	20.03, 24.49	19.96, 24.01	
	Min, Max	16.00, 33.20	12.84, 34.63	15.95, 36.73	
	<18.5	15 (12.00%)	28 (11.16%)	13 (10.32%)	0.2973[a]
	>=18.5-<24	85 (68.00%)	142 (56.57%)	81 (64.29%)	
	>=24-<28	19 (15.20%)	64 (25.50%)	24 (19.05%)	
	>=28	6 (4.80%)	17 (6.77%)	8 (6.35%)	
	Total	125 (100.00%)	251 (100.00%)	126 (100.00%)	
Smoking history	Never smoking	111 (88.80%)	220 (87.65%)	113 (89.68%)	0.9897[b]
	Used to smoke, given up now	5 (4.00%)	11 (4.38%)	4 (3.17%)	
	Still smoking	9 (7.20%)	20 (7.97%)	9 (7.14%)	
	Total	125 (100.00%)	251 (100.00%)	126 (100.00%)	

Footnote: The smoking history information were from 'Life History' page in CRF.

N, number of patients in population; nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.
The percentage denominator is the number of patients with non-missing value.
P values for continuous values were from Wilcoxon rank sum test.
a:P values for categorical values were from Chi-squared test. b:P values for categorical values were from Fisher exact tests.
Q1=125, Q3=126

Table ANN. 141 Rheumatoid Arthritis Diagnosis (Baseline SDAI Subgroups, Effectiveness Analyses Population)

		Effectiveness Analyses Population			
		<Q1 (N=125)	*>=Q1 and <Q3 (N=251)*	*>=Q3 (N=126)*	*P value*
Months from the onset date of RA to ICF (months)	n (nmiss)	125 (0)	251 (0)	126 (0)	0.1002
	Mean (Std)	85.74 (97.98)	104.69 (104.65)	112.25 (111.10)	
	Median	47.64	72.28	71.41	
	Q1, Q3	20.76, 120.61	22.83, 152.02	23.98, 158.36	
	Min, Max	0, 504.34	0, 623.67	2.04, 454.37	
Duration of RA (months)	n (nmiss)	125 (0)	251 (0)	126 (0)	0.1640
	Mean (Std)	73.58 (89.50)	88.89 (100.58)	101.18 (111.93)	
	Median	39.23	50.27	60.42	
	Q1, Q3	13.01, 101.22	13.80, 131.19	14.95, 145.58	
	Min, Max	0, 489.99	0, 623.67	0, 453.36	
	<=1 year	31 (24.80%)	54 (21.51%)	27 (21.43%)	0.7084[a]
	>1-<=3 years	29 (23.20%)	51 (20.32%)	22 (17.46%)	
	>3-<=10 years	38 (30.40%)	74 (29.48%)	38 (30.16%)	
	>10 years	27 (21.60%)	72 (28.69%)	39 (30.95%)	
	Total	125 (100.00%)	251 (100.00%)	126 (100.00%)	
Meet the ACR/EULAR 2010 criteria and number of points	Yes	125 (100.00%)	251 (100.00%)	126 (100.00%)	NA[b]
	n (nmiss)	125 (0)	251 (0)	126 (0)	
	Mean (Std)	8.02 (1.55)	8.31 (1.45)	9.07 (1.21)	
	Median	8.00	8.00	10.00	
	Q1, Q3	7.00, 10.00	7.00, 10.00	8.00, 10.00	
	Min, Max	6, 10	6, 10	6, 10	
	Total	125 (100.00%)	251 (100.00%)	126 (100.00%)	

Footnote: The duration of RA (months) = (Date of informed consent – date of diagnosis of RA) / 30.4375, round to 2 decimal place. Months from the onset date of RA to ICF (months) = (Date of informed consent – the onset date of RA) / 30.4375, round to 2 decimal place.
N, number of patients in population; nmiss, no. of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range. The percentage denominator is the number of patients with non-missing value.
P values for continuous values were from Wilcoxon rank sum test.
a:P values for categorical values were from Chi-squared test. b:P values for categorical values were from Fisher exact tests.
Q1=125, Q3=126

Table ANN. 142 **Drug Exposure (Baseline SDAI subgroups, Effectiveness Analyses Population)**

		Effectiveness Analyses Population			
		<Q1 (N=125)	*≥Q1 and <Q3 (N=251)*	*≥Q3. (N=126)*	*P value*
Overall Olumiant exposure (days)	n (nmiss)	125 (0)	250 (1)	126 (0)	0.2240
	Mean (Std)	163.49 (35.15)	166.28 (32.82)	160.80 (28.45)	
	Median	171.00	171.00	169.00	
	Q1, Q3	151.00, 183.00	159.00, 180.00	154.00, 177.00	
	Min, Max	79, 232	1, 314	55, 224	
Olumiant exposure (days)	n (nmiss)	125 (0)	250 (1)	126 (0)	0.3719
	Mean (Std)	161.48 (34.97)	164.07 (34.40)	159.32 (29.60)	
	Median	169.00	169.00	168.50	
	Q1, Q3	151.00, 182.00	156.00, 179.00	148.00, 176.00	
	Min, Max	79, 232	1, 314	55, 224	
Total patient year exposure		56.0	113.8	55.5	
Number of patients administered only 2mg Olumiant	n (%)	108 (86.40%)	226 (90.04%)	113 (89.68%)	0.5378
Number of patients administered only 4mg Olumiant	n (%)	10 (8.00%)	11 (4.38%)	6 (4.76%)	0.3043
Number of patients administered mixed dosage of Olumiant	n (%)	7 (5.60%)	14 (5.58%)	7 (5.56%)	>.9999

Footnote: N, number of patients in population; nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.
Overall Olumiant exposure (days) = Olumiant discontinue date in study termination page – the earliest start date of treatment in treatment information page +1.
Olumiant exposure (days) = sum of (end date of treatment - start date of treatment +1). The start and end date of treatment are from the same record in treatment information page.
The sum are based on all records in this page.
Total patient year exposure = sum of all patients' year exposure. Patient year exposure = overall Olumiant exposure in days for the patient / 365.25, keep 1 decimal place.
P values for continuous values were from Wilcoxon rank sum test. P values for categorical values were from Fisher exact tests.
Q1=125, Q3=126

Table ANN. 143 **DAS28-CRP Score (Baseline SDAI Subgroups, Effectiveness Analyses Population)**

		observed				*change (post −baseline)*			
visit		*Baseline SDAI<Q1 (N=125)*	*Baseline SDAI>=Q1 and <Q3 (N=251)*	*Baseline SDAI>=Q3 (N=126)*	*P value**	*Baseline SDAI<Q1 (N=125)*	*Baseline SDAI>=Q1 and <Q3 (N=251)*	*Baseline SDAI>=Q3 (N=126)*	*P value**
Baseline	n (nmiss)	125 (0)	251 (0)	126 (0)	<0.0001				
	Mean	2.24	4.86	6.74					
	(Std)	(1.38)	(0.72)	(0.63)					
	Median	2.56	4.81	6.71					
	Q1, Q3	0.56, 3.39	4.36, 5.33	6.29, 7.25					
	Min, Max	0.25, 4.70	2.96, 6.35	5.26, 8.02					
12-weeks	n (nmiss)	104 (21)	211 (40)	98 (28)	<0.0001	104 (21)	211 (40)	98 (28)	<0.0001
	Mean	1.77	3.23	4.21		-0.44	-1.62	-2.56	
	(Std)	(1.43)	(1.26)	(1.76)		(0.84)	(1.39)	(1.71)	
	Median	1.61	3.19	4.12		-0.29	-1.72	-2.42	
	Q1, Q3	0.33, 2.70	2.14, 4.17	2.70, 5.81		-0.84, -0.08	-2.82, -0.58	-4.07, -1.13	
	Min, Max	0.11, 6.00	1.18, 6.67	1.32, 7.88		-3.53, 3.58	-4.33, 2.43	-5.71, 0.68	
	P value					<.0001[b]	<.0001[b]	<.0001[b]	
24-weeks	n (nmiss)	88 (37)	178 (73)	84 (42)	<0.0001	88 (37)	178 (73)	84 (42)	<0.0001
	Mean	1.65	2.90	3.46		-0.67	-1.98	-3.29	
	(Std)	(1.23)	(1.24)	(1.69)		(0.92)	(1.42)	(1.72)	
	Median	1.69	2.70	3.12		-0.39	-2.22	-3.60	
	Q1, Q3	0.33, 2.40	1.83, 3.80	2.17, 4.81		-1.28, -0.18	-3.06, -0.94	-4.62, -1.93	
	Min, Max	0.11, 5.55	1.03, 6.75	1.14, 7.12		-3.67, 2.58	-4.43, 2.15	-6.01, 0.41	
	P value					<.0001[b]	<.0001[b]	<.0001[b]	

Footnote: CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Kruskal-Wallis tests.

Table ANN. 144 **DAS28-CRP Score (DAS28-CRP ≤3.2, Baseline SDAI Subgroups, Effectiveness Analyses Population)**

visit		*observed*				*change (post −baseline)*			
		Baseline SDAI<Q1 (N=125)	*Baseline SDAI>=Q 1 and <Q3 (N=251)*	*Baseline SDAI>=Q 3 (N=126)*	*P value**	*Baseline SDAI<Q1 (N=125)*	*Baseline SDAI>=Q 1 and <Q3 (N=251)*	*Baseline SDAI>=Q 3 (N=126)*	*P value**
Baseline	n (nmiss)	80 (45)	4 (247)	0 (126)	0.0025				
	%	64.00%	1.59%	0					
	Mean	1.45	3.06	NA (NA)					
	(Std)	(1.07)	(0.08)						
	Median	0.69	3.07	NA					
	Q1, Q3	0.44, 2.50	3.01, 3.12	NA					
	Min, Max	0.25, 3.13	2.96, 3.15	NA					
12-weeks	n (nmiss)	85 (40)	106 (145)	32 (94)	<0.0001	85 (40)	106 (145)	32 (94)	<0.0001
	%	81.73%	50.24%	32.65%		81.73%	50.24%	32.65%	
	Mean	1.25	2.18	2.24		-0.62	-2.59	-4.42	
	(Std)	(0.97)	(0.58)	(0.54)		(0.66)	(0.87)	(0.82)	
	Median	1.25	2.14	2.20		-0.34	-2.68	-4.26	
	Q1, Q3	0.29, 2.05	1.69, 2.70	1.79, 2.61		-0.96, -0.15	-3.32, -1.93	-4.99, -3.91	
	Min, Max	0.11, 2.96	1.18, 3.19	1.32, 3.13		-3.53, 0.55	-4.33, -0.60	-5.71, -2.21	
	P value					<.0001[b]	<.0001[a]	<.0001[a]	
24-weeks	n (nmiss)	79 (46)	111 (140)	43 (83)	<0.0001	79 (46)	111 (140)	43 (83)	<0.0001
	%	89.77%	62.36%	51.19%		89.77%	62.36%	51.19%	
	Mean	1.37	2.08	2.13		-0.81	-2.83	-4.60	
	(Std)	(0.94)	(0.57)	(0.60)		(0.79)	(0.83)	(0.74)	
	Median	1.53	1.98	2.25		-0.52	-2.89	-4.56	
	Q1, Q3	0.31, 2.19	1.62, 2.60	1.54, 2.61		-1.45, -0.19	-3.39, -2.34	-5.12, -4.15	
	Min, Max	0.11, 2.97	1.03, 3.13	1.14, 3.14		-3.67, 0.19	-4.43, -0.18	-6.01, -2.98	
	P value					<.0001[b]	<.0001[a]	<.0001[a]	

Footnote: CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
The numerator of percentage was n. The denominator of percentage for observed value was the number of patients with non-missing observed value at the visit in the subgroup. The denominator of
percentage for change from baseline was the number of patients with non-missing change at the visit in the subgroup.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Kruskal-Wallis tests.

Table ANN. 145 DAS28-CRP Score Summary by Category and Visit (Baseline SDAI <Q1, Effectiveness Analyses Population)

Visit	*<2.6*	*>=2.6 to <=3.2*	*>3.2 to <=5.1*	*>5.1*	*<=3.2*	*>3.2*	*Non-missing Total*
Baseline	64 (51.20%)	16 (12.80%)	45 (36.00%)	0	80 (64.00%)	45 (36.00%)	125 (100.00%)
12-weeks	73 (70.19%)	12 (11.54%)	17 (16.35%)	2 (1.92%)	85 (81.73%)	19 (18.27%)	104 (100.00%)
24-weeks	70 (79.55%)	9 (10.23%)	8 (9.09%)	1 (1.14%)	79 (89.77%)	9 (10.23%)	88 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 146 **DAS28-CRP Score Summary by Category and Visit (Baseline SDAI ≥Q1 and <Q3, Effectiveness Analyses Population)**

Visit	*<2.6*	*>=2.6 to <=3.2*	*>3.2 to <=5.1*	*>5.1*	*<=3.2*	*>3.2*	*Non-missing Total*
Baseline	0	4 (1.59%)	161 (64.14%)	86 (34.26%)	4 (1.59%)	247 (98.41%)	251 (100.00%)
12-weeks	75 (35.55%)	31 (14.69%)	86 (40.76%)	19 (9.00%)	106 (50.24%)	105 (49.76%)	211 (100.00%)
24-weeks	83 (46.63%)	28 (15.73%)	57 (32.02%)	10 (5.62%)	111 (62.36%)	67 (37.64%)	178 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 147 DAS28-CRP Score Summary by Category and Visit (Baseline SDAI ≥Q3, Effectiveness Analyses Population)

Visit	*<2.6*	*>=2.6 to <=3.2*	*>3.2 to <=5.1*	*>5.1*	*<=3.2*	*>3.2*	*Non-missing Total*
Baseline	0	0	0	126 (100.00%)	0	126 (100.00%)	126 (100.00%)
12-weeks	24 (24.49%)	8 (8.16%)	31 (31.63%)	35 (35.71%)	32 (32.65%)	66 (67.35%)	98 (100.00%)
24-weeks	30 (35.71%)	13 (15.48%)	22 (26.19%)	19 (22.62%)	43 (51.19%)	41 (48.81%)	84 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 148 DAS28-CRP Score Mixed-Effects Model Analysis (Baseline SDAI <Q1, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=125)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.32	0.063	<.0001	-0.4488,-0.2009
week 12	-0.05	0.142	0.7244	-0.3318,0.2314
week 24	0.09	0.168	0.5966	-0.2440,0.4225
baseline*week 12	0.15	0.068	0.0265	0.0182,0.2876
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of DAS28-CRP at 12 weeks	-0.44	0.077	<.0001	-0.5894,-0.2862
the least-squares mean of the change of DAS28-CRP at 24 weeks	-0.64	0.086	<.0001	-0.8132,-0.4725

Footnote: CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; N, number of patients in Baseline SDAI<Q1 population.
MMRM is applied by using the change of DAS28-CRP Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline DAS28 score and baseline DAS28 score-by-week-interaction.

Table ANN. 149 DAS28-CRP Score Mixed-Effects Model Analysis (Baseline SDAI ≥Q1 and <Q3, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=251)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.92	0.119	<.0001	-1.1561,-0.6868
week 12	2.24	0.589	0.0002	1.0784,3.4004
week 24	2.52	0.586	<.0001	1.3647,3.6755
baseline*week 12	0.13	0.092	0.1533	-0.0496,0.3138
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of DAS28-CRP at 12 weeks	-1.60	0.087	<.0001	-1.7726,-1.4283
the least-squares mean of the change of DAS28-CRP at 24 weeks	-1.96	0.086	<.0001	-2.1321,-1.7931

Footnote: CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; N, number of patients in Baseline SDAI>=Q1 and <Q3 population.
MMRM is applied by using the change of DAS28-CRP Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline DAS28 score and baseline DAS28 score-by-week-interaction.

Table ANN. 150 DAS28-CRP Score Mixed-Effects Model Analysis (Baseline SDAI ≥Q3, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=126)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.50	0.276	0.0728	-1.0476,0.0472
week 12	-0.33	1.803	0.8548	-3.9057,3.2442
week 24	0.12	1.872	0.9504	-3.5967,3.8300
baseline*week 12	0.17	0.255	0.4956	-0.3313,0.6801
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of DAS28-CRP at 12 weeks	-2.53	0.171	<.0001	-2.8739,-2.1951
the least-squares mean of the change of DAS28-CRP at 24 weeks	-3.27	0.175	<.0001	-3.6142,-2.9187

Footnote: CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; N, number of patients in Baseline SDAI>=Q3 population.
MMRM is applied by using the change of DAS28-CRP Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline DAS28 score and baseline DAS28 score-by-week-interaction.

Table ANN. 151 **SDAI Score (Baseline SDAI Subgroups, Effectiveness Analyses Population)**

visit		*observed*				*change (post −baseline)*			
		Baseline SDAI<Q1 (N=125)	*Baseline SDAI>=Q1 and <Q3 (N=251)*	*Baseline SDAI>=Q3 (N=126)*	*P value**	*Baseline SDAI<Q1 (N=125)*	*Baseline SDAI>=Q1 and <Q3 (N=251)*	*Baseline SDAI>=Q3 (N=126)*	*P value**
Baseline	n (nmiss)	125 (0)	251 (0)	126 (0)	<0.0001				
	Mean	9.74	29.39	57.10					
	(Std)	(5.76)	(6.68)	(9.79)					
	Median	10.92	28.32	55.17					
	Q1, Q3	3.97, 15.13	23.75, 34.39	48.40, 63.48					
	Min, Max	1.23, 18.22	18.86, 43.89	43.95, 85.92					
12-weeks	n (nmiss)	104 (21)	211 (40)	98 (28)	<0.0001	104 (21)	211 (40)	98 (28)	<0.0001
	Mean	6.43	14.59	27.37		-3.43	-14.56	-30.78	
	(Std)	(6.55)	(10.96)	(21.09)		(5.22)	(11.49)	(19.87)	
	Median	4.25	11.08	20.64		-3.00	-15.88	-32.26	
	Q1, Q3	1.29, 9.03	6.10, 22.14	10.00, 42.84		-6.23, 0.84	-23.08, 6.76	-46.25, 13.95	
	Min, Max	0.01, 32.24	0.10, 60.70	2.05, 75.30		-16.50, 20.44	-35.73, 25.74	-83.51, 5.15	
	P value					<.0001[b]	<.0001[b]	<.0001[b]	
24-weeks	n (nmiss)	88 (37)	178 (73)	84 (42)	<0.0001	88 (37)	178 (73)	84 (42)	<0.0001
	Mean	5.49	11.56	19.34		-4.38	-17.72	-38.56	
	(Std)	(6.83)	(10.57)	(19.29)		(6.84)	(11.69)	(19.14)	
	Median	3.81	7.84	11.51		-3.77	-18.82	-41.92	
	Q1, Q3	1.03, 7.18	3.40, 17.00	4.72, 27.39		-8.98, 1.28	-26.08, 10.09	-53.07, 30.44	
	Min, Max	0.02, 46.71	0.02, 47.12	0.16, 66.11		-17.39, 31.01	-40.15, 15.00	-83.91, 13.75	
	P value					<.0001[b]	<.0001[b]	<.0001[b]	

Footnote: nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Kruskal-Wallis tests.

Table ANN. 152 **SDAI Score (SDAI ≤11, Baseline SDAI subgroups, Effectiveness Analyses Population)**

visit		*observed*				*change (post −baseline)*			
		Baseline SDAI<Q1 (N=125)	*Baseline SDAI>=Q1 and <Q3 (N=251)*	*Baseline SDAI>=Q3 (N=126)*	*P value**	*Baseline SDAI<Q1 (N=125)*	*Baseline SDAI>=Q1 and <Q3 (N=251)*	*Baseline SDAI>=Q3 (N=126)*	*P value**
Baseline	n (nmiss)	63 (62)	0 (251)	0 (126)	NA				
	%	50.40%	0	0					
	Mean (Std)	4.60 (2.83)	NA (NA)	NA (NA)					
	Median	3.97	NA	NA					
	Q1, Q3	2.01, 6.12	NA	NA					
	Min, Max	1.23, 10.92	NA	NA					
12-weeks	n (nmiss)	82 (43)	104 (147)	30 (96)	<0.0001	82 (43)	104 (147)	30 (96)	<0.0001
	%	78.85%	49.29%	30.61%		78.85%	49.29%	30.61%	
	Mean (Std)	3.62 (3.01)	5.93 (3.02)	6.37 (3.28)		-4.64 (4.01)	-22.68 (6.41)	-51.54 (11.06)	
	Median	2.13	6.09	7.39		-3.52	-22.49	-53.05	
	Q1, Q3	1.05, 6.45	3.51, 8.34	3.17, 9.31		-7.00, -1.40	-27.11, -17.28	-58.24, -40.86	
	Min, Max	0.01, 10.66	0.10, 10.93	2.05, 10.88		-16.50, 0.81	-35.73, -10.32	-83.51, -33.66	
	P value					<.0001[b]	<.0001[b]	<.0001[a]	
24-weeks	n (nmiss)	79 (46)	105 (146)	42 (84)	0.0811	79 (46)	105 (146)	42 (84)	<0.0001
	%	89.77%	58.99%	50.00%		89.77%	58.99%	50.00%	
	Mean (Std)	3.69 (2.93)	4.41 (2.89)	4.93 (3.23)		-5.69 (4.72)	-24.68 (6.79)	-51.46 (10.23)	
	Median	3.37	4.00	4.72		-4.30	-23.88	-51.80	
	Q1, Q3	0.96, 6.30	2.32, 6.47	2.05, 7.05		-9.86, -1.63	-30.06, -19.10	-56.59, -43.59	
	Min, Max	0.02, 10.86	0.02, 10.95	0.16, 10.99		-17.39, 0.41	-40.15, -9.56	-83.91, -35.37	
	P value					<.0001[b]	<.0001[a]	<.0001[a]	

Footnote: nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
The numerator of percentage was n. The denominator of percentage for observed value was the number of patients with non-missing observed value at the visit in the subgroup. The denominator of
percentage for change from baseline was the number of patients with non-missing change at the visit in the subgroup.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Wilcoxon rank sum tests or Kruskal-Wallis tests.

Table ANN. 153 SDAI Score Summary by Category and Visit (Baseline SDAI <Q1, Effectiveness Analyses Population)

Visit	*<=3.3*	*>3.3 to <=11.0*	*>11.0 to <=26.0*	*>26.0*	*<=11.0*	*>11.0*	*Non-missing Total*
Baseline	24 (19.20%)	39 (31.20%)	62 (49.60%)	0	63 (50.40%)	62 (49.60%)	125 (100.00%)
12-weeks	49 (47.12%)	33 (31.73%)	20 (19.23%)	2 (1.92%)	82 (78.85%)	22 (21.15%)	104 (100.00%)
24-weeks	39 (44.32%)	40 (45.45%)	7 (7.95%)	2 (2.27%)	79 (89.77%)	9 (10.23%)	88 (100.00%)

Footnote: Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 154 SDAI Score Summary by Category and Visit (Baseline SDAI ≥Q1 and <Q3, Effectiveness Analyses Population)

Visit	*<=3.3*	*>3.3 to <=11.0*	*>11.0 to <=26.0*	*>26.0*	*<=11.0*	*>11.0*	*Non-missing Total*
Baseline	0	0	95 (37.85%)	156 (62.15%)	0	251 (100.00%)	251 (100.00%)
12-weeks	25 (11.85%)	79 (37.44%)	71 (33.65%)	36 (17.06%)	104 (49.29%)	107 (50.71%)	211 (100.00%)
24-weeks	43 (24.16%)	62 (34.83%)	54 (30.34%)	19 (10.67%)	105 (58.99%)	73 (41.01%)	178 (100.00%)

Footnote: Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 155 SDAI Score Summary by Category and Visit (Baseline SDAI ≥Q3, Effectiveness Analyses Population)

Visit	*<=3.3*	*>3.3 to <=11.0*	*>11.0 to <=26.0*	*>26.0*	*<=11.0*	*>11.0*	*Non-missing Total*
Baseline	0	0	0	126 (100.00%)	0	126 (100.00%)	126 (100.00%)
12-weeks	8 (8.16%)	22 (22.45%)	28 (28.57%)	40 (40.82%)	30 (30.61%)	68 (69.39%)	98 (100.00%)
24-weeks	14 (16.67%)	28 (33.33%)	20 (23.81%)	22 (26.19%)	42 (50.00%)	42 (50.00%)	84 (100.00%)

Footnote: Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 156 SDAI Score Mixed-Effects Model Analysis (Baseline SDAI <Q1, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=125)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.52	0.117	<.0001	-0.7538,-0.2901
week 12	-0.58	0.919	0.5320	-2.3971,1.2448
week 24	0.81	1.317	0.5400	-1.7999,3.4189
baseline*week 12	0.24	0.120	0.0527	-0.0028,0.4730
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of SDAI at 12 weeks	-3.40	0.471	<.0001	-4.3374,-2.4724
the least-squares mean of the change of SDAI at 24 weeks	-4.34	0.653	<.0001	-5.6328,-3.0434

Footnote: SDAI, Simplified Disease Activity Index; N, number of patients in Baseline SDAI<Q1 population.
MMRM is applied by using the change of SDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline SDAI score and baseline SDAI score-by-week-interaction.

Table ANN. 157 SDAI Score Mixed-Effects Model Analysis (Baseline SDAI ≥Q1 and <Q3, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=251)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.77	0.109	<.0001	-0.9851,-0.5565
week 12	2.40	3.418	0.4831	-4.3342,9.1365
week 24	4.94	3.261	0.1312	-1.4861,11.3677
baseline*week 12	0.20	0.079	0.0113	0.0463,0.3581
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of SDAI at 12 weeks	-14.21	0.754	<.0001	-15.6979,-12.7250
the least-squares mean of the change of SDAI at 24 weeks	-17.58	0.717	<.0001	-18.9914,-16.1652

Footnote: SDAI, Simplified Disease Activity Index; N, number of patients in Baseline SDAI>=Q1 and <Q3 population.
MMRM is applied by using the change of SDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline SDAI score and baseline SDAI score-by-week-interaction.

Table ANN. 158 SDAI Score Mixed-Effects Model Analysis (Baseline SDAI ≥Q3, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=126)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.39	0.197	0.0487	-0.7855,-0.0023
week 12	-15.24	11.954	0.2051	-38.9492,8.4654
week 24	-15.68	11.599	0.1795	-38.6803,7.3279
baseline*week 12	0.13	0.185	0.4754	-0.2347,0.5002
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of SDAI at 12 weeks	-30.40	1.992	<.0001	-34.3504,-26.4510
the least-squares mean of the change of SDAI at 24 weeks	-38.54	1.930	<.0001	-42.3656,-34.7093

Footnote: SDAI, Simplified Disease Activity Index; N, number of patients in Baseline SDAI>=Q3 population.
MMRM is applied by using the change of SDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline SDAI score and baseline SDAI score-by-week-interaction.

Table ANN. 159 **CDAI Score (Baseline SDAI Subgroups, Effectiveness Analyses Population)**

visit		*observed*				*change (post −baseline)*			
		Baseline SDAIQ1 (N=125)	*Baseline SDAI>=Q1 and <Q3 (N=251)*	*Baseline SDAI>=Q3 (N=126)*	*P value**	*Baseline SDAIQ1 (N=125)*	*Baseline SDAI>=Q1 and <Q3 (N=251)*	*Baseline SDAI>=Q3 (N=126)*	*P value**
Baseline	n (nmiss)	125 (0)	251 (0)	126 (0)	<0.0001				
	Mean	9.16	26.88	53.36					
	(Std)	(5.43)	(6.44)	(9.52)					
	Median	10.20	26.00	52.25					
	Q1, Q3	3.60, 14.00	22.00, 31.10	45.80, 60.00					
	Min, Max	1.20, 18.00	12.70, 43.50	30.00, 74.00					
12-weeks	n (nmiss)	106 (19)	214 (37)	112 (14)	<0.0001	106 (19)	214 (37)	112 (14)	<0.0001
	Mean	6.20	13.56	26.15		-3.18	-13.10	-27.45	
	(Std)	(6.03)	(10.53)	(19.80)		(4.90)	(10.51)	(18.30)	
	Median	4.40	10.35	21.20		-2.65	-14.35	-27.95	
	Q1, Q3	1.20, 9.20	5.80, 19.70	9.15, 42.00		-5.50, 0.80	-21.00, 5.20	-41.70, 10.30	
	Min, Max	0.000, 31.00	0.000, 60.00	0.000, 71.60		-16.50, 21.00	-35.10, 25.90	-66.20, 5.40	
	P value					<.0001[b]	<.0001[b]	<.0001[b]	
24-weeks	n (nmiss)	90 (35)	188 (63)	99 (27)	<0.0001	90 (35)	188 (63)	99 (27)	<0.0001
	Mean	4.83	10.88	20.23		-4.36	-15.95	-33.67	
	(Std)	(6.26)	(10.42)	(18.86)		(6.42)	(11.13)	(17.34)	
	Median	3.35	7.85	13.00		-3.45	-17.85	-35.00	
	Q1, Q3	1.00, 7.00	2.70, 16.00	4.20, 38.50		-8.50, 1.50	-23.50, 7.45	-46.00, 22.90	
	Min, Max	0.000, 46.60	0.000, 45.80	0.000, 66.00		-15.50, 32.50	-38.00, 15.00	-67.60, 14.00	
	P value					<.0001[b]	<.0001[b]	<.0001[b]	

Footnote: nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Kruskal-Wallis tests.

Table ANN. 160 **CDAI Score (CDAI ≤10, Baseline SDAI Subgroups, Effectiveness Analyses Population)**

visit		*observed*				*change (post −baseline)*			
		Baseline SDAI<Q1 (N=125)	*Baseline SDAI>=Q1 and <Q3 (N=251)*	*Baseline SDAI>=Q3 (N=126)*	*P value**	*Baseline SDAI<Q1 (N=125)*	*Baseline SDAI>=Q1 and <Q3 (N=251)*	*Baseline SDAI>=Q3 (N=126)*	*P value**
Baseline	n (nmiss)	61 (64)	0 (251)	0 (126)	NA				
	%	48.80%	0	0					
	Mean (Std)	4.15 (2.50)	NA (NA)	NA (NA)					
	Median	3.60	NA	NA					
	Q1, Q3	1.90, 5.80	NA	NA					
	Min, Max	1.20, 10.00	NA	NA					
12-weeks	n (nmiss)	83 (42)	105 (146)	31 (95)	<0.0001	83 (42)	105 (146)	31 (95)	<0.0001
	%	78.30%	49.07%	27.68%		78.30%	49.07%	27.68%	
	Mean (Std)	3.61 (3.02)	5.32 (2.76)	5.50 (2.96)		-4.26 (3.82)	-20.46 (5.98)	-46.90 (10.75)	
	Median	2.00	5.70	6.80		-3.10	-20.00	-47.30	
	Q1, Q3	1.00, 6.40	3.00, 7.50	2.30, 8.00		-6.90, -1.10	-24.00, -16.00	-55.00, -38.20	
	Min, Max	0.000, 10.00	0.000, 10.00	0.000, 10.00		-16.50, 1.60	-35.10, -7.20	-66.20, -23.00	
	P value					<.0001[b]	<.0001[a]	<.0001[a]	
24-weeks	n (nmiss)	82 (43)	114 (137)	44 (82)	0.1275	82 (43)	114 (137)	44 (82)	<0.0001
	%	91.11%	60.64%	44.44%		91.11%	60.64%	44.44%	
	Mean (Std)	3.43 (2.88)	4.11 (2.91)	4.42 (3.21)		-5.39 (4.40)	-22.41 (6.45)	-46.78 (9.15)	
	Median	2.75	3.55	4.00		-3.95	-22.00	-45.60	
	Q1, Q3	0.80, 6.00	2.00, 6.50	1.70, 7.00		-9.10, -1.60	-26.10, -18.00	-53.30, -40.45	
	Min, Max	0.000, 10.00	0.000, 10.00	0.000, 10.00		-15.50, 0.50	-38.00, -6.70	-67.60, -26.00	
	P value					<.0001[b]	<.0001[a]	<.0001[a]	

Footnote: nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
The numerator of percentage was n. The denominator of percentage for observed value was the number of patients with non-missing observed value at the visit in the subgroup. The denominator of
percentage for change from baseline was the number of patients with non-missing change at the visit in the subgroup.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Wilcoxon rank sum tests or Kruskal-Wallis tests.

Table ANN. 161 CDAI Score Summary by Category and Visit (Baseline SDAI <Q1, Effectiveness Analyses Population)

Visit	*<=2.8*	*>2.8 to <=10.0*	*>10.0 to <=22.0*	*>22.0*	*<=10.0*	*>10.0*	*Non-missing Total*
Baseline	24 (19.20%)	37 (29.60%)	64 (51.20%)	0	61 (48.80%)	64 (51.20%)	125 (100.00%)
12-weeks	45 (42.45%)	38 (35.85%)	21 (19.81%)	2 (1.89%)	83 (78.30%)	23 (21.70%)	106 (100.00%)
24-weeks	41 (45.56%)	41 (45.56%)	6 (6.67%)	2 (2.22%)	82 (91.11%)	8 (8.89%)	90 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 162 CDAI Score Summary by Category and Visit (Baseline SDAI ≥Q1 and <Q3, Effectiveness Analyses Population)

Visit	*<=2.8*	*>2.8 to <=10.0*	*>10.0 to <=22.0*	*>22.0*	*<=10.0*	*>10.0*	*Non-missing Total*
Baseline	0	0	68 (27.09%)	183 (72.91%)	0	251 (100.00%)	251 (100.00%)
12-weeks	25 (11.68%)	80 (37.38%)	67 (31.31%)	42 (19.63%)	105 (49.07%)	109 (50.93%)	214 (100.00%)
24-weeks	48 (25.53%)	66 (35.11%)	50 (26.60%)	24 (12.77%)	114 (60.64%)	74 (39.36%)	188 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 163 CDAI Score Summary by Category and Visit (Baseline SDAI ≥Q3, Effectiveness Analyses Population)

Visit	*<=2.8*	*>2.8 to <=10.0*	*>10.0 to <=22.0*	*>22.0*	*<=10.0*	*>10.0*	*Non-missing Total*
Baseline	0	0	0	126 (100.00%)	0	126 (100.00%)	126 (100.00%)
12-weeks	8 (7.14%)	23 (20.54%)	27 (24.11%)	54 (48.21%)	31 (27.68%)	81 (72.32%)	112 (100.00%)
24-weeks	15 (15.15%)	29 (29.29%)	22 (22.22%)	33 (33.33%)	44 (44.44%)	55 (55.56%)	99 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 164 CDAI Score Mixed-Effects Model Analysis (Baseline SDAI <Q1, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=125)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.56	0.117	<.0001	-0.7913,-0.3259
week 12	-0.25	0.860	0.7754	-1.9502,1.4581
week 24	0.78	1.230	0.5247	-1.6511,3.2204
baseline*week 12	0.25	0.123	0.0483	0.0019,0.4906
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of CDAI at 12 weeks	-3.15	0.437	<.0001	-4.0140,-2.2813
the least-squares mean of the change of CDAI at 24 weeks	-4.40	0.601	<.0001	-5.5959,-3.2136

Footnote: CDAI, Clinical Disease Activity Index; N, number of patients in Baseline SDAI<Q1 population.
MMRM is applied by using the change of CDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline CDAI score and baseline CDAI score-by-week-interaction.

Table ANN. 165 CDAI Score Mixed-Effects Model Analysis (Baseline SDAI ≥Q1 and <Q3, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=251)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.66	0.109	<.0001	-0.8790,-0.4479
week 12	-0.68	3.008	0.8221	-6.6047,5.2508
week 24	1.92	3.006	0.5245	-4.0077,7.8398
baseline*week 12	0.21	0.069	0.0026	0.0735,0.3441
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of CDAI at 12 weeks	-12.83	0.693	<.0001	-14.1999,-11.4671
the least-squares mean of the change of CDAI at 24 weeks	-15.82	0.690	<.0001	-17.1850,-14.4641

Footnote: CDAI, Clinical Disease Activity Index; N, number of patients in Baseline SDAI>=Q1 and <Q3 population.
MMRM is applied by using the change of CDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline CDAI score and baseline CDAI score-by-week-interaction.

Table ANN. 166 CDAI Score Mixed-Effects Model Analysis (Baseline SDAI ≥Q3, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=126)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.22	0.178	0.2158	-0.5734,0.1309
week 12	-17.11	9.657	0.0792	-36.2375,2.0245
week 24	-22.15	9.704	0.0243	-41.3773,-2.9295
baseline*week 12	0.03	0.159	0.8538	-0.2861,0.3449
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of CDAI at 12 weeks	-27.42	1.708	<.0001	-30.7990,-24.0338
the least-squares mean of the change of CDAI at 24 weeks	-34.04	1.692	<.0001	-37.3967,-30.6920

Footnote: CDAI, Clinical Disease Activity Index; N, number of patients in Baseline SDAI>=Q3 population.
MMRM is applied by using the change of CDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline CDAI score and baseline CDAI score-by-week-interaction.

Table ANN. 167 Demographics (Baseline RF and Anti-CCP Subgroups, Effectiveness Analyses Population)

		Effectiveness Analyses Population		
		both negative (N=19)	*any positive (N=355)*	*P value*
Age (years)	n (nmiss)	19 (0)	355 (0)	0.1867
	Mean (Std)	50.11 (9.73)	53.68 (12.44)	
	Median	51.00	55.00	
	Q1, Q3	48.00, 60.00	46.00, 63.00	
	Min, Max	32, 63	20, 85	
	18-34	3 (15.79%)	29 (8.17%)	0.1061[b]
	35-44	1 (5.26%)	51 (14.37%)	
	45-64	15 (78.95%)	206 (58.03%)	
	65-74	0	57 (16.06%)	
	>=75	0	12 (3.38%)	
	Total	19 (100.00%)	355 (100.00%)	
Sex	Male	2 (10.53%)	67 (18.87%)	0.5459[b]
	Female	17 (89.47%)	288 (81.13%)	
	Total	19 (100.00%)	355 (100.00%)	
Height (cm)	n (nmiss)	19 (0)	355 (0)	0.3892
	Mean (Std)	159.68 (6.30)	160.63 (6.92)	
	Median	158.00	160.00	
	Q1, Q3	156.00, 162.00	156.00, 165.00	
	Min, Max	150, 174	144, 198	
Weight (kg)	n (nmiss)	19 (0)	355 (0)	0.1922
	Mean (Std)	54.37 (8.71)	57.46 (9.81)	
	Median	53.00	56.00	
	Q1, Q3	49.00, 64.00	50.00, 64.00	
	Min, Max	40.0, 72.5	34.0, 100.0	
BMI (kg/m^2)	n (nmiss)	19 (0)	355 (0)	0.1938
	Mean (Std)	21.25 (2.70)	22.23 (3.29)	
	Median	20.58	21.64	
	Q1, Q3	19.10, 23.95	19.98, 24.02	
	Min, Max	16.65, 26.04	15.95, 36.73	
	<18.5	1 (5.26%)	40 (11.27%)	0.7747[b]
	>=18.5-<24	14 (73.68%)	225 (63.38%)	
	>=24-<28	4 (21.05%)	68 (19.15%)	
	>=28	0	22 (6.20%)	
	Total	19 (100.00%)	355 (100.00%)	
Smoking history	Never smoking	16 (84.21%)	310 (87.32%)	0.2504[b]
	Used to smoke, given up now	2 (10.53%)	14 (3.94%)	
	Still smoking	1 (5.26%)	31 (8.73%)	
	Total	19 (100.00%)	355 (100.00%)	

Footnote: The smoking history information were from 'Life History' page in CRF.
N, number of patients in population; nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.

The percentage denominator is the number of patients with non-missing value.
P values for continuous values were from Wilcoxon rank sum test. b: P values for categorical values were from Fisher exact tests.

Table ANN. 168 Rheumatoid Arthritis Diagnosis (Baseline RF and Anti-CCP Subgroups, Effectiveness Analyses Population)

		Effectiveness Analyses Population		
		both negative (N=19)	*any positive (N=355)*	*P value*
Months from the onset date of RA to ICF (months)	n (nmiss)	19 (0)	355 (0)	0.4017
	Mean (Std)	92.61 (107.51)	103.78 (109.65)	
	Median	41.72	64.36	
	Q1, Q3	10.81, 149.39	22.83, 145.58	
	Min, Max	2.37, 335.84	0, 623.67	
Duration of RA (months)	n (nmiss)	19 (0)	355 (0)	0.0833
	Mean (Std)	70.48 (107.15)	92.01 (107.47)	
	Median	14.65	52.40	
	Q1, Q3	2.37, 103.26	14.19, 132.50	
	Min, Max	0.46, 335.84	0, 623.67	
	<=1 year	7 (36.84%)	77 (21.69%)	0.1098[b]
	>1-<=3 years	6 (31.58%)	71 (20.00%)	
	>3-<=10 years	2 (10.53%)	106 (29.86%)	
	>10 years	4 (21.05%)	101 (28.45%)	
	Total	19 (100.00%)	355 (100.00%)	
Meet the ACR/EULAR 2010 criteria and number of points	Yes	19 (100.00%)	355 (100.00%)	NA[b]
	n (nmiss)	19 (0)	355 (0)	
	Mean (Std)	7.37 (1.12)	8.55 (1.48)	
	Median	7.00	9.00	
	Q1, Q3	7.00, 7.00	7.00, 10.00	
	Min, Max	6, 10	6, 10	
	Total	19 (100.00%)	355 (100.00%)	

Footnote: The duration of RA (months) = (Date of informed consent – date of diagnosis of RA) / 30.4375, round to 2 decimal place. Months from the onset date of RA to ICF (months) = (Date of informed consent – the onset date of RA) / 30.4375, round to 2 decimal place.
N, number of patients in population; nmiss, no. of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range. The percentage denominator is the number of patients with non-missing value.
P values for continuous values were from Wilcoxon rank sum test. b: P values for categorical values were from Fisher exact tests.

Table ANN. 169 Drug Exposure (Baseline RF and Anti-CCP Subgroups, Effectiveness Analyses Population)

		Effectiveness Analyses Population		
		both negative (N=19)	*any positive (N=355)*	*P value*
Overall Olumiant exposure (days)	n (nmiss)	19 (0)	354 (1)	0.9382
	Mean (Std)	165.37 (23.43)	163.46 (33.25)	
	Median	170.00	169.00	
	Q1, Q3	158.00, 177.00	156.00, 179.00	
	Min, Max	82, 194	1, 314	
Olumiant exposure (days)	n (nmiss)	19 (0)	354 (1)	0.9061
	Mean (Std)	164.11 (23.04)	161.48 (34.44)	
	Median	170.00	169.00	
	Q1, Q3	157.00, 174.00	155.00, 179.00	
	Min, Max	82, 194	1, 314	
Total patient year exposure		8.6	158.4	
Number of patients administered only 2mg Olumiant	n (%)	19 (100.00%)	319 (89.86%)	0.2370
Number of patients administered only 4mg Olumiant	n (%)	0	19 (5.35%)	0.6122
Number of patients administered mixed dosage of Olumiant	n (%)	0	17 (4.79%)	>.9999

Footnote: N, number of patients in population; nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.
Overall Olumiant exposure (days) = Olumiant discontinue date in study termination page – the earliest start date of treatment in treatment information page +1.
Olumiant exposure (days) = sum of (end date of treatment - start date of treatment +1). The start and end date of treatment are from the same record in treatment information page.
The sum are based on all records in this page.
Total patient year exposure = sum of all patients' year exposure. Patient year exposure = overall Olumiant exposure in days for the patient / 365.25, keep 1 decimal place.
P values for continuous values were from Wilcoxon rank sum test. P values for categorical values were from Fisher exact tests.

Table ANN. 170 **DAS28-CRP Score (Baseline RF and Anti-CCP Subgroups, Effectiveness Analyses Population)**

visit		*observed*			*change (post −baseline)*		
		Baseline RF and anti-CCP both negative (N=19)	*Baseline RF and anti-CCP any positive (N=355)*	*P value**	*Baseline RF and anti-CCP both negative (N=19)*	*Baseline RF and anti-CCP any positive (N=355)*	*P value**
Baseline	n (nmiss)	19 (0)	352 (3)	0.4960			
	Mean (Std)	3.71 (2.95)	4.72 (1.80)				
	Median	4.90	4.83				
	Q1, Q3	0.54, 6.74	3.83, 6.01				
	Min, Max	0.35, 7.33	0.25, 8.02				
12-weeks	n (nmiss)	17 (2)	291 (64)	0.0008	17 (2)	291 (64)	0.8997
	Mean (Std)	1.60 (1.52)	3.02 (1.60)		-1.78 (1.77)	-1.69 (1.50)	
	Median	1.34	2.84		-1.22	-1.52	
	Q1, Q3	0.33, 2.51	1.84, 4.09		-2.65, -0.25	-2.88, -0.55	
	Min, Max	0.24, 5.24	0.11, 7.88		-5.12, -0.02	-5.71, 2.12	
	P value				<.0001[b]	<.0001[b]	
24-weeks	n (nmiss)	14 (5)	247 (108)	0.0304	14 (5)	247 (108)	0.4491
	Mean (Std)	1.76 (1.63)	2.68 (1.43)		-1.82 (1.82)	-2.06 (1.57)	
	Median	1.49	2.56		-1.15	-2.01	
	Q1, Q3	0.32, 2.82	1.67, 3.58		-3.38, -0.24	-3.30, -0.73	
	Min, Max	0.17, 5.17	0.11, 7.12		-5.37, -0.03	-6.01, 1.98	
	P value				0.0001[b]	<.0001[b]	

Footnote: CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Wilcoxon rank sum tests.

Table ANN. 171 **DAS28-CRP Score (DAS28-CRP ≤3.2, Baseline RF and Anti-CCP Subgroups, Effectiveness Analyses Population)**

visit		*observed*			*change (post −baseline)*		
		Baseline RF and anti-CCP both negative (N=14)	*Baseline RF and anti-CCP any positive (N=247)*	*P value**	*Baseline RF and anti-CCP both negative (N=14)*	*Baseline RF and anti-CCP any positive (N=247)*	*P value**
Baseline	n (nmiss)	9 (10)	56 (299)	0.2624			
	%	47.37%	15.91%				
	Mean (Std)	0.77 (0.68)	1.62 (1.14)				
	Median	0.54	2.07				
	Q1, Q3	0.50, 0.68	0.40, 2.72				
	Min, Max	0.35, 2.56	0.25, 3.15				
12-weeks	n (nmiss)	14 (5)	166 (189)	0.0036	14 (5)	166 (189)	0.1577
	%	82.35%	57.04%		82.35%	57.04%	
	Mean (Std)	1.05 (0.93)	1.89 (0.84)		-1.64 (1.93)	-2.18 (1.48)	
	Median	0.41	1.99		-0.42	-2.10	
	Q1, Q3	0.28, 1.92	1.47, 2.53		-3.41, -0.20	-3.33, -0.92	
	Min, Max	0.24, 2.60	0.11, 3.19		-5.12, -0.02	-5.71, 0.20	
	P value				0.0001[b]	<.0001[b]	
24-weeks	n (nmiss)	11 (8)	169 (186)	0.0140	11 (8)	169 (186)	0.1301
	%	78.57%	68.42%		78.57%	68.42%	
	Mean (Std)	1.10 (1.02)	1.91 (0.77)		-1.70 (2.03)	-2.50 (1.49)	
	Median	0.37	1.90		-0.48	-2.60	
	Q1, Q3	0.32, 2.08	1.49, 2.57		-3.74, -0.22	-3.59, -1.37	
	Min, Max	0.17, 2.82	0.11, 3.14		-5.37, -0.03	-6.01, 0.19	
	P value				0.0010[b]	<.0001[b]	

Footnote: CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
The numerator of percentage was n. The denominator of percentage for observed value was the number of patients with non-missing observed value at the visit in the subgroup. The denominator of
percentage for change from baseline was the number of patients with non-missing change at the visit in the subgroup.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Wilcoxon rank sum tests.

Table ANN. 172 DAS28-CRP Score Summary by Category and Visit (Baseline RF and Anti-CCP Both Negative, Effectiveness Analyses Population)

Visit	*<2.6*	*>=2.6 to <=3.2*	*>3.2 to <=5.1*	*>5.1*	*<=3.2*	*>3.2*	*Non-missing Total*
Baseline	9 (47.37%)	0	1 (5.26%)	9 (47.37%)	9 (47.37%)	10 (52.63%)	19 (100.00%)
12-weeks	13 (76.47%)	1 (5.88%)	2 (11.76%)	1 (5.88%)	14 (82.35%)	3 (17.65%)	17 (100.00%)
24-weeks	10 (71.43%)	1 (7.14%)	2 (14.29%)	1 (7.14%)	11 (78.57%)	3 (21.43%)	14 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 173 DAS28-CRP Score Summary by Category and Visit (Baseline RF and Anti-CCP Any Positive, Effectiveness Analyses Population)

Visit	*<2.6*	*>=2.6 to <=3.2*	*>3.2 to <=5.1*	*>5.1*	*<=3.2*	*>3.2*	*Non-missing Total*
Baseline	40 (11.36%)	16 (4.55%)	146 (41.48%)	150 (42.61%)	56 (15.91%)	296 (84.09%)	352 (100.00%)
12-weeks	128 (43.99%)	38 (13.06%)	94 (32.30%)	31 (10.65%)	166 (57.04%)	125 (42.96%)	291 (100.00%)
24-weeks	129 (52.23%)	40 (16.19%)	63 (25.51%)	15 (6.07%)	169 (68.42%)	78 (31.58%)	247 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 174 DAS28-CRP Score Mixed-Effects Model Analysis (Baseline RF and Anti-CCP Both Negative, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=19)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.52	0.090	<.0001	-0.7050,-0.3269
week 12	0.07	0.282	0.7950	-0.5197,0.6683
week 24	0.08	0.417	0.8514	-0.8011,0.9599
baseline*week 12	-0.03	0.096	0.7268	-0.2354,0.1676
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of DAS28-CRP at 12 weeks	-1.83	0.181	<.0001	-2.2166,-1.4523
the least-squares mean of the change of DAS28-CRP at 24 weeks	-1.71	0.254	<.0001	-2.2469,-1.1763

Footnote: CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; N, number of patients in RF and anti-CCP both negative population.
MMRM is applied by using the change of DAS28-CRP Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline DAS28 score and baseline DAS28 score-by-week-interaction.

Table ANN. 175 DAS28-CRP Score Mixed-Effects Model Analysis (Baseline RF and Anti-CCP Any Positive, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=355)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.56	0.042	<.0001	-0.6407,-0.4764
week 12	0.45	0.206	0.0295	0.0451,0.8560
week 24	0.58	0.210	0.0063	0.1646,0.9929
baseline*week 12	0.11	0.037	0.0037	0.0351,0.1795
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of DAS28-CRP at 12 weeks	-1.68	0.074	<.0001	-1.8260,-1.5364
the least-squares mean of the change of DAS28-CRP at 24 weeks	-2.06	0.073	<.0001	-2.2044,-1.9156

Footnote: CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; N, number of patients in RF and anti-CCP any positive population.
MMRM is applied by using the change of DAS28-CRP Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline DAS28 score and baseline DAS28 score-by-week-interaction.

Table ANN. 176 **SDAI Score (Baseline RF and Anti-CCP Subgroups, Effectiveness Analyses Population)**

visit		*observed*			*change (post −baseline)*		
		Baseline RF and anti-CCP both negative (N=19)	*Baseline RF and anti-CCP any positive (N=355)*	*P value**	*Baseline RF and anti-CCP both negative (N=19)*	*Baseline RF and anti-CCP any positive (N=355)*	*P value**
Baseline	n (nmiss)	19 (0)	352 (3)	0.3911			
	Mean (Std)	27.90 (24.54)	31.34 (18.37)				
	Median	23.70	28.23				
	Q1, Q3	4.29, 51.14	18.90, 42.65				
	Min, Max	2.23, 66.73	1.23, 85.92				
12-weeks	n (nmiss)	17 (2)	291 (64)	0.0049	17 (2)	291 (64)	0.9955
	Mean (Std)	7.36 (9.83)	14.55 (14.27)		-18.36 (18.99)	-16.72 (15.65)	
	Median	3.79	10.24		-7.00	-14.61	
	Q1, Q3	1.39, 8.56	4.63, 19.93		-33.70, -3.26	-25.26, -4.66	
	Min, Max	0.91, 39.31	0.01, 75.30		-57.57, -0.20	-83.51, 20.44	
	P value				<.0001[b]	<.0001[b]	
24-weeks	n (nmiss)	14 (5)	247 (108)	0.0627	14 (5)	247 (108)	0.9927
	Mean (Std)	6.53 (8.18)	11.24 (12.76)		-20.42 (18.72)	-19.95 (16.95)	
	Median	1.61	6.75		-16.28	-17.50	
	Q1, Q3	1.30, 10.14	3.15, 15.37		-33.63, -2.62	-30.34, -6.65	
	Min, Max	0.43, 27.73	0.02, 66.11		-50.60, -1.68	-83.91, 18.44	
	P value				0.0001[b]	<.0001[b]	

Footnote: nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Wilcoxon rank sum tests.

Table ANN. 177 **SDAI Score (SDAI ≤11, Baseline RF and Anti-CCP Subgroups, Effectiveness Analyses Population)**

visit		*observed*			*change (post −baseline)*		
		Baseline RF and anti-CCP both negative (N=14)	*Baseline RF and anti-CCP any positive (N=247)*	*P value**	*Baseline RF and anti-CCP both negative (N=14)*	*Baseline RF and anti-CCP any positive (N=247)*	*P value**
Baseline	n (nmiss)	9 (10)	40 (315)	0.2839			
	%	47.37%	11.36%				
	Mean (Std)	5.03 (2.59)	4.47 (3.09)				
	Median	4.29	3.44				
	Q1, Q3	3.43, 5.83	1.86, 6.13				
	Min, Max	2.23, 10.92	1.23, 10.69				
12-weeks	n (nmiss)	13 (6)	159 (196)	0.0134	13 (6)	159 (196)	0.0496
	%	76.47%	54.64%		76.47%	54.64%	
	Mean (Std)	2.99 (2.35)	5.31 (3.27)		-13.97 (19.73)	-20.24 (16.08)	
	Median	1.43	5.11		-4.71	-17.34	
	Q1, Q3	1.27, 3.92	2.19, 8.25		-17.60, -2.14	-29.21, -6.67	
	Min, Max	0.91, 8.56	0.01, 10.93		-57.57, -0.20	-83.51, 0.81	
	P value				0.0002[b]	<.0001[b]	
24-weeks	n (nmiss)	11 (8)	164 (191)	0.0835	11 (8)	164 (191)	0.1360
	%	78.57%	66.40%		78.57%	66.40%	
	Mean (Std)	3.06 (3.56)	4.46 (2.98)		-15.38 (17.46)	-23.03 (16.77)	
	Median	1.53	4.05		-5.01	-21.76	
	Q1, Q3	0.96, 4.40	2.04, 6.74		-30.16, -2.57	-32.99, -9.86	
	Min, Max	0.43, 10.14	0.02, 10.99		-49.61, -1.68	-83.91, 0.17	
	P value				0.0010[b]	<.0001[b]	

Footnote: nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
The numerator of percentage was n. The denominator of percentage for observed value was the number of patients with non-missing observed value at the visit in the subgroup. The denominator of
percentage for change from baseline was the number of patients with non-missing change at the visit in the subgroup.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Wilcoxon rank sum tests.

Table ANN. 178 SDAI Score Summary by Category and Visit (Baseline RF and Anti-CCP Both Negative, Effectiveness Analyses Population)

Visit	*<=3.3*	*>3.3 to <=11.0*	*>11.0 to <=26.0*	*>26.0*	*<=11.0*	*>11.0*	*Non-missing Total*
Baseline	2 (10.53%)	7 (36.84%)	1 (5.26%)	9 (47.37%)	9 (47.37%)	10 (52.63%)	19 (100.00%)
12-weeks	8 (47.06%)	5 (29.41%)	3 (17.65%)	1 (5.88%)	13 (76.47%)	4 (23.53%)	17 (100.00%)
24-weeks	8 (57.14%)	3 (21.43%)	2 (14.29%)	1 (7.14%)	11 (78.57%)	3 (21.43%)	14 (100.00%)

Footnote: Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 179 SDAI Score Summary by Category and Visit (Baseline RF and Anti-CCP Any Positive, Effectiveness Analyses Population)

Visit	*<=3.3*	*>3.3 to <=11.0*	*>11.0 to <=26.0*	*>26.0*	*<=11.0*	*>11.0*	*Non-missing Total*
Baseline	19 (5.40%)	21 (5.97%)	117 (33.24%)	195 (55.40%)	40 (11.36%)	312 (88.64%)	352 (100.00%)
12-weeks	56 (19.24%)	103 (35.40%)	84 (28.87%)	48 (16.49%)	159 (54.64%)	132 (45.36%)	291 (100.00%)
24-weeks	65 (26.32%)	99 (40.08%)	59 (23.89%)	24 (9.72%)	164 (66.40%)	83 (33.60%)	247 (100.00%)

Footnote: Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 180 SDAI Score Mixed-Effects Model Analysis (Baseline RF and Anti-CCP Both Negative, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=19)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.82	0.074	<.0001	-0.9717,-0.6608
week 12	-0.10	2.370	0.9652	-5.1061,4.8964
week 24	0.43	2.628	0.8708	-5.1103,5.9785
baseline*week 12	0.10	0.128	0.4350	-0.1681,0.3733
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of SDAI at 12 weeks	-18.86	1.603	<.0001	-22.2389,-15.4743
the least-squares mean of the change of SDAI at 24 weeks	-21.01	1.734	<.0001	-24.6723,-17.3538

Footnote: SDAI, Simplified Disease Activity Index; N, number of patients in RF and anti-CCP both negative population.
MMRM is applied by using the change of SDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline SDAI score and baseline SDAI score-by-week-interaction.

Table ANN. 181 SDAI Score Mixed-Effects Model Analysis (Baseline RF and Anti-CCP Any Positive, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=355)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.67	0.037	<.0001	-0.7472,-0.6017
week 12	0.81	1.347	0.5488	-1.8419,3.4586
week 24	0.99	1.337	0.4595	-1.6407,3.6211
baseline*week 12	0.12	0.032	0.0003	0.0546,0.1817
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of SDAI at 12 weeks	-16.56	0.686	<.0001	-17.9137,-15.2141
the least-squares mean of the change of SDAI at 24 weeks	-20.07	0.680	<.0001	-21.4107,-18.7358

Footnote: SDAI, Simplified Disease Activity Index; N, number of patients in RF and anti-CCP any positive population.
MMRM is applied by using the change of SDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline SDAI score and baseline SDAI score-by-week-interaction.

Table ANN. 182 **CDAI Score (Baseline RF and Anti-CCP subgroups, Effectiveness Analyses Population)**

visit		*observed*			*change (post −baseline)*		
		Baseline RF and anti-CCP both negative (N=19)	*Baseline RF and anti-CCP any positive (N=355)*	*P value**	*Baseline RF and anti-CCP both negative (N=19)*	*Baseline RF and anti-CCP any positive (N=355)*	*P value**
Baseline	n (nmiss)	19 (0)	353 (2)	0.3692			
	Mean (Std)	26.04 (22.99)	28.79 (17.19)				
	Median	22.50	26.00				
	Q1, Q3	4.10, 48.00	16.50, 38.90				
	Min, Max	2.20, 62.20	1.20, 74.00				
12-weeks	n (nmiss)	18 (1)	304 (51)	0.0076	18 (1)	303 (52)	0.8231
	Mean (Std)	7.47 (9.62)	14.01 (13.81)		-17.35 (17.85)	-15.30 (14.38)	
	Median	3.55	9.30		-11.75	-13.60	
	Q1, Q3	1.30, 13.10	4.60, 19.00		-27.30, -3.10	-22.60, -4.00	
	Min, Max	0.90, 39.00	0.000, 71.60		-57.60, -0.20	-66.20, 21.00	
	P value				<.0001[b]	<.0001[b]	
24-weeks	n (nmiss)	16 (3)	261 (94)	0.1258	16 (3)	261 (94)	0.8546
	Mean (Std)	7.92 (10.95)	10.84 (12.78)		-19.40 (16.33)	-18.41 (15.25)	
	Median	2.05	6.70		-20.65	-17.10	
	Q1, Q3	1.10, 11.00	2.60, 13.20		-33.30, -3.60	-26.50, -6.60	
	Min, Max	0.40, 39.10	0.000, 66.00		-50.20, -1.80	-67.60, 19.00	
	P value				0.0003[a]	<.0001[b]	

Footnote: nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Wilcoxon rank sum tests.

Table ANN. 183 **CDAI Score (CDAI ≤10, Baseline RF and Anti-CCP Subgroups, Effectiveness Analyses Population)**

visit		*observed*			*change (post −baseline)*		
		Baseline RF and anti-CCP both negative (N=16)	*Baseline RF and anti-CCP any positive (N=261)*	*P value**	*Baseline RF and anti-CCP both negative (N=16)*	*Baseline RF and anti-CCP any positive (N=261)*	*P value**
Baseline	n (nmiss)	8 (11)	40 (315)	0.4712			
	%	42.11%	11.33%				
	Mean (Std)	4.19 (1.41)	4.15 (2.81)				
	Median	3.75	3.05				
	Q1, Q3	3.30, 5.50	1.70, 6.00				
	Min, Max	2.20, 6.20	1.20, 10.00				
12-weeks	n (nmiss)	13 (6)	162 (193)	0.0141	13 (6)	162 (193)	0.0713
	%	72.22%	53.29%		72.22%	53.47%	
	Mean (Std)	2.77 (2.31)	4.86 (3.01)		-13.55 (19.57)	-17.89 (14.44)	
	Median	1.40	5.00		-4.40	-16.00	
	Q1, Q3	1.20, 3.90	2.00, 7.50		-16.50, -2.10	-24.00, -6.00	
	Min, Max	0.90, 8.50	0.000, 10.00		-57.60, -0.20	-66.20, 0.80	
	P value				0.0002[b]	<.0001[b]	
24-weeks	n (nmiss)	12 (7)	174 (181)	0.0865	12 (7)	174 (181)	0.1550
	%	75.00%	66.67%		75.00%	66.67%	
	Mean (Std)	2.80 (3.31)	4.12 (2.96)		-14.36 (14.62)	-20.85 (14.98)	
	Median	1.40	4.00		-6.05	-20.30	
	Q1, Q3	0.90, 2.95	1.60, 6.70		-23.75, -2.55	-28.50, -8.50	
	Min, Max	0.40, 10.00	0.000, 10.00		-43.20, -1.80	-67.60, 0.000	
	P value				0.0005[b]	<.0001[b]	

Footnote: nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
The numerator of percentage was n. The denominator of percentage for observed value was the number of patients with non-missing observed value at the visit in the subgroup. The denominator of
percentage for change from baseline was the number of patients with non-missing change at the visit in the subgroup.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Wilcoxon rank sum tests.

Table ANN. 184 CDAI Score Summary by Category and Visit (Baseline RF and Anti-CCP Both Negative, Effectiveness Analyses Population)

Visit	*<=2.8*	*>2.8 to <=10.0*	*>10.0 to <=22.0*	*>22.0*	*<=10.0*	*>10.0*	*Non-missing Total*
Baseline	1 (5.26%)	7 (36.84%)	1 (5.26%)	10 (52.63%)	8 (42.11%)	11 (57.89%)	19 (100.00%)
12-weeks	8 (44.44%)	5 (27.78%)	4 (22.22%)	1 (5.56%)	13 (72.22%)	5 (27.78%)	18 (100.00%)
24-weeks	9 (56.25%)	3 (18.75%)	2 (12.50%)	2 (12.50%)	12 (75.00%)	4 (25.00%)	16 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 185 CDAI Score Summary by Category and Visit (Baseline RF and Anti-CCP Any Positive, Effectiveness Analyses Population)

Visit	*<=2.8*	*>2.8 to <=10.0*	*>10.0 to <=22.0*	*>22.0*	*<=10.0*	*>10.0*	*Non-missing Total*
Baseline	20 (5.67%)	20 (5.67%)	100 (28.33%)	213 (60.34%)	40 (11.33%)	313 (88.67%)	353 (100.00%)
12-weeks	53 (17.43%)	109 (35.86%)	81 (26.64%)	61 (20.07%)	162 (53.29%)	142 (46.71%)	304 (100.00%)
24-weeks	69 (26.44%)	105 (40.23%)	55 (21.07%)	32 (12.26%)	174 (66.67%)	87 (33.33%)	261 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 186 CDAI Score Mixed-Effects Model Analysis (Baseline RF and Anti-CCP Both Negative, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=19)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.64	0.078	<.0001	-0.8020,-0.4727
week 12	0.36	2.543	0.8903	-5.0089,5.7211
week 24	-1.96	2.732	0.4824	-7.7250,3.8015
baseline*week 12	-0.08	0.082	0.3638	-0.2482,0.0960
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of CDAI at 12 weeks	-18.19	1.705	<.0001	-21.7864,-14.5938
the least-squares mean of the change of CDAI at 24 weeks	-18.53	1.756	<.0001	-22.2338,-14.8248

Footnote: CDAI, Clinical Disease Activity Index; N, number of patients in RF and anti-CCP both negative population.
MMRM is applied by using the change of CDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline CDAI score and baseline CDAI score-by-week-interaction.

Table ANN. 187 CDAI Score Mixed-Effects Model Analysis (Baseline RF and Anti-CCP Any Positive, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=355)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.64	0.037	<.0001	-0.7081,-0.5636
week 12	0.38	1.197	0.7540	-1.9796,2.7304
week 24	-0.11	1.244	0.9297	-2.5571,2.3373
baseline*week 12	0.10	0.030	0.0012	0.0391,0.1583
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of CDAI at 12 weeks	-15.31	0.616	<.0001	-16.5238,-14.0993
the least-squares mean of the change of CDAI at 24 weeks	-18.68	0.638	<.0001	-19.9363,-17.4246

Footnote: CDAI, Clinical Disease Activity Index; N, number of patients in RF and anti-CCP any positive population.
MMRM is applied by using the change of CDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline CDAI score and baseline CDAI score-by-week-interaction.

Table ANN. 188 Demographics (TNF-IR Subgroups, Effectiveness Analyses Population)

		Effectiveness Analyses Population		
		yes (N=23)	*no (N=491)*	*P value*
Age (years)	n (nmiss)	23 (0)	491 (0)	0.5577
	Mean (Std)	51.04 (13.46)	52.94 (12.57)	
	Median	55.00	54.00	
	Q1, Q3	44.00, 59.00	46.00, 62.00	
	Min, Max	25, 80	20, 85	
	18-34	4 (17.39%)	45 (9.16%)	0.0764[b]
	35-44	2 (8.70%)	71 (14.46%)	
	45-64	16 (69.57%)	284 (57.84%)	
	65-74	0	78 (15.89%)	
	>=75	1 (4.35%)	13 (2.65%)	
	Total	23 (100.00%)	491 (100.00%)	
Sex	Male	5 (21.74%)	81 (16.50%)	0.5650[b]
	Female	18 (78.26%)	410 (83.50%)	
	Total	23 (100.00%)	491 (100.00%)	
Height (cm)	n (nmiss)	23 (0)	491 (0)	0.5413
	Mean (Std)	161.30 (6.67)	160.41 (6.76)	
	Median	160.00	160.00	
	Q1, Q3	155.00, 167.00	156.00, 165.00	
	Min, Max	149, 180	144, 198	
Weight (kg)	n (nmiss)	23 (0)	491 (0)	0.6587
	Mean (Std)	58.09 (8.60)	57.48 (10.03)	
	Median	60.00	56.00	
	Q1, Q3	50.00, 64.00	50.00, 64.00	
	Min, Max	44.0, 75.0	27.0, 100.0	
BMI (kg/m^2)	n (nmiss)	23 (0)	491 (0)	0.9473
	Mean (Std)	22.40 (3.63)	22.28 (3.32)	
	Median	21.51	21.78	
	Q1, Q3	19.53, 25.64	19.97, 24.22	
	Min, Max	17.72, 31.22	12.84, 36.73	
	<18.5	5 (21.74%)	51 (10.39%)	0.1627[b]
	>=18.5-<24	10 (43.48%)	304 (61.91%)	
	>=24-<28	7 (30.43%)	106 (21.59%)	
	>=28	1 (4.35%)	30 (6.11%)	
	Total	23 (100.00%)	491 (100.00%)	
Smoking history	Never smoking	20 (86.96%)	435 (88.59%)	0.7638[b]
	Used to smoke, given up now	1 (4.35%)	20 (4.07%)	
	Still smoking	2 (8.70%)	36 (7.33%)	
	Total	23 (100.00%)	491 (100.00%)	

Footnote: The smoking history information were from 'Life History' page in CRF.
N, number of patients in population; nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.
The percentage denominator is the number of patients with non-missing value.
P values for continuous values were from Wilcoxon rank sum test. b: P values for categorical values were from Fisher exact tests.

Table ANN. 189 Rheumatoid Arthritis Diagnosis (TNF-IR Subgroups, Effectiveness Analyses Population)

		Effectiveness Analyses Population		
		yes (N=23)	*no (N=491)*	*P value*
Months from the onset date of RA to ICF (months)	n (nmiss)	23 (0)	491 (0)	0.3647
	Mean (Std)	116.51 (110.20)	100.76 (104.41)	
	Median	79.01	61.60	
	Q1, Q3	31.77, 162.73	21.91, 141.77	
	Min, Max	6.18, 411.27	0, 623.67	
Duration of RA (months)	n (nmiss)	23 (0)	491 (0)	0.3319
	Mean (Std)	107.03 (111.74)	87.13 (100.49)	
	Median	79.01	48.30	
	Q1, Q3	22.08, 142.52	13.57, 125.93	
	Min, Max	0, 411.27	0, 623.67	
	<=1 year	4 (17.39%)	109 (22.20%)	0.8270[b]
	>1-<=3 years	5 (21.74%)	98 (19.96%)	
	>3-<=10 years	6 (26.09%)	153 (31.16%)	
	>10 years	8 (34.78%)	131 (26.68%)	
	Total	23 (100.00%)	491 (100.00%)	
Meet the ACR/EULAR 2010 criteria and number of points	Yes	23 (100.00%)	491 (100.00%)	NA[b]
	n (nmiss)	23 (0)	491 (0)	
	Mean (Std)	8.57 (1.59)	8.42 (1.47)	
	Median	10.00	8.00	
	Q1, Q3	7.00, 10.00	7.00, 10.00	
	Min, Max	6, 10	6, 10	
	Total	23 (100.00%)	491 (100.00%)	

Footnote: The duration of RA (months) = (Date of informed consent – date of diagnosis of RA) / 30.4375, round to 2 decimal place. Months from the onset date of RA to ICF (months) = (Date of informed consent – the onset date of RA) / 30.4375, round to 2 decimal place.
N, number of patients in population; nmiss, no. of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range. The percentage denominator is the number of patients with non-missing value.
P values for continuous values were from Wilcoxon rank sum test. b: P values for categorical values were from Fisher exact tests.

Table ANN. 190 Drug Exposure (TNF-IR Subgroups, Effectiveness Analyses Population)

		Effectiveness Analyses Population		
		yes (N=23)	*no (N=491)*	*P value*
Overall Olumiant exposure (days)	n (nmiss)	23 (0)	490 (1)	0.7684
	Mean (Std)	163.91 (26.74)	164.36 (32.81)	
	Median	168.00	170.00	
	Q1, Q3	157.00, 182.00	156.00, 181.00	
	Min, Max	93, 208	1, 314	
Olumiant exposure (days)	n (nmiss)	23 (0)	490 (1)	0.9690
	Mean (Std)	162.61 (28.64)	162.41 (33.75)	
	Median	168.00	169.00	
	Q1, Q3	157.00, 182.00	154.00, 180.00	
	Min, Max	93, 208	1, 314	
Total patient year exposure		10.3	220.5	
Number of patients administered only 2mg Olumiant	n (%)	20 (86.96%)	438 (89.21%)	0.7293
Number of patients administered only 4mg Olumiant	n (%)	1 (4.35%)	27 (5.50%)	>.9999
Number of patients administered mixed dosage of Olumiant	n (%)	2 (8.70%)	26 (5.30%)	0.3606

Footnote: N, number of patients in population; nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.
Overall Olumiant exposure (days) = Olumiant discontinue date in study termination page – the earliest start date of treatment in treatment information page +1.
Olumiant exposure (days) = sum of (end date of treatment - start date of treatment +1). The start and end date of treatment are from the same record in treatment information page.
The sum are based on all records in this page.
Total patient year exposure = sum of all patients' year exposure. Patient year exposure = overall Olumiant exposure in days for the patient / 365.25, keep 1 decimal place.
P values for continuous values were from Wilcoxon rank sum test. P values for categorical values were from Fisher exact tests.

Table ANN. 191 **DAS28-CRP Score (TNF-IR Subgroups, Effectiveness Analyses Population)**

		observed			*change (post −baseline)*		
visit		*TNF-IR yes (N=23)*	*TNF-IR no (N=491)*	*P value**	*TNF-IR yes (N=23)*	*TNF-IR no (N=491)*	*P value**
Baseline	n (nmiss)	23 (0)	479 (12)	0.0326			
	Mean (Std)	5.31 (1.91)	4.65 (1.84)				
	Median	5.82	4.81				
	Q1, Q3	4.49, 6.66	3.71, 6.01				
	Min, Max	0.59, 7.69	0.25, 8.02				
12-weeks	n (nmiss)	17 (6)	400 (91)	0.8711	17 (6)	396 (95)	0.0267
	Mean (Std)	2.99 (1.65)	3.09 (1.67)		-2.46 (1.74)	-1.51 (1.53)	
	Median	2.94	3.01		-1.89	-1.29	
	Q1, Q3	1.75, 3.92	1.88, 4.23		-4.02, -1.26	-2.65, -0.30	
	Min, Max	0.25, 5.81	0.11, 7.88		-5.71, -0.30	-5.63, 3.58	
	P value				<.0001[a]	<.0001[b]	
24-weeks	n (nmiss)	18 (5)	335 (156)	0.8310	18 (5)	332 (159)	0.1144
	Mean (Std)	2.76 (1.84)	2.72 (1.50)		-2.60 (1.74)	-1.93 (1.66)	
	Median	2.14	2.56		-2.21	-1.87	
	Q1, Q3	1.63, 4.45	1.65, 3.64		-3.94, -0.76	-3.12, -0.53	
	Min, Max	0.11, 5.96	0.13, 7.12		-5.73, -0.47	-6.01, 2.58	
	P value				<.0001[a]	<.0001[b]	

Footnote: CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Wilcoxon rank sum tests.

Table ANN. 192 **DAS28-CRP Score (DAS28-CRP ≤3.2, TNF-IR Subgroups, Effectiveness Analyses Population)**

		observed			*change (post −baseline)*		
visit		*TNF-IR yes (N=18)*	*TNF-IR no (N=332)*	*P value**	*TNF-IR yes (N=18)*	*TNF-IR no (N=332)*	*P value**
Baseline	n (nmiss)	3 (20)	81 (410)	0.8095			
	%	13.04%	16.91%				
	Mean (Std)	1.34 (1.06)	1.53 (1.11)				
	Median	0.87	1.53				
	Q1, Q3	0.59, 2.55	0.44, 2.56				
	Min, Max	0.59, 2.55	0.25, 3.15				
12-weeks	n (nmiss)	9 (14)	217 (274)	0.8575	9 (14)	214 (277)	0.0626
	%	52.94%	54.25%		52.94%	54.04%	
	Mean (Std)	1.77 (0.99)	1.84 (0.88)		-3.17 (2.01)	-2.06 (1.50)	
	Median	1.75	1.95		-4.02	-1.92	
	Q1, Q3	1.49, 2.46	1.39, 2.52		-4.78, -1.55	-3.30, -0.68	
	Min, Max	0.25, 2.94	0.11, 3.19		-5.71, -0.30	-5.63, 0.55	
	P value				0.0015[a]	<.0001[b]	
24-weeks	n (nmiss)	12 (11)	223 (268)	0.3310	12 (11)	221 (270)	0.0488
	%	66.67%	66.57%		66.67%	66.57%	
	Mean (Std)	1.64 (0.89)	1.86 (0.80)		-3.35 (1.66)	-2.42 (1.56)	
	Median	1.71	1.90		-3.60	-2.49	
	Q1, Q3	1.23, 2.14	1.46, 2.56		-4.69, -2.21	-3.57, -1.02	
	Min, Max	0.11, 3.09	0.13, 3.14		-5.73, -0.47	-6.01, 0.19	
	P value				<.0001[a]	<.0001[b]	

Footnote: CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
The numerator of percentage was n. The denominator of percentage for observed value was the number of patients with non-missing observed value at the visit in the subgroup. The denominator of
percentage for change from baseline was the number of patients with non-missing change at the visit in the subgroup.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Wilcoxon rank sum tests.

Table ANN. 193 DAS28-CRP Score Summary by Category and Visit (TNF-IR Yes, Effectiveness Analyses Population)

Visit	*<2.6*	*>=2.6 to <=3.2*	*>3.2 to <=5.1*	*>5.1*	*<=3.2*	*>3.2*	*Non-missing Total*
Baseline	3 (13.04%)	0	5 (21.74%)	15 (65.22%)	3 (13.04%)	20 (86.96%)	23 (100.00%)
12-weeks	7 (41.18%)	2 (11.76%)	6 (35.29%)	2 (11.76%)	9 (52.94%)	8 (47.06%)	17 (100.00%)
24-weeks	10 (55.56%)	2 (11.11%)	3 (16.67%)	3 (16.67%)	12 (66.67%)	6 (33.33%)	18 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 194 DAS28-CRP Score Summary by Category and Visit (TNF-IR No, Effectiveness Analyses Population)

Visit	*<2.6*	*>=2.6 to <=3.2*	*>3.2 to <=5.1*	*>5.1*	*<=3.2*	*>3.2*	*Non-missing Total*
Baseline	61 (12.73%)	20 (4.18%)	201 (41.96%)	197 (41.13%)	81 (16.91%)	398 (83.09%)	479 (100.00%)
12-weeks	167 (41.75%)	50 (12.50%)	129 (32.25%)	54 (13.50%)	217 (54.25%)	183 (45.75%)	400 (100.00%)
24-weeks	175 (52.24%)	48 (14.33%)	85 (25.37%)	27 (8.06%)	223 (66.57%)	112 (33.43%)	335 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 195 DAS28-CRP Score Mixed-Effects Model Analysis (TNF-IR Yes, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=23)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.40	0.192	0.0517	-0.8031,0.0032
week 12	0.32	1.026	0.7606	-1.8385,2.4733
week 24	-0.37	1.102	0.7384	-2.6880,1.9408
baseline*week 12	-0.10	0.143	0.4992	-0.3983,0.2014
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of DAS28-CRP at 12 weeks	-2.37	0.342	<.0001	-3.0921,-1.6549
the least-squares mean of the change of DAS28-CRP at 24 weeks	-2.53	0.360	<.0001	-3.2886,-1.7776

Footnote: CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; N, number of patients in TNF-IR yes population.
MMRM is applied by using the change of DAS28-CRP Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline DAS28 score and baseline DAS28 score-by-week-interaction.

Table ANN. 196 DAS28-CRP Score Mixed-Effects Model Analysis (TNF-IR No, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=491)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.57	0.037	<.0001	-0.6406,-0.4966
week 12	0.51	0.175	0.0036	0.1681,0.8563
week 24	0.72	0.182	<.0001	0.3598,1.0760
baseline*week 12	0.14	0.032	<.0001	0.0725,0.1979
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of DAS28-CRP at 12 weeks	-1.49	0.065	<.0001	-1.6203,-1.3645
the least-squares mean of the change of DAS28-CRP at 24 weeks	-1.91	0.067	<.0001	-2.0427,-1.7812

Footnote: CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; N, number of patients in TNF-IR no population.
MMRM is applied by using the change of DAS28-CRP Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline DAS28 score and baseline DAS28 score-by-week-interaction.

Table ANN. 197 **SDAI Score (TNF-IR subgroups, Effectiveness Analyses Population)**

visit		*observed*			*change (post −baseline)*		
		TNF-IR yes (N=23)	*TNF-IR no (N=491)*	*P value**	*TNF-IR yes (N=23)*	*TNF-IR no (N=491)*	*P value**
Baseline	n (nmiss)	23 (0)	479 (12)	0.0612			
	Mean (Std)	39.39 (21.46)	31.07 (18.21)				
	Median	37.07	28.26				
	Q1, Q3	23.17, 59.45	18.08, 43.25				
	Min, Max	1.78, 85.92	1.23, 77.80				
12-weeks	n (nmiss)	17 (6)	400 (91)	0.6925	17 (6)	396 (95)	0.0096
	Mean (Std)	13.67 (12.92)	15.66 (15.29)		-28.34 (22.39)	-15.06 (15.60)	
	Median	10.42	10.48		-23.60	-11.67	
	Q1, Q3	2.50, 17.75	4.82, 22.19		-36.06, -15.20	-24.18, -3.28	
	Min, Max	0.93, 46.55	0.01, 75.30		-83.51, -0.77	-66.20, 25.74	
	P value				<.0001[a]	<.0001[b]	
24-weeks	n (nmiss)	18 (5)	335 (156)	0.7203	18 (5)	332 (159)	0.0996
	Mean (Std)	13.23 (15.33)	11.85 (13.37)		-27.16 (21.26)	-18.94 (17.47)	
	Median	4.84	7.00		-23.11	-16.59	
	Q1, Q3	1.12, 22.80	3.00, 16.39		-35.79, -16.26	-30.20, -5.01	
	Min, Max	0.03, 46.79	0.02, 66.11		-83.91, -0.37	-69.88, 31.01	
	P value				<.0001[a]	<.0001[b]	

Footnote: nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Wilcoxon rank sum tests.

Table ANN. 198 **SDAI Score (SDAI ≤11, TNF-IR subgroups, Effectiveness Analyses Population)**

		observed			*change (post −baseline)*		
visit		*TNF-IR yes (N=18)*	*TNF-IR no (N=332)*	*P value**	*TNF-IR yes (N=18)*	*TNF-IR no (N=332)*	*P value**
Baseline	n (nmiss)	2 (21)	61 (430)	0.5434			
	%	8.70%	12.73%				
	Mean (Std)	3.07 (1.82)	4.65 (2.85)				
	Median	3.07	3.97				
	Q1, Q3	1.78, 4.36	2.03, 6.12				
	Min, Max	1.78, 4.36	1.23, 10.92				
12-weeks	n (nmiss)	9 (14)	209 (282)	0.5527	9 (14)	207 (284)	0.1116
	%	52.94%	52.25%		52.94%	52.27%	
	Mean (Std)	4.48 (3.75)	5.13 (3.24)		-34.42 (27.88)	-19.21 (15.70)	
	Median	2.50	5.05		-34.38	-17.25	
	Q1, Q3	2.19, 6.83	2.05, 8.04		-57.57, -15.20	-27.02, -5.16	
	Min, Max	0.93, 10.42	0.01, 10.93		-83.51, -0.77	-66.20, 0.81	
	P value				0.0060[a]	<.0001[b]	
24-weeks	n (nmiss)	11 (12)	217 (274)	0.0769	11 (12)	215 (276)	0.1856
	%	61.11%	64.78%		61.11%	64.76%	
	Mean (Std)	2.94 (3.16)	4.32 (2.98)		-31.65 (23.98)	-22.58 (17.05)	
	Median	2.01	4.00		-26.39	-20.54	
	Q1, Q3	0.55, 3.50	1.67, 6.57		-43.99, -16.26	-32.85, -8.55	
	Min, Max	0.03, 10.69	0.02, 10.99		-83.91, -1.75	-69.88, 0.41	
	P value				0.0014[a]	<.0001[b]	

Footnote: nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
The numerator of percentage was n. The denominator of percentage for observed value was the number of patients with non-missing observed value at the visit in the subgroup. The denominator of
percentage for change from baseline was the number of patients with non-missing change at the visit in the subgroup.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Wilcoxon rank sum tests.

Table ANN. 199 **SDAI Score Summary by Category and Visit (TNF-IR Yes, Effectiveness Analyses Population)**

Visit	*<=3.3*	*>3.3 to <=11.0*	*>11.0 to <=26.0*	*>26.0*	*<=11.0*	*>11.0*	*Non-missing Total*
Baseline	1 (4.35%)	1 (4.35%)	5 (21.74%)	16 (69.57%)	2 (8.70%)	21 (91.30%)	23 (100.00%)
12-weeks	5 (29.41%)	4 (23.53%)	6 (35.29%)	2 (11.76%)	9 (52.94%)	8 (47.06%)	17 (100.00%)
24-weeks	6 (33.33%)	5 (27.78%)	4 (22.22%)	3 (16.67%)	11 (61.11%)	7 (38.89%)	18 (100.00%)

Footnote: Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 200 SDAI Score Summary by Category and Visit (TNF-IR No, Effectiveness Analyses Population)

Visit	*<=3.3*	*>3.3 to <=11.0*	*>11.0 to <=26.0*	*>26.0*	*<=11.0*	*>11.0*	*Non-missing Total*
Baseline	23 (4.80%)	38 (7.93%)	152 (31.73%)	266 (55.53%)	61 (12.73%)	418 (87.27%)	479 (100.00%)
12-weeks	78 (19.50%)	131 (32.75%)	113 (28.25%)	78 (19.50%)	209 (52.25%)	191 (47.75%)	400 (100.00%)
24-weeks	91 (27.16%)	126 (37.61%)	77 (22.99%)	41 (12.24%)	217 (64.78%)	118 (35.22%)	335 (100.00%)

Footnote: Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 201 SDAI Score Mixed-Effects Model Analysis (TNF-IR Yes, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=23)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.68	0.153	0.0003	-0.9984,-0.3564
week 12	4.97	7.025	0.4884	-9.7902,19.7274
week 24	1.00	7.120	0.8895	-13.9555,15.9615
baseline*week 12	-0.09	0.090	0.3241	-0.2814,0.0982
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of SDAI at 12 weeks	-26.69	3.267	<.0001	-33.5563,-19.8279
the least-squares mean of the change of SDAI at 24 weeks	-26.89	3.304	<.0001	-33.8283,-19.9447

Footnote: SDAI, Simplified Disease Activity Index; N, number of patients in TNF-IR yes population.
MMRM is applied by using the change of SDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline SDAI score and baseline SDAI score-by-week-interaction.

Table ANN. 202 SDAI Score Mixed-Effects Model Analysis (TNF-IR No, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=491)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.69	0.034	<.0001	-0.7547,-0.6191
week 12	0.81	1.225	0.5086	-1.5975,3.2186
week 24	2.23	1.230	0.0700	-0.1833,4.6523
baseline*week 12	0.18	0.030	<.0001	0.1179,0.2371
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of SDAI at 12 weeks	-14.85	0.625	<.0001	-16.0782,-13.6220
the least-squares mean of the change of SDAI at 24 weeks	-18.88	0.626	<.0001	-20.1121,-17.6521

Footnote: SDAI, Simplified Disease Activity Index; N, number of patients in TNF-IR no population.
MMRM is applied by using the change of SDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline SDAI score and baseline SDAI score-by-week-interaction.

Table ANN. 203 **CDAI Score (TNF-IR Subgroups, Effectiveness Analyses Population)**

		observed			*change (post −baseline)*		
visit		*TNF-IR yes (N=23)*	*TNF-IR no (N=491)*	*P value**	*TNF-IR yes (N=23)*	*TNF-IR no (N=491)*	*P value**
Baseline	n (nmiss)	23 (0)	485 (6)	0.0604			
	Mean (Std)	35.90 (18.58)	28.86 (17.15)				
	Median	33.50	26.00				
	Q1, Q3	22.20, 49.80	16.00, 39.20				
	Min, Max	1.70, 66.10	1.20, 74.00				
12-weeks	n (nmiss)	20 (3)	419 (72)	0.8392	20 (3)	415 (76)	0.0588
	Mean (Std)	15.71 (14.65)	15.19 (14.89)		-21.78 (18.02)	-13.94 (14.68)	
	Median	12.75	10.00		-19.20	-10.70	
	Q1, Q3	2.00, 20.90	4.80, 22.00		-31.75, -4.30	-22.00, -2.80	
	Min, Max	0.90, 48.60	0.000, 71.60		-58.00, 0.000	-66.20, 25.90	
	P value				<.0001[a]	<.0001[b]	
24-weeks	n (nmiss)	19 (4)	362 (129)	0.8474	19 (4)	359 (132)	0.1282
	Mean (Std)	13.36 (15.51)	11.91 (13.66)		-23.31 (16.05)	-17.50 (16.13)	
	Median	6.00	7.00		-21.50	-15.60	
	Q1, Q3	1.00, 23.00	2.50, 16.00		-34.60, -7.50	-26.90, -4.60	
	Min, Max	0.000, 46.00	0.000, 66.00		-57.00, 0.20	-67.60, 32.50	
	P value				<.0001[a]	<.0001[b]	

Footnote: nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Wilcoxon rank sum tests.

Table ANN. 204 **CDAI Score (CDAI ≤10, TNF-IR Subgroups, Effectiveness Analyses Population)**

visit		*observed*			*change (post −baseline)*		
		TNF-IR yes (N=19)	*TNF-IR no (N=359)*	*P value**	*TNF-IR yes (N=19)*	*TNF-IR no (N=359)*	*P value**
Baseline	n (nmiss)	2 (21)	59 (432)	0.5842			
	%	8.70%	12.16%				
	Mean (Std)	3.00 (1.84)	4.19 (2.52)				
	Median	3.00	3.60				
	Q1, Q3	1.70, 4.30	1.90, 6.00				
	Min, Max	1.70, 4.30	1.20, 10.00				
12-weeks	n (nmiss)	9 (14)	212 (279)	0.4639	9 (14)	210 (281)	0.1439
	%	45.00%	50.60%		45.00%	50.60%	
	Mean (Std)	3.99 (3.72)	4.71 (2.97)		-28.10 (21.35)	-17.63 (14.83)	
	Median	2.00	5.00		-27.00	-15.80	
	Q1, Q3	2.00, 6.00	2.00, 7.30		-43.00, -15.20	-23.70, -4.70	
	Min, Max	0.90, 10.00	0.000, 10.00		-58.00, -0.70	-66.20, 1.60	
	P value				0.0042[a]	<.0001[b]	
24-weeks	n (nmiss)	11 (12)	231 (260)	0.1003	11 (12)	229 (262)	0.2560
	%	57.89%	63.81%		57.89%	63.79%	
	Mean (Std)	2.66 (3.02)	3.99 (2.95)		-26.19 (16.87)	-20.82 (15.70)	
	Median	1.60	3.50		-24.60	-19.00	
	Q1, Q3	0.40, 3.20	1.40, 6.40		-43.00, -16.30	-28.50, -8.00	
	Min, Max	0.000, 10.00	0.000, 10.00		-57.00, -1.68	-67.60, 0.50	
	P value				0.0004[a]	<.0001[b]	

Footnote: nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
The numerator of percentage was n. The denominator of percentage for observed value was the number of patients with non-missing observed value at the visit in the subgroup. The denominator of
percentage for change from baseline was the number of patients with non-missing change at the visit in the subgroup.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Wilcoxon rank sum tests.

Table ANN. 205 CDAI Score Summary by Category and Visit (TNF-IR Yes, Effectiveness Analyses Population)

Visit	*<=2.8*	*>2.8 to <=10.0*	*>10.0 to <=22.0*	*>22.0*	*<=10.0*	*>10.0*	*Non-missing Total*
Baseline	1 (4.35%)	1 (4.35%)	3 (13.04%)	18 (78.26%)	2 (8.70%)	21 (91.30%)	23 (100.00%)
12-weeks	6 (30.00%)	3 (15.00%)	6 (30.00%)	5 (25.00%)	9 (45.00%)	11 (55.00%)	20 (100.00%)
24-weeks	6 (31.58%)	5 (26.32%)	3 (15.79%)	5 (26.32%)	11 (57.89%)	8 (42.11%)	19 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 206 CDAI Score Summary by Category and Visit (TNF-IR No, Effectiveness Analyses Population)

Visit	*<=2.8*	*>2.8 to <=10.0*	*>10.0 to <=22.0*	*>22.0*	*<=10.0*	*>10.0*	*Non-missing Total*
Baseline	23 (4.74%)	36 (7.42%)	129 (26.60%)	297 (61.24%)	59 (12.16%)	426 (87.84%)	485 (100.00%)
12-weeks	73 (17.42%)	139 (33.17%)	109 (26.01%)	98 (23.39%)	212 (50.60%)	207 (49.40%)	419 (100.00%)
24-weeks	99 (27.35%)	132 (36.46%)	75 (20.72%)	56 (15.47%)	231 (63.81%)	131 (36.19%)	362 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 207 CDAI Score Mixed-Effects Model Analysis (TNF-IR Yes, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=23)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.52	0.155	0.0033	-0.8427,-0.1943
week 12	1.64	6.380	0.8002	-11.6732,14.9455
week 24	-3.61	6.400	0.5790	-16.9589,9.7400
baseline*week 12	-0.12	0.093	0.2302	-0.3098,0.0791
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of CDAI at 12 weeks	-21.87	2.879	<.0001	-27.8783,-15.8674
the least-squares mean of the change of CDAI at 24 weeks	-22.84	2.863	<.0001	-28.8118,-16.8681

Footnote: CDAI, Clinical Disease Activity Index; N, number of patients in TNF-IR yes population.
MMRM is applied by using the change of CDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline CDAI score and baseline CDAI score-by-week-interaction.

Table ANN. 208 CDAI Score Mixed-Effects Model Analysis (TNF-IR No, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=491)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.64	0.034	<.0001	-0.7041,-0.5686
week 12	0.61	1.124	0.5890	-1.6011,2.8165
week 24	1.11	1.167	0.3421	-1.1837,3.4036
baseline*week 12	0.14	0.029	<.0001	0.0843,0.1969
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of CDAI at 12 weeks	-13.86	0.576	<.0001	-14.9955,-12.7305
the least-squares mean of the change of CDAI at 24 weeks	-17.47	0.598	<.0001	-18.6402,-16.2906

Footnote: CDAI, Clinical Disease Activity Index; N, number of patients in TNF-IR no population.
MMRM is applied by using the change of CDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline CDAI score and baseline CDAI score-by-week-interaction.

Table ANN. 209 Demographics (1st Dosage Subgroups, Effectiveness Analyses Population)

		Effectiveness Analyses Population			
		2 mg only (N=458)	*4 mg only (N=28)*	*both dosages (N=28)*	*P value*
Age (years)	n (nmiss)	458 (0)	28 (0)	28 (0)	0.3512
	Mean (Std)	53.15 (12.51)	50.71 (11.08)	50.29 (15.39)	
	Median	55.00	53.00	51.50	
	Q1, Q3	46.00, 62.00	40.50, 59.00	40.00, 57.50	
	Min, Max	20, 85	29, 67	21, 84	
	18-34	42 (9.17%)	2 (7.14%)	5 (17.86%)	0.2838[a]
	35-44	60 (13.10%)	8 (28.57%)	5 (17.86%)	
	45-64	273 (59.61%)	15 (53.57%)	12 (42.86%)	
	65-74	70 (15.28%)	3 (10.71%)	5 (17.86%)	
	>=75	13 (2.84%)	0	1 (3.57%)	
	Total	458 (100.00%)	28 (100.00%)	28 (100.00%)	
Sex	Male	74 (16.16%)	8 (28.57%)	4 (14.29%)	0.2457[b]
	Female	384 (83.84%)	20 (71.43%)	24 (85.71%)	
	Total	458 (100.00%)	28 (100.00%)	28 (100.00%)	
Height (cm)	n (nmiss)	458 (0)	28 (0)	28 (0)	0.1118
	Mean (Std)	160.29 (6.85)	161.88 (5.77)	161.75 (5.89)	
	Median	160.00	161.50	161.50	
	Q1, Q3	156.00, 165.00	158.00, 166.25	158.00, 165.50	
	Min, Max	144, 198	148, 172	150, 173	
Weight (kg)	n (nmiss)	458 (0)	28 (0)	28 (0)	0.2652
	Mean (Std)	57.27 (9.91)	59.93 (11.01)	58.98 (9.75)	
	Median	56.00	60.00	60.00	
	Q1, Q3	50.00, 64.00	50.00, 66.00	51.50, 61.75	
	Min, Max	27.0, 100.0	39.0, 90.0	42.0, 90.0	
BMI (kg/m^2)	n (nmiss)	458 (0)	28 (0)	28 (0)	0.6926
	Mean (Std)	22.24 (3.33)	22.83 (3.77)	22.49 (3.07)	
	Median	21.64	22.67	22.40	
	Q1, Q3	19.97, 24.22	19.62, 25.59	20.03, 24.55	
	Min, Max	12.84, 36.73	17.72, 31.14	18.18, 30.07	
	<18.5	47 (10.26%)	5 (17.86%)	4 (14.29%)	0.6869[a]
	>=18.5-<24	285 (62.23%)	14 (50.00%)	15 (53.57%)	
	>=24-<28	100 (21.83%)	6 (21.43%)	7 (25.00%)	
	>=28	26 (5.68%)	3 (10.71%)	2 (7.14%)	
	Total	458 (100.00%)	28 (100.00%)	28 (100.00%)	
Smoking history	Never smoking	408 (89.08%)	22 (78.57%)	25 (89.29%)	0.2864[b]
	Used to smoke, given up now	17 (3.71%)	3 (10.71%)	1 (3.57%)	
	Still smoking	33 (7.21%)	3 (10.71%)	2 (7.14%)	
	Total	458 (100.00%)	28 (100.00%)	28 (100.00%)	

Footnote: The smoking history information were from 'Life History' page in CRF.

N, number of patients in population; nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.
The percentage denominator is the number of patients with non-missing value.
P values for continuous values were from Wilcoxon rank sum test.
a:P values for categorical values were from Chi-squared test. b:P values for categorical values were from Fisher exact tests.
Both dosages subgroup includes 2 mg to 4 mg and other mixed dosage subgroups.

Table ANN. 210 Demographics (2nd Dosage Subgroups, Effectiveness Analyses Population)

		Effectiveness Analyses Population				
		2 mg only (N=458)	*4 mg only (N=28)*	*2mg to 4mg (N=12)*	*other mixed dosage (N=16)*	*P value*
Age (years)	n (nmiss)	458 (0)	28 (0)	12 (0)	16 (0)	0.2484
	Mean (Std)	53.15 (12.51)	50.71 (11.08)	47.00 (16.41)	52.75 (14.62)	
	Median	55.00	53.00	49.00	55.00	
	Q1, Q3	46.00, 62.00	40.50, 59.00	35.00, 54.50	40.50, 68.00	
	Min, Max	20, 85	29, 67	21, 84	25, 71	
	18-34	42 (9.17%)	2 (7.14%)	3 (25.00%)	2 (12.50%)	0.1412[a]
	35-44	60 (13.10%)	8 (28.57%)	2 (16.67%)	3 (18.75%)	
	45-64	273 (59.61%)	15 (53.57%)	6 (50.00%)	6 (37.50%)	
	65-74	70 (15.28%)	3 (10.71%)	0	5 (31.25%)	
	>=75	13 (2.84%)	0	1 (8.33%)	0	
	Total	458 (100.00%)	28 (100.00%)	12 (100.00%)	16 (100.00%)	
Sex	Male	74 (16.16%)	8 (28.57%)	2 (16.67%)	2 (12.50%)	0.3675[b]
	Female	384 (83.84%)	20 (71.43%)	10 (83.33%)	14 (87.50%)	
	Total	458 (100.00%)	28 (100.00%)	12 (100.00%)	16 (100.00%)	
Height (cm)	n (nmiss)	458 (0)	28 (0)	12 (0)	16 (0)	0.1628
	Mean (Std)	160.29 (6.85)	161.88 (5.77)	163.17 (6.19)	160.69 (5.62)	
	Median	160.00	161.50	163.00	160.50	
	Q1, Q3	156.00, 165.00	158.00, 166.25	158.50, 167.50	158.00, 165.00	
	Min, Max	144, 198	148, 172	152, 173	150, 172	
Weight (kg)	n (nmiss)	458 (0)	28 (0)	12 (0)	16 (0)	0.4379
	Mean (Std)	57.27 (9.91)	59.93 (11.01)	60.79 (13.41)	57.63 (5.89)	
	Median	56.00	60.00	60.00	59.50	
	Q1, Q3	50.00, 64.00	50.00, 66.00	51.50, 68.75	53.00, 61.00	
	Min, Max	27.0, 100.0	39.0, 90.0	42.0, 90.0	47.0, 67.0	
BMI (kg/m^2)	n (nmiss)	458 (0)	28 (0)	12 (0)	16 (0)	0.8605
	Mean (Std)	22.24 (3.33)	22.83 (3.77)	22.71 (4.07)	22.33 (2.17)	
	Median	21.64	22.67	23.23	22.30	
	Q1, Q3	19.97, 24.22	19.62, 25.59	18.57, 25.07	20.88, 23.97	
	Min, Max	12.84, 36.73	17.72, 31.14	18.18, 30.07	18.29, 26.17	
	<18.5	47 (10.26%)	5 (17.86%)	3 (25.00%)	1 (6.25%)	0.2966[a]
	>=18.5-<24	285 (62.23%)	14 (50.00%)	4 (33.33%)	11 (68.75%)	
	>=24-<28	100 (21.83%)	6 (21.43%)	3 (25.00%)	4 (25.00%)	
	>=28	26 (5.68%)	3 (10.71%)	2 (16.67%)	0	
	Total	458 (100.00%)	28 (100.00%)	12 (100.00%)	16 (100.00%)	
Smoking history	Never smoking	408 (89.08%)	22 (78.57%)	10 (83.33%)	15 (93.75%)	0.3112[b]

Used to smoke, given up now	17 (3.71%)	3 (10.71%)	1 (8.33%)	0
Still smoking	33 (7.21%)	3 (10.71%)	1 (8.33%)	1 (6.25%)
Total	458 (100.00%)	28 (100.00%)	12 (100.00%)	16 (100.00%)

Footnote: The smoking history information were from 'Life History' page in CRF.
N, number of patients in population; nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.
The percentage denominator is the number of patients with non-missing value.
P values for continuous values were from Wilcoxon rank sum test.
a:P values for categorical values were from Chi-squared test. b:P values for categorical values were from Fisher exact tests.

Table ANN. 211 **Rheumatoid Arthritis Diagnosis (1st Dosage Subgroups, Effectiveness Analyses Population)**

		Effectiveness Analyses Population			
		2 mg only (N=458)	*4 mg only (N=28)*	*both dosages (N=28)*	*P value*
Months from the onset date of RA to ICF (months)	n (nmiss)	458 (0)	28 (0)	28 (0)	0.9890
	Mean (Std)	102.64 (106.66)	93.40 (84.76)	90.28 (89.37)	
	Median	62.56	70.56	47.10	
	Q1, Q3	22.57, 142.52	21.37, 150.20	29.11, 141.05	
	Min, Max	0, 623.67	2.60, 360.48	3.22, 360.15	
Duration of RA (months)	n (nmiss)	458 (0)	28 (0)	28 (0)	0.9839
	Mean (Std)	88.61 (102.66)	82.98 (84.75)	83.56 (90.26)	
	Median	48.42	61.72	47.10	
	Q1, Q3	13.57, 127.57	16.71, 124.59	18.14, 140.08	
	Min, Max	0, 623.67	0, 360.48	1.22, 360.15	
	<=1 year	102 (22.27%)	6 (21.43%)	5 (17.86%)	0.9862[a]
	>1-<=3 years	91 (19.87%)	5 (17.86%)	7 (25.00%)	
	>3-<=10 years	141 (30.79%)	10 (35.71%)	8 (28.57%)	
	>10 years	124 (27.07%)	7 (25.00%)	8 (28.57%)	
	Total	458 (100.00%)	28 (100.00%)	28 (100.00%)	
Meet the ACR/EULAR 2010 criteria and number of points	Yes	458 (100.00%)	28 (100.00%)	28 (100.00%)	NA[b]
	n (nmiss)	458 (0)	28 (0)	28 (0)	
	Mean (Std)	8.42 (1.47)	8.43 (1.50)	8.43 (1.53)	
	Median	8.00	9.00	8.00	
	Q1, Q3	7.00, 10.00	7.00, 10.00	7.00, 10.00	
	Min, Max	6, 10	6, 10	6, 10	
	Total	458 (100.00%)	28 (100.00%)	28 (100.00%)	

Footnote: The duration of RA (months) = (Date of informed consent – date of diagnosis of RA) / 30.4375, round to 2 decimal place. Months from the onset date of RA to ICF (months) = (Date of informed consent – the onset date of RA) / 30.4375, round to 2 decimal place.
N, number of patients in population; nmiss, no. of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range. The percentage denominator is the number of patients with non-missing value.
P values for continuous values were from Wilcoxon rank sum test.
a:P values for categorical values were from Chi-squared test. b:P values for categorical values were from Fisher exact tests.
Both dosages subgroup includes 2 mg to 4 mg and other mixed dosage subgroups.

Table ANN. 212 **Rheumatoid Arthritis Diagnosis (2nd Dosage Subgroups, Effectiveness Analyses Population)**

		Effectiveness Analyses Population				
		2 mg only (N=458)	*4 mg only (N=28)*	*2mg to 4mg (N=12)*	*other mixed dosage (N=16)*	*P value*
Months from the onset date of RA to ICF (months)	n (nmiss)	458 (0)	28 (0)	12 (0)	16 (0)	0.9882
	Mean (Std)	102.64 (106.66)	93.40 (84.76)	81.95 (82.90)	96.52 (96.12)	
	Median	62.56	70.56	52.72	43.67	
	Q1, Q3	22.57, 142.52	21.37, 150.20	27.71, 100.50	31.21, 155.76	
	Min, Max	0, 623.67	2.60, 360.48	6.24, 277.68	3.22, 360.15	
Duration of RA (months)	n (nmiss)	458 (0)	28 (0)	12 (0)	16 (0)	0.9933
	Mean (Std)	88.61 (102.66)	82.98 (84.75)	77.03 (82.76)	88.45 (97.89)	
	Median	48.42	61.72	52.23	42.50	
	Q1, Q3	13.57, 127.57	16.71, 124.59	16.95, 100.50	18.14, 150.26	
	Min, Max	0, 623.67	0, 360.48	3.12, 262.70	1.22, 360.15	
	<=1 year	102 (22.27%)	6 (21.43%)	3 (25.00%)	2 (12.50%)	0.8784[a]
	>1-<=3 years	91 (19.87%)	5 (17.86%)	2 (16.67%)	5 (31.25%)	
	>3-<=10 years	141 (30.79%)	10 (35.71%)	5 (41.67%)	3 (18.75%)	
	>10 years	124 (27.07%)	7 (25.00%)	2 (16.67%)	6 (37.50%)	
	Total	458 (100.00%)	28 (100.00%)	12 (100.00%)	16 (100.00%)	
Meet the ACR/EULAR 2010 criteria and number of points	Yes	458 (100.00%)	28 (100.00%)	12 (100.00%)	16 (100.00%)	NA[b]
	n (nmiss)	458 (0)	28 (0)	12 (0)	16 (0)	
	Mean (Std)	8.42 (1.47)	8.43 (1.50)	8.75 (1.36)	8.19 (1.64)	
	Median	8.00	9.00	9.00	8.00	
	Q1, Q3	7.00, 10.00	7.00, 10.00	7.50, 10.00	7.00, 10.00	
	Min, Max	6, 10	6, 10	7, 10	6, 10	
	Total	458 (100.00%)	28 (100.00%)	12 (100.00%)	16 (100.00%)	

Footnote: The duration of RA (months) = (Date of informed consent – date of diagnosis of RA) / 30.4375, round to 2 decimal place. Months from the onset date of RA to ICF (months) = (Date of informed consent – the onset date of RA) / 30.4375, round to 2 decimal place.
N, number of patients in population; nmiss, no. of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range. The percentage denominator is the number of patients with non-missing value.
P values for continuous values were from Wilcoxon rank sum test.
a:P values for categorical values were from Chi-squared test. b:P values for categorical values were from Fisher exact tests.

Table ANN. 213 **Drug Exposure (1st Dosage Subgroups, Effectiveness Analyses Population)**

		Effectiveness Analyses Population			
		2 mg only (N=458)	*4 mg only years (N=28)*	*Both dosages (N=28)*	*P value*
Overall Olumiant exposure (days)	n (nmiss)	457 (1)	28 (0)	28 (0)	0.2760
	Mean (Std)	164.59 (32.66)	168.14 (28.39)	156.54 (34.31)	
	Median	170.00	172.00	165.50	
	Q1, Q3	156.00, 181.00	156.00, 182.00	155.00, 171.50	
	Min, Max	1, 314	87, 252	55, 203	
Olumiant exposure (days)	n (nmiss)	457 (1)	28 (0)	28 (0)	0.2544
	Mean (Std)	162.58 (33.80)	166.64 (28.60)	155.46 (33.42)	
	Median	169.00	169.00	165.50	
	Q1, Q3	154.00, 180.00	155.50, 182.00	155.50, 172.00	
	Min, Max	1, 314	87, 249	55, 203	
Total patient year exposure		205.9	12.9	12.0	
Number of patients administered only 2mg Olumiant	n (%)	458 (100.00%)	0	0	<.0001
Number of patients administered only 4mg Olumiant	n (%)	0	28 (100.00%)	0	<.0001
Number of patients administered mixed dosage of Olumiant	n (%)	0	0	28 (100.00%)	<.0001

Footnote: N, number of patients in population; nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.
Overall Olumiant exposure (days) = Olumiant discontinue date in study termination page – the earliest start date of treatment in treatment information page +1.
Olumiant exposure (days) = sum of (end date of treatment - start date of treatment +1). The start and end date of treatment are from the same record in treatment information page.
The sum are based on all records in this page.
Total patient year exposure = sum of all patients' year exposure. Patient year exposure = overall Olumiant exposure in days for the patient / 365.25, keep 1 decimal place.
P values for continuous values were from Wilcoxon rank sum test. P values for categorical values were from Fisher exact tests.
Both dosages subgroup includes 2 mg to 4 mg and other mixed dosage subgroups.

Table ANN. 214 **Drug Exposure (2nd Dosage Subgroups, Effectiveness Analyses Population)**

		Effectiveness Analyses Population				
		2 mg only (N=458)	*4 mg only years (N=28)*	*2mg to 4mg (N=12)*	*other mixed dosage (N=16)*	*P value*
Overall Olumiant exposure (days)	n (nmiss)	457 (1)	28 (0)	12 (0)	16 (0)	0.4554
	Mean (Std)	164.59 (32.66)	168.14 (28.39)	156.08 (38.29)	156.88 (32.31)	
	Median	170.00	172.00	167.50	164.50	
	Q1, Q3	156.00, 181.00	156.00, 182.00	149.50, 171.50	155.00, 170.50	
	Min, Max	1, 314	87, 252	79, 203	55, 194	
Olumiant exposure (days)	n (nmiss)	457 (1)	28 (0)	12 (0)	16 (0)	0.4170
	Mean (Std)	162.58 (33.80)	166.64 (28.60)	154.83 (37.01)	155.94 (31.70)	
	Median	169.00	169.00	167.50	165.00	
	Q1, Q3	154.00, 180.00	155.50, 182.00	149.50, 172.00	155.50, 169.00	
	Min, Max	1, 314	87, 249	79, 203	55, 195	
Total patient year exposure		205.9	12.9	5.1	6.9	
Number of patients administered only 2mg Olumiant	n (%)	458 (100.00%)	0	0	0	<.0001
Number of patients administered only 4mg Olumiant	n (%)	0	28 (100.00%)	0	0	<.0001
Number of patients administered mixed dosage of Olumiant	n (%)	0	0	12 (100.00%)	16 (100.00%)	<.0001

Footnote: N, number of patients in population; nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.
Overall Olumiant exposure (days) = Olumiant discontinue date in study termination page – the earliest start date of treatment in treatment information page +1.
Olumiant exposure (days) = sum of (end date of treatment - start date of treatment +1). The start and end date of treatment are from the same record in treatment information page.
The sum are based on all records in this page.
Total patient year exposure = sum of all patients' year exposure. Patient year exposure = overall Olumiant exposure in days for the patient / 365.25, keep 1 decimal place.
P values for continuous values were from Wilcoxon rank sum test. P values for categorical values were from Fisher exact tests.

Table ANN. 215 **DAS28-CRP Score (1st Dosage Subgroups, Effectiveness Analyses Population)**

		observed				*change (post −baseline)*			
visit		*2 mg only (N=458)*	*4 mg only (N=28)*	*both dosages (N=28)*	*P value**	*2 mg only (N=458)*	*4 mg only (N=28)*	*both dosages (N=28)*	*P value**
Baseline	n (nmiss)	447 (11)	27 (1)	28 (0)	0.9240				
	Mean	4.69	4.53	4.67					
	(Std)	(1.83)	(2.04)	(1.86)					
	Median	4.81	4.59	4.89					
	Q1, Q3	3.81, 6.06	3.00, 6.06	3.45, 5.95					
	Min, Max	0.25, 8.02	0.45, 7.56	0.30, 7.82					
12-weeks	n (nmiss)	373 (85)	18 (10)	26 (2)	0.3445	369 (89)	18 (10)	26 (2)	0.7476
	Mean	3.05	3.37	3.39		-1.58	-1.53	-1.14	
	(Std)	(1.68)	(1.42)	(1.75)		(1.57)	(1.52)	(1.33)	
	Median	2.91	3.30	3.44		-1.32	-1.11	-1.40	
	Q1, Q3	1.84, 4.18	2.68, 4.46	2.59, 4.34		-2.77, -0.32	-2.64, 0.56	-1.83, 0.29	
	Min, Max	0.11, 7.88	0.31, 5.64	0.29, 7.27		-5.71, 2.43	-5.00, 0.99	-3.10, 3.58	
	P value					<.0001[b]	0.0005[a]	<.0001[b]	
24-weeks	n (nmiss)	312 (146)	21 (7)	20 (8)	0.5049	309 (149)	21 (7)	20 (8)	0.9132
	Mean	2.75	2.25	2.64		-1.95	-2.13	-2.07	
	(Std)	(1.56)	(0.81)	(1.33)		(1.68)	(1.73)	(1.37)	
	Median	2.56	2.22	2.52		-1.93	-1.64	-1.86	
	Q1, Q3	1.65, 3.75	1.94, 2.61	1.54, 3.68		-3.20, -0.58	-3.09, 0.47	-2.66, 1.36	
	Min, Max	0.11, 7.12	0.31, 3.97	0.23, 5.47		-5.81, 2.58	-6.01, 0.000	-4.95, 0.20	
	P value					<.0001[b]	<.0001[a]	<.0001[a]	

Footnote: CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
Both dosages subgroup includes 2 mg to 4 mg and other mixed dosage subgroups.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Kruskal-Wallis tests.

Table ANN. 216 **DAS28-CRP Score (2nd Dosage Subgroups, Effectiveness Analyses Population)**

visit		*observed*					*change (post −baseline)*				
		2 mg only (N=458)	*4 mg only (N=28)*	*2 mg to 4 mg (N=12)*	*other mixed dosage (N=16)*	*P value**	*2 mg only (N=458)*	*4 mg only (N=28)*	*2 mg to 4 mg (N=12)*	*other mixed dosage (N=16)*	*P value**
Baseline	n	447	27 (1)	12 (0)	16 (0)	0.8854					
	(nmiss)	(11)									
	Mean	4.69	4.53	4.25	4.98						
	(Std)	(1.83)	(2.04)	(2.21)	(1.54)						
	Median	4.81	4.59	4.76	4.89						
	Q1, Q3	3.81, 6.06	3.00, 6.06	2.88, 5.85	4.00, 6.05						
	Min, Max	0.25, 8.02	0.45, 7.56	0.30, 7.46	2.10, 7.82						
12-weeks	n	373	18 (10)	11 (1)	15 (1)	0.5422	369	18 (10)	11 (1)	15 (1)	0.5342
	(nmiss)	(85)					(89)				
	Mean	3.05	3.37	3.44	3.35		-1.58	-1.53	-0.62	-1.53	
	(Std)	(1.68)	(1.42)	(2.13)	(1.49)		(1.57)	(1.52)	(1.58)	(1.00)	
	Median	2.91	3.30	3.48	3.22		-1.32	-1.11	-1.28	-1.47	
	Q1, Q3	1.84, 4.18	2.68, 4.46	1.57, 4.34	2.59, 4.54		-2.77, 0.32	-2.64, 0.56	-1.50, 0.19	-2.29, 0.85	
	Min, Max	0.11, 7.88	0.31, 5.64	0.29, 7.27	0.98, 6.58		-5.71, 2.43	-5.00, 0.99	-2.20, 3.58	-3.10, 0.35	
	P value						<.0001[b]	0.0005[a]	0.0537[b]	<.0001[a]	
24-weeks	n	312	21 (7)	8 (4)	12 (4)	0.2196	309	21 (7)	8 (4)	12 (4)	0.6239
	(nmiss)	(146)					(149)				
	Mean	2.75	2.25	3.25	2.23		-1.95	-2.13	-1.49	-2.46	
	(Std)	(1.56)	(0.81)	(1.65)	(0.94)		(1.68)	(1.73)	(1.14)	(1.41)	
	Median	2.56	2.22	3.69	1.97		-1.93	-1.64	-1.36	-2.22	
	Q1, Q3	1.65, 3.75	1.94, 2.61	2.18, 4.30	1.40, 3.13		-3.20, 0.58	-3.09, 0.47	-1.87, 0.58	-3.22, 1.69	
	Min, Max	0.11, 7.12	0.31, 3.97	0.23, 5.47	1.14, 3.76		-5.81, 2.58	-6.01, 0.000	-3.91, 0.39	-4.95, 0.20	
	P value						<.0001[b]	<.0001[a]	0.0077[a]	<.0001[a]	

Footnote: nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Kruskal-Wallis tests.

Table ANN. 217 **DAS28-CRP Score (DAS28-CRP ≤3.2, 1st dosage subgroups, Effectiveness Analyses Population)**

		observed				*change (post −baseline)*			
visit		*2 mg only (N=458)*	*4 mg only (N=28)*	*both dosages (N=28)*	*P value**	*2 mg only (N=458)*	*4 mg only (N=28)*	*both dosages (N=28)*	*P value**
Baseline	n (nmiss)	72 (386)	7 (21)	5 (23)	0.8350				
	%	16.11%	25.93%	17.86%					
	Mean	1.49	1.81	1.65					
	(Std)	(1.12)	(1.01)	(1.12)					
	Median	0.69	2.36	2.10					
	Q1, Q3	0.43, 2.60	0.50, 2.45	0.62, 2.42					
	Min, Max	0.25, 3.15	0.45, 3.00	0.30, 2.82					
12-weeks	n (nmiss)	208 (250)	7 (21)	11 (17)	0.6583	205 (253)	7 (21)	11 (17)	0.2892
	%	55.76%	38.89%	42.31%		55.56%	38.89%	42.31%	
	Mean	1.83	2.08	1.86		-2.15	-1.63	-1.48	
	(Std)	(0.87)	(1.02)	(1.05)		(1.54)	(1.79)	(0.99)	
	Median	1.95	2.66	1.81		-2.12	-0.92	-1.72	
	Q1, Q3	1.41, 2.49	1.25, 2.71	0.98, 2.75		-3.36, -0.68	-2.99, 0.28	-1.84, 0.75	
	Min, Max	0.11, 3.19	0.31, 3.18	0.29, 3.14		-5.71, 0.55	-5.00, 0.19	-3.10, 0.01	
	P value					<.0001[b]	0.0530[a]	0.0006[a]	
24-weeks	n (nmiss)	204 (254)	19 (9)	12 (16)	0.2798	202 (256)	19 (9)	12 (16)	0.7360
	%	65.38%	90.48%	60.00%		65.37%	90.48%	60.00%	
	Mean	1.83	2.09	1.74		-2.49	-2.26	-2.54	
	(Std)	(0.82)	(0.64)	(0.74)		(1.56)	(1.77)	(1.49)	
	Median	1.86	2.20	1.68		-2.60	-2.11	-2.22	
	Q1, Q3	1.45, 2.54	1.75, 2.61	1.29, 2.32		-3.63, -1.02	-3.09, 0.36	-3.68, 1.58	
	Min, Max	0.11, 3.14	0.31, 3.00	0.23, 2.94		-5.81, 0.19	-6.01, 0.000	-4.95, 0.39	
	P value					<.0001[b]	<.0001[a]	0.0001[a]	

Footnote: CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
Both dosages subgroup includes 2 mg to 4 mg and other mixed dosage subgroups.
The numerator of percentage was n. The denominator of percentage for observed value was the number of patients with non-missing observed value at the visit in the subgroup. The denominator of
percentage for change from baseline was the number of patients with non-missing change at the visit in the subgroup.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Kruskal-Wallis tests.

Table ANN. 218 **DAS28-CRP Score (DAS28-CRP ≤3.2, 2nd dosage subgroups, Effectiveness Analyses Population)**

visit		*observed*					*change (post −baseline)*				
		2 mg only (N=458)	*4 mg only (N=28)*	*2 mg to 4 mg (N=12)*	*other mixed dosage (N=16)*	*P value**	*2 mg only (N=458)*	*4 mg only (N=28)*	*2 mg to 4 mg (N=12)*	*other mixed dosage (N=16)*	*P value**
Baseline	n (nmiss)	72 (386)	7 (21)	3 (9)	2 (14)	0.6159					
	%	16.11%	25.93%	25.00%	12.50%						
	Mean	1.49	1.81	1.11	2.46						
	(Std)	(1.12)	(1.01)	(1.14)	(0.51)						
	Median	0.69	2.36	0.62	2.46						
	Q1, Q3	0.43, 2.60	0.50, 2.45	0.30, 2.42	2.10, 2.82						
	Min, Max	0.25, 3.15	0.45, 3.00	0.30, 2.42	2.10, 2.82						
12-weeks	n (nmiss)	208 (250)	7 (21)	4 (8)	7 (9)	0.5298	205 (253)	7 (21)	4 (8)	7 (9)	0.2514
	%	55.76%	38.89%	36.36%	46.67%		55.56%	38.89%	36.36%	46.67%	
	Mean	1.83	2.08	1.35	2.16		-2.15	-1.63	-0.82	-1.85	
	(Std)	(0.87)	(1.02)	(1.32)	(0.82)		(1.54)	(1.79)	(0.84)	(0.90)	
	Median	1.95	2.66	0.99	2.59		-2.12	-0.92	-0.75	-1.83	
	Q1, Q3	1.41, 2.49	1.25, 2.71	0.35, 2.35	1.25, 2.75		-3.36, 0.68	-2.99, 0.28	-1.52, 0.12	-2.89, 0.85	
	Min, Max	0.11, 3.19	0.31, 3.18	0.29, 3.13	0.98, 3.14		-5.71, 0.55	-5.00, 0.19	-1.76, 0.01	-3.10, 0.75	
	P value						<.0001[b]	0.0530[a]	0.1464[a]	0.0016[a]	
24-weeks	n (nmiss)	204 (254)	19 (9)	3 (9)	9 (7)	0.4668	202 (256)	19 (9)	3 (9)	9 (7)	0.6917
	%	65.38%	90.48%	37.50%	75.00%		65.37%	90.48%	37.50%	75.00%	
	Mean	1.83	2.09	1.53	1.81		-2.49	-2.26	-1.61	-2.84	
	(Std)	(0.82)	(0.64)	(1.16)	(0.63)		(1.56)	(1.77)	(2.00)	(1.28)	
	Median	1.86	2.20	1.90	1.61		-2.60	-2.11	-0.52	-2.24	
	Q1, Q3	1.45, 2.54	1.75, 2.61	0.23, 2.45	1.32, 2.19		-3.63, 1.02	-3.09, 0.36	-3.91, 0.39	-3.44, 1.92	
	Min, Max	0.11, 3.14	0.31, 3.00	0.23, 2.45	1.14, 2.94		-5.81, 0.19	-6.01, 0.000	-3.91, 0.39	-4.95, 1.57	
	P value						<.0001[b]	<.0001[a]	0.2979[a]	0.0002[a]	

Footnote: nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
The numerator of percentage was n. The denominator of percentage for observed value was the number of patients with non-missing observed value at the visit in the subgroup. The denominator of
percentage for change from baseline was the number of patients with non-missing change at the visit in the subgroup.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Kruskal-Wallis tests.

Table ANN. 219 **DAS28-CRP Score Summary by Category and Visit (2 mg Only, Effectiveness Analyses Population)**

Visit	*<2.6*	*>=2.6 to <=3.2*	*>3.2 to <=5.1*	*>5.1*	*<=3.2*	*>3.2*	*Non-missing Total*
Baseline	54 (12.08%)	18 (4.03%)	185 (41.39%)	190 (42.51%)	72 (16.11%)	375 (83.89%)	447 (100.00%)
12-weeks	164 (43.97%)	44 (11.80%)	115 (30.83%)	50 (13.40%)	208 (55.76%)	165 (44.24%)	373 (100.00%)
24-weeks	160 (51.28%)	44 (14.10%)	79 (25.32%)	29 (9.29%)	204 (65.38%)	108 (34.62%)	312 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 220 DAS28-CRP Score Summary by Category and Visit (4 mg Only, Effectiveness Analyses Population)

Visit	*<2.6*	*>=2.6 to <=3.2*	*>3.2 to <=5.1*	*>5.1*	*<=3.2*	*>3.2*	*Non-missing Total*
Baseline	6 (22.22%)	1 (3.70%)	9 (33.33%)	11 (40.74%)	7 (25.93%)	20 (74.07%)	27 (100.00%)
12-weeks	3 (16.67%)	4 (22.22%)	8 (44.44%)	3 (16.67%)	7 (38.89%)	11 (61.11%)	18 (100.00%)
24-weeks	14 (66.67%)	5 (23.81%)	2 (9.52%)	0	19 (90.48%)	2 (9.52%)	21 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 221 DAS28-CRP Score Summary by Category and Visit (Both Dosages, Effectiveness Analyses Population)

Visit	*<2.6*	*>=2.6 to <=3.2*	*>3.2 to <=5.1*	*>5.1*	*<=3.2*	*>3.2*	*Non-missing Total*
Baseline	4 (14.29%)	1 (3.57%)	12 (42.86%)	11 (39.29%)	5 (17.86%)	23 (82.14%)	28 (100.00%)
12-weeks	7 (26.92%)	4 (15.38%)	12 (46.15%)	3 (11.54%)	11 (42.31%)	15 (57.69%)	26 (100.00%)
24-weeks	11 (55.00%)	1 (5.00%)	7 (35.00%)	1 (5.00%)	12 (60.00%)	8 (40.00%)	20 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 222 DAS28-CRP Score Summary by Category and Visit (2 mg to 4 mg, Effectiveness Analyses Population)

Visit	*<2.6*	*>=2.6 to <=3.2*	*>3.2 to <=5.1*	*>5.1*	*<=3.2*	*>3.2*	*Non-missing Total*
Baseline	3 (25.00%)	0	5 (41.67%)	4 (33.33%)	3 (25.00%)	9 (75.00%)	12 (100.00%)
12-weeks	3 (27.27%)	1 (9.09%)	5 (45.45%)	2 (18.18%)	4 (36.36%)	7 (63.64%)	11 (100.00%)
24-weeks	3 (37.50%)	0	4 (50.00%)	1 (12.50%)	3 (37.50%)	5 (62.50%)	8 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 223 DAS28-CRP Score Summary by Category and Visit (Other Mixed Dosages, Effectiveness Analyses Population)

Visit	*<2.6*	*>=2.6 to <=3.2*	*>3.2 to <=5.1*	*>5.1*	*<=3.2*	*>3.2*	*Non-missing Total*
Baseline	1 (6.25%)	1 (6.25%)	7 (43.75%)	7 (43.75%)	2 (12.50%)	14 (87.50%)	16 (100.00%)
12-weeks	4 (26.67%)	3 (20.00%)	7 (46.67%)	1 (6.67%)	7 (46.67%)	8 (53.33%)	15 (100.00%)
24-weeks	8 (66.67%)	1 (8.33%)	3 (25.00%)	0	9 (75.00%)	3 (25.00%)	12 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 224 DAS28-CRP Score Mixed-Effects Model Analysis (2 mg Only, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=458)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.55	0.039	<.0001	-0.6293,-0.4777
week 12	0.51	0.185	0.0064	0.1434,0.8712
week 24	0.67	0.194	0.0006	0.2904,1.0528
baseline*week 12	0.11	0.032	0.0006	0.0472,0.1727
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of DAS28-CRP at 12 weeks	-1.56	0.069	<.0001	-1.6975,-1.4269
the least-squares mean of the change of DAS28-CRP at 24 weeks	-1.91	0.071	<.0001	-2.0503,-1.7717

Footnote: CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; N, number of patients in 2 mg only population.
MMRM is applied by using the change of DAS28-CRP Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline DAS28 score and baseline DAS28 score-by-week-interaction.

Table ANN. 225 DAS28-CRP Score Mixed-Effects Model Analysis (4 mg Only, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=28)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.82	0.097	<.0001	-1.0256,-0.6237
week 12	1.33	0.685	0.0653	-0.0915,2.7491
week 24	1.45	0.479	0.0062	0.4575,2.4441
baseline*week 12	0.25	0.100	0.0210	0.0413,0.4564
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of DAS28-CRP at 12 weeks	-1.33	0.241	<.0001	-1.8324,-0.8324
the least-squares mean of the change of DAS28-CRP at 24 weeks	-2.36	0.177	<.0001	-2.7279,-1.9931

Footnote: CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; N, number of patients in 4 mg only population.
MMRM is applied by using the change of DAS28-CRP Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline DAS28 score and baseline DAS28 score-by-week-interaction.

Table ANN. 226 DAS28-CRP Score Mixed-Effects Model Analysis (Both Dosages, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=28)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.48	0.161	0.0062	-0.8119,-0.1485
week 12	0.29	0.639	0.6547	-1.0240,1.6019
week 24	0.19	0.796	0.8101	-1.4438,1.8304
baseline*week 12	0.16	0.185	0.3907	-0.2192,0.5427
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of DAS28-CRP at 12 weeks	-1.18	0.238	<.0001	-1.6694,-0.6890
the least-squares mean of the change of DAS28-CRP at 24 weeks	-2.02	0.249	<.0001	-2.5323,-1.5091

Footnote: CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; N, number of patients in both dosages population.
MMRM is applied by using the change of DAS28-CRP Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline DAS28 score and baseline DAS28 score-by-week-interaction.

Table ANN. 227 DAS28-CRP Score Mixed-Effects Model Analysis (2 mg to 4 mg, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=12)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.25	0.049	0.0003	-0.3578,-0.1441
week 12	0.56	1.055	0.6043	-1.7586,2.8841
week 24	-0.03	0.242	0.9171	-0.5591,0.5075
baseline*week 12	-0.04	0.230	0.8626	-0.5480,0.4663
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of DAS28-CRP at 12 weeks	-0.71	0.491	0.1784	-1.7864,0.3748
the least-squares mean of the change of DAS28-CRP at 24 weeks	-1.12	0.104	<.0001	-1.3459,-0.8879

Footnote: CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; N, number of patients in 2 mg to 4 mg population.
MMRM is applied by using the change of DAS28-CRP Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline DAS28 score and baseline DAS28 score-by-week-interaction.

Table ANN. 228 DAS28-CRP Score Mixed-Effects Model Analysis (Other Mixed Dosages, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=16)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.97	0.282	0.0039	-1.5785,-0.3689
week 12	-0.34	0.852	0.6964	-2.1674,1.4884
week 24	2.12	1.352	0.1394	-0.7812,5.0181
baseline*week 12	0.73	0.307	0.0320	0.0724,1.3871
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of DAS28-CRP at 12 weeks	-1.51	0.249	<.0001	-2.0438,-0.9748
the least-squares mean of the change of DAS28-CRP at 24 weeks	-2.55	0.283	<.0001	-3.1568,-1.9445

Footnote: CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; N, number of patients in other mixed dosage population.
MMRM is applied by using the change of DAS28-CRP Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline DAS28 score and baseline DAS28 score-by-week-interaction.

Table ANN. 229 **SDAI Score (1st Dosage Subgroups, Effectiveness Analyses Population)**

visit		*observed*				*change (post −baseline)*			
		2 mg only (N=458)	*4 mg only (N=28)*	*both dosages (N=28)*	*P value**	*2 mg only (N=458)*	*4 mg only (N=28)*	*both dosages (N=28)*	*P value**
Baseline	n (nmiss)	447 (11)	27 (1)	28 (0)	0.8769				
	Mean	31.60	29.89	30.61					
	(Std)	(18.38)	(20.49)	(17.62)					
	Median	29.00	28.13	27.02					
	Q1, Q3	19.26, 44.09	12.16, 43.38	18.69, 42.58					
	Min, Max	1.42, 85.92	2.72, 66.85	1.23, 67.80					
12-weeks	n (nmiss)	373 (85)	18 (10)	26 (2)	0.6970	369 (89)	18 (10)	26 (2)	0.7611
	Mean	15.53	15.27	16.50		-15.69	-18.00	-12.82	
	(Std)	(15.37)	(10.81)	(15.65)		(16.43)	(16.86)	(10.01)	
	Median	10.34	12.93	12.36		-12.01	-11.33	-10.86	
	Q1, Q3	4.55, 21.95	8.33, 23.00	6.52, 23.23		-24.72, -3.28	-27.53, -5.13	-19.00, -4.08	
	Min, Max	0.05, 75.30	1.23, 35.20	0.01, 62.61		-83.51, 25.74	-58.91, 1.40	-35.22, 0.18	
	P value					<.0001[b]	0.0003[a]	<.0001[a]	
24-weeks	n (nmiss)	312 (146)	21 (7)	20 (8)	0.1861	309 (149)	21 (7)	20 (8)	0.7439
	Mean	12.50	5.59	9.56		-19.13	-22.02	-20.25	
	(Std)	(13.99)	(4.27)	(8.72)		(17.93)	(19.23)	(13.15)	
	Median	7.05	4.37	6.42		-17.14	-16.49	-17.64	
	Q1, Q3	2.76, 17.26	3.55, 5.77	2.50, 16.43		-30.16, -4.66	-34.50, -8.61	-28.06, -10.41	
	Min, Max	0.02, 66.11	1.02, 17.85	0.80, 32.54		-83.91, 31.01	-57.91, 0.41	-43.99, -2.13	
	P value					<.0001[b]	<.0001[b]	<.0001[a]	

Footnote: nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
Both dosages subgroup includes 2 mg to 4 mg and other mixed dosage subgroups.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Kruskal-Wallis tests.

Table ANN. 230 **SDAI Score (2nd Dosage Subgroups, Effectiveness Analyses Population)**

		observed					*change (post −baseline)*				
visit		*2 mg only (N=458)*	*4 mg only (N=28)*	*2 mg to 4 mg (N=12)*	*other mixed dosage (N=16)*	*P value**	*2 mg only (N=458)*	*4 mg only (N=28)*	*2 mg to 4 mg (N=12)*	*other mixed dosage (N=16)*	*P value**
Baseline	n	447	27 (1)	12 (0)	16 (0)	0.8465					
	(nmiss)	(11)									
	Mean	31.60	29.89	27.53	32.91						
	(Std)	(18.38)	(20.49)	(18.48)	(17.18)						
	Median	29.00	28.13	26.67	30.75						
	Q1, Q3	19.26, 44.09	12.16, 43.38	13.58, 37.02	21.47, 45.58						
	Min, Max	1.42, 85.92	2.72, 66.85	1.23, 64.78	6.01, 67.80						
12-weeks	n	373	18 (10)	11 (1)	15 (1)	0.8680	369	18 (10)	11 (1)	15 (1)	0.5128
	(nmiss)	(85)					(89)				
	Mean	15.53	15.27	16.45	16.54		-15.69	-18.00	-9.25	-15.43	
	(Std)	(15.37)	(10.81)	(17.08)	(15.13)		(16.43)	(16.86)	(8.69)	(10.37)	
	Median	10.34	12.93	13.73	10.26		-12.01	-11.33	-5.91	-16.54	
	Q1, Q3	4.55, 21.95	8.33, 23.00	3.22, 17.75	6.52, 27.50		-24.72, -3.28	-27.53, -5.13	-19.00, -2.17	-22.50, -7.09	
	Min, Max	0.05, 75.30	1.23, 35.20	1.41, 62.61	0.01, 51.26		-83.51, 25.74	-58.91, 1.40	-23.24, 0.18	-35.22, -2.29	
	P value						<.0001[b]	0.0003[a]	0.0054[a]	<.0001[a]	
24-weeks	n	312	21 (7)	8 (4)	12 (4)	0.0904	309	21 (7)	8 (4)	12 (4)	0.7491
	(nmiss)	(146)					(149)				
	Mean	12.50	5.59	14.17	6.49		-19.13	-22.02	-16.94	-22.45	
	(Std)	(13.99)	(4.27)	(10.17)	(6.30)		(17.93)	(19.23)	(13.44)	(13.05)	
	Median	7.05	4.37	13.33	3.60		-17.14	-16.49	-16.25	-20.79	
	Q1, Q3	2.76, 17.26	3.55, 5.77	6.42, 20.27	2.03, 11.01		-30.16, -4.66	-34.50, -8.61	-24.68, -5.02	-30.76, -14.35	
	Min, Max	0.02, 66.11	1.02, 17.85	0.80, 32.54	1.03, 18.17		-83.91, 31.01	-57.91, 0.41	-40.44, -3.17	-43.99, -2.13	
	P value						<.0001[b]	<.0001[b]	0.0092[a]	<.0001[a]	

Footnote: nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Kruskal-Wallis tests.

Table ANN. 231 **SDAI Score (SDAI ≤11, 1st Dosage Subgroups, Effectiveness Analyses Population)**

		observed				*change (post −baseline)*			
visit		*2 mg only (N=458)*	*4 mg only (N=28)*	*both dosages (N=28)*	*P value**	*2 mg only (N=458)*	*4 mg only (N=28)*	*both dosages (N=28)*	*P value**
Baseline	n (nmiss)	52 (406)	6 (22)	5 (23)	0.5535				
	%	11.63%	22.22%	17.86%					
	Mean	4.43	4.84	6.09					
	(Std)	(2.83)	(2.11)	(3.66)					
	Median	3.60	4.65	6.01					
	Q1, Q3	1.94, 6.10	2.73, 6.05	3.97, 9.13					
	Min, Max	1.42, 10.92	2.72, 8.23	1.23, 10.10					
12-weeks	n (nmiss)	198 (260)	8 (20)	12 (16)	0.5332	196 (262)	8 (20)	12 (16)	0.2702
	%	53.08%	44.44%	46.15%		53.12%	44.44%	46.15%	
	Mean	5.04	6.34	5.26		-20.18	-23.09	-12.20	
	(Std)	(3.21)	(3.74)	(3.83)		(16.77)	(19.11)	(8.47)	
	Median	4.94	8.19	4.87		-17.91	-24.12	-13.37	
	Q1, Q3	2.08, 7.82	2.28, 9.02	1.80, 8.92		-29.37, -5.20	-32.04, -6.00	-17.16, -4.94	
	Min, Max	0.05, 10.93	1.23, 10.52	0.01, 10.26		-83.51, 0.81	-58.91, -1.49	-26.55, 0.18	
	P value					<.0001[b]	0.0112[a]	0.0004[a]	
24-weeks	n (nmiss)	197 (261)	19 (9)	12 (16)	0.6698	195 (263)	19 (9)	12 (16)	0.9358
	%	63.14%	90.48%	60.00%		63.11%	90.48%	60.00%	
	Mean	4.28	4.37	3.57		-23.03	-22.89	-23.04	
	(Std)	(3.10)	(1.97)	(2.55)		(17.46)	(20.02)	(14.98)	
	Median	3.95	4.15	3.03		-20.77	-16.49	-21.10	
	Q1, Q3	1.59, 6.69	3.50, 5.25	1.40, 5.01		-32.72, -9.35	-35.75, -4.03	-39.04, -10.41	
	Min, Max	0.02, 10.99	1.02, 8.23	0.80, 8.74		-83.91, 0.17	-57.91, 0.41	-43.99, -3.17	
	P value					<.0001[b]	<.0001[b]	0.0002[a]	

Footnote: nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
Both dosages subgroup includes 2 mg to 4 mg and other mixed dosage subgroups.
The numerator of percentage was n. The denominator of percentage for observed value was the number of patients with non-missing observed value at the visit in the subgroup. The denominator of
percentage for change from baseline was the number of patients with non-missing change at the visit in the subgroup.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Wilcoxon rank sum tests or Kruskal-Wallis tests.

Table ANN. 232 **SDAI Score (SDAI ≤11, 2nd Dosage Subgroups, Effectiveness Analyses Population)**

		observed					*change (post −baseline)*				
visit		*2 mg only (N=458)*	*4 mg only (N=28)*	*2 mg to 4 mg (N=12)*	*other mixed dosage (N=16)*	*P value**	*2 mg only (N=458)*	*4 mg only (N=28)*	*2 mg to 4 mg (N=12)*	*other mixed dosage (N=16)*	*P value**
Baseline	n	52	6 (22)	3 (9)	2 (14)	0.3971					
	(nmiss)	(406)									
	%	11.63%	22.22%	25.00%	12.50%						
	Mean	4.43	4.84	4.78	8.06						
	(Std)	(2.83)	(2.11)	(4.01)	(2.89)						
	Median	3.60	4.65	3.97	8.06						
	Q1, Q3	1.94, 6.10	2.73, 6.05	1.23, 9.13	6.01, 10.10						
	Min, Max	1.42, 10.92	2.72, 8.23	1.23, 9.13	6.01, 10.10						
12-weeks	n	198	8 (20)	4 (8)	8 (8)	0.5715	196	8 (20)	4 (8)	8 (8)	0.2314
	(nmiss)	(260)					(262)				
	%	53.08%	44.44%	36.36%	53.33%		53.12%	44.44%	36.36%	53.33%	
	Mean	5.04	6.34	4.09	5.85		-20.18	-23.09	-6.28	-15.17	
	(Std)	(3.21)	(3.74)	(4.15)	(3.80)		(16.77)	(19.11)	(7.53)	(7.63)	
	Median	4.94	8.19	2.38	7.01		-17.91	-24.12	-4.17	-16.86	
	Q1, Q3	2.08, 7.82	2.28, 9.02	1.48, 6.71	2.34, 8.92		-29.37, -5.20	-32.04, -6.00	-11.43, -1.13	-19.88, -8.68	
	Min, Max	0.05, 10.93	1.23, 10.52	1.41, 10.20	0.01, 10.26		-83.51, 0.81	-58.91, -1.49	-16.94, 0.18	-26.55, -3.96	
	P value						<.0001[b]	0.0112[a]	0.1944[a]	0.0008[a]	
24-weeks	n	197	19 (9)	3 (9)	9 (7)	0.7332	195	19 (9)	3 (9)	9 (7)	0.7829
	(nmiss)	(261)					(263)				
	%	63.14%	90.48%	37.50%	75.00%		63.11%	90.48%	37.50%	75.00%	
	Mean	4.28	4.37	4.55	3.25		-23.03	-22.89	-15.74	-25.47	
	(Std)	(3.10)	(1.97)	(3.36)	(2.37)		(17.46)	(20.02)	(21.39)	(12.95)	
	Median	3.95	4.15	5.53	2.50		-20.77	-16.49	-3.60	-22.26	
	Q1, Q3	1.59, 6.69	3.50, 5.25	0.80, 7.31	1.55, 3.64		-32.72, -9.35	-35.75, -4.03	-40.44, -3.17	-37.63, -18.16	
	Min, Max	0.02, 10.99	1.02, 8.23	0.80, 7.31	1.03, 8.74		-83.91, 0.17	-57.91, 0.41	-40.44, -3.17	-43.99, -8.55	
	P value						<.0001[b]	<.0001[b]	0.2500[b]	0.0004[a]	

Footnote: nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
The numerator of percentage was n. The denominator of percentage for observed value was the number of patients with non-missing observed value at the visit in the subgroup. The denominator of
percentage for change from baseline was the number of patients with non-missing change at the visit in the subgroup.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Kruskal-Wallis tests.

Table ANN. 233 SDAI Score Summary by Category and Visit (2 mg Only, Effectiveness Analyses Population)

Visit	*<=3.3*	*>3.3 to <=11.0*	*>11.0 to <=26.0*	*>26.0*	*<=11.0*	*>11.0*	*Non-missing Total*
Baseline	21 (4.70%)	31 (6.94%)	144 (32.21%)	251 (56.15%)	52 (11.63%)	395 (88.37%)	447 (100.00%)
12-weeks	74 (19.84%)	124 (33.24%)	105 (28.15%)	70 (18.77%)	198 (53.08%)	175 (46.92%)	373 (100.00%)
24-weeks	87 (27.88%)	110 (35.26%)	72 (23.08%)	43 (13.78%)	197 (63.14%)	115 (36.86%)	312 (100.00%)

Footnote: Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 234 SDAI Score Summary by Category and Visit (4 mg Only, Effectiveness Analyses Population)

Visit	*<=3.3*	*>3.3 to <=11.0*	*>11.0 to <=26.0*	*>26.0*	*<=11.0*	*>11.0*	*Non-missing Total*
Baseline	2 (7.41%)	4 (14.81%)	7 (25.93%)	14 (51.85%)	6 (22.22%)	21 (77.78%)	27 (100.00%)
12-weeks	3 (16.67%)	5 (27.78%)	6 (33.33%)	4 (22.22%)	8 (44.44%)	10 (55.56%)	18 (100.00%)
24-weeks	4 (19.05%)	15 (71.43%)	2 (9.52%)	0	19 (90.48%)	2 (9.52%)	21 (100.00%)

Footnote: Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 235 SDAI Score Summary by Category and Visit (Both Dosages, Effectiveness Analyses Population)

Visit	*<=3.3*	*>3.3 to <=11.0*	*>11.0 to <=26.0*	*>26.0*	*<=11.0*	*>11.0*	*Non-missing Total*
Baseline	1 (3.57%)	4 (14.29%)	6 (21.43%)	17 (60.71%)	5 (17.86%)	23 (82.14%)	28 (100.00%)
12-weeks	6 (23.08%)	6 (23.08%)	8 (30.77%)	6 (23.08%)	12 (46.15%)	14 (53.85%)	26 (100.00%)
24-weeks	6 (30.00%)	6 (30.00%)	7 (35.00%)	1 (5.00%)	12 (60.00%)	8 (40.00%)	20 (100.00%)

Footnote: Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 236 SDAI Score Summary by Category and Visit (2 mg to 4 mg, Effectiveness Analyses Population)

Visit	*<=3.3*	*>3.3 to <=11.0*	*>11.0 to <=26.0*	*>26.0*	*<=11.0*	*>11.0*	*Non-missing Total*
Baseline	1 (8.33%)	2 (16.67%)	2 (16.67%)	7 (58.33%)	3 (25.00%)	9 (75.00%)	12 (100.00%)
12-weeks	3 (27.27%)	1 (9.09%)	5 (45.45%)	2 (18.18%)	4 (36.36%)	7 (63.64%)	11 (100.00%)
24-weeks	1 (12.50%)	2 (25.00%)	4 (50.00%)	1 (12.50%)	3 (37.50%)	5 (62.50%)	8 (100.00%)

Footnote: Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 237 SDAI Score Summary by Category and Visit (Other Mixed Dosages, Effectiveness Analyses Population)

Visit	*<=3.3*	*>3.3 to <=11.0*	*>11.0 to <=26.0*	*>26.0*	*<=11.0*	*>11.0*	*Non-missing Total*
Baseline	0	2 (12.50%)	4 (25.00%)	10 (62.50%)	2 (12.50%)	14 (87.50%)	16 (100.00%)
12-weeks	3 (20.00%)	5 (33.33%)	3 (20.00%)	4 (26.67%)	8 (53.33%)	7 (46.67%)	15 (100.00%)
24-weeks	5 (41.67%)	4 (33.33%)	3 (25.00%)	0	9 (75.00%)	3 (25.00%)	12 (100.00%)

Footnote: Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 238 SDAI Score Mixed-Effects Model Analysis (2 mg Only, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=458)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.67	0.036	<.0001	-0.7427,-0.6012
week 12	1.44	1.313	0.2728	-1.1397,4.0235
week 24	2.17	1.314	0.0990	-0.4104,4.7582
baseline*week 12	0.13	0.030	<.0001	0.0727,0.1918
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of SDAI at 12 weeks	-15.50	0.672	<.0001	-16.8216,-14.1781
the least-squares mean of the change of SDAI at 24 weeks	-18.92	0.669	<.0001	-20.2357,-17.6038

Footnote: SDAI, Simplified Disease Activity Index; N, number of patients in 2 mg only population.
MMRM is applied by using the change of SDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline SDAI score and baseline SDAI score-by-week-interaction.

Table ANN. 239 SDAI Score Mixed-Effects Model Analysis (4 mg Only, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=28)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-1.00	0.062	<.0001	-1.1275,-0.8683
week 12	7.74	4.657	0.1105	-1.9143,17.4016
week 24	5.53	2.263	0.0230	0.8361,10.2240
baseline*week 12	0.22	0.110	0.0558	-0.0061,0.4521
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of SDAI at 12 weeks	-15.67	2.167	<.0001	-20.1670,-11.1779
the least-squares mean of the change of SDAI at 24 weeks	-24.63	1.121	<.0001	-26.9501,-22.3003

Footnote: SDAI, Simplified Disease Activity Index; N, number of patients in 4 mg only population.
MMRM is applied by using the change of SDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline SDAI score and baseline SDAI score-by-week-interaction.

Table ANN. 240 SDAI Score Mixed-Effects Model Analysis (Both Dosages, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=28)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.74	0.117	<.0001	-0.9845,-0.5018
week 12	-4.91	3.457	0.1675	-12.0131,2.1968
week 24	2.19	3.883	0.5777	-5.7919,10.1702
baseline*week 12	0.47	0.135	0.0018	0.1930,0.7482
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of SDAI at 12 weeks	-12.96	1.754	<.0001	-16.5631,-9.3525
the least-squares mean of the change of SDAI at 24 weeks	-19.76	1.731	<.0001	-23.3164,-16.1991

Footnote: SDAI, Simplified Disease Activity Index; N, number of patients in both dosages population.
MMRM is applied by using the change of SDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline SDAI score and baseline SDAI score-by-week-interaction.

Table ANN. 241 SDAI Score Mixed-Effects Model Analysis (2 mg to 4 mg, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=12)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.50	0.051	<.0001	-0.6112,-0.3883
week 12	-4.81	5.255	0.3795	-16.3793,6.7552
week 24	0.59	1.747	0.7413	-3.2539,4.4372
baseline*week 12	0.33	0.179	0.0948	-0.0669,0.7231
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of SDAI at 12 weeks	-9.61	2.966	0.0079	-16.1431,-3.0865
the least-squares mean of the change of SDAI at 24 weeks	-13.39	0.955	<.0001	-15.4906,-11.2885

Footnote: SDAI, Simplified Disease Activity Index; N, number of patients in 2 mg to 4 mg population.
MMRM is applied by using the change of SDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline SDAI score and baseline SDAI score-by-week-interaction.

Table ANN. 242 SDAI Score Mixed-Effects Model Analysis (Other Mixed Dosages, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=16)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-1.01	0.168	<.0001	-1.3663,-0.6461
week 12	-5.88	5.185	0.2756	-17.0031,5.2382
week 24	6.70	5.232	0.2213	-4.5236,17.9178
baseline*week 12	0.71	0.199	0.0032	0.2808,1.1341
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of SDAI at 12 weeks	-15.03	2.415	<.0001	-20.2123,-9.8515
the least-squares mean of the change of SDAI at 24 weeks	-24.12	1.909	<.0001	-28.2127,-20.0259

Footnote: SDAI, Simplified Disease Activity Index; N, number of patients in other mixed dosage population.
MMRM is applied by using the change of SDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline SDAI score and baseline SDAI score-by-week-interaction.

Table ANN. 243 **CDAI Score (1st Dosage Subgroups, Effectiveness Analyses Population)**

visit		*observed*				*change (post −baseline)*			
		2 mg only (N=458)	*4 mg only (N=28)*	*both dosages (N=28)*	*P value**	*2 mg only (N=458)*	*4 mg only (N=28)*	*both dosages (N=28)*	*P value**
Baseline	n (nmiss)	453 (5)	27 (1)	28 (0)	0.7232				
	Mean	29.39	26.84	28.04					
	(Std)	(17.27)	(18.81)	(15.97)					
	Median	26.50	26.00	25.75					
	Q1, Q3	17.00, 40.70	11.00, 37.10	18.65, 41.75					
	Min, Max	1.40, 74.00	2.60, 61.00	1.20, 58.70					
12-weeks	n (nmiss)	395 (63)	18 (10)	26 (2)	0.9170	391 (67)	18 (10)	26 (2)	0.7686
	Mean	15.30	13.36	15.19		-14.38	-16.34	-11.60	
	(Std)	(15.11)	(8.82)	(14.77)		(15.16)	(16.21)	(9.41)	
	Median	10.00	12.00	10.05		-11.00	-9.60	-11.00	
	Q1, Q3	4.30, 22.00	7.40, 22.00	7.00, 17.00		-22.50, 2.80	-25.60, 3.50	-18.00, 3.50	
	Min, Max	0.000, 71.60	1.20, 29.10	0.000, 57.60		-66.20, 25.90	-58.00, 1.40	-32.50, 1.60	
	P value					<.0001[b]	<.0001[b]	<.0001[a]	
24-weeks	n (nmiss)	337 (121)	22 (6)	22 (6)	0.0705	334 (124)	22 (6)	22 (6)	0.7374
	Mean	12.54	4.67	10.77		-17.56	-20.08	-19.00	
	(Std)	(14.16)	(3.51)	(11.60)		(16.24)	(17.94)	(13.07)	
	Median	7.00	4.00	7.65		-16.30	-13.50	-17.60	
	Q1, Q3	2.50, 16.80	2.60, 6.10	2.00, 14.30		-26.50, 4.50	-29.20, 7.50	-28.50, 8.50	
	Min, Max	0.000, 66.00	0.000, 17.00	0.80, 49.40		-67.60, 32.50	-57.00, 0.50	-43.00, 2.30	
	P value					<.0001[b]	<.0001[b]	<.0001[a]	

Footnote: nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
Both dosages subgroup includes 2 mg to 4 mg and other mixed dosage subgroups.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Kruskal-Wallis tests.

Table ANN. 244 **CDAI Score (2nd Dosage Subgroups, Effectiveness Analyses Population)**

		observed					*change (post −baseline)*				
visit		*2 mg only (N=458)*	*4 mg only (N=28)*	*2 mg to 4 mg (N=12)*	*other mixed dosage (N=16)*	*P value**	*2 mg only (N=458)*	*4 mg only (N=28)*	*2 mg to 4 mg (N=12)*	*other mixed dosage (N=16)*	*P value**
Baseline	n (nmiss)	453 (5)	27 (1)	12 (0)	16 (0)	0.8213					
	Mean (Std)	29.39 (17.27)	26.84 (18.81)	25.60 (16.79)	29.88 (15.62)						
	Median	26.50	26.00	25.75	25.75						
	Q1, Q3	17.00, 40.70	11.00, 37.10	13.00, 34.75	19.90, 43.75						
	Min, Max	1.40, 74.00	2.60, 61.00	1.20, 58.20	6.00, 58.70						
12-weeks	n (nmiss)	395 (63)	18 (10)	11 (1)	15 (1)	0.9483	391 (67)	18 (10)	11 (1)	15 (1)	0.3883
	Mean (Std)	15.30 (15.11)	13.36 (8.82)	15.85 (15.48)	14.71 (14.76)		-14.38 (15.16)	-16.34 (16.21)	-7.98 (8.88)	-14.26 (9.16)	
	Median	10.00	12.00	13.00	8.00		-11.00	-9.60	-5.00	-13.00	
	Q1, Q3	4.30, 22.00	7.40, 22.00	9.00, 17.00	6.40, 22.00		-22.50, -2.80	-25.60, -3.50	-18.50, 0.20	-18.00, -7.00	
	Min, Max	0.000, 71.60	1.20, 29.10	1.20, 57.60	0.000, 49.70		-66.20, 25.90	-58.00, 1.40	-20.20, 1.60	-32.50, -2.30	
	P value						<.0001[b]	<.0001[b]	0.0186[b]	<.0001[a]	
24-weeks	n (nmiss)	337 (121)	22 (6)	8 (4)	14 (2)	0.1070	334 (124)	22 (6)	8 (4)	14 (2)	0.8541
	Mean (Std)	12.54 (14.16)	4.67 (3.51)	11.39 (8.64)	10.41 (13.30)		-17.56 (16.24)	-20.08 (17.94)	-16.93 (12.39)	-20.19 (13.76)	
	Median	7.00	4.00	10.50	3.75		-16.30	-13.50	-17.35	-18.00	
	Q1, Q3	2.50, 16.80	2.60, 6.10	6.15, 13.65	2.00, 17.00		-26.50, -4.50	-29.20, -7.50	-25.00, -5.10	-31.10, -9.30	
	Min, Max	0.000, 66.00	0.000, 17.00	0.80, 29.70	1.00, 49.40		-67.60, 32.50	-57.00, 0.50	-37.70, -2.80	-43.00, -2.30	
	P value						<.0001[b]	<.0001[b]	0.0062[a]	0.0001[a]	

Footnote: nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Kruskal-Wallis tests.

Table ANN. 245 **CDAI Score (CDAI ≤10, 1st Dosage Subgroups, Effectiveness Analyses Population)**

		observed				*change (post −baseline)*			
visit		*2 mg only (N=458)*	*4 mg only (N=28)*	*both dosages (N=28)*	*P value**	*2 mg only (N=458)*	*4 mg only (N=28)*	*both dosages (N=28)*	*P value**
Baseline	n (nmiss)	50 (408)	6 (22)	5 (23)	0.3216				
	%	11.04%	22.22%	17.86%					
	Mean	3.94	4.55	5.76					
	(Std)	(2.45)	(1.78)	(3.48)					
	Median	3.40	4.50	6.00					
	Q1, Q3	1.90, 5.50	2.70, 6.00	3.60, 8.00					
	Min, Max	1.40, 10.00	2.60, 7.00	1.20, 10.00					
12-weeks	n (nmiss)	200 (258)	8 (20)	13 (15)	0.3656	198 (260)	8 (20)	13 (15)	0.2041
	%	50.63%	44.44%	50.00%		50.64%	44.44%	50.00%	
	Mean	4.59	5.56	5.51		-18.43	-20.59	-10.86	
	(Std)	(2.95)	(3.37)	(3.59)		(15.42)	(18.05)	(7.79)	
	Median	4.60	6.50	7.00		-16.05	-20.45	-13.00	
	Q1, Q3	2.00, 7.00	2.00, 8.50	2.00, 8.00		-25.00, -5.00	-26.20, -6.00	-17.00, -4.00	
	Min, Max	0.000, 10.00	1.20, 9.30	0.000, 9.60		-66.20, 0.80	-58.00, -1.40	-22.00, 1.60	
	P value					<.0001[b]	0.0145[a]	0.0003[a]	
24-weeks	n (nmiss)	208 (250)	21 (7)	13 (15)	0.8029	206 (252)	21 (7)	13 (15)	0.8719
	%	61.72%	95.45%	59.09%		61.68%	95.45%	59.09%	
	Mean	3.92	4.08	3.74		-21.05	-20.61	-21.92	
	(Std)	(3.05)	(2.23)	(2.81)		(15.66)	(18.20)	(14.18)	
	Median	3.30	4.00	3.50		-20.00	-15.00	-18.50	
	Q1, Q3	1.30, 6.40	2.60, 5.50	1.50, 5.00		-28.50, -8.00	-29.20, -7.50	-37.70, -12.00	
	Min, Max	0.000, 10.00	0.000, 8.00	0.80, 9.00		-67.60, 0.000	-57.00, 0.50	-43.00, -2.80	
	P value					<.0001[b]	<.0001[b]	0.0001[a]	

Footnote: nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
Both dosages subgroup includes 2 mg to 4 mg and other mixed dosage subgroups.
The numerator of percentage was n. The denominator of percentage for observed value was the number of patients with non-missing observed value at the visit in the subgroup. The denominator of
percentage for change from baseline was the number of patients with non-missing change at the visit in the subgroup.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Wilcoxon rank sum tests or Kruskal-Wallis tests.

Table ANN. 246 **CDAI Score (CDAI ≤10, 2nd Dosage Subgroups, Effectiveness Analyses Population)**

visit		*observed*					*change (post −baseline)*				
		2 mg only (N=458)	*4 mg only (N=28)*	*2 mg to 4 mg (N=12)*	*other mixed dosage (N=16)*	*P value**	*2 mg only (N=458)*	*4 mg only (N=28)*	*2 mg to 4 mg (N=12)*	*other mixed dosage (N=16)*	*P value**
Baseline	n (nmiss)	50 (408)	6 (22)	3 (9)	2 (14)	0.1964					
	%	11.04%	22.22%	25.00%	12.50%						
	Mean	3.94	4.55	4.27	8.00						
	(Std)	(2.45)	(1.78)	(3.45)	(2.83)						
	Median	3.40	4.50	3.60	8.00						
	Q1, Q3	1.90, 5.50	2.70, 6.00	1.20, 8.00	6.00, 10.00						
	Min, Max	1.40, 10.00	2.60, 7.00	1.20, 8.00	6.00, 10.00						
12-weeks	n (nmiss)	200 (258)	8 (20)	4 (8)	9 (7)	0.5617	198 (260)	8 (20)	4 (8)	9 (7)	0.1277
	%	50.63%	44.44%	36.36%	60.00%		50.64%	44.44%	36.36%	60.00%	
	Mean	4.59	5.56	5.30	5.60		-18.43	-20.59	-4.40	-13.73	
	(Std)	(2.95)	(3.37)	(4.63)	(3.36)		(15.42)	(18.05)	(8.56)	(5.79)	
	Median	4.60	6.50	5.20	7.00		-16.05	-20.45	-1.10	-15.60	
	Q1, Q3	2.00, 7.00	2.00, 8.50	1.30, 9.30	2.00, 8.00		-25.00, -5.00	-26.20, -6.00	-9.70, 0.90	-18.00, -10.00	
	Min, Max	0.000, 10.00	1.20, 9.30	1.20, 9.60	0.000, 9.50		-66.20, 0.80	-58.00, -1.40	-17.00, 1.60	-22.00, -4.00	
	P value						<.0001[b]	0.0145[a]	0.3797[a]	0.0001[a]	
24-weeks	n (nmiss)	208 (250)	21 (7)	4 (8)	9 (7)	0.5473	206 (252)	21 (7)	4 (8)	9 (7)	0.6605
	%	61.72%	95.45%	50.00%	64.29%		61.68%	95.45%	50.00%	64.29%	
	Mean	3.92	4.08	5.53	2.94		-21.05	-20.61	-15.13	-24.94	
	(Std)	(3.05)	(2.23)	(3.55)	(2.20)		(15.66)	(18.20)	(16.45)	(12.92)	
	Median	3.30	4.00	6.15	2.00		-20.00	-15.00	-10.00	-22.00	
	Q1, Q3	1.30, 6.40	2.60, 5.50	2.90, 8.15	1.50, 3.50		-28.50, -8.00	-29.20, -7.50	-27.35, -2.90	-38.00, -17.50	
	Min, Max	0.000, 10.00	0.000, 8.00	0.80, 9.00	1.00, 8.00		-67.60, 0.000	-57.00, 0.50	-37.70, -2.80	-43.00, -8.50	
	P value						<.0001[b]	<.0001[b]	0.1633[a]	0.0004[a]	

Footnote: nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
The numerator of percentage was n. The denominator of percentage for observed value was the number of patients with non-missing observed value at the visit in the subgroup. The denominator of
percentage for change from baseline was the number of patients with non-missing change at the visit in the subgroup.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Kruskal-Wallis tests.

Table ANN. 247 CDAI Score Summary by Category and Visit (2 mg Only, Effectiveness Analyses Population)

Visit	*<=2.8*	*>2.8 to <=10.0*	*>10.0 to <=22.0*	*>22.0*	*<=10.0*	*>10.0*	*Non-missing Total*
Baseline	21 (4.64%)	29 (6.40%)	120 (26.49%)	283 (62.47%)	50 (11.04%)	403 (88.96%)	453 (100.00%)
12-weeks	71 (17.97%)	129 (32.66%)	101 (25.57%)	94 (23.80%)	200 (50.63%)	195 (49.37%)	395 (100.00%)
24-weeks	93 (27.60%)	115 (34.12%)	70 (20.77%)	59 (17.51%)	208 (61.72%)	129 (38.28%)	337 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 248 CDAI Score Summary by Category and Visit (4 mg Only, Effectiveness Analyses Population)

Visit	*<=2.8*	*>2.8 to <=10.0*	*>10.0 to <=22.0*	*>22.0*	*<=10.0*	*>10.0*	*Non-missing Total*
Baseline	2 (7.41%)	4 (14.81%)	6 (22.22%)	15 (55.56%)	6 (22.22%)	21 (77.78%)	27 (100.00%)
12-weeks	3 (16.67%)	5 (27.78%)	6 (33.33%)	4 (22.22%)	8 (44.44%)	10 (55.56%)	18 (100.00%)
24-weeks	6 (27.27%)	15 (68.18%)	1 (4.55%)	0	21 (95.45%)	1 (4.55%)	22 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 249 CDAI Score Summary by Category and Visit (Both Dosages, Effectiveness Analyses Population)

Visit	*<=2.8*	*>2.8 to <=10.0*	*>10.0 to <=22.0*	*>22.0*	*<=10.0*	*>10.0*	*Non-missing Total*
Baseline	1 (3.57%)	4 (14.29%)	6 (21.43%)	17 (60.71%)	5 (17.86%)	23 (82.14%)	28 (100.00%)
12-weeks	5 (19.23%)	8 (30.77%)	8 (30.77%)	5 (19.23%)	13 (50.00%)	13 (50.00%)	26 (100.00%)
24-weeks	6 (27.27%)	7 (31.82%)	7 (31.82%)	2 (9.09%)	13 (59.09%)	9 (40.91%)	22 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 250 CDAI Score Summary by Category and Visit (2 mg to 4 mg, Effectiveness Analyses Population)

Visit	*<=2.8*	*>2.8 to <=10.0*	*>10.0 to <=22.0*	*>22.0*	*<=10.0*	*>10.0*	*Non-missing Total*
Baseline	1 (8.33%)	2 (16.67%)	2 (16.67%)	7 (58.33%)	3 (25.00%)	9 (75.00%)	12 (100.00%)
12-weeks	2 (18.18%)	2 (18.18%)	5 (45.45%)	2 (18.18%)	4 (36.36%)	7 (63.64%)	11 (100.00%)
24-weeks	1 (12.50%)	3 (37.50%)	3 (37.50%)	1 (12.50%)	4 (50.00%)	4 (50.00%)	8 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 251 CDAI Score Summary by Category and Visit (Other Mixed Dosage, Effectiveness Analyses Population)

Visit	*<=2.8*	*>2.8 to <=10.0*	*>10.0 to <=22.0*	*>22.0*	*<=10.0*	*>10.0*	*Non-missing Total*
Baseline	0	2 (12.50%)	4 (25.00%)	10 (62.50%)	2 (12.50%)	14 (87.50%)	16 (100.00%)
12-weeks	3 (20.00%)	6 (40.00%)	3 (20.00%)	3 (20.00%)	9 (60.00%)	6 (40.00%)	15 (100.00%)
24-weeks	5 (35.71%)	4 (28.57%)	4 (28.57%)	1 (7.14%)	9 (64.29%)	5 (35.71%)	14 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 252 CDAI Score Mixed-Effects Model Analysis (2 mg Only, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=458)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.62	0.036	<.0001	-0.6873,-0.5460
week 12	0.80	1.197	0.5064	-1.5571,3.1494
week 24	0.92	1.242	0.4602	-1.5240,3.3605
baseline*week 12	0.11	0.029	0.0002	0.0524,0.1656
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of CDAI at 12 weeks	-14.34	0.612	<.0001	-15.5393,-13.1334
the least-squares mean of the change of CDAI at 24 weeks	-17.46	0.632	<.0001	-18.7044,-16.2209

Footnote: CDAI, Clinical Disease Activity Index; N, number of patients in 2 mg only population.
MMRM is applied by using the change of CDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline CDAI score and baseline CDAI score-by-week-interaction.

Table ANN. 253 CDAI Score Mixed-Effects Model Analysis (4 mg Only, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=28)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-1.01	0.053	<.0001	-1.1244,-0.9046
week 12	8.40	3.759	0.0359	0.6068,16.1979
week 24	5.13	1.736	0.0073	1.5293,8.7277
baseline*week 12	0.18	0.105	0.1006	-0.0377,0.3968
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of CDAI at 12 weeks	-14.12	1.825	<.0001	-17.9058,-10.3365
the least-squares mean of the change of CDAI at 24 weeks	-22.24	0.891	<.0001	-24.0856,-20.3909

Footnote: CDAI, Clinical Disease Activity Index; N, number of patients in 4 mg only population.
MMRM is applied by using the change of CDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline CDAI score and baseline CDAI score-by-week-interaction.

Table ANN. 254 CDAI Score Mixed-Effects Model Analysis (Both Dosages, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=28)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.61	0.131	<.0001	-0.8749,-0.3370
week 12	-4.93	3.436	0.1631	-11.9937,2.1304
week 24	-0.69	4.373	0.8760	-9.6776,8.2991
baseline*week 12	0.35	0.141	0.0196	0.0610,0.6416
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of CDAI at 12 weeks	-12.10	1.729	<.0001	-15.6585,-8.5485
the least-squares mean of the change of CDAI at 24 weeks	-17.75	2.028	<.0001	-21.9223,-13.5846

Footnote: CDAI, Clinical Disease Activity Index; N, number of patients in both dosages population.
MMRM is applied by using the change of CDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline CDAI score and baseline CDAI score-by-week-interaction.

Table ANN. 255 CDAI Score Mixed-Effects Model Analysis (2 mg to 4 mg, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=12)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.56	0.065	<.0001	-0.6998,-0.4131
week 12	-2.90	5.083	0.5798	-14.0868,8.2877
week 24	0.47	1.967	0.8149	-3.8573,4.8005
baseline*week 12	0.33	0.146	0.0440	0.0106,0.6525
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of CDAI at 12 weeks	-8.68	2.801	0.0101	-14.8496,-2.5185
the least-squares mean of the change of CDAI at 24 weeks	-13.84	1.068	<.0001	-16.1908,-11.4901

Footnote: CDAI, Clinical Disease Activity Index; N, number of patients in 2 mg to 4 mg population.
MMRM is applied by using the change of CDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline CDAI score and baseline CDAI score-by-week-interaction.

Table ANN. 256 CDAI Score Mixed-Effects Model Analysis (Other Mixed Dosages, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=16)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.55	0.215	0.0237	-1.0091,-0.0848
week 12	-7.63	4.860	0.1388	-18.0504,2.7954
week 24	-3.29	7.264	0.6574	-18.8714,12.2891
baseline*week 12	0.32	0.220	0.1707	-0.1543,0.7902
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of CDAI at 12 weeks	-14.44	2.260	<.0001	-19.2889,-9.5937
the least-squares mean of the change of CDAI at 24 weeks	-19.57	3.122	<.0001	-26.2634,-12.8700

Footnote: CDAI, Clinical Disease Activity Index; N, number of patients in Other mixed dosage population.
MMRM is applied by using the change of CDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline CDAI score and baseline CDAI score-by-week-interaction.

Table ANN. 257 Demographics (RA Duration Subgroups, Effectiveness Analyses Population)

		Effectiveness Analyses Population				
		<=1 year (N=113)	*>1 and <=5 years (N=167)*	*>5 and <=10 years (N=95)*	*>10 years (N=139)*	*P value*
Age (years)	n (nmiss)	113 (0)	167 (0)	95 (0)	139 (0)	0.0763
	Mean (Std)	52.79 (12.84)	51.22 (13.46)	52.72 (12.52)	54.98 (11.16)	
	Median	55.00	52.00	53.00	56.00	
	Q1, Q3	44.00, 63.00	42.00, 60.00	42.00, 61.00	49.00, 63.00	
	Min, Max	21, 85	20, 81	21, 84	23, 80	
	18-34	10 (8.85%)	23 (13.77%)	8 (8.42%)	8 (5.76%)	0.0081[a]
	35-44	19 (16.81%)	27 (16.17%)	16 (16.84%)	11 (7.91%)	
	45-64	59 (52.21%)	89 (53.29%)	59 (62.11%)	93 (66.91%)	
	65-74	24 (21.24%)	22 (13.17%)	7 (7.37%)	25 (17.99%)	
	>=75	1 (0.88%)	6 (3.59%)	5 (5.26%)	2 (1.44%)	
	Total	113 (100.00%)	167 (100.00%)	95 (100.00%)	139 (100.00%)	
Sex	Male	27 (23.89%)	31 (18.56%)	16 (16.84%)	12 (8.63%)	0.0082[b]
	Female	86 (76.11%)	136 (81.44%)	79 (83.16%)	127 (91.37%)	
	Total	113 (100.00%)	167 (100.00%)	95 (100.00%)	139 (100.00%)	
Height (cm)	n (nmiss)	113 (0)	167 (0)	95 (0)	139 (0)	0.4305
	Mean (Std)	161.02 (6.45)	160.64 (6.98)	160.76 (7.79)	159.57 (5.89)	
	Median	160.00	160.00	160.00	160.00	
	Q1, Q3	157.00, 165.00	156.00, 165.00	156.00, 165.00	156.00, 164.00	
	Min, Max	147, 180	146, 198	145, 198	144, 178	
Weight (kg)	n (nmiss)	113 (0)	167 (0)	95 (0)	139 (0)	0.5142
	Mean (Std)	58.29 (10.19)	57.83 (9.96)	57.59 (9.54)	56.41 (10.09)	
	Median	58.00	56.00	58.00	55.00	
	Q1, Q3	50.00, 65.00	50.00, 64.00	50.00, 65.00	50.00, 61.00	
	Min, Max	39.0, 90.0	34.0, 90.0	40.0, 90.0	27.0, 100.0	
BMI (kg/m^2)	n (nmiss)	113 (0)	167 (0)	95 (0)	139 (0)	0.8127
	Mean (Std)	22.44 (3.40)	22.36 (3.26)	22.25 (3.09)	22.11 (3.55)	
	Median	22.03	21.79	22.03	21.48	
	Q1, Q3	19.96, 24.61	20.00, 24.44	19.81, 24.24	19.83, 23.71	
	Min, Max	16.00, 33.87	15.95, 31.22	16.38, 30.07	12.84, 36.73	

Footnote: The smoking history information were from 'Life History' page in CRF.
N, number of patients in population; nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.
The percentage denominator is the number of patients with non-missing value.
P values for continuous values were from Wilcoxon rank sum test.
a:P values for categorical values were from Chi-squared test. b:P values for categorical values were from Fisher exact tests.

		Effectiveness Analyses Population				
		<=1 year (N=113)	*>1 and <=5 years (N=167)*	*>5 and <=10 years (N=95)*	*>10 years (N=139)*	*P value*
	<18.5	13 (11.50%)	18 (10.78%)	10 (10.53%)	15 (10.79%)	0.8818[a]
	>=18.5-<24	64 (56.64%)	100 (59.88%)	58 (61.05%)	92 (66.19%)	
	>=24-<28	30 (26.55%)	38 (22.75%)	22 (23.16%)	23 (16.55%)	
	>=28	6 (5.31%)	11 (6.59%)	5 (5.26%)	9 (6.47%)	
	Total	113 (100.00%)	167 (100.00%)	95 (100.00%)	139 (100.00%)	
Smoking history	Never smoking	92 (81.42%)	145 (86.83%)	85 (89.47%)	133 (95.68%)	0.0014[b]
	Used to smoke, given up now	7 (6.19%)	5 (2.99%)	4 (4.21%)	5 (3.60%)	
	Still smoking	14 (12.39%)	17 (10.18%)	6 (6.32%)	1 (0.72%)	
	Total	113 (100.00%)	167 (100.00%)	95 (100.00%)	139 (100.00%)	

Footnote: The smoking history information were from 'Life History' page in CRF.
N, number of patients in population; nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.
The percentage denominator is the number of patients with non-missing value.
P values for continuous values were from Wilcoxon rank sum test.
a:P values for categorical values were from Chi-squared test. b:P values for categorical values were from Fisher exact tests.

Table ANN. 258 **Rheumatoid Arthritis Diagnosis (RA Duration Subgroups, Effectiveness Analyses Population)**

		Effectiveness Analyses Population				
		<=1 year (N=113)	*>1 and <=5 years (N=167)*	*>5 and <=10 years (N=95)*	*>10 years (N=139)*	*P value*
Months from the onset date of RA to ICF (months)	n (nmiss)	113 (0)	167 (0)	95 (0)	139 (0)	<.0001
	Mean (Std)	22.79 (61.99)	45.56 (35.42)	103.91 (42.37)	230.92 (95.37)	
	Median	8.54	36.63	97.74	205.67	
	Q1, Q3	4.57, 14.42	23.98, 54.24	76.55, 119.00	152.48, 277.68	
	Min, Max	0, 504.34	12.19, 264.31	60.02, 324.47	120.38, 623.67	
Duration of RA (months)	n (nmiss)	113 (0)	167 (0)	95 (0)	139 (0)	<.0001
	Mean (Std)	4.34 (3.70)	31.18 (14.36)	88.95 (18.08)	223.71 (96.12)	
	Median	3.29	27.24	91.93	194.89	
	Q1, Q3	0.85, 7.43	18.43, 42.18	72.64, 103.69	145.02, 266.38	
	Min, Max	0, 11.83	12.12, 59.79	60.02, 119.36	120.18, 623.67	
	<=1 year	113 (100.00%)	0	0	0	<.0001[a]
	>1-<=3 years	0	103 (61.68%)	0	0	
	>3-<=10 years	0	64 (38.32%)	95 (100.00%)	0	
	>10 years	0	0	0	139 (100.00%)	
	Total	113 (100.00%)	167 (100.00%)	95 (100.00%)	139 (100.00%)	
Meet the ACR/EULAR 2010 criteria and number of points	Yes	113 (100.00%)	167 (100.00%)	95 (100.00%)	139 (100.00%)	NA[b]
	n (nmiss)	113 (0)	167 (0)	95 (0)	139 (0)	
	Mean (Std)	8.38 (1.48)	8.32 (1.48)	8.53 (1.49)	8.52 (1.44)	
	Median	8.00	8.00	9.00	9.00	
	Q1, Q3	7.00, 10.00	7.00, 10.00	7.00, 10.00	7.00, 10.00	
	Min, Max	6, 10	6, 10	6, 10	6, 10	
	Total	113 (100.00%)	167 (100.00%)	95 (100.00%)	139 (100.00%)	

Footnote: The duration of RA (months) = (Date of informed consent – date of diagnosis of RA) / 30.4375, round to 2 decimal place. Months from the onset date of RA to ICF (months) = (Date of informed consent – the onset date of RA) / 30.4375, round to 2 decimal place.
N, number of patients in population; nmiss, no. of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range. The percentage denominator is the number of patients with non-missing value.
P values for continuous values were from Wilcoxon rank sum test.
a:P values for categorical values were from Chi-squared test. b:P values for categorical values were from Fisher exact tests.

Table ANN. 259 **Rheumatoid Arthritis Diagnosis (RA Duration Subgroups, Effectiveness Analyses Population)**

		Effectiveness Analyses Population				
		≤1 year (N=113)	*>1 and ≤5 years (N=167)*	*>5 and ≤10 years (N=95)*	*>10 years(N=139)*	*P value*
Overall Olumiant exposure (days)	n (nmiss)	113 (0)	166 (1)	95 (0)	139 (0)	0.6061
	Mean (Std)	166.14 (33.24)	162.53 (35.19)	164.52 (31.30)	164.92 (29.60)	
	Median	172.00	169.00	171.00	169.00	
	Q1, Q3	157.00, 182.00	155.00, 181.00	158.00, 181.00	155.00, 179.00	
	Min, Max	75, 252	55, 314	1, 218	71, 285	
Olumiant exposure (days)	n (nmiss)	113 (0)	166 (1)	95 (0)	139 (0)	0.6868
	Mean (Std)	164.57 (33.80)	160.88 (35.08)	161.92 (32.86)	162.84 (32.02)	
	Median	171.00	168.00	170.00	169.00	
	Q1, Q3	155.00, 181.00	154.00, 180.00	156.00, 181.00	153.00, 179.00	
	Min, Max	75, 249	55, 314	1, 218	46, 285	
Total patient year exposure		51.4	73.9	42.8	62.8	
Number of patients administered only 2mg Olumiant	n (%)	102 (90.27%)	147 (88.02%)	85 (89.47%)	124 (89.21%)	0.9544
Number of patients administered only 4mg Olumiant	n (%)	6 (5.31%)	8 (4.79%)	7 (7.37%)	7 (5.04%)	0.8353
Number of patients administered mixed dosage of Olumiant	n (%)	5 (4.42%)	12 (7.19%)	3 (3.16%)	8 (5.76%)	0.5706

Footnote: N, number of patients in population; nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.
Overall Olumiant exposure (days) = Olumiant discontinue date in study termination page – the earliest start date of treatment in treatment information page +1.
Olumiant exposure (days) = sum of (end date of treatment - start date of treatment +1). The start and end date of treatment are from the same record in treatment information page.
The sum are based on all records in this page.
Total patient year exposure = sum of all patients' year exposure. Patient year exposure = overall Olumiant exposure in days for the patient / 365.25, keep 1 decimal place.
P values for continuous values were from Wilcoxon rank sum test. P values for categorical values were from Fisher exact tests.

Table ANN. 260 **DAS28-CRP Score (RA Duration Subgroups, Effectiveness Analyses Population)**

		observed					*change (post −baseline)*				
visit		*<=1 year (N=113)*	*>1 and <=5 years (N=167)*	*>5 and <=10 years (N=95)*	*>10 years (N=139)*	*P value**	*<=1 year (N=113)*	*>1 and <=5 years (N=167)*	*>5 and <=10 years (N=95)*	*>10 years (N=139)*	*P value**
Baseline	n (nmiss)	112 (1)	162 (5)	90 (5)	138 (1)	0.2371					
	Mean (Std)	4.68 (1.88)	4.46 (1.89)	4.74 (1.82)	4.89 (1.77)						
	Median	4.93	4.65	4.86	4.93						
	Q1, Q3	3.69, 6.08	3.57, 5.73	3.73, 6.05	4.17, 6.23						
	Min, Max	0.30, 8.02	0.35, 7.89	0.25, 7.83	0.32, 7.96						
12-weeks	n (nmiss)	92 (21)	131 (36)	77 (18)	117 (22)	0.0257	92 (21)	129 (38)	75 (20)	117 (22)	0.1187
	Mean (Std)	2.80 (1.45)	2.92 (1.76)	3.20 (1.61)	3.42 (1.72)		-1.88 (1.55)	-1.38 (1.47)	-1.45 (1.59)	-1.54 (1.60)	
	Median	2.66	2.70	3.18	3.39		-1.72	-0.96	-1.31	-1.44	
	Q1, Q3	1.68, 3.78	1.60, 4.04	2.01, 4.29	2.19, 4.66		-2.92, 0.53	-2.47, 0.25	-2.53, 0.29	-2.84, 0.38	
	Min, Max	0.24, 7.72	0.11, 7.88	0.18, 6.59	0.19, 7.56		-5.63, 0.87	-5.71, 2.43	-5.61, 3.58	-5.52, 2.12	
	P value						<.0001[b]	<.0001[b]	<.0001[a]	<.0001[a]	
24-weeks	n (nmiss)	79 (34)	105 (62)	66 (29)	103 (36)	0.1896	79 (34)	104 (63)	64 (31)	103 (36)	0.2024
	Mean (Std)	2.46 (1.22)	2.63 (1.57)	2.78 (1.45)	2.97 (1.67)		-2.28 (1.65)	-1.73 (1.67)	-2.01 (1.51)	-1.93 (1.75)	
	Median	2.19	2.27	2.48	2.71		-2.21	-1.63	-2.05	-1.73	
	Q1, Q3	1.55, 3.24	1.64, 3.58	1.75, 3.90	1.63, 3.96		-3.44, 0.73	-3.01, 0.32	-3.16, 0.71	-3.20, 0.59	
	Min, Max	0.17, 5.84	0.12, 7.12	0.16, 6.60	0.11, 7.09		-5.60, 0.82	-5.73, 2.58	-5.26, 0.67	-6.01, 1.98	
	P value						<.0001[a]	<.0001[a]	<.0001[a]	<.0001[a]	

Footnote: CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Kruskal-Wallis tests.

Table ANN. 261 **DAS28-CRP Score (DAS28-CRP ≤3.2, RA Duration Subgroups, Effectiveness Analyses Population)**

		observed					*change (post −baseline)*				
visit		*<=1 year (N=113)*	*>1 and <=5 years (N=167)*	*>5 and <=10 years (N=95)*	*>10 years (N=139)*	*P value**	*<=1 year (N=113)*	*>1 and <=5 years (N=167)*	*>5 and <=10 years (N=95)*	*>10 years (N=139)*	*P value**
Baseline	n	21 (92)	31	15 (80)	17	0.8884					
	(nmiss)		(136)		(122)						
	%	18.75%	19.14%	16.67%	12.32%						
	Mean	1.61	1.45	1.66	1.45						
	(Std)	(1.09)	(1.17)	(1.09)	(1.08)						
	Median	2.03	0.59	2.14	0.87						
	Q1, Q3	0.55, 2.52	0.40, 2.83	0.46, 2.55	0.51, 2.36						
	Min, Max	0.30, 3.12	0.35, 3.08	0.25, 3.15	0.32, 3.13						
12-weeks	n	56 (57)	78 (89)	39 (56)	53 (86)	0.5890	56 (57)	76 (91)	38 (57)	53 (86)	0.5728
	(nmiss)										
	%	60.87%	59.54%	50.65%	45.30%		60.87%	58.91%	50.67%	45.30%	
	Mean	1.86	1.74	1.91	1.89		-2.27	-1.93	-2.01	-2.24	
	(Std)	(0.80)	(0.92)	(0.92)	(0.88)		(1.64)	(1.49)	(1.61)	(1.43)	
	Median	1.97	1.82	2.01	2.13		-2.06	-1.72	-1.85	-2.41	
	Q1, Q3	1.46, 2.48	1.25, 2.48	1.42, 2.67	1.45, 2.60		-3.62, 0.77	-3.32, 0.50	-3.41, 0.56	-3.06, 0.96	
	Min, Max	0.24, 3.19	0.11, 3.14	0.18, 3.18	0.19, 3.14		-5.63, 0.02	-5.71, 0.10	-5.61, 0.55	-5.52, 0.02	
	P value						<.0001[b]	<.0001[b]	<.0001[a]	<.0001[a]	
24-weeks	n	59 (54)	72 (95)	40 (55)	64 (75)	0.8385	59 (54)	71 (96)	39 (56)	64 (75)	0.5131
	(nmiss)										
	%	74.68%	68.57%	60.61%	62.14%		74.68%	68.27%	60.94%	62.14%	
	Mean	1.89	1.77	1.81	1.91		-2.60	-2.25	-2.47	-2.60	
	(Std)	(0.70)	(0.83)	(0.78)	(0.87)		(1.58)	(1.53)	(1.54)	(1.65)	
	Median	1.84	1.90	1.90	1.98		-2.60	-2.46	-2.71	-2.85	
	Q1, Q3	1.45, 2.54	1.51, 2.35	1.56, 2.28	1.38, 2.66		-3.89, 1.05	-3.46, 0.79	-3.67, 1.19	-3.66, 1.17	
	Min, Max	0.17, 3.13	0.12, 3.12	0.16, 3.12	0.11, 3.14		-5.60, 0.02	-5.73, 0.000	-5.26, 0.19	-6.01, 0.05	
	P value						<.0001[a]	<.0001[b]	<.0001[a]	<.0001[b]	

Footnote: CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
The numerator of percentage was n. The denominator of percentage for observed value was the number of patients with non-missing observed value at the visit in the subgroup. The denominator of
percentage for change from baseline was the number of patients with non-missing change at the visit in the subgroup.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Kruskal-Wallis tests.

Table ANN. 262 DAS28-CRP Score Summary by Category and Visit (RA Duration ≤1 Year, Effectiveness Analyses Population)

Visit	*<2.6*	*>=2.6 to <=3.2*	*>3.2 to <=5.1*	*>5.1*	*<=3.2*	*>3.2*	*Non-missing Total*
Baseline	16 (14.29%)	5 (4.46%)	40 (35.71%)	51 (45.54%)	21 (18.75%)	91 (81.25%)	112 (100.00%)
12-weeks	45 (48.91%)	11 (11.96%)	32 (34.78%)	4 (4.35%)	56 (60.87%)	36 (39.13%)	92 (100.00%)
24-weeks	47 (59.49%)	12 (15.19%)	17 (21.52%)	3 (3.80%)	59 (74.68%)	20 (25.32%)	79 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 263 DAS28-CRP Score Summary by Category and Visit (RA Duration >1 and ≤5 Years, Effectiveness Analyses Population)

Visit	*<2.6*	*>=2.6 to <=3.2*	*>3.2 to <=5.1*	*>5.1*	*<=3.2*	*>3.2*	*Non-missing Total*
Baseline	23 (14.20%)	8 (4.94%)	71 (43.83%)	60 (37.04%)	31 (19.14%)	131 (80.86%)	162 (100.00%)
12-weeks	61 (46.56%)	17 (12.98%)	35 (26.72%)	18 (13.74%)	78 (59.54%)	53 (40.46%)	131 (100.00%)
24-weeks	60 (57.14%)	12 (11.43%)	24 (22.86%)	9 (8.57%)	72 (68.57%)	33 (31.43%)	105 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 264 DAS28-CRP Score Summary by Category and Visit (RA Duration >5 and ≤10 years, Effectiveness Analyses Population)

Visit	*<2.6*	*>=2.6 to <=3.2*	*>3.2 to <=5.1*	*>5.1*	*<=3.2*	*>3.2*	*Non-missing Total*
Baseline	12 (13.33%)	3 (3.33%)	37 (41.11%)	38 (42.22%)	15 (16.67%)	75 (83.33%)	90 (100.00%)
12-weeks	29 (37.66%)	10 (12.99%)	28 (36.36%)	10 (12.99%)	39 (50.65%)	38 (49.35%)	77 (100.00%)
24-weeks	34 (51.52%)	6 (9.09%)	22 (33.33%)	4 (6.06%)	40 (60.61%)	26 (39.39%)	66 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 265 DAS28-CRP Score Summary by Category and Visit (RA Duration >10 Years, Effectiveness Analyses Population)

Visit	*<2.6*	*>=2.6 to <=3.2*	*>3.2 to <=5.1*	*>5.1*	*<=3.2*	*>3.2*	*Non-missing Total*
Baseline	13 (9.42%)	4 (2.90%)	58 (42.03%)	63 (45.65%)	17 (12.32%)	121 (87.68%)	138 (100.00%)
12-weeks	39 (33.33%)	14 (11.97%)	40 (34.19%)	24 (20.51%)	53 (45.30%)	64 (54.70%)	117 (100.00%)
24-weeks	44 (42.72%)	20 (19.42%)	25 (24.27%)	14 (13.59%)	64 (62.14%)	39 (37.86%)	103 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 266 DAS28-CRP Score Mixed-Effects Model Analysis (RA Duration ≤1 Year, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=113)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.70	0.065	<.0001	-0.8288,-0.5700
week 12	0.71	0.347	0.0426	0.0242,1.4014
week 24	0.99	0.328	0.0032	0.3406,1.6425
baseline*week 12	0.16	0.061	0.0123	0.0347,0.2784
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of DAS28-CRP at 12 weeks	-1.84	0.127	<.0001	-2.0962,-1.5914
the least-squares mean of the change of DAS28-CRP at 24 weeks	-2.30	0.113	<.0001	-2.5272,-2.0780

Footnote: CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; N, number of patients in RA duration <=1 year population.
MMRM is applied by using the change of DAS28-CRP Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline DAS28 score and baseline DAS28 score-by-week-interaction.

Table ANN. 267 **DAS28-CRP Score Mixed-Effects Model Analysis (RA Duration >1 and ≤5 years, Effectiveness Analyses Population)**

variable	*Effectiveness Analyses Population (N=167)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.55	0.062	<.0001	-0.6755,-0.4297
week 12	0.21	0.277	0.4594	-0.3427,0.7542
week 24	0.66	0.295	0.0260	0.0805,1.2472
baseline*week 12	0.19	0.054	0.0006	0.0830,0.2947
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of DAS28-CRP at 12 weeks	-1.37	0.113	<.0001	-1.5920,-1.1454
the least-squares mean of the change of DAS28-CRP at 24 weeks	-1.73	0.119	<.0001	-1.9636,-1.4929

Footnote: CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; N, number of patients in RA duration >1 and <=5 years population.
MMRM is applied by using the change of DAS28-CRP Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline DAS28 score and baseline DAS28 score-by-week-interaction.

Table ANN. 268 **DAS28-CRP Score Mixed-Effects Model Analysis (RA Duration >5 and ≤10 years, Effectiveness Analyses Population)**

variable	*Effectiveness Analyses Population (N=95)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.50	0.085	<.0001	-0.6725,-0.3359
week 12	0.89	0.407	0.0327	0.0750,1.6958
week 24	0.45	0.430	0.2940	-0.4016,1.3097
baseline*week 12	0.00	0.089	0.9618	-0.1726,0.1811
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of DAS28-CRP at 12 weeks	-1.48	0.148	<.0001	-1.7761,-1.1860
the least-squares mean of the change of DAS28-CRP at 24 weeks	-1.93	0.147	<.0001	-2.2255,-1.6397

Footnote: CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; N, number of patients in RA duration >5 and <=10 years population.
MMRM is applied by using the change of DAS28-CRP Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline DAS28 score and baseline DAS28 score-by-week-interaction.

Table ANN. 269 **DAS28-CRP Score Mixed-Effects Model Analysis (RA Duration >10 years, Effectiveness Analyses Population)**

variable	*Effectiveness Analyses Population (N=139)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.52	0.076	<.0001	-0.6721,-0.3698
week 12	0.61	0.380	0.1087	-0.1383,1.3677
week 24	0.66	0.399	0.1000	-0.1286,1.4523
baseline*week 12	0.09	0.055	0.0905	-0.0151,0.2031
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of DAS28-CRP at 12 weeks	-1.49	0.127	<.0001	-1.7403,-1.2371
the least-squares mean of the change of DAS28-CRP at 24 weeks	-1.90	0.136	<.0001	-2.1748,-1.6348

Footnote: CRP, C-reactive protein; DAS28, Disease Activity Score modified to include the 28 diarthrodial joint count; N, number of patients in RA duration >10 years population.
MMRM is applied by using the change of DAS28-CRP Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline DAS28 score and baseline DAS28 score-by-week-interaction.

Table ANN. 270 **SDAI Score (RA Duration Subgroups, Effectiveness Analyses Population)**

		observed					*change (post −baseline)*				
visit		*<=1 year (N=113)*	*>1 and <=5 years (N=167)*	*>5 and <=10 years (N=95)*	*>10 years (N=139)*	*P value**	*<=1 year (N=113)*	*>1 and <=5 years (N=167)*	*>5 and <=10 years (N=95)*	*>10 years (N=139)*	*P value**
Baseline	n (nmiss)	112 (1)	162 (5)	90 (5)	138 (1)	0.1404					
	Mean (Std)	31.14 (17.68)	29.21 (18.08)	31.85 (18.74)	34.08 (19.07)						
	Median	29.70	26.16	27.19	31.81						
	Q1, Q3	17.44, 42.16	16.55, 40.13	20.05, 45.60	21.29, 45.70						
	Min, Max	1.23, 77.80	1.63, 85.92	1.42, 73.57	1.73, 76.88						
12-weeks	n (nmiss)	92 (21)	131 (36)	77 (18)	117 (22)	0.0315	92 (21)	129 (38)	75 (20)	117 (22)	0.0941
	Mean (Std)	12.35 (12.84)	14.79 (15.12)	15.64 (13.86)	18.95 (17.19)		-18.49 (16.16)	-13.21 (14.76)	-15.61 (16.15)	-15.99 (17.25)	
	Median	8.19	10.24	12.24	13.55		-15.94	-9.29	-11.51	-12.83	
	Q1, Q3	4.26, 17.20	3.68, 19.72	4.55, 21.95	6.52, 27.75		-27.42, -5.68	-20.90, -2.29	-22.86, -3.52	-26.84, -3.32	
	Min, Max	0.17, 70.53	0.05, 75.30	0.18, 59.05	0.01, 72.19		-60.41, 5.93	-83.51, 19.00	-59.35, 12.08	-66.20, 25.74	
	P value						<.0001[b]	<.0001[b]	<.0001[b]	<.0001[b]	
24-weeks	n (nmiss)	79 (34)	105 (62)	66 (29)	103 (36)	0.1799	79 (34)	104 (63)	64 (31)	103 (36)	0.2786
	Mean (Std)	9.41 (10.48)	11.28 (13.52)	12.14 (12.82)	14.37 (15.44)		-21.55 (16.71)	-17.03 (18.09)	-20.01 (17.70)	-19.64 (18.17)	
	Median	6.42	6.23	7.05	8.02		-19.35	-15.87	-17.90	-17.12	
	Q1, Q3	3.15, 13.64	2.31, 14.44	3.91, 17.00	3.60, 20.42		-33.13, -6.79	-26.91, -2.65	-30.04, -6.04	-32.15, -4.66	
	Min, Max	0.09, 55.06	0.12, 62.56	0.02, 66.11	0.02, 63.58		-59.71, 5.93	-83.91, 31.01	-68.39, 13.75	-69.88, 18.44	
	P value						<.0001[b]	<.0001[b]	<.0001[b]	<.0001[b]	

Footnote: nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Kruskal-Wallis tests.

Table ANN. 271 **SDAI Score (SDAI ≤11, RA Duration Subgroups, Effectiveness Analyses Population)**

		observed					*change (post −baseline)*				
visit		*<=1 year (N=113)*	*>1 and <=5 years (N=167)*	*>5 and <=10 years (N=95)*	*>10 years (N=139)*	*P value**	*<=1 year (N=113)*	*>1 and <=5 years (N=167)*	*>5 and <=10 years (N=95)*	*>10 years (N=139)*	*P value**
Baseline	n	12	23	12 (83)	16	0.5895					
	(nmiss)	(101)	(144)		(123)						
	%	10.71%	14.20%	13.33%	11.59%						
	Mean	4.32	4.08	5.11	5.16						
	(Std)	(2.60)	(2.77)	(3.11)	(2.97)						
	Median	3.77	3.32	4.85	4.93						
	Q1, Q3	2.37, 5.54	1.93, 5.42	2.17, 7.43	2.13, 6.87						
	Min, Max	1.23, 10.69	1.63, 10.92	1.42, 10.47	1.73, 10.10						
12-weeks	n	56 (57)	71 (96)	37 (58)	54 (85)	0.7652	56 (57)	70 (97)	36 (59)	54 (85)	0.0969
	(nmiss)										
	%	60.87%	54.20%	48.05%	46.15%		60.87%	54.26%	48.00%	46.15%	
	Mean	5.09	4.85	5.02	5.49		-20.75	-17.03	-18.90	-23.18	
	(Std)	(2.97)	(3.39)	(3.30)	(3.37)		(16.03)	(15.76)	(17.88)	(17.00)	
	Median	5.19	4.49	4.55	6.24		-17.43	-16.26	-15.00	-22.81	
	Q1, Q3	2.19, 7.58	1.68, 8.11	2.02, 8.27	2.19, 8.05		-30.43, -7.47	-23.08, -3.43	-23.80, -3.16	-31.40, -9.00	
	Min, Max	0.17, 10.52	0.05, 10.88	0.18, 10.93	0.01, 10.90		-58.91, 0.18	-83.51, 0.81	-59.35, -0.20	-66.20, -0.57	
	P value						<.0001[b]	<.0001[b]	<.0001[b]	<.0001[b]	
24-weeks	n	58 (55)	72 (95)	38 (57)	60 (79)	0.8323	58 (55)	71 (96)	37 (58)	60 (79)	0.3609
	(nmiss)										
	%	73.42%	68.57%	57.58%	58.25%		73.42%	68.27%	57.81%	58.25%	
	Mean	4.50	4.08	3.95	4.40		-24.20	-20.54	-23.00	-24.82	
	(Std)	(3.04)	(3.02)	(2.77)	(3.09)		(15.75)	(17.24)	(18.56)	(18.76)	
	Median	3.75	3.49	4.02	4.16		-23.45	-18.69	-20.72	-22.70	
	Q1, Q3	2.67, 6.73	1.66, 6.36	1.37, 5.53	1.66, 7.15		-35.37, -10.92	-30.06, -6.06	-29.20, -6.65	-35.72, -9.03	
	Min, Max	0.09, 10.69	0.12, 10.86	0.02, 10.99	0.02, 10.70		-57.91, -1.47	-83.91, 0.06	-68.39, 0.41	-69.88, -0.06	
	P value						<.0001[b]	<.0001[b]	<.0001[b]	<.0001[b]	

Footnote: nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
The numerator of percentage was n. The denominator of percentage for observed value was the number of patients with non-missing observed value at the visit in the subgroup. The denominator of
percentage for change from baseline was the number of patients with non-missing change at the visit in the subgroup.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Kruskal-Wallis tests.

Table ANN. 272 SDAI Score Summary by Category and Visit (RA Duration ≤1 Year, Effectiveness Analyses Population)

Visit	*<=3.3*	*>3.3 to <=11.0*	*>11.0 to <=26.0*	*>26.0*	*<=11.0*	*>11.0*	*Non-missing Total*
Baseline	4 (3.57%)	8 (7.14%)	36 (32.14%)	64 (57.14%)	12 (10.71%)	100 (89.29%)	112 (100.00%)
12-weeks	21 (22.83%)	35 (38.04%)	26 (28.26%)	10 (10.87%)	56 (60.87%)	36 (39.13%)	92 (100.00%)
24-weeks	21 (26.58%)	37 (46.84%)	16 (20.25%)	5 (6.33%)	58 (73.42%)	21 (26.58%)	79 (100.00%)

Footnote: Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 273 SDAI Score Summary by Category and Visit (RA Duration >1 and ≤5 Years, Effectiveness Analyses Population)

Visit	*<=3.3*	*>3.3 to <=11.0*	*>11.0 to <=26.0*	*>26.0*	*<=11.0*	*>11.0*	*Non-missing Total*
Baseline	11 (6.79%)	12 (7.41%)	58 (35.80%)	81 (50.00%)	23 (14.20%)	139 (85.80%)	162 (100.00%)
12-weeks	30 (22.90%)	41 (31.30%)	36 (27.48%)	24 (18.32%)	71 (54.20%)	60 (45.80%)	131 (100.00%)
24-weeks	35 (33.33%)	37 (35.24%)	20 (19.05%)	13 (12.38%)	72 (68.57%)	33 (31.43%)	105 (100.00%)

Footnote: Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 274 SDAI Score Summary by Category and Visit (RA Duration >5 and ≤10 Years, Effectiveness Analyses Population)

Visit	*<=3.3*	*>3.3 to <=11.0*	*>11.0 to <=26.0*	*>26.0*	*<=11.0*	*>11.0*	*Non-missing Total*
Baseline	4 (4.44%)	8 (8.89%)	27 (30.00%)	51 (56.67%)	12 (13.33%)	78 (86.67%)	90 (100.00%)
12-weeks	14 (18.18%)	23 (29.87%)	26 (33.77%)	14 (18.18%)	37 (48.05%)	40 (51.95%)	77 (100.00%)
24-weeks	16 (24.24%)	22 (33.33%)	21 (31.82%)	7 (10.61%)	38 (57.58%)	28 (42.42%)	66 (100.00%)

Footnote: Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 275 **SDAI Score Summary by Category and Visit (RA Duration >10 Years, Effectiveness Analyses Population)**

Visit	*<=3.3*	*>3.3 to <=11.0*	*>11.0 to <=26.0*	*>26.0*	*<=11.0*	*>11.0*	*Non-missing Total*
Baseline	5 (3.62%)	11 (7.97%)	36 (26.09%)	86 (62.32%)	16 (11.59%)	122 (88.41%)	138 (100.00%)
12-weeks	18 (15.38%)	36 (30.77%)	31 (26.50%)	32 (27.35%)	54 (46.15%)	63 (53.85%)	117 (100.00%)
24-weeks	25 (24.27%)	35 (33.98%)	24 (23.30%)	19 (18.45%)	60 (58.25%)	43 (41.75%)	103 (100.00%)

Footnote: Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 276 SDAI Score Mixed-Effects Model Analysis (RA Duration ≤1 Year, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=113)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.84	0.060	<.0001	-0.9539,-0.7162
week 12	2.25	2.487	0.3683	-2.6869,7.1823
week 24	3.72	2.107	0.0804	-0.4594,7.9051
baseline*week 12	0.18	0.058	0.0031	0.0613,0.2928
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of SDAI at 12 weeks	-18.08	1.215	<.0001	-20.4902,-15.6694
the least-squares mean of the change of SDAI at 24 weeks	-22.08	1.007	<.0001	-24.0730,-20.0773

Footnote: SDAI, Simplified Disease Activity Index; N, number of patients in RA duration <=1 year population.
MMRM is applied by using the change of SDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline SDAI score and baseline SDAI score-by-week-interaction.

Table ANN. 277 **SDAI Score Mixed-Effects Model Analysis (RA Duration >1 and ≤5 Years, Effectiveness Analyses Population)**

variable	*Effectiveness Analyses Population (N=167)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.72	0.060	<.0001	-0.8418,-0.6036
week 12	0.20	1.908	0.9173	-3.5752,3.9724
week 24	3.17	2.028	0.1205	-0.8417,7.1793
baseline*week 12	0.25	0.051	<.0001	0.1491,0.3514
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of SDAI at 12 weeks	-13.10	1.046	<.0001	-15.1665,-11.0278
the least-squares mean of the change of SDAI at 24 weeks	-17.17	1.112	<.0001	-19.3691,-14.9709

Footnote: SDAI, Simplified Disease Activity Index; N, number of patients in RA duration >1 and <=5 years population.
MMRM is applied by using the change of SDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline SDAI score and baseline SDAI score-by-week-interaction.

Table ANN. 278 SDAI Score Mixed-Effects Model Analysis (RA Duration >5 and ≤10 Years, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=95)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.69	0.078	<.0001	-0.8455,-0.5368
week 12	3.17	2.613	0.2281	-2.0279,8.3767
week 24	2.56	2.846	0.3709	-3.1048,8.2279
baseline*week 12	0.09	0.077	0.2379	-0.0619,0.2456
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of SDAI at 12 weeks	-15.75	1.336	<.0001	-18.4068,-13.0891
the least-squares mean of the change of SDAI at 24 weeks	-19.26	1.427	<.0001	-22.1026,-16.4204

Footnote: SDAI, Simplified Disease Activity Index; N, number of patients in RA duration >5 and <=10 years population.
MMRM is applied by using the change of SDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline SDAI score and baseline SDAI score-by-week-interaction.

Table ANN. 279 SDAI Score Mixed-Effects Model Analysis (RA Duration >10 Years, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=139)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.58	0.067	<.0001	-0.7141,-0.4499
week 12	1.46	2.756	0.5975	-3.9963,6.9142
week 24	0.67	2.624	0.7987	-4.5230,5.8643
baseline*week 12	0.09	0.053	0.0889	-0.0139,0.1945
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of SDAI at 12 weeks	-15.51	1.320	<.0001	-18.1214,-12.8946
the least-squares mean of the change of SDAI at 24 weeks	-19.41	1.279	<.0001	-21.9432,-16.8807

Footnote: SDAI, Simplified Disease Activity Index; N, number of patients in RA duration >10 years population.
MMRM is applied by using the change of SDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline SDAI score and baseline SDAI score-by-week-interaction.

Table ANN. 280 **CDAI Score (RA Duration Subgroups, Effectiveness Analyses Population)**

visit		*observed*					*change (post −baseline)*				
		<=1 year (N=113)	*>1 and <=5 years (N=167)*	*>5 and <=10 years (N=95)*	*>10 years (N=139)*	*P value**	*<=1 year (N=113)*	*>1 and <=5 years (N=167)*	*>5 and <=10 years (N=95)*	*>10 years (N=139)*	*P value**
Baseline	n (nmiss)	113 (0)	165 (2)	92 (3)	138 (1)	0.2285					
	Mean	28.51	27.20	29.84	31.66						
	(Std)	(16.28)	(16.39)	(17.92)	(18.44)						
	Median	27.40	25.00	25.25	29.00						
	Q1, Q3	16.00, 36.60	16.00, 37.10	16.00, 44.05	19.00, 43.50						
	Min, Max	1.20, 68.30	1.50, 72.30	1.40, 63.60	1.70, 74.00						
12-weeks	n (nmiss)	95 (18)	136 (31)	84 (11)	124 (15)	0.0224	95 (18)	135 (32)	81 (14)	124 (15)	0.1488
	Mean	11.81	14.46	15.98	18.13		-16.50	-12.16	-14.01	-15.12	
	(Std)	(12.51)	(14.65)	(14.19)	(16.64)		(14.57)	(12.90)	(15.41)	(16.67)	
	Median	8.00	10.00	13.25	12.50		-15.00	-8.50	-10.40	-12.90	
	Q1, Q3	4.20, 16.00	3.55, 19.90	4.85, 22.00	6.40, 25.50		-24.30, -4.50	-20.20, -2.10	-21.10, -2.50	-24.69, -2.90	
	Min, Max	0.000, 63.00	0.000, 71.60	0.000, 59.00	0.000, 68.00		-58.00, 2.50	-53.70, 19.00	-57.60, 12.20	-66.20, 25.90	
	P value						<.0001[b]	<.0001[b]	<.0001[b]	<.0001[b]	
24-weeks	n (nmiss)	84 (29)	115 (52)	72 (23)	110 (29)	0.0800	84 (29)	114 (53)	70 (25)	110 (29)	0.4568
	Mean	8.91	11.39	12.78	14.43		-19.57	-15.89	-17.99	-18.29	
	(Std)	(10.52)	(13.71)	(13.84)	(15.45)		(14.78)	(15.93)	(17.34)	(16.63)	
	Median	5.75	6.70	7.05	8.20		-19.00	-14.30	-13.95	-17.00	
	Q1, Q3	2.55, 12.00	2.00, 16.00	3.80, 16.15	3.00, 21.50		-28.00, -6.45	-24.40, -3.90	-28.00, -4.70	-27.00, -4.60	
	Min, Max	0.000, 55.00	0.000, 59.10	0.000, 66.00	0.000, 62.00		-57.00, 1.00	-64.00, 32.50	-60.20, 14.00	-67.60, 19.00	
	P value						<.0001[b]	<.0001[b]	<.0001[b]	<.0001[b]	

Footnote: nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Kruskal-Wallis tests.

Table ANN. 281 **CDAI Score (CDAI ≤10, RA Duration Subgroups, Effectiveness Analyses Population)**

visit		*observed*					*change (post −baseline)*				
		<=1 year (N=113)	*>1 and <=5 years (N=167)*	*>5 and <=10 years (N=95)*	*>10 years (N=139)*	*P value**	*<=1 year (N=113)*	*>1 and <=5 years (N=167)*	*>5 and <=10 years (N=95)*	*>10 years (N=139)*	*P value**
Baseline	n	12	22	11 (84)	16	0.4228					
	(nmiss)	(101)	(145)		(123)						
	%	10.62%	13.33%	11.96%	11.59%						
	Mean	3.57	3.75	4.33	5.01						
	(Std)	(1.77)	(2.50)	(2.47)	(2.92)						
	Median	3.50	3.10	4.00	4.90						
	Q1, Q3	1.85, 5.30	1.90, 5.00	1.50, 6.00	2.10, 6.50						
	Min, Max	1.20, 6.20	1.50, 10.00	1.40, 8.00	1.70, 10.00						
12-weeks	n	58 (55)	70 (97)	37 (58)	56 (83)	0.8492	58 (55)	69 (98)	36 (59)	56 (83)	0.1029
	(nmiss)										
	%	61.05%	51.47%	44.05%	45.16%		61.05%	51.11%	44.44%	45.16%	
	Mean	4.77	4.47	4.59	4.92		-18.50	-14.91	-17.61	-21.78	
	(Std)	(2.85)	(3.22)	(2.97)	(2.94)		(14.70)	(12.37)	(17.66)	(16.76)	
	Median	5.00	3.95	4.30	6.00		-16.25	-15.20	-14.35	-21.05	
	Q1, Q3	2.00, 7.00	1.50, 7.90	2.00, 7.40	2.10, 7.25		-25.00, -7.30	-22.00, -3.40	-22.05, -2.65	-27.65, -9.10	
	Min, Max	0.000, 10.00	0.000, 10.00	0.000, 10.00	0.000, 9.60		-58.00, 0.20	-53.70, 0.80	-57.60, 1.60	-66.20, -0.70	
	P value						<.0001[b]	<.0001[b]	<.0001[b]	<.0001[b]	
24-weeks	n	61 (52)	78 (89)	41 (54)	62 (77)	0.9853	61 (52)	77 (90)	40 (55)	62 (77)	0.5009
	(nmiss)										
	%	72.62%	67.83%	56.94%	56.36%		72.62%	67.54%	57.14%	56.36%	
	Mean	3.97	3.86	3.85	4.02		-21.76	-18.94	-21.21	-22.91	
	(Std)	(3.02)	(3.08)	(2.73)	(2.98)		(14.43)	(14.66)	(17.58)	(17.11)	
	Median	3.20	2.55	4.00	4.00		-20.60	-18.00	-20.00	-22.00	
	Q1, Q3	1.40, 6.00	1.40, 7.00	1.00, 5.50	1.40, 7.00		-29.20, -10.60	-26.00, -6.70	-28.65, -5.85	-32.00, -9.50	
	Min, Max	0.000, 10.00	0.000, 10.00	0.000, 10.00	0.000, 9.70		-57.00, -0.30	-64.00, 0.000	-60.20, 0.50	-67.60, -0.10	
	P value						<.0001[b]	<.0001[b]	<.0001[b]	<.0001[b]	

Footnote: nmiss, number of data missing patients; Std, standard deviation; Q1 and Q3, interquartile range.
The numerator of percentage was n. The denominator of percentage for observed value was the number of patients with non-missing observed value at the visit in the subgroup. The denominator of
percentage for change from baseline was the number of patients with non-missing change at the visit in the subgroup.
Superscript a: Paired t test is used. Superscript b: Wilcoxon signed - rank test is used.
*P value for continuous values from Kruskal-Wallis tests.

Table ANN. 282 CDAI Score Summary by Category and Visit (RA Duration ≤1 Year, Effectiveness Analyses Population)

Visit	*<=2.8*	*>2.8 to <=10.0*	*>10.0 to <=22.0*	*>22.0*	*<=10.0*	*>10.0*	*Non-missing Total*
Baseline	5 (4.42%)	7 (6.19%)	31 (27.43%)	70 (61.95%)	12 (10.62%)	101 (89.38%)	113 (100.00%)
12-weeks	20 (21.05%)	38 (40.00%)	23 (24.21%)	14 (14.74%)	58 (61.05%)	37 (38.95%)	95 (100.00%)
24-weeks	23 (27.38%)	38 (45.24%)	16 (19.05%)	7 (8.33%)	61 (72.62%)	23 (27.38%)	84 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 283 CDAI Score Summary by Category and Visit (RA Duration >1 and ≤5 Years, Effectiveness Analyses Population)

Visit	*<=2.8*	*>2.8 to <=10.0*	*>10.0 to <=22.0*	*>22.0*	*<=10.0*	*>10.0*	*Non-missing Total*
Baseline	10 (6.06%)	12 (7.27%)	47 (28.48%)	96 (58.18%)	22 (13.33%)	143 (86.67%)	165 (100.00%)
12-weeks	30 (22.06%)	40 (29.41%)	36 (26.47%)	30 (22.06%)	70 (51.47%)	66 (48.53%)	136 (100.00%)
24-weeks	40 (34.78%)	38 (33.04%)	19 (16.52%)	18 (15.65%)	78 (67.83%)	37 (32.17%)	115 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 284 CDAI Score Summary by Category and Visit (RA Duration >5 and ≤10 Years, Effectiveness Analyses Population)

Visit	*<=2.8*	*>2.8 to <=10.0*	*>10.0 to <=22.0*	*>22.0*	*<=10.0*	*>10.0*	*Non-missing Total*
Baseline	4 (4.35%)	7 (7.61%)	24 (26.09%)	57 (61.96%)	11 (11.96%)	81 (88.04%)	92 (100.00%)
12-weeks	12 (14.29%)	25 (29.76%)	27 (32.14%)	20 (23.81%)	37 (44.05%)	47 (55.95%)	84 (100.00%)
24-weeks	16 (22.22%)	25 (34.72%)	20 (27.78%)	11 (15.28%)	41 (56.94%)	31 (43.06%)	72 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 285 CDAI Score Summary by Category and Visit (RA Duration >10 Years, Effectiveness Analyses Population)

Visit	*<=2.8*	*>2.8 to <=10.0*	*>10.0 to <=22.0*	*>22.0*	*<=10.0*	*>10.0*	*Non-missing Total*
Baseline	5 (3.62%)	11 (7.97%)	30 (21.74%)	92 (66.67%)	16 (11.59%)	122 (88.41%)	138 (100.00%)
12-weeks	17 (13.71%)	39 (31.45%)	29 (23.39%)	39 (31.45%)	56 (45.16%)	68 (54.84%)	124 (100.00%)
24-weeks	26 (23.64%)	36 (32.73%)	23 (20.91%)	25 (22.73%)	62 (56.36%)	48 (43.64%)	110 (100.00%)

Denominators are the number of patients with non-missing values at the visit in effectiveness analyses population.

Table ANN. 286 CDAI Score Mixed-Effects Model Analysis (RA Duration ≤1 Year, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=113)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.74	0.062	<.0001	-0.8672,-0.6225
week 12	1.13	2.346	0.6324	-3.5276,5.7782
week 24	1.26	1.997	0.5293	-2.7007,5.2219
baseline*week 12	0.14	0.060	0.0266	0.0161,0.2559
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of CDAI at 12 weeks	-16.16	1.140	<.0001	-18.4222,-13.8974
the least-squares mean of the change of CDAI at 24 weeks	-19.88	0.957	<.0001	-21.7815,-17.9864

Footnote: CDAI, Clinical Disease Activity Index; N, number of patients in RA duration <=1 year population.
MMRM is applied by using the change of CDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline CDAI score and baseline CDAI score-by-week-interaction.

Table ANN. 287 CDAI Score Mixed-Effects Model Analysis (RA Duration >1 and ≤5 Years, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=167)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.66	0.063	<.0001	-0.7812,-0.5310
week 12	-1.16	1.744	0.5060	-4.6093,2.2843
week 24	1.69	2.008	0.4013	-2.2791,5.6599
baseline*week 12	0.24	0.050	<.0001	0.1450,0.3444
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of CDAI at 12 weeks	-12.26	0.925	<.0001	-14.0934,-10.4342
the least-squares mean of the change of CDAI at 24 weeks	-16.01	1.063	<.0001	-18.1143,-13.9129

Footnote: CDAI, Clinical Disease Activity Index; N, number of patients in RA duration >1 and <=5 years population.
MMRM is applied by using the change of CDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline CDAI score and baseline CDAI score-by-week-interaction.

Table ANN. 288 CDAI Score Mixed-Effects Model Analysis (RA Duration >5 and ≤10 Years, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=95)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.65	0.079	<.0001	-0.8086,-0.4936
week 12	3.35	2.405	0.1673	-1.4326,8.1338
week 24	2.29	2.768	0.4113	-3.2182,7.7891
baseline*week 12	0.07	0.070	0.3396	-0.0721,0.2068
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of CDAI at 12 weeks	-14.11	1.252	<.0001	-16.6041,-11.6258
the least-squares mean of the change of CDAI at 24 weeks	-17.20	1.410	<.0001	-19.9988,-14.3914

Footnote: CDAI, Clinical Disease Activity Index; N, number of patients in RA duration >5 and <=10 years population.
MMRM is applied by using the change of CDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline CDAI score and baseline CDAI score-by-week-interaction.

Table ANN. 289 CDAI Score Mixed-Effects Model Analysis (RA Duration >10 Years, Effectiveness Analyses Population)

variable	*Effectiveness Analyses Population (N=139)*			
	Estimate	*Standard Error*	*P value*	*95%CI*
baseline	-0.56	0.064	<.0001	-0.6863,-0.4336
week 12	1.58	2.474	0.5234	-3.3121,6.4776
week 24	0.10	2.405	0.9671	-4.6586,4.8574
baseline*week 12	0.06	0.048	0.2306	-0.0369,0.1519
baseline*week 24	0.00	NA	NA	NA
the least-squares mean of the change of CDAI at 12 weeks	-15.00	1.214	<.0001	-17.4004,-12.5971
the least-squares mean of the change of CDAI at 24 weeks	-18.38	1.198	<.0001	-20.7486,-16.0094

Footnote: CDAI, Clinical Disease Activity Index; N, number of patients in RA duration >10 years population.
MMRM is applied by using the change of CDAI Score from baseline as the response variable, the fixed effects including categorical week (12 weeks, 24 weeks) and the continuous
fixed covariates of baseline CDAI score and baseline CDAI score-by-week-interaction.

Table ANN. 290 Demographics (Age Subgroups, Safety Analyses Population)

		Safety Analyses Population			
		<65 years (N=542)	*>=65 and <75 years (N=106)*	*>=75 years (N=19)*	*P value*
Age (years)	n (nmiss)	542 (0)	106 (0)	19 (0)	<.0001
	Mean (Std)	49.34 (10.34)	68.78 (2.60)	78.11 (2.88)	
	Median	52.00	69.00	78.00	
	Q1, Q3	42.00, 57.00	67.00, 70.00	76.00, 80.00	
	Min, Max	20, 64	65, 74	75, 85	
	18-34	61 (11.25%)	0	0	<.0001[a]
	35-44	92 (16.97%)	0	0	
	45-64	389 (71.77%)	0	0	
	65-74	0	106 (100.00%)	0	
	>=75	0	0	19 (100.00%)	
	Total	542 (100.00%)	106 (100.00%)	19 (100.00%)	
Sex	Male	93 (17.16%)	19 (17.92%)	6 (31.58%)	0.2586[b]
	Female	449 (82.84%)	87 (82.08%)	13 (68.42%)	
	Total	542 (100.00%)	106 (100.00%)	19 (100.00%)	
Height (cm)	n (nmiss)	541 (1)	106 (0)	19 (0)	0.0331
	Mean (Std)	160.65 (6.76)	158.80 (6.69)	159.84 (8.46)	
	Median	160.00	158.50	159.00	
	Q1, Q3	156.00, 164.00	155.00, 163.00	155.00, 165.00	
	Min, Max	144, 198	146, 176	142, 175	
Weight (kg)	n (nmiss)	541 (1)	106 (0)	19 (0)	0.0714
	Mean (Std)	57.68 (10.02)	55.87 (9.99)	60.66 (11.46)	
	Median	56.00	55.00	61.00	
	Q1, Q3	50.00, 64.00	49.00, 60.00	50.00, 65.00	
	Min, Max	27.0, 101.0	34.0, 100.0	45.0, 90.0	
BMI (kg/m^2)	n (nmiss)	541 (1)	106 (0)	19 (0)	0.1793
	Mean (Std)	22.31 (3.42)	22.10 (3.36)	23.66 (3.48)	
	Median	21.88	21.55	23.81	
	Q1, Q3	19.81, 24.34	19.98, 24.09	21.22, 25.71	
	Min, Max	12.84, 39.45	15.94, 36.73	18.03, 30.42	
	<18.5	64 (11.83%)	10 (9.43%)	2 (10.53%)	0.5799[a]
	>=18.5-<24	320 (59.15%)	69 (65.09%)	10 (52.63%)	
	>=24-<28	125 (23.11%)	22 (20.75%)	4 (21.05%)	
	>=28	32 (5.91%)	5 (4.72%)	3 (15.79%)	
	Total	541 (100.00%)	106 (100.00%)	19 (100.00%)	
	Missing	1	0	0	
Smoking history	Never smoking	476 (87.82%)	92 (86.79%)	17 (89.47%)	0.6453[b]
	Used to smoke, given up now	21 (3.87%)	7 (6.60%)	1 (5.26%)	
	Still smoking	45 (8.30%)	7 (6.60%)	1 (5.26%)	
	Total	542 (100.00%)	106 (100.00%)	19 (100.00%)	

Footnote: The smoking history information were from 'Life History' page in CRF.

N, number of patients in population; nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.
The percentage denominator is the number of patients with non-missing value.
P values for continuous values were from Wilcoxon rank sum test.
a:P values for categorical values were from Chi-squared test. b:P values for categorical values were from Fisher exact tests.

Table ANN. 291 **Rheumatoid Arthritis Diagnosis (Age Subgroups, Safety Analyses Population)**

		Safety Analyses Population			
		<65 years (N=542)	*>=65 and <75 years (N=106)*	*>=75 years (N=19)*	*P value*
Months from the onset date of RA to ICF (months)	n (nmiss)	542 (0)	106 (0)	19 (0)	0.3582
	Mean (Std)	96.37 (95.01)	125.94 (137.49)	127.61 (125.60)	
	Median	60.96	67.75	84.01	
	Q1, Q3	23.43, 142.52	24.74, 180.86	29.57, 204.32	
	Min, Max	0, 492.02	0.23, 623.67	2.50, 440.97	
Duration of RA (months)	n (nmiss)	542 (0)	106 (0)	19 (0)	0.7992
	Mean (Std)	82.65 (90.79)	104.96 (132.54)	107.65 (128.02)	
	Median	46.38	48.15	68.24	
	Q1, Q3	13.86, 122.38	11.20, 139.63	18.37, 110.78	
	Min, Max	0, 489.99	0, 623.67	2.50, 435.94	
	<=1 year	115 (21.22%)	27 (25.47%)	2 (10.53%)	0.3205[a]
	>1-<=3 years	113 (20.85%)	21 (19.81%)	6 (31.58%)	
	>3-<=10 years	172 (31.73%)	24 (22.64%)	7 (36.84%)	
	>10 years	142 (26.20%)	34 (32.08%)	4 (21.05%)	
	Total	542 (100.00%)	106 (100.00%)	19 (100.00%)	
Meet the ACR/EULAR 2010 criteria and number of points	Yes	542 (100.00%)	106 (100.00%)	19 (100.00%)	NA[b]
	n (nmiss)	542 (0)	106 (0)	19 (0)	
	Mean (Std)	8.24 (1.53)	8.75 (1.31)	9.16 (1.21)	
	Median	8.00	9.00	10.00	
	Q1, Q3	7.00, 10.00	8.00, 10.00	8.00, 10.00	
	Min, Max	6, 10	6, 10	7, 10	
	Total	542 (100.00%)	106 (100.00%)	19 (100.00%)	

Footnote: The duration of RA (months) = (Date of informed consent – date of diagnosis of RA) / 30.4375, round to 2 decimal place. Months from the onset date of RA to ICF (months) = (Date of informed consent – the onset date of RA) / 30.4375, round to 2 decimal place.
N, number of patients in population; nmiss, no. of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range. The percentage denominator is the number of patients with non-missing value.
P values for continuous values were from Wilcoxon rank sum test.
a:P values for categorical values were from Chi-squared test. b:P values for categorical values were from Fisher exact tests.

Table ANN. 292 Drug Exposure (Age Subgroups, Safety Analyses Population)

		Safety Analyses Population			
		<65 years (N=542)	*≥65 and <75 years (N=106)*	*≥75 years (N=19)*	*P value*
Overall Olumiant exposure (days)	n (nmiss)	540 (2)	106 (0)	19 (0)	0.4954
	Mean (Std)	144.46 (56.18)	142.14 (59.96)	139.26 (49.67)	
	Median	168.00	165.00	156.00	
	Q1, Q3	126.50, 179.00	101.00, 177.00	128.00, 173.00	
	Min, Max	1, 285	2, 314	19, 185	
Olumiant exposure (days)	n (nmiss)	540 (2)	106 (0)	19 (0)	0.6331
	Mean (Std)	142.76 (55.97)	140.25 (61.26)	136.42 (51.09)	
	Median	165.50	165.00	156.00	
	Q1, Q3	118.00, 178.00	93.00, 177.00	105.00, 173.00	
	Min, Max	1, 285	2, 314	19, 185	
Total patient year exposure		213.6	41.3	7.2	
Number of patients administered only 2mg Olumiant	n (%)	465 (85.79%)	97 (91.51%)	18 (94.74%)	0.2098
Number of patients administered only 4mg Olumiant	n (%)	49 (9.04%)	4 (3.77%)	0	0.0963
Number of patients administered mixed dosage of Olumiant	n (%)	28 (5.17%)	5 (4.72%)	1 (5.26%)	>.9999

Footnote: N, number of patients in population; nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.
Overall Olumiant exposure (days) = Olumiant discontinue date in study termination page – the earliest start date of treatment in treatment information page +1.
Olumiant exposure (days) = sum of (end date of treatment - start date of treatment +1). The start and end date of treatment are from the same record in treatment information page.
The sum are based on all records in this page.
Total patient year exposure = sum of all patients' year exposure. Patient year exposure = overall Olumiant exposure in days for the patient / 365.25, keep 1 decimal place.
P values for continuous values were from Wilcoxon rank sum test. P values for categorical values were from Fisher exact tests.

Table ANN. 293 AE Summary (Age Subgroups, Safety Analyses Population)

		Safety Analyses Population (N=667)						
	Age subgroup	*Event*	*n*	*Patient-year of observation time*	*Patient-year of exposure time*	*Percentage and 95% CI*	*Incidence rate and 95% CI*	*EAIR and 95% CI*
AEs over a period of 12 weeks	<65 years (Nx=542)	240	165	106.72	102.54	30.44% (26.59%, 34.51%)	154.61 (131.92, 180.08)	160.91 (137.30, 187.43)
	>=65 and <75 years (Nx=106)	73	41	19.24	17.99	38.68% (29.38%, 48.63%)	213.10 (152.92, 289.09)	227.90 (163.55, 309.18)
	>=75 years (Nx=19)	16	8	3.59	3.51	42.11% (20.25%, 66.50%)	222.84 (96.21, 439.09)	227.92 (98.40, 449.09)
AEs over a period of 24 weeks	<65 years (Nx=542)	328	196	172.05	164.08	36.16% (32.11%, 40.37%)	113.92 (98.53, 131.03)	119.45 (103.32, 137.40)
	>=65 and <75 years (Nx=106)	79	45	31.00	29.38	42.45% (32.91%, 52.43%)	145.16 (105.88, 194.24)	153.17 (111.72, 204.95)
	>=75 years (Nx=19)	21	9	5.50	5.12	47.37% (24.45%, 71.14%)	163.64 (74.82, 310.63)	175.78 (80.38, 333.69)
AEs related to study treatment as judged by the investigator over a period of 12 weeks	<65 years (Nx=542)	82	73	119.92	114.70	13.47% (10.71%, 16.63%)	60.87 (47.72, 76.54)	63.64 (49.89, 80.02)
	>=65 and <75 years (Nx=106)	25	18	22.81	21.32	16.98% (10.39%, 25.50%)	78.91 (46.77, 124.72)	84.43 (50.04, 133.43)
	>=75 years (Nx=19)	4	4	4.14	3.97	21.05% (6.05%, 45.57%)	96.62 (26.33, 247.38)	100.76 (27.45, 257.97)

Footnote: The number of event for each patient counts the event which happened during the 12-weeks/ 24-weeks observation time. The percentage denominator is the number of analyses population and the numerator is the number of patients with corresponding events.
AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; n, the number of patients with events; SAE, serious adverse event.
The percentage of AEs/SAEs over a period of 12/24 weeks = Number of patients with at least one AE/SAE over a period of 12/24 weeks ÷number of patients in safety analyses population ×100, results round to 2 decimal places.
The incidence rates of AEs/SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ observation time
of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places. The EAIR of AEs /SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at
least one AE/SAE over an observation period of 12/24 weeks ÷ overall exposure time of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The calculation of observation time and exposure time could refer to definition in the main body of SAP.

AEs related to study treatment as judged by the investigator are the AEs whose relationship with olumiant are not 'No'. Drug adjustment includes dose increase, dose reduce and temporary discontinuation.
Death is from SAE which the reason is death or AE whose outcome is fatal or death recorded in the page of study termination.

		Safety Analyses Population (N=667)						
	Age subgroup	*Event*	*n*	*Patient-year of observation time*	*Patient-year of exposure time*	*Percentage and 95% CI*	*Incidence rate and 95% CI*	*EAIR and 95% CI*
AEs related to study treatment as judged by the investigator over a period of 24 weeks	<65 years (Nx=542)	113	93	204.27	194.34	17.16% (14.08%, 20.60%)	45.53 (36.75, 55.77)	47.85 (38.62, 58.62)
	>=65 and <75 years (Nx=106)	27	20	38.55	36.33	18.87% (11.92%, 27.62%)	51.88 (31.69, 80.13)	55.05 (33.63, 85.02)
	>=75 years (Nx=19)	7	7	6.43	5.97	36.84% (16.29%, 61.64%)	108.86 (43.77, 224.30)	117.25 (47.14, 241.59)
Death	<65 years (Nx=542)	0	0	224.96	213.14	0.00% (0%, 0.68%)	0.00 (NA, 1.64)	0.00 (NA, 1.73)
	>=65 and <75 years (Nx=106)	2	2	43.53	40.91	1.89% (0.23%, 6.65%)	4.59 (0.56, 16.60)	4.89 (0.59, 17.66)
	>=75 years (Nx=19)	0	0	7.95	7.24	0.00% (0%, 17.65%)	0.00 (NA, 46.40)	0.00 (NA, 50.95)
SAEs over a period of 12 weeks	<65 years (Nx=542)	11	10	126.32	120.30	1.85% (0.89%, 3.37%)	7.92 (3.80, 14.56)	8.31 (3.99, 15.29)
	>=65 and <75 years (Nx=106)	11	11	23.79	22.34	10.38% (5.30%, 17.81%)	46.24 (23.08, 82.73)	49.24 (24.58, 88.10)

Footnote: The number of event for each patient counts the event which happened during the 12-weeks/ 24-weeks observation time. The percentage denominator is the number of analyses population and the numerator is the number of patients with corresponding events.
AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; n, the number of patients with events; SAE, serious adverse event.
The percentage of AEs/SAEs over a period of 12/24 weeks = Number of patients with at least one AE/SAE over a period of 12/24 weeks ÷number of patients in safety analyses population ×100, results round to 2 decimal places.
The incidence rates of AEs/SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ observation time
of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places. The EAIR of AEs /SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at
least one AE/SAE over an observation period of 12/24 weeks ÷ overall exposure time of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The calculation of observation time and exposure time could refer to definition in the main body of SAP.
AEs related to study treatment as judged by the investigator are the AEs whose relationship with olumiant are not 'No'. Drug adjustment includes dose increase, dose reduce and temporary discontinuation.
Death is from SAE which the reason is death or AE whose outcome is fatal or death recorded in the page of study termination.

		Safety Analyses Population (N=667)						
	Age subgroup	*Event*	*n*	*Patient-year of observation time*	*Patient-year of exposure time*	*Percentage and 95% CI*	*Incidence rate and 95% CI*	*EAIR and 95% CI*
	>=75 years (Nx=19)	1	1	4.64	4.39	5.26% (0.13%, 26.03%)	21.55 (0.55, 120.08)	22.78 (0.58, 126.92)
SAEs over a period of 24 weeks	<65 years (Nx=542)	19	16	221.91	210.63	2.95% (1.70%, 4.75%)	7.21 (4.12, 11.71)	7.60 (4.34, 12.34)
	>=65 and <75 years (Nx=106)	11	11	41.43	39.20	10.38% (5.30%, 17.81%)	26.55 (13.25, 47.51)	28.06 (14.01, 50.21)
	>=75 years (Nx=19)	1	1	7.60	6.89	5.26% (0.13%, 26.03%)	13.16 (0.33, 73.31)	14.51 (0.37, 80.87)
SAEs related to study treatment as judged by the investigator over a period of 12 weeks	<65 years (Nx=542)	5	5	126.93	120.76	0.92% (0.30%, 2.14%)	3.94 (1.28, 9.19)	4.14 (1.34, 9.66)
	>=65 and <75 years (Nx=106)	3	3	24.74	23.10	2.83% (0.59%, 8.05%)	12.13 (2.50, 35.44)	12.99 (2.68, 37.95)
	>=75 years (Nx=19)	0	0	4.71	4.46	0.00% (0%, 17.65%)	0.00 (NA, 78.32)	0.00 (NA, 82.71)
SAEs related to study treatment as judged by the investigator	<65 years (Nx=542)	7	7	223.93	212.35	1.29% (0.52%, 2.64%)	3.13 (1.26, 6.44)	3.30 (1.33, 6.79)

over a period of 24 weeks

Footnote: The number of event for each patient counts the event which happened during the 12-weeks/ 24-weeks observation time. The percentage denominator is the number of analyses population and the numerator is the number of patients with corresponding events.

AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; n, the number of patients with events; SAE, serious adverse event.

The percentage of AEs/SAEs over a period of 12/24 weeks = Number of patients with at least one AE/SAE over a period of 12/24 weeks ÷number of patients in safety analyses population ×100, results round to 2 decimal places.

The incidence rates of AEs/SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ observation time of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places. The EAIR of AEs /SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ overall exposure time of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.

The calculation of observation time and exposure time could refer to definition in the main body of SAP.

AEs related to study treatment as judged by the investigator are the AEs whose relationship with olumiant are not 'No'. Drug adjustment includes dose increase, dose reduce and temporary discontinuation.

Death is from SAE which the reason is death or AE whose outcome is fatal or death recorded in the page of study termination.

		Safety Analyses Population (N=667)						
	Age subgroup	*Event*	*n*	*Patient-year of observation time*	*Patient-year of exposure time*	*Percentage and 95% CI*	*Incidence rate and 95% CI*	*EAIR and 95% CI*
	>=65 and <75 years (Nx=106)	3	3	43.29	40.70	2.83% (0.59%, 8.05%)	6.93 (1.43, 20.25)	7.37 (1.52, 21.54)
	>=75 years (Nx=19)	0	0	7.95	7.24	0.00% (0%, 17.65%)	0.00 (NA, 46.40)	0.00 (NA, 50.95)
AEs leading to drug adjustment over a period of 12 weeks	<65 years (Nx=542)	25	21	124.28	118.43	3.87% (2.41%, 5.86%)	16.90 (10.46, 25.83)	17.73 (10.98, 27.11)
	>=65 and <75 years (Nx=106)	10	8	24.10	22.43	7.55% (3.31%, 14.33%)	33.20 (14.33, 65.41)	35.67 (15.40, 70.28)
	>=75 years (Nx=19)	1	1	4.60	4.35	5.26% (0.13%, 26.03%)	21.74 (0.55, 121.12)	22.99 (0.58, 128.08)
AEs leading to drug adjustment over a period of 24 weeks	<65 years (Nx=542)	33	29	218.25	207.41	5.35% (3.61%, 7.59%)	13.29 (8.90, 19.08)	13.98 (9.36, 20.08)
	>=65 and <75 years (Nx=106)	11	9	41.47	38.97	8.49% (3.96%, 15.51%)	21.70 (9.92, 41.20)	23.09 (10.56, 43.84)
	>=75 years (Nx=19)	1	1	7.71	7.09	5.26% (0.13%, 26.03%)	12.97 (0.33, 72.27)	14.10 (0.36, 78.58)

Footnote: The number of event for each patient counts the event which happened during the 12-weeks/ 24-weeks observation time. The percentage denominator is the number of analyses population and the numerator is the number of patients with corresponding events.
AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; n, the number of patients with events; SAE, serious adverse event.
The percentage of AEs/SAEs over a period of 12/24 weeks = Number of patients with at least one AE/SAE over a period of 12/24 weeks ÷number of patients in safety analyses population ×100, results round to 2 decimal places.
The incidence rates of AEs/SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ observation time
of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places. The EAIR of AEs /SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at
least one AE/SAE over an observation period of 12/24 weeks ÷ overall exposure time of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The calculation of observation time and exposure time could refer to definition in the main body of SAP.
AEs related to study treatment as judged by the investigator are the AEs whose relationship with olumiant are not 'No'. Drug adjustment includes dose increase, dose reduce and temporary discontinuation.
Death is from SAE which the reason is death or AE whose outcome is fatal or death recorded in the page of study termination.

		Safety Analyses Population (N=667)						
	Age subgroup	*Event*	*n*	*Patient-year of observation time*	*Patient-year of exposure time*	*Percentage and 95% CI*	*Incidence rate and 95% CI*	*EAIR and 95% CI*
AEs leading to drug permanent discontinuation over a period of 12 weeks	<65 years (Nx=542)	15	14	126.44	120.84	2.58% (1.42%, 4.30%)	11.07 (6.05, 18.58)	11.59 (6.33, 19.44)
	>=65 and <75 years (Nx=106)	6	5	24.31	22.89	4.72% (1.55%, 10.67%)	20.57 (6.68, 48.00)	21.84 (7.09, 50.98)
	>=75 years (Nx=19)	1	1	4.62	4.46	5.26% (0.13%, 26.03%)	21.65 (0.55, 120.60)	22.42 (0.57, 124.92)
AEs leading to drug permanent discontinuation over a period of 24 weeks	<65 years (Nx=542)	17	16	223.63	212.87	2.95% (1.70%, 4.75%)	7.15 (4.09, 11.62)	7.52 (4.30, 12.21)
	>=65 and <75 years (Nx=106)	6	5	43.03	40.68	4.72% (1.55%, 10.67%)	11.62 (3.77, 27.12)	12.29 (3.99, 28.68)
	>=75 years (Nx=19)	3	3	7.78	7.24	15.79% (3.38%, 39.58%)	38.56 (7.95, 112.69)	41.44 (8.55, 121.09)

Footnote: The number of event for each patient counts the event which happened during the 12-weeks/ 24-weeks observation time. The percentage denominator is the number of analyses population and the numerator is the number of patients with corresponding events.
AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; n, the number of patients with events; SAE, serious adverse event.
The percentage of AEs/SAEs over a period of 12/24 weeks = Number of patients with at least one AE/SAE over a period of 12/24 weeks ÷number of patients in safety analyses population ×100, results round to 2 decimal places.
The incidence rates of AEs/SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ observation time
of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places. The EAIR of AEs /SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at
least one AE/SAE over an observation period of 12/24 weeks ÷ overall exposure time of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The calculation of observation time and exposure time could refer to definition in the main body of SAP.
AEs related to study treatment as judged by the investigator are the AEs whose relationship with olumiant are not 'No'. Drug adjustment includes dose increase, dose reduce and temporary discontinuation.
Death is from SAE which the reason is death or AE whose outcome is fatal or death recorded in the page of study termination.

Table ANN. 294 **Summary of AE with Special Interest Based on the Judgment of Investigator (<65 Years, Safety Analyses Population)**

	Safety Analyses Population (N=542)						
	Event	*n*	*Patient-year of observation time*	*Patient-year of exposure time*	*Percentage and 95% CI*	*Incidence rate and 95% CI*	*EAIR and 95% CI*
AEs with special interest over a period of 12 weeks	14	13	125.85	119.67	2.40% (1.28%, 4.07%)	10.33 (5.50, 17.66)	10.86 (5.78, 18.58)
Serious infection	1	1	127.28	120.95	0.18% (0.005%, 1.02%)	0.79 (0.02, 4.38)	0.83 (0.02, 4.61)
Hepatotoxicity	13	12	126.03	119.77	2.21% (1.15%, 3.84%)	9.52 (4.92, 16.63)	10.02 (5.18, 17.50)
VTE	0	0	127.46	121.05	0.00% (0%, 0.68%)	0.00 (NA, 2.89)	0.00 (NA, 3.05)
AEs with special interest over a period of 24 weeks	24	20	220.87	209.38	3.69% (2.27%, 5.64%)	9.06 (5.53, 13.98)	9.55 (5.83, 14.75)
Serious infection	2	2	224.58	212.84	0.37% (0.04%, 1.33%)	0.89 (0.11, 3.22)	0.94 (0.11, 3.39)
Hepatotoxicity	22	19	221.05	209.48	3.51% (2.12%, 5.42%)	8.60 (5.17, 13.42)	9.07 (5.46, 14.16)
VTE	0	0	224.96	213.14	0.00% (0%, 0.68%)	0.00 (NA, 1.64)	0.00 (NA, 1.73)
AEs with special interest related to study treatment as judged by the investigator over a period of 12 weeks	11	10	126.21	120.04	1.85% (0.89%, 3.37%)	7.92 (3.80, 14.57)	8.33 (3.99, 15.32)
Serious infection	1	1	127.28	120.95	0.18% (0.005%, 1.02%)	0.79 (0.02, 4.38)	0.83 (0.02, 4.61)
Hepatotoxicity	10	9	126.39	120.13	1.66% (0.76%, 3.13%)	7.12 (3.26, 13.52)	7.49 (3.43, 14.22)
VTE	0	0	127.46	121.05	0.00% (0%, 0.68%)	0.00 (NA, 2.89)	0.00 (NA, 3.05)
AEs with special interest related to study treatment as judged by the investigator over a period of 24 weeks	19	16	221.87	210.29	2.95% (1.70%, 4.75%)	7.21 (4.12, 11.71)	7.61 (4.35, 12.36)
Serious infection	2	2	224.58	212.84	0.37% (0.04%, 1.33%)	0.89 (0.11, 3.22)	0.94 (0.11, 3.39)
Hepatotoxicity	17	15	222.05	210.39	2.77% (1.56%, 4.52%)	6.76 (3.78, 11.14)	7.13 (3.99, 11.76)
VTE	0	0	224.96	213.14	0.00% (0%, 0.68%)	0.00 (NA, 1.64)	0.00 (NA, 1.73)

Footnote: The percentage denominator is the number of analyses population and the numerator is the number of patients with corresponding events.
AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; n, the number of patients with events; SAE, serious adverse event; VTE, venous thromboembolism.
The percentage of AEs/SAEs over a period of 12/24 weeks = Number of patients with at least one AE/SAE over a period of 12/24 weeks ÷number of patients in safety analyses population ×100, results round to 2 decimal places.
The incidence rates of AEs/SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ observation time
of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The EAIR of AEs /SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ overall exposure time of
AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The calculation of observation time and exposure time could refer to definition in the main body of SAP.
AEs related to study treatment as judged by the investigator are the AEs whose relationship with olumiant are not 'No'.
AE with special interest is based on the judgement of investigator recorded in EDC.

	Safety Analyses Population (N=542)						
	Event	*n*	*Patient-year of observation time*	*Patient-year of exposure time*	*Percentage and 95% CI*	*Incidence rate and 95% CI*	*EAIR and 95% CI*
SAEs with special interest over a period of 12 weeks	2	2	127.12	120.87	0.37% (0.04%, 1.33%)	1.57 (0.19, 5.68)	1.65 (0.20, 5.98)
Serious infection	1	1	127.28	120.95	0.18% (0.005%, 1.02%)	0.79 (0.02, 4.38)	0.83 (0.02, 4.61)
Hepatotoxicity	1	1	127.30	120.97	0.18% (0.005%, 1.02%)	0.79 (0.02, 4.38)	0.83 (0.02, 4.61)
VTE	0	0	127.46	121.05	0.00% (0%, 0.68%)	0.00 (NA, 2.89)	0.00 (NA, 3.05)
SAEs with special interest over a period of 24 weeks	3	3	224.42	212.76	0.55% (0.11%, 1.61%)	1.34 (0.28, 3.91)	1.41 (0.29, 4.12)
Serious infection	2	2	224.58	212.84	0.37% (0.04%, 1.33%)	0.89 (0.11, 3.22)	0.94 (0.11, 3.39)
Hepatotoxicity	1	1	224.80	213.06	0.18% (0.005%, 1.02%)	0.44 (0.01, 2.48)	0.47 (0.01, 2.62)
VTE	0	0	224.96	213.14	0.00% (0%, 0.68%)	0.00 (NA, 1.64)	0.00 (NA, 1.73)

Footnote: The percentage denominator is the number of analyses population and the numerator is the number of patients with corresponding events.
AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; n, the number of patients with events; SAE, serious adverse event; VTE, venous thromboembolism.
The percentage of AEs/SAEs over a period of 12/24 weeks = Number of patients with at least one AE/SAE over a period of 12/24 weeks ÷number of patients in safety analyses population ×100, results round to 2 decimal places.
The incidence rates of AEs/SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ observation time
of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The EAIR of AEs /SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ overall exposure time of
AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The calculation of observation time and exposure time could refer to definition in the main body of SAP.
AEs related to study treatment as judged by the investigator are the AEs whose relationship with olumiant are not 'No'.
AE with special interest is based on the judgement of investigator recorded in EDC.

Table ANN. 295 **Summary of AE with Special Interest Based on the Judgement of Investigator (≥65 and <75 Years, Safety Analyses Population)**

	Safety Analyses Population (N=106)						
	Event	*n*	*Patient-year of observation time*	*Patient-year of exposure time*	*Percentage and 95% CI*	*Incidence rate and 95% CI*	*EAIR and 95% CI*
AEs with special interest over a period of 12 weeks	5	4	24.66	23.01	3.77% (1.04%, 9.38%)	16.22 (4.42, 41.53)	17.38 (4.74, 44.51)
Serious infection	3	2	24.75	23.11	1.89% (0.23%, 6.65%)	8.08 (0.98, 29.19)	8.65 (1.05, 31.26)
Hepatotoxicity	2	2	24.76	23.03	1.89% (0.23%, 6.65%)	8.08 (0.98, 29.18)	8.68 (1.05, 31.37)
VTE	0	0	24.85	23.12	0.00% (0%, 3.42%)	0.00 (NA, 14.84)	0.00 (NA, 15.96)
AEs with special interest over a period of 24 weeks	5	4	43.01	40.42	3.77% (1.04%, 9.38%)	9.30 (2.53, 23.81)	9.90 (2.70, 25.34)
Serious infection	3	2	43.49	40.90	1.89% (0.23%, 6.65%)	4.60 (0.56, 16.61)	4.89 (0.59, 17.66)
Hepatotoxicity	2	2	43.19	40.44	1.89% (0.23%, 6.65%)	4.63 (0.56, 16.73)	4.95 (0.60, 17.87)
VTE	0	0	43.67	40.91	0.00% (0%, 3.42%)	0.00 (NA, 8.45)	0.00 (NA, 9.02)
AEs with special interest related to study treatment as judged by the investigator over a period of 12 weeks	5	4	24.66	23.01	3.77% (1.04%, 9.38%)	16.22 (4.42, 41.53)	17.38 (4.74, 44.51)
Serious infection	3	2	24.75	23.11	1.89% (0.23%, 6.65%)	8.08 (0.98, 29.19)	8.65 (1.05, 31.26)
Hepatotoxicity	2	2	24.76	23.03	1.89% (0.23%, 6.65%)	8.08 (0.98, 29.18)	8.68 (1.05, 31.37)
VTE	0	0	24.85	23.12	0.00% (0%, 3.42%)	0.00 (NA, 14.84)	0.00 (NA, 15.96)
AEs with special interest related to study treatment as judged by the investigator over a period of 24 weeks	5	4	43.01	40.42	3.77% (1.04%, 9.38%)	9.30 (2.53, 23.81)	9.90 (2.70, 25.34)
Serious infection	3	2	43.49	40.90	1.89% (0.23%, 6.65%)	4.60 (0.56, 16.61)	4.89 (0.59, 17.66)
Hepatotoxicity	2	2	43.19	40.44	1.89% (0.23%, 6.65%)	4.63 (0.56, 16.73)	4.95 (0.60, 17.87)
VTE	0	0	43.67	40.91	0.00% (0%, 3.42%)	0.00 (NA, 8.45)	0.00 (NA, 9.02)

Footnote: The percentage denominator is the number of analyses population and the numerator is the number of patients with corresponding events.

AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; n, the number of patients with events; SAE, serious adverse event; VTE, venous thromboembolism.
The percentage of AEs/SAEs over a period of 12/24 weeks = Number of patients with at least one AE/SAE over a period of 12/24 weeks ÷number of patients in safety analyses population ×100, results round to 2 decimal places.
The incidence rates of AEs/SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ observation time
of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The EAIR of AEs /SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ overall exposure time of
AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The calculation of observation time and exposure time could refer to definition in the main body of SAP.
AEs related to study treatment as judged by the investigator are the AEs whose relationship with olumiant are not 'No'.
AE with special interest is based on the judgement of investigator recorded in EDC.

	Safety Analyses Population (N=106)						
	Event	*n*	*Patient-year of observation time*	*Patient-year of exposure time*	*Percentage and 95% CI*	*Incidence rate and 95% CI*	*EAIR and 95% CI*
SAEs with special interest over a period of 12 weeks	2	2	24.77	23.12	1.89% (0.23%, 6.65%)	8.07 (0.98, 29.17)	8.65 (1.05, 31.25)
Serious infection	2	2	24.77	23.12	1.89% (0.23%, 6.65%)	8.07 (0.98, 29.17)	8.65 (1.05, 31.25)
Hepatotoxicity	0	0	24.85	23.12	0.00% (0%, 3.42%)	0.00 (NA, 14.84)	0.00 (NA, 15.96)
VTE	0	0	24.85	23.12	0.00% (0%, 3.42%)	0.00 (NA, 14.84)	0.00 (NA, 15.96)
SAEs with special interest over a period of 24 weeks	2	2	43.50	40.91	1.89% (0.23%, 6.65%)	4.60 (0.56, 16.61)	4.89 (0.59, 17.66)
Serious infection	2	2	43.50	40.91	1.89% (0.23%, 6.65%)	4.60 (0.56, 16.61)	4.89 (0.59, 17.66)
Hepatotoxicity	0	0	43.67	40.91	0.00% (0%, 3.42%)	0.00 (NA, 8.45)	0.00 (NA, 9.02)
VTE	0	0	43.67	40.91	0.00% (0%, 3.42%)	0.00 (NA, 8.45)	0.00 (NA, 9.02)

Footnote: The percentage denominator is the number of analyses population and the numerator is the number of patients with corresponding events.
AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; n, the number of patients with events; SAE, serious adverse event; VTE, venous thromboembolism.
The percentage of AEs/SAEs over a period of 12/24 weeks = Number of patients with at least one AE/SAE over a period of 12/24 weeks ÷number of patients in safety analyses population ×100, results round to 2 decimal places.
The incidence rates of AEs/SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ observation time
of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The EAIR of AEs /SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ overall exposure time of
AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The calculation of observation time and exposure time could refer to definition in the main body of SAP.
AEs related to study treatment as judged by the investigator are the AEs whose relationship with olumiant are not 'No'.
AE with special interest is based on the judgement of investigator recorded in EDC.

Table ANN. 296 **Summary of AE with Special Interest Based on the Judgement of Investigator (≥75 years, Safety Analyses Population)**

	Safety Analyses Population (N=19)						
	Event	*n*	*Patient-year of observation time*	*Patient-year of exposure time*	*Percentage and 95% CI*	*Incidence rate and 95% CI*	*EAIR and 95% CI*
AEs with special interest over a period of 12 weeks	2	2	4.58	4.33	10.53% (1.30%, 33.14%)	43.67 (5.29, 157.74)	46.19 (5.59, 166.85)
Serious infection	0	0	4.71	4.46	0.00% (0%, 17.65%)	0.00 (NA, 78.32)	0.00 (NA, 82.71)
Hepatotoxicity	2	2	4.58	4.33	10.53% (1.30%, 33.14%)	43.67 (5.29, 157.74)	46.19 (5.59, 166.85)
VTE	0	0	4.71	4.46	0.00% (0%, 17.65%)	0.00 (NA, 78.32)	0.00 (NA, 82.71)
AEs with special interest over a period of 24 weeks	2	2	7.46	6.84	10.53% (1.30%, 33.14%)	26.81 (3.25, 96.85)	29.24 (3.54, 105.62)
Serious infection	0	0	7.95	7.24	0.00% (0%, 17.65%)	0.00 (NA, 46.40)	0.00 (NA, 50.95)
Hepatotoxicity	2	2	7.46	6.84	10.53% (1.30%, 33.14%)	26.81 (3.25, 96.85)	29.24 (3.54, 105.62)
VTE	0	0	7.95	7.24	0.00% (0%, 17.65%)	0.00 (NA, 46.40)	0.00 (NA, 50.95)
AEs with special interest related to study treatment as judged by the investigator over a period of 12 weeks	1	1	4.58	4.33	5.26% (0.13%, 26.03%)	21.83 (0.55, 121.65)	23.09 (0.58, 128.68)
Serious infection	0	0	4.71	4.46	0.00% (0%, 17.65%)	0.00 (NA, 78.32)	0.00 (NA, 82.71)
Hepatotoxicity	1	1	4.58	4.33	5.26% (0.13%, 26.03%)	21.83 (0.55, 121.65)	23.09 (0.58, 128.68)
VTE	0	0	4.71	4.46	0.00% (0%, 17.65%)	0.00 (NA, 78.32)	0.00 (NA, 82.71)
AEs with special interest related to study treatment as judged by the investigator over a period of 24 weeks	1	1	7.58	6.88	5.26% (0.13%, 26.03%)	13.19 (0.33, 73.50)	14.53 (0.37, 80.98)
Serious infection	0	0	7.95	7.24	0.00% (0%, 17.65%)	0.00 (NA, 46.40)	0.00 (NA, 50.95)
Hepatotoxicity	1	1	7.58	6.88	5.26% (0.13%, 26.03%)	13.19 (0.33, 73.50)	14.53 (0.37, 80.98)
VTE	0	0	7.95	7.24	0.00% (0%, 17.65%)	0.00 (NA, 46.40)	0.00 (NA, 50.95)

Footnote: The percentage denominator is the number of analyses population and the numerator is the number of patients with corresponding events.
AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; n, the number of patients with events; SAE, serious adverse event; VTE, venous thromboembolism.
The percentage of AEs/SAEs over a period of 12/24 weeks = Number of patients with at least one AE/SAE over a period of 12/24 weeks ÷number of patients in safety analyses population ×100, results round to 2 decimal places.
The incidence rates of AEs/SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ observation time
of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The EAIR of AEs /SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ overall exposure time of
AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The calculation of observation time and exposure time could refer to definition in the main body of SAP.
AEs related to study treatment as judged by the investigator are the AEs whose relationship with olumiant are not 'No'.
AE with special interest is based on the judgement of investigator recorded in EDC.

	Safety Analyses Population (N=19)						
	Event	*n*	*Patient-year of observation time*	*Patient-year of exposure time*	*Percentage and 95% CI*	*Incidence rate and 95% CI*	*EAIR and 95% CI*
SAEs with special interest over a period of 12 weeks	0	0	4.71	4.46	0.00% (0%, 17.65%)	0.00 (NA, 78.32)	0.00 (NA, 82.71)
Serious infection	0	0	4.71	4.46	0.00% (0%, 17.65%)	0.00 (NA, 78.32)	0.00 (NA, 82.71)
Hepatotoxicity	0	0	4.71	4.46	0.00% (0%, 17.65%)	0.00 (NA, 78.32)	0.00 (NA, 82.71)
VTE	0	0	4.71	4.46	0.00% (0%, 17.65%)	0.00 (NA, 78.32)	0.00 (NA, 82.71)
SAEs with special interest over a period of 24 weeks	0	0	7.95	7.24	0.00% (0%, 17.65%)	0.00 (NA, 46.40)	0.00 (NA, 50.95)
Serious infection	0	0	7.95	7.24	0.00% (0%, 17.65%)	0.00 (NA, 46.40)	0.00 (NA, 50.95)
Hepatotoxicity	0	0	7.95	7.24	0.00% (0%, 17.65%)	0.00 (NA, 46.40)	0.00 (NA, 50.95)
VTE	0	0	7.95	7.24	0.00% (0%, 17.65%)	0.00 (NA, 46.40)	0.00 (NA, 50.95)

Footnote: The percentage denominator is the number of analyses population and the numerator is the number of patients with corresponding events.
AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; n, the number of patients with events; SAE, serious adverse event; VTE, venous thromboembolism.
The percentage of AEs/SAEs over a period of 12/24 weeks = Number of patients with at least one AE/SAE over a period of 12/24 weeks ÷number of patients in safety analyses population ×100, results round to 2 decimal places.
The incidence rates of AEs/SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ observation time
of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The EAIR of AEs /SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ overall exposure time of
AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The calculation of observation time and exposure time could refer to definition in the main body of SAP.
AEs related to study treatment as judged by the investigator are the AEs whose relationship with olumiant are not 'No'.
AE with special interest is based on the judgement of investigator recorded in EDC.

Table ANN. 297 **AEs over a Period of 12 Weeks by Maximum Severity — MedDRA Preferred Term by Decreasing Frequency, Within System Organ Class (<65 Years, Safety Analyses Population)**

	Safety Analyses Population (N=542)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
AE	240	165 (30.44%)	180	112 (20.66%)	48	43 (7.93%)	12	10 (1.85%)
Investigations	56	42 (7.75%)	56	42 (7.75%)	0	0	0	0
Platelet count increased	13	13 (2.40%)	13	13 (2.40%)	0	0	0	0
Lymphocyte count decreased	6	6 (1.11%)	6	6 (1.11%)	0	0	0	0
Neutrophil count increased	6	6 (1.11%)	6	6 (1.11%)	0	0	0	0
White blood cell count increased	6	6 (1.11%)	6	6 (1.11%)	0	0	0	0
Alanine aminotransferase increased	5	5 (0.92%)	5	5 (0.92%)	0	0	0	0
White blood cell count decreased	5	5 (0.92%)	5	5 (0.92%)	0	0	0	0
Neutrophil percentage increased	3	3 (0.55%)	3	3 (0.55%)	0	0	0	0
Aspartate aminotransferase increased	2	2 (0.37%)	2	2 (0.37%)	0	0	0	0
Fibrin D dimer increased	2	2 (0.37%)	2	2 (0.37%)	0	0	0	0
Blood creatine phosphokinase increased	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Blood pressure increased	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Blood triglycerides increased	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Coagulation test abnormal	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Haemoglobin decreased	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Lipids increased	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Red blood cells urine positive	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Weight increased	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=542)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Infections and infestations	44	39 (7.20%)	28	23 (4.24%)	14	14 (2.58%)	2	2 (0.37%)
Upper respiratory tract infection	18	17 (3.14%)	13	12 (2.21%)	5	5 (0.92%)	0	0
Urinary tract infection	7	7 (1.29%)	4	4 (0.74%)	3	3 (0.55%)	0	0
Pneumonia	3	3 (0.55%)	0	0	2	2 (0.37%)	1	1 (0.18%)
Herpes zoster	2	2 (0.37%)	0	0	2	2 (0.37%)	0	0
Pharyngitis	2	2 (0.37%)	0	0	2	2 (0.37%)	0	0
Enterovirus infection	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Herpes ophthalmic	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Herpes simplex	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Herpes virus infection	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Otitis media	1	1 (0.18%)	0	0	0	0	1	1 (0.18%)
Periodontitis	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Pulmonary tuberculosis	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Pulpitis dental	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Streptococcal infection	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Tonsillitis	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Urethritis	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Vulvovaginal mycotic infection	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=542)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Gastrointestinal disorders	19	19 (3.51%)	17	17 (3.14%)	2	2 (0.37%)	0	0
Gastrointestinal disorder	4	4 (0.74%)	4	4 (0.74%)	0	0	0	0
Diarrhoea	3	3 (0.55%)	3	3 (0.55%)	0	0	0	0
Nausea	2	2 (0.37%)	2	2 (0.37%)	0	0	0	0
Abdominal discomfort	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Abdominal distension	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Aphthous ulcer	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Functional gastrointestinal disorder	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Gastritis	1	1 (0.18%)	0	0	1	1 (0.18%)	0	0
Haemorrhagic erosive gastritis	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Mouth ulceration	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Noninfective gingivitis	1	1 (0.18%)	0	0	1	1 (0.18%)	0	0
Oral blood blister	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Toothache	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Musculoskeletal and connective tissue disorders	19	17 (3.14%)	6	5 (0.92%)	9	8 (1.48%)	4	4 (0.74%)
Rheumatoid arthritis	7	7 (1.29%)	1	1 (0.18%)	3	3 (0.55%)	3	3 (0.55%)
Arthralgia	6	6 (1.11%)	2	2 (0.37%)	3	3 (0.55%)	1	1 (0.18%)
Joint swelling	2	2 (0.37%)	1	1 (0.18%)	1	1 (0.18%)	0	0
Back pain	1	1 (0.18%)	0	0	1	1 (0.18%)	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=542)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Intervertebral disc protrusion	1	1 (0.18%)	0	0	1	1 (0.18%)	0	0
Pain in extremity	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Spinal osteoarthritis	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Metabolism and nutrition disorders	16	16 (2.95%)	13	13 (2.40%)	3	3 (0.55%)	0	0
Hyperlipidaemia	7	7 (1.29%)	5	5 (0.92%)	2	2 (0.37%)	0	0
Hyperuricaemia	3	3 (0.55%)	3	3 (0.55%)	0	0	0	0
Decreased appetite	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Dyslipidaemia	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Hypercholesterolaemia	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Hypertriglyceridaemia	1	1 (0.18%)	0	0	1	1 (0.18%)	0	0
Hypocalcaemia	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Vitamin D deficiency	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Blood and lymphatic system disorders	15	15 (2.77%)	14	14 (2.58%)	1	1 (0.18%)	0	0
Anaemia	6	6 (1.11%)	6	6 (1.11%)	0	0	0	0
Leukopenia	2	2 (0.37%)	2	2 (0.37%)	0	0	0	0
Thrombocytosis	2	2 (0.37%)	2	2 (0.37%)	0	0	0	0
Coagulopathy	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Eosinophilia	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=542)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Monocytosis	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Myelosuppression	1	1 (0.18%)	0	0	1	1 (0.18%)	0	0
Thrombocytopenia	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Hepatobiliary disorders	16	15 (2.77%)	10	10 (1.85%)	4	4 (0.74%)	2	1 (0.18%)
Hepatic function abnormal	14	14 (2.58%)	10	10 (1.85%)	4	4 (0.74%)	0	0
Drug-induced liver injury	2	1 (0.18%)	0	0	0	0	2	1 (0.18%)
Skin and subcutaneous tissue disorders	13	12 (2.21%)	9	8 (1.48%)	4	4 (0.74%)	0	0
Alopecia	4	4 (0.74%)	3	3 (0.55%)	1	1 (0.18%)	0	0
Acne	3	3 (0.55%)	2	2 (0.37%)	1	1 (0.18%)	0	0
Dermatitis	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Eczema	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Pruritus	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Rash	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Skin erosion	1	1 (0.18%)	0	0	1	1 (0.18%)	0	0
Skin ulcer	1	1 (0.18%)	0	0	1	1 (0.18%)	0	0
Respiratory, thoracic and mediastinal disorders	9	8 (1.48%)	4	3 (0.55%)	4	4 (0.74%)	1	1 (0.18%)
Cough	3	3 (0.55%)	1	1 (0.18%)	2	2 (0.37%)	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=542)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Bronchiectasis	1	1 (0.18%)	0	0	1	1 (0.18%)	0	0
Chronic obstructive pulmonary disease	1	1 (0.18%)	0	0	0	0	1	1 (0.18%)
Interstitial lung disease	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Laryngeal pain	1	1 (0.18%)	0	0	1	1 (0.18%)	0	0
Oropharyngeal pain	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Productive cough	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
General disorders and administration site conditions	7	6 (1.11%)	6	5 (0.92%)	1	1 (0.18%)	0	0
Asthenia	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Chest discomfort	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Chest pain	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Chills	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Face oedema	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Oedema peripheral	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Peripheral swelling	1	1 (0.18%)	0	0	1	1 (0.18%)	0	0
Nervous system disorders	5	5 (0.92%)	4	4 (0.74%)	0	0	1	1 (0.18%)
Headache	2	2 (0.37%)	2	2 (0.37%)	0	0	0	0
Carotid artery aneurysm	1	1 (0.18%)	0	0	0	0	1	1 (0.18%)
Dizziness	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=542)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Somnolence	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Reproductive system and breast disorders	6	5 (0.92%)	5	4 (0.74%)	1	1 (0.18%)	0	0
Abnormal uterine bleeding	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Adenomyosis	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Dysmenorrhoea	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Ectropion of cervix	1	1 (0.18%)	0	0	1	1 (0.18%)	0	0
Menstrual disorder	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Vaginal discharge	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Endocrine disorders	5	4 (0.74%)	3	2 (0.37%)	1	1 (0.18%)	1	1 (0.18%)
Hypothyroidism	2	2 (0.37%)	1	1 (0.18%)	1	1 (0.18%)	0	0
Thyroid mass	3	2 (0.37%)	2	1 (0.18%)	0	0	1	1 (0.18%)
Ear and labyrinth disorders	3	3 (0.55%)	0	0	2	2 (0.37%)	1	1 (0.18%)
Vertigo	2	2 (0.37%)	0	0	2	2 (0.37%)	0	0
Otolithiasis	1	1 (0.18%)	0	0	0	0	1	1 (0.18%)
Vascular disorders	4	3 (0.55%)	3	2 (0.37%)	1	1 (0.18%)	0	0
Hypertension	4	3 (0.55%)	3	2 (0.37%)	1	1 (0.18%)	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=542)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Cardiac disorders	1	1 (0.18%)	0	0	1	1 (0.18%)	0	0
Arteriosclerosis coronary artery	1	1 (0.18%)	0	0	1	1 (0.18%)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Thyroid cancer	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Psychiatric disorders	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Sleep disorder	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

Table ANN. 298 **AEs over a Period of 12 Weeks by Maximum Severity — MedDRA Preferred Term by Decreasing Frequency, Within System Organ Class (≥65 and <75 years, Safety Analyses Population)**

	Safety Analyses Population (N=106)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
AE	73	41 (38.68%)	47	21 (19.81%)	17	11 (10.38%)	9	9 (8.49%)
Gastrointestinal disorders	13	11 (10.38%)	9	7 (6.60%)	2	2 (1.89%)	2	2 (1.89%)
Abdominal pain upper	3	3 (2.83%)	2	2 (1.89%)	1	1 (0.94%)	0	0
Abdominal discomfort	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Diarrhoea	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Dry mouth	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Ileus paralytic	1	1 (0.94%)	0	0	0	0	1	1 (0.94%)
Mouth ulceration	2	1 (0.94%)	2	1 (0.94%)	0	0	0	0
Nausea	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Pancreatitis acute	1	1 (0.94%)	0	0	0	0	1	1 (0.94%)
Periodontal disease	1	1 (0.94%)	0	0	1	1 (0.94%)	0	0
Stomatitis	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Metabolism and nutrition disorders	14	11 (10.38%)	11	9 (8.49%)	2	1 (0.94%)	1	1 (0.94%)
Decreased appetite	3	3 (2.83%)	3	3 (2.83%)	0	0	0	0
Hyperuricaemia	2	2 (1.89%)	2	2 (1.89%)	0	0	0	0
Hypocalcaemia	2	2 (1.89%)	2	2 (1.89%)	0	0	0	0
Hypokalaemia	2	2 (1.89%)	2	2 (1.89%)	0	0	0	0
Diabetes mellitus	1	1 (0.94%)	0	0	1	1 (0.94%)	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=106)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Hyperkalaemia	1	1 (0.94%)	0	0	0	0	1	1 (0.94%)
Hyperlipidaemia	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Hypoalbuminaemia	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Hypoglycaemia	1	1 (0.94%)	0	0	1	1 (0.94%)	0	0
Infections and infestations	11	8 (7.55%)	5	3 (2.83%)	4	3 (2.83%)	2	2 (1.89%)
Pneumonia	4	3 (2.83%)	0	0	2	1 (0.94%)	2	2 (1.89%)
Urinary tract infection	3	3 (2.83%)	2	2 (1.89%)	1	1 (0.94%)	0	0
Bronchitis	1	1 (0.94%)	0	0	1	1 (0.94%)	0	0
Gingivitis	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Otitis externa	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Pharyngitis	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Investigations	10	6 (5.66%)	9	5 (4.72%)	1	1 (0.94%)	0	0
White blood cell count increased	3	3 (2.83%)	3	3 (2.83%)	0	0	0	0
Blood albumin decreased	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Blood pressure increased	1	1 (0.94%)	0	0	1	1 (0.94%)	0	0
Lymphocyte count increased	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Lymphocyte percentage increased	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Neutrophil count increased	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=106)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Neutrophil percentage increased	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Platelet count increased	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Blood and lymphatic system disorders	5	5 (4.72%)	3	3 (2.83%)	2	2 (1.89%)	0	0
Anaemia	2	2 (1.89%)	1	1 (0.94%)	1	1 (0.94%)	0	0
Thrombocytosis	2	2 (1.89%)	2	2 (1.89%)	0	0	0	0
Myelosuppression	1	1 (0.94%)	0	0	1	1 (0.94%)	0	0
General disorders and administration site conditions	3	3 (2.83%)	1	1 (0.94%)	1	1 (0.94%)	1	1 (0.94%)
Chest pain	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Death	1	1 (0.94%)	0	0	0	0	1	1 (0.94%)
Oedema peripheral	1	1 (0.94%)	0	0	1	1 (0.94%)	0	0
Musculoskeletal and connective tissue disorders	3	3 (2.83%)	0	0	1	1 (0.94%)	2	2 (1.89%)
Arthralgia	1	1 (0.94%)	0	0	1	1 (0.94%)	0	0
Intervertebral disc protrusion	1	1 (0.94%)	0	0	0	0	1	1 (0.94%)
Rheumatoid arthritis	1	1 (0.94%)	0	0	0	0	1	1 (0.94%)
Eye disorders	2	2 (1.89%)	2	2 (1.89%)	0	0	0	0
Cataract	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class

All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.

The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.

MedDRA English version 25.1

	Safety Analyses Population (N=106)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Eyelid oedema	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Hepatobiliary disorders	2	2 (1.89%)	2	2 (1.89%)	0	0	0	0
Hepatic function abnormal	2	2 (1.89%)	2	2 (1.89%)	0	0	0	0
Nervous system disorders	2	2 (1.89%)	0	0	2	2 (1.89%)	0	0
Neuropathy peripheral	1	1 (0.94%)	0	0	1	1 (0.94%)	0	0
Optic neuritis	1	1 (0.94%)	0	0	1	1 (0.94%)	0	0
Renal and urinary disorders	2	2 (1.89%)	1	1 (0.94%)	1	1 (0.94%)	0	0
Renal failure	1	1 (0.94%)	0	0	1	1 (0.94%)	0	0
Renal impairment	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Vascular disorders	2	2 (1.89%)	1	1 (0.94%)	1	1 (0.94%)	0	0
Hypertension	2	2 (1.89%)	1	1 (0.94%)	1	1 (0.94%)	0	0
Ear and labyrinth disorders	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Cerumen impaction	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Injury, poisoning and procedural complications	1	1 (0.94%)	0	0	0	0	1	1 (0.94%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=106)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Lumbar vertebral fracture	1	1 (0.94%)	0	0	0	0	1	1 (0.94%)
Respiratory, thoracic and mediastinal disorders	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Cough	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Skin and subcutaneous tissue disorders	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Night sweats	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

Table ANN. 299 **AEs over a Period of 12 Weeks by Maximum Severity — MedDRA Preferred Term by Decreasing Frequency, Within System Organ Class (≥75 years, Safety Analyses Population)**

	Safety Analyses Population (N=19)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
AE	16	8 (42.11%)	10	3 (15.79%)	5	4 (21.05%)	1	1 (5.26%)
Blood and lymphatic system disorders	2	2 (10.53%)	2	2 (10.53%)	0	0	0	0
Anaemia	2	2 (10.53%)	2	2 (10.53%)	0	0	0	0
Hepatobiliary disorders	2	2 (10.53%)	0	0	2	2 (10.53%)	0	0
Hepatic function abnormal	2	2 (10.53%)	0	0	2	2 (10.53%)	0	0
Infections and infestations	2	2 (10.53%)	1	1 (5.26%)	1	1 (5.26%)	0	0
Herpes zoster	1	1 (5.26%)	0	0	1	1 (5.26%)	0	0
Urinary tract infection	1	1 (5.26%)	1	1 (5.26%)	0	0	0	0
Metabolism and nutrition disorders	3	2 (10.53%)	2	1 (5.26%)	1	1 (5.26%)	0	0
Electrolyte imbalance	3	2 (10.53%)	2	1 (5.26%)	1	1 (5.26%)	0	0
Vascular disorders	2	2 (10.53%)	1	1 (5.26%)	1	1 (5.26%)	0	0
Arteriosclerosis	1	1 (5.26%)	1	1 (5.26%)	0	0	0	0
Hypertension	1	1 (5.26%)	0	0	1	1 (5.26%)	0	0
Gastrointestinal disorders	1	1 (5.26%)	1	1 (5.26%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=19)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Gastrooesophageal reflux disease	1	1 (5.26%)	1	1 (5.26%)	0	0	0	0
Investigations	1	1 (5.26%)	1	1 (5.26%)	0	0	0	0
Lymphocyte count decreased	1	1 (5.26%)	1	1 (5.26%)	0	0	0	0
Musculoskeletal and connective tissue disorders	3	1 (5.26%)	2	0	0	0	1	1 (5.26%)
Intervertebral disc protrusion	1	1 (5.26%)	1	1 (5.26%)	0	0	0	0
Lumbar spinal stenosis	1	1 (5.26%)	0	0	0	0	1	1 (5.26%)
Spinal osteoarthritis	1	1 (5.26%)	1	1 (5.26%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

Table ANN. 300 **AEs over a Period of 24 Weeks by Maximum Severity — MedDRA Preferred Term by Decreasing Frequency, Within System Organ Class (<65 Years, Safety Analyses Population)**

	Safety Analyses Population (N=542)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
AE	328	196 (36.16%)	240	131 (24.17%)	69	50 (9.23%)	19	15 (2.77%)
Investigations	73	53 (9.78%)	73	53 (9.78%)	0	0	0	0
Platelet count increased	15	15 (2.77%)	15	15 (2.77%)	0	0	0	0
Lymphocyte count decreased	7	7 (1.29%)	7	7 (1.29%)	0	0	0	0
White blood cell count increased	9	7 (1.29%)	9	7 (1.29%)	0	0	0	0
Neutrophil count increased	7	6 (1.11%)	7	6 (1.11%)	0	0	0	0
White blood cell count decreased	6	6 (1.11%)	6	6 (1.11%)	0	0	0	0
Alanine aminotransferase increased	5	5 (0.92%)	5	5 (0.92%)	0	0	0	0
Aspartate aminotransferase increased	3	3 (0.55%)	3	3 (0.55%)	0	0	0	0
Neutrophil percentage increased	3	3 (0.55%)	3	3 (0.55%)	0	0	0	0
Blood bilirubin increased	2	2 (0.37%)	2	2 (0.37%)	0	0	0	0
Fibrin D dimer increased	2	2 (0.37%)	2	2 (0.37%)	0	0	0	0
Blood creatine phosphokinase increased	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Blood pressure increased	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Blood triglycerides increased	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Coagulation test abnormal	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Haemoglobin decreased	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Lipids increased	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Liver function test abnormal	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=542)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Neutrophil count decreased	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Platelet count decreased	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Protein urine present	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Red blood cells urine positive	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Rheumatoid factor increased	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Weight decreased	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Weight increased	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Infections and infestations	57	50 (9.23%)	33	27 (4.98%)	20	19 (3.51%)	4	4 (0.74%)
Upper respiratory tract infection	20	17 (3.14%)	14	12 (2.21%)	6	5 (0.92%)	0	0
Urinary tract infection	9	9 (1.66%)	6	6 (1.11%)	3	3 (0.55%)	0	0
Herpes zoster	6	6 (1.11%)	2	2 (0.37%)	4	4 (0.74%)	0	0
Pneumonia	5	5 (0.92%)	0	0	4	4 (0.74%)	1	1 (0.18%)
Pharyngitis	2	2 (0.37%)	0	0	2	2 (0.37%)	0	0
Appendicitis	1	1 (0.18%)	0	0	0	0	1	1 (0.18%)
Enterovirus infection	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Herpes ophthalmic	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Herpes simplex	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Herpes virus infection	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Influenza	1	1 (0.18%)	0	0	0	0	1	1 (0.18%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=542)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Laryngopharyngitis	1	1 (0.18%)	0	0	1	1 (0.18%)	0	0
Otitis media	1	1 (0.18%)	0	0	0	0	1	1 (0.18%)
Periodontitis	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Pulmonary tuberculosis	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Pulpitis dental	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Streptococcal infection	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Tonsillitis	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Urethritis	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Vulvovaginal mycotic infection	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Musculoskeletal and connective tissue disorders	33	27 (4.98%)	12	10 (1.85%)	15	11 (2.03%)	6	6 (1.11%)
Arthralgia	11	9 (1.66%)	3	3 (0.55%)	6	4 (0.74%)	2	2 (0.37%)
Rheumatoid arthritis	9	9 (1.66%)	3	3 (0.55%)	3	3 (0.55%)	3	3 (0.55%)
Back pain	2	2 (0.37%)	1	1 (0.18%)	1	1 (0.18%)	0	0
Joint swelling	2	2 (0.37%)	1	1 (0.18%)	1	1 (0.18%)	0	0
Osteonecrosis	2	2 (0.37%)	1	1 (0.18%)	0	0	1	1 (0.18%)
Synovial cyst	2	2 (0.37%)	1	1 (0.18%)	1	1 (0.18%)	0	0
Arthropathy	1	1 (0.18%)	0	0	1	1 (0.18%)	0	0
Intervertebral disc protrusion	1	1 (0.18%)	0	0	1	1 (0.18%)	0	0
Pain in extremity	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=542)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Palindromic rheumatism	1	1 (0.18%)	0	0	1	1 (0.18%)	0	0
Spinal osteoarthritis	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Gastrointestinal disorders	24	21 (3.87%)	20	19 (3.51%)	4	2 (0.37%)	0	0
Gastrointestinal disorder	4	4 (0.74%)	4	4 (0.74%)	0	0	0	0
Diarrhoea	3	3 (0.55%)	3	3 (0.55%)	0	0	0	0
Abdominal discomfort	2	2 (0.37%)	2	2 (0.37%)	0	0	0	0
Nausea	2	2 (0.37%)	2	2 (0.37%)	0	0	0	0
Abdominal distension	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Abdominal pain upper	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Aphthous ulcer	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Functional gastrointestinal disorder	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Gastritis	1	1 (0.18%)	0	0	1	1 (0.18%)	0	0
Gastritis erosive	2	1 (0.18%)	0	0	2	1 (0.18%)	0	0
Haemorrhagic erosive gastritis	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Mouth ulceration	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Noninfective gingivitis	1	1 (0.18%)	0	0	1	1 (0.18%)	0	0
Oral blood blister	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Oral mucosal eruption	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Toothache	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0

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	Safety Analyses Population (N=542)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Hepatobiliary disorders	24	21 (3.87%)	15	14 (2.58%)	7	6 (1.11%)	2	1 (0.18%)
Hepatic function abnormal	20	18 (3.32%)	14	13 (2.40%)	6	5 (0.92%)	0	0
Drug-induced liver injury	3	2 (0.37%)	0	0	1	1 (0.18%)	2	1 (0.18%)
Liver injury	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Blood and lymphatic system disorders	21	20 (3.69%)	19	18 (3.32%)	2	2 (0.37%)	0	0
Anaemia	11	10 (1.85%)	10	9 (1.66%)	1	1 (0.18%)	0	0
Coagulopathy	2	2 (0.37%)	2	2 (0.37%)	0	0	0	0
Leukopenia	2	2 (0.37%)	2	2 (0.37%)	0	0	0	0
Thrombocytosis	2	2 (0.37%)	2	2 (0.37%)	0	0	0	0
Eosinophilia	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Monocytosis	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Myelosuppression	1	1 (0.18%)	0	0	1	1 (0.18%)	0	0
Thrombocytopenia	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Metabolism and nutrition disorders	21	20 (3.69%)	18	17 (3.14%)	3	3 (0.55%)	0	0
Hyperlipidaemia	8	8 (1.48%)	6	6 (1.11%)	2	2 (0.37%)	0	0
Hyperuricaemia	4	4 (0.74%)	4	4 (0.74%)	0	0	0	0
Decreased appetite	2	2 (0.37%)	2	2 (0.37%)	0	0	0	0

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All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
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MedDRA English version 25.1

	Safety Analyses Population (N=542)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Dyslipidaemia	2	2 (0.37%)	2	2 (0.37%)	0	0	0	0
Glucose tolerance impaired	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Hypercholesterolaemia	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Hypertriglyceridaemia	1	1 (0.18%)	0	0	1	1 (0.18%)	0	0
Hypocalcaemia	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Vitamin D deficiency	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Skin and subcutaneous tissue disorders	14	13 (2.40%)	9	8 (1.48%)	5	5 (0.92%)	0	0
Alopecia	5	5 (0.92%)	3	3 (0.55%)	2	2 (0.37%)	0	0
Acne	3	3 (0.55%)	2	2 (0.37%)	1	1 (0.18%)	0	0
Dermatitis	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Eczema	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Pruritus	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Rash	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Skin erosion	1	1 (0.18%)	0	0	1	1 (0.18%)	0	0
Skin ulcer	1	1 (0.18%)	0	0	1	1 (0.18%)	0	0
Respiratory, thoracic and mediastinal disorders	12	11 (2.03%)	7	6 (1.11%)	4	4 (0.74%)	1	1 (0.18%)
Cough	5	5 (0.92%)	3	3 (0.55%)	2	2 (0.37%)	0	0
Bronchiectasis	2	2 (0.37%)	1	1 (0.18%)	1	1 (0.18%)	0	0

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All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
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	Safety Analyses Population (N=542)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Chronic obstructive pulmonary disease	1	1 (0.18%)	0	0	0	0	1	1 (0.18%)
Interstitial lung disease	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Laryngeal pain	1	1 (0.18%)	0	0	1	1 (0.18%)	0	0
Oropharyngeal pain	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Productive cough	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
General disorders and administration site conditions	9	8 (1.48%)	8	7 (1.29%)	1	1 (0.18%)	0	0
Asthenia	2	2 (0.37%)	2	2 (0.37%)	0	0	0	0
Chest discomfort	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Chest pain	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Chills	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Face oedema	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Oedema peripheral	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Peripheral swelling	1	1 (0.18%)	0	0	1	1 (0.18%)	0	0
Pyrexia	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Nervous system disorders	6	6 (1.11%)	4	4 (0.74%)	1	1 (0.18%)	1	1 (0.18%)
Headache	3	3 (0.55%)	2	2 (0.37%)	1	1 (0.18%)	0	0
Carotid artery aneurysm	1	1 (0.18%)	0	0	0	0	1	1 (0.18%)
Dizziness	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0

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	Safety Analyses Population (N=542)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Somnolence	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Reproductive system and breast disorders	7	6 (1.11%)	6	5 (0.92%)	1	1 (0.18%)	0	0
Abnormal uterine bleeding	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Adenomyosis	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Breast mass	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Dysmenorrhoea	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Ectropion of cervix	1	1 (0.18%)	0	0	1	1 (0.18%)	0	0
Menstrual disorder	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Vaginal discharge	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Ear and labyrinth disorders	4	4 (0.74%)	1	1 (0.18%)	2	2 (0.37%)	1	1 (0.18%)
Vertigo	3	3 (0.55%)	1	1 (0.18%)	2	2 (0.37%)	0	0
Otolithiasis	1	1 (0.18%)	0	0	0	0	1	1 (0.18%)
Endocrine disorders	5	4 (0.74%)	3	2 (0.37%)	1	1 (0.18%)	1	1 (0.18%)
Hypothyroidism	2	2 (0.37%)	1	1 (0.18%)	1	1 (0.18%)	0	0
Thyroid mass	3	2 (0.37%)	2	1 (0.18%)	0	0	1	1 (0.18%)
Psychiatric disorders	4	4 (0.74%)	4	4 (0.74%)	0	0	0	0

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	Safety Analyses Population (N=542)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Sleep disorder	2	2 (0.37%)	2	2 (0.37%)	0	0	0	0
Anxiety disorder	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Insomnia	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Eye disorders	4	3 (0.55%)	2	2 (0.37%)	0	0	2	1 (0.18%)
Cataract	2	1 (0.18%)	0	0	0	0	2	1 (0.18%)
Dry eye	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Ocular discomfort	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Injury, poisoning and procedural complications	3	3 (0.55%)	2	2 (0.37%)	1	1 (0.18%)	0	0
Limb injury	1	1 (0.18%)	0	0	1	1 (0.18%)	0	0
Nail injury	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Tendon injury	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Vascular disorders	4	3 (0.55%)	3	2 (0.37%)	1	1 (0.18%)	0	0
Hypertension	4	3 (0.55%)	3	2 (0.37%)	1	1 (0.18%)	0	0
Cardiac disorders	1	1 (0.18%)	0	0	1	1 (0.18%)	0	0
Arteriosclerosis coronary artery	1	1 (0.18%)	0	0	1	1 (0.18%)	0	0

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	Safety Analyses Population (N=542)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Thyroid cancer	1	1 (0.18%)	1	1 (0.18%)	0	0	0	0
Pregnancy, puerperium and perinatal conditions	1	1 (0.18%)	0	0	0	0	1	1 (0.18%)
Abortion threatened	1	1 (0.18%)	0	0	0	0	1	1 (0.18%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
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Table ANN. 301 **AEs over a Period of 24 Weeks by Maximum Severity — MedDRA Preferred Term by Decreasing Frequency, Within System Organ Class (≥65 and <75 Years, Safety Analyses Population)**

	Safety Analyses Population (N=106)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
AE	79	45 (42.45%)	51	24 (22.64%)	19	12 (11.32%)	9	9 (8.49%)
Metabolism and nutrition disorders	15	12 (11.32%)	12	10 (9.43%)	2	1 (0.94%)	1	1 (0.94%)
Decreased appetite	3	3 (2.83%)	3	3 (2.83%)	0	0	0	0
Hyperlipidaemia	2	2 (1.89%)	2	2 (1.89%)	0	0	0	0
Hyperuricaemia	2	2 (1.89%)	2	2 (1.89%)	0	0	0	0
Hypocalcaemia	2	2 (1.89%)	2	2 (1.89%)	0	0	0	0
Hypokalaemia	2	2 (1.89%)	2	2 (1.89%)	0	0	0	0
Diabetes mellitus	1	1 (0.94%)	0	0	1	1 (0.94%)	0	0
Hyperkalaemia	1	1 (0.94%)	0	0	0	0	1	1 (0.94%)
Hypoalbuminaemia	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Hypoglycaemia	1	1 (0.94%)	0	0	1	1 (0.94%)	0	0
Gastrointestinal disorders	13	11 (10.38%)	9	7 (6.60%)	2	2 (1.89%)	2	2 (1.89%)
Abdominal pain upper	3	3 (2.83%)	2	2 (1.89%)	1	1 (0.94%)	0	0
Abdominal discomfort	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Diarrhoea	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Dry mouth	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Ileus paralytic	1	1 (0.94%)	0	0	0	0	1	1 (0.94%)
Mouth ulceration	2	1 (0.94%)	2	1 (0.94%)	0	0	0	0

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	Safety Analyses Population (N=106)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Nausea	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Pancreatitis acute	1	1 (0.94%)	0	0	0	0	1	1 (0.94%)
Periodontal disease	1	1 (0.94%)	0	0	1	1 (0.94%)	0	0
Stomatitis	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Infections and infestations	13	10 (9.43%)	7	5 (4.72%)	4	3 (2.83%)	2	2 (1.89%)
Urinary tract infection	4	4 (3.77%)	3	3 (2.83%)	1	1 (0.94%)	0	0
Pneumonia	4	3 (2.83%)	0	0	2	1 (0.94%)	2	2 (1.89%)
Bronchitis	1	1 (0.94%)	0	0	1	1 (0.94%)	0	0
Gingivitis	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Otitis externa	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Pharyngitis	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Upper respiratory tract infection	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Investigations	12	8 (7.55%)	10	6 (5.66%)	2	2 (1.89%)	0	0
White blood cell count increased	3	3 (2.83%)	3	3 (2.83%)	0	0	0	0
Lymphocyte count decreased	2	2 (1.89%)	1	1 (0.94%)	1	1 (0.94%)	0	0
Blood albumin decreased	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Blood pressure increased	1	1 (0.94%)	0	0	1	1 (0.94%)	0	0
Lymphocyte count increased	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0

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	Safety Analyses Population (N=106)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Lymphocyte percentage increased	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Neutrophil count increased	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Neutrophil percentage increased	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Platelet count increased	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Blood and lymphatic system disorders	5	5 (4.72%)	3	3 (2.83%)	2	2 (1.89%)	0	0
Anaemia	2	2 (1.89%)	1	1 (0.94%)	1	1 (0.94%)	0	0
Thrombocytosis	2	2 (1.89%)	2	2 (1.89%)	0	0	0	0
Myelosuppression	1	1 (0.94%)	0	0	1	1 (0.94%)	0	0
Musculoskeletal and connective tissue disorders	4	4 (3.77%)	0	0	2	2 (1.89%)	2	2 (1.89%)
Arthralgia	1	1 (0.94%)	0	0	1	1 (0.94%)	0	0
Intervertebral disc protrusion	1	1 (0.94%)	0	0	0	0	1	1 (0.94%)
Palindromic rheumatism	1	1 (0.94%)	0	0	1	1 (0.94%)	0	0
Rheumatoid arthritis	1	1 (0.94%)	0	0	0	0	1	1 (0.94%)
General disorders and administration site conditions	3	3 (2.83%)	1	1 (0.94%)	1	1 (0.94%)	1	1 (0.94%)
Chest pain	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Death	1	1 (0.94%)	0	0	0	0	1	1 (0.94%)
Oedema peripheral	1	1 (0.94%)	0	0	1	1 (0.94%)	0	0

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All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
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	Safety Analyses Population (N=106)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Eye disorders	2	2 (1.89%)	2	2 (1.89%)	0	0	0	0
Cataract	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Eyelid oedema	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Hepatobiliary disorders	2	2 (1.89%)	2	2 (1.89%)	0	0	0	0
Hepatic function abnormal	2	2 (1.89%)	2	2 (1.89%)	0	0	0	0
Nervous system disorders	2	2 (1.89%)	0	0	2	2 (1.89%)	0	0
Neuropathy peripheral	1	1 (0.94%)	0	0	1	1 (0.94%)	0	0
Optic neuritis	1	1 (0.94%)	0	0	1	1 (0.94%)	0	0
Renal and urinary disorders	2	2 (1.89%)	1	1 (0.94%)	1	1 (0.94%)	0	0
Renal failure	1	1 (0.94%)	0	0	1	1 (0.94%)	0	0
Renal impairment	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Vascular disorders	2	2 (1.89%)	1	1 (0.94%)	1	1 (0.94%)	0	0
Hypertension	2	2 (1.89%)	1	1 (0.94%)	1	1 (0.94%)	0	0
Ear and labyrinth disorders	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=106)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Cerumen impaction	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Injury, poisoning and procedural complications	1	1 (0.94%)	0	0	0	0	1	1 (0.94%)
Lumbar vertebral fracture	1	1 (0.94%)	0	0	0	0	1	1 (0.94%)
Respiratory, thoracic and mediastinal disorders	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Cough	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Skin and subcutaneous tissue disorders	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0
Night sweats	1	1 (0.94%)	1	1 (0.94%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

Table ANN. 302 AEs over a Period of 24 Weeks by Maximum Severity — MedDRA Preferred Term by Decreasing Frequency, Within System Organ Class (≥75 years, Safety Analyses Population)

	Safety Analyses Population (N=19)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
AE	21	9 (47.37%)	14	3 (15.79%)	6	5 (26.32%)	1	1 (5.26%)
Infections and infestations	4	4 (21.05%)	3	3 (15.79%)	1	1 (5.26%)	0	0
Urinary tract infection	2	2 (10.53%)	2	2 (10.53%)	0	0	0	0
Herpes zoster	1	1 (5.26%)	0	0	1	1 (5.26%)	0	0
Pneumonia	1	1 (5.26%)	1	1 (5.26%)	0	0	0	0
Metabolism and nutrition disorders	4	3 (15.79%)	3	2 (10.53%)	1	1 (5.26%)	0	0
Electrolyte imbalance	3	2 (10.53%)	2	1 (5.26%)	1	1 (5.26%)	0	0
Hyperlipidaemia	1	1 (5.26%)	1	1 (5.26%)	0	0	0	0
Blood and lymphatic system disorders	2	2 (10.53%)	2	2 (10.53%)	0	0	0	0
Anaemia	2	2 (10.53%)	2	2 (10.53%)	0	0	0	0
Hepatobiliary disorders	2	2 (10.53%)	0	0	2	2 (10.53%)	0	0
Hepatic function abnormal	2	2 (10.53%)	0	0	2	2 (10.53%)	0	0
Musculoskeletal and connective tissue disorders	4	2 (10.53%)	2	0	1	1 (5.26%)	1	1 (5.26%)
Intervertebral disc protrusion	1	1 (5.26%)	1	1 (5.26%)	0	0	0	0
Lumbar spinal stenosis	1	1 (5.26%)	0	0	0	0	1	1 (5.26%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=19)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Rheumatoid arthritis	1	1 (5.26%)	0	0	1	1 (5.26%)	0	0
Spinal osteoarthritis	1	1 (5.26%)	1	1 (5.26%)	0	0	0	0
Vascular disorders	2	2 (10.53%)	1	1 (5.26%)	1	1 (5.26%)	0	0
Arteriosclerosis	1	1 (5.26%)	1	1 (5.26%)	0	0	0	0
Hypertension	1	1 (5.26%)	0	0	1	1 (5.26%)	0	0
Gastrointestinal disorders	1	1 (5.26%)	1	1 (5.26%)	0	0	0	0
Gastrooesophageal reflux disease	1	1 (5.26%)	1	1 (5.26%)	0	0	0	0
Investigations	1	1 (5.26%)	1	1 (5.26%)	0	0	0	0
Lymphocyte count decreased	1	1 (5.26%)	1	1 (5.26%)	0	0	0	0
Skin and subcutaneous tissue disorders	1	1 (5.26%)	1	1 (5.26%)	0	0	0	0
Rash	1	1 (5.26%)	1	1 (5.26%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

Table ANN. 303 AEs over a Period of 12 Weeks — MedDRA Preferred Term by Decreasing Frequency (<65 Years, Safety Analyses Population)

	Safety Analyses Population (N=542)	
PT	*Event*	*n (%)*
AE	240	165 (30.44%)
Upper respiratory tract infection	18	17 (3.14%)
Hepatic function abnormal	14	14 (2.58%)
Platelet count increased	13	13 (2.40%)
Hyperlipidaemia	7	7 (1.29%)
Rheumatoid arthritis	7	7 (1.29%)
Urinary tract infection	7	7 (1.29%)
Anaemia	6	6 (1.11%)
Arthralgia	6	6 (1.11%)
Lymphocyte count decreased	6	6 (1.11%)
Neutrophil count increased	6	6 (1.11%)
White blood cell count increased	6	6 (1.11%)
Alanine aminotransferase increased	5	5 (0.92%)
White blood cell count decreased	5	5 (0.92%)
Alopecia	4	4 (0.74%)
Gastrointestinal disorder	4	4 (0.74%)
Acne	3	3 (0.55%)
Cough	3	3 (0.55%)
Diarrhoea	3	3 (0.55%)
Hypertension	4	3 (0.55%)
Hyperuricaemia	3	3 (0.55%)
Neutrophil percentage increased	3	3 (0.55%)
Pneumonia	3	3 (0.55%)
Aspartate aminotransferase increased	2	2 (0.37%)
Fibrin D dimer increased	2	2 (0.37%)
Headache	2	2 (0.37%)
Herpes zoster	2	2 (0.37%)
Hypothyroidism	2	2 (0.37%)
Joint swelling	2	2 (0.37%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

	Safety Analyses Population (N=542)	
PT	*Event*	*n (%)*
Leukopenia	2	2 (0.37%)
Nausea	2	2 (0.37%)
Pharyngitis	2	2 (0.37%)
Thrombocytosis	2	2 (0.37%)
Thyroid mass	3	2 (0.37%)
Vertigo	2	2 (0.37%)
Abdominal discomfort	1	1 (0.18%)
Abdominal distension	1	1 (0.18%)
Abnormal uterine bleeding	1	1 (0.18%)
Adenomyosis	1	1 (0.18%)
Aphthous ulcer	1	1 (0.18%)
Arteriosclerosis coronary artery	1	1 (0.18%)
Asthenia	1	1 (0.18%)
Back pain	1	1 (0.18%)
Blood creatine phosphokinase increased	1	1 (0.18%)
Blood pressure increased	1	1 (0.18%)
Blood triglycerides increased	1	1 (0.18%)
Bronchiectasis	1	1 (0.18%)
Carotid artery aneurysm	1	1 (0.18%)
Chest discomfort	1	1 (0.18%)
Chest pain	1	1 (0.18%)
Chills	1	1 (0.18%)
Chronic obstructive pulmonary disease	1	1 (0.18%)
Coagulation test abnormal	1	1 (0.18%)
Coagulopathy	1	1 (0.18%)
Decreased appetite	1	1 (0.18%)
Dermatitis	1	1 (0.18%)
Dizziness	1	1 (0.18%)
Drug-induced liver injury	2	1 (0.18%)
Dyslipidaemia	1	1 (0.18%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

	Safety Analyses Population (N=542)	
PT	*Event*	*n (%)*
Dysmenorrhoea	1	1 (0.18%)
Ectropion of cervix	1	1 (0.18%)
Eczema	1	1 (0.18%)
Enterovirus infection	1	1 (0.18%)
Eosinophilia	1	1 (0.18%)
Face oedema	1	1 (0.18%)
Functional gastrointestinal disorder	1	1 (0.18%)
Gastritis	1	1 (0.18%)
Haemoglobin decreased	1	1 (0.18%)
Haemorrhagic erosive gastritis	1	1 (0.18%)
Herpes ophthalmic	1	1 (0.18%)
Herpes simplex	1	1 (0.18%)
Herpes virus infection	1	1 (0.18%)
Hypercholesterolaemia	1	1 (0.18%)
Hypertriglyceridaemia	1	1 (0.18%)
Hypocalcaemia	1	1 (0.18%)
Interstitial lung disease	1	1 (0.18%)
Intervertebral disc protrusion	1	1 (0.18%)
Laryngeal pain	1	1 (0.18%)
Lipids increased	1	1 (0.18%)
Menstrual disorder	1	1 (0.18%)
Monocytosis	1	1 (0.18%)
Mouth ulceration	1	1 (0.18%)
Myelosuppression	1	1 (0.18%)
Noninfective gingivitis	1	1 (0.18%)
Oedema peripheral	1	1 (0.18%)
Oral blood blister	1	1 (0.18%)
Oropharyngeal pain	1	1 (0.18%)
Otitis media	1	1 (0.18%)
Otolithiasis	1	1 (0.18%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

	Safety Analyses Population (N=542)	
PT	*Event*	*n (%)*
Pain in extremity	1	1 (0.18%)
Periodontitis	1	1 (0.18%)
Peripheral swelling	1	1 (0.18%)
Productive cough	1	1 (0.18%)
Pruritus	1	1 (0.18%)
Pulmonary tuberculosis	1	1 (0.18%)
Pulpitis dental	1	1 (0.18%)
Rash	1	1 (0.18%)
Red blood cells urine positive	1	1 (0.18%)
Skin erosion	1	1 (0.18%)
Skin ulcer	1	1 (0.18%)
Sleep disorder	1	1 (0.18%)
Somnolence	1	1 (0.18%)
Spinal osteoarthritis	1	1 (0.18%)
Streptococcal infection	1	1 (0.18%)
Thrombocytopenia	1	1 (0.18%)
Thyroid cancer	1	1 (0.18%)
Tonsillitis	1	1 (0.18%)
Toothache	1	1 (0.18%)
Urethritis	1	1 (0.18%)
Vaginal discharge	1	1 (0.18%)
Vitamin D deficiency	1	1 (0.18%)
Vulvovaginal mycotic infection	1	1 (0.18%)
Weight increased	1	1 (0.18%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

Table ANN. 304 AEs over a Period of 12 Weeks — MedDRA Preferred Term by Decreasing Frequency (≥65 and <75 Years, Safety Analyses Population)

	Safety Analyses Population (N=106)	
PT	*Event*	*n (%)*
AE	73	41 (38.68%)
Abdominal pain upper	3	3 (2.83%)
Decreased appetite	3	3 (2.83%)
Pneumonia	4	3 (2.83%)
Urinary tract infection	3	3 (2.83%)
White blood cell count increased	3	3 (2.83%)
Anaemia	2	2 (1.89%)
Hepatic function abnormal	2	2 (1.89%)
Hypertension	2	2 (1.89%)
Hyperuricaemia	2	2 (1.89%)
Hypocalcaemia	2	2 (1.89%)
Hypokalaemia	2	2 (1.89%)
Thrombocytosis	2	2 (1.89%)
Abdominal discomfort	1	1 (0.94%)
Arthralgia	1	1 (0.94%)
Blood albumin decreased	1	1 (0.94%)
Blood pressure increased	1	1 (0.94%)
Bronchitis	1	1 (0.94%)
Cataract	1	1 (0.94%)
Cerumen impaction	1	1 (0.94%)
Chest pain	1	1 (0.94%)
Cough	1	1 (0.94%)
Death	1	1 (0.94%)
Diabetes mellitus	1	1 (0.94%)
Diarrhoea	1	1 (0.94%)
Dry mouth	1	1 (0.94%)
Eyelid oedema	1	1 (0.94%)
Gingivitis	1	1 (0.94%)
Hyperkalaemia	1	1 (0.94%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

	Safety Analyses Population (N=106)	
PT	*Event*	*n (%)*
Hyperlipidaemia	1	1 (0.94%)
Hypoalbuminaemia	1	1 (0.94%)
Hypoglycaemia	1	1 (0.94%)
Ileus paralytic	1	1 (0.94%)
Intervertebral disc protrusion	1	1 (0.94%)
Lumbar vertebral fracture	1	1 (0.94%)
Lymphocyte count increased	1	1 (0.94%)
Lymphocyte percentage increased	1	1 (0.94%)
Mouth ulceration	2	1 (0.94%)
Myelosuppression	1	1 (0.94%)
Nausea	1	1 (0.94%)
Neuropathy peripheral	1	1 (0.94%)
Neutrophil count increased	1	1 (0.94%)
Neutrophil percentage increased	1	1 (0.94%)
Night sweats	1	1 (0.94%)
Oedema peripheral	1	1 (0.94%)
Optic neuritis	1	1 (0.94%)
Otitis externa	1	1 (0.94%)
Pancreatitis acute	1	1 (0.94%)
Periodontal disease	1	1 (0.94%)
Pharyngitis	1	1 (0.94%)
Platelet count increased	1	1 (0.94%)
Renal failure	1	1 (0.94%)
Renal impairment	1	1 (0.94%)
Rheumatoid arthritis	1	1 (0.94%)
Stomatitis	1	1 (0.94%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

Table ANN. 305 AEs over a Period of 12 Weeks — MedDRA Preferred Term by Decreasing Frequency (≥75 Years, Safety Analyses Population)

	Safety Analyses Population (N=19)	
PT	*Event*	*n (%)*
AE	16	8 (42.11%)
Anaemia	2	2 (10.53%)
Electrolyte imbalance	3	2 (10.53%)
Hepatic function abnormal	2	2 (10.53%)
Arteriosclerosis	1	1 (5.26%)
Gastrooesophageal reflux disease	1	1 (5.26%)
Herpes zoster	1	1 (5.26%)
Hypertension	1	1 (5.26%)
Intervertebral disc protrusion	1	1 (5.26%)
Lumbar spinal stenosis	1	1 (5.26%)
Lymphocyte count decreased	1	1 (5.26%)
Spinal osteoarthritis	1	1 (5.26%)
Urinary tract infection	1	1 (5.26%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

Table ANN. 306 AEs over a Period of 24 Weeks — MedDRA Preferred Term by Decreasing Frequency (<65 Years, Safety Analyses Population)

	Safety Analyses Population (N=542)	
PT	*Event*	*n (%)*
AE	328	196 (36.16%)
Hepatic function abnormal	20	18 (3.32%)
Upper respiratory tract infection	20	17 (3.14%)
Platelet count increased	15	15 (2.77%)
Anaemia	11	10 (1.85%)
Arthralgia	11	9 (1.66%)
Rheumatoid arthritis	9	9 (1.66%)
Urinary tract infection	9	9 (1.66%)
Hyperlipidaemia	8	8 (1.48%)
Lymphocyte count decreased	7	7 (1.29%)
White blood cell count increased	9	7 (1.29%)
Herpes zoster	6	6 (1.11%)
Neutrophil count increased	7	6 (1.11%)
White blood cell count decreased	6	6 (1.11%)
Alanine aminotransferase increased	5	5 (0.92%)
Alopecia	5	5 (0.92%)
Cough	5	5 (0.92%)
Pneumonia	5	5 (0.92%)
Gastrointestinal disorder	4	4 (0.74%)
Hyperuricaemia	4	4 (0.74%)
Acne	3	3 (0.55%)
Aspartate aminotransferase increased	3	3 (0.55%)
Diarrhoea	3	3 (0.55%)
Headache	3	3 (0.55%)
Hypertension	4	3 (0.55%)
Neutrophil percentage increased	3	3 (0.55%)
Vertigo	3	3 (0.55%)
Abdominal discomfort	2	2 (0.37%)
Asthenia	2	2 (0.37%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

	Safety Analyses Population (N=542)	
PT	*Event*	*n (%)*
Back pain	2	2 (0.37%)
Blood bilirubin increased	2	2 (0.37%)
Bronchiectasis	2	2 (0.37%)
Coagulopathy	2	2 (0.37%)
Decreased appetite	2	2 (0.37%)
Drug-induced liver injury	3	2 (0.37%)
Dyslipidaemia	2	2 (0.37%)
Fibrin D dimer increased	2	2 (0.37%)
Hypothyroidism	2	2 (0.37%)
Joint swelling	2	2 (0.37%)
Leukopenia	2	2 (0.37%)
Nausea	2	2 (0.37%)
Osteonecrosis	2	2 (0.37%)
Pharyngitis	2	2 (0.37%)
Sleep disorder	2	2 (0.37%)
Synovial cyst	2	2 (0.37%)
Thrombocytosis	2	2 (0.37%)
Thyroid mass	3	2 (0.37%)
Abdominal distension	1	1 (0.18%)
Abdominal pain upper	1	1 (0.18%)
Abnormal uterine bleeding	1	1 (0.18%)
Abortion threatened	1	1 (0.18%)
Adenomyosis	1	1 (0.18%)
Anxiety disorder	1	1 (0.18%)
Aphthous ulcer	1	1 (0.18%)
Appendicitis	1	1 (0.18%)
Arteriosclerosis coronary artery	1	1 (0.18%)
Arthropathy	1	1 (0.18%)
Blood creatine phosphokinase increased	1	1 (0.18%)
Blood pressure increased	1	1 (0.18%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

	Safety Analyses Population (N=542)	
PT	*Event*	*n (%)*
Blood triglycerides increased	1	1 (0.18%)
Breast mass	1	1 (0.18%)
Carotid artery aneurysm	1	1 (0.18%)
Cataract	2	1 (0.18%)
Chest discomfort	1	1 (0.18%)
Chest pain	1	1 (0.18%)
Chills	1	1 (0.18%)
Chronic obstructive pulmonary disease	1	1 (0.18%)
Coagulation test abnormal	1	1 (0.18%)
Dermatitis	1	1 (0.18%)
Dizziness	1	1 (0.18%)
Dry eye	1	1 (0.18%)
Dysmenorrhoea	1	1 (0.18%)
Ectropion of cervix	1	1 (0.18%)
Eczema	1	1 (0.18%)
Enterovirus infection	1	1 (0.18%)
Eosinophilia	1	1 (0.18%)
Face oedema	1	1 (0.18%)
Functional gastrointestinal disorder	1	1 (0.18%)
Gastritis	1	1 (0.18%)
Gastritis erosive	2	1 (0.18%)
Glucose tolerance impaired	1	1 (0.18%)
Haemoglobin decreased	1	1 (0.18%)
Haemorrhagic erosive gastritis	1	1 (0.18%)
Herpes ophthalmic	1	1 (0.18%)
Herpes simplex	1	1 (0.18%)
Herpes virus infection	1	1 (0.18%)
Hypercholesterolaemia	1	1 (0.18%)
Hypertriglyceridaemia	1	1 (0.18%)
Hypocalcaemia	1	1 (0.18%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

	Safety Analyses Population (N=542)	
PT	*Event*	*n (%)*
Influenza	1	1 (0.18%)
Insomnia	1	1 (0.18%)
Interstitial lung disease	1	1 (0.18%)
Intervertebral disc protrusion	1	1 (0.18%)
Laryngeal pain	1	1 (0.18%)
Laryngopharyngitis	1	1 (0.18%)
Limb injury	1	1 (0.18%)
Lipids increased	1	1 (0.18%)
Liver function test abnormal	1	1 (0.18%)
Liver injury	1	1 (0.18%)
Menstrual disorder	1	1 (0.18%)
Monocytosis	1	1 (0.18%)
Mouth ulceration	1	1 (0.18%)
Myelosuppression	1	1 (0.18%)
Nail injury	1	1 (0.18%)
Neutrophil count decreased	1	1 (0.18%)
Noninfective gingivitis	1	1 (0.18%)
Ocular discomfort	1	1 (0.18%)
Oedema peripheral	1	1 (0.18%)
Oral blood blister	1	1 (0.18%)
Oral mucosal eruption	1	1 (0.18%)
Oropharyngeal pain	1	1 (0.18%)
Otitis media	1	1 (0.18%)
Otolithiasis	1	1 (0.18%)
Pain in extremity	1	1 (0.18%)
Palindromic rheumatism	1	1 (0.18%)
Periodontitis	1	1 (0.18%)
Peripheral swelling	1	1 (0.18%)
Platelet count decreased	1	1 (0.18%)
Productive cough	1	1 (0.18%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

	Safety Analyses Population (N=542)	
PT	*Event*	*n (%)*
Protein urine present	1	1 (0.18%)
Pruritus	1	1 (0.18%)
Pulmonary tuberculosis	1	1 (0.18%)
Pulpitis dental	1	1 (0.18%)
Pyrexia	1	1 (0.18%)
Rash	1	1 (0.18%)
Red blood cells urine positive	1	1 (0.18%)
Rheumatoid factor increased	1	1 (0.18%)
Skin erosion	1	1 (0.18%)
Skin ulcer	1	1 (0.18%)
Somnolence	1	1 (0.18%)
Spinal osteoarthritis	1	1 (0.18%)
Streptococcal infection	1	1 (0.18%)
Tendon injury	1	1 (0.18%)
Thrombocytopenia	1	1 (0.18%)
Thyroid cancer	1	1 (0.18%)
Tonsillitis	1	1 (0.18%)
Toothache	1	1 (0.18%)
Urethritis	1	1 (0.18%)
Vaginal discharge	1	1 (0.18%)
Vitamin D deficiency	1	1 (0.18%)
Vulvovaginal mycotic infection	1	1 (0.18%)
Weight decreased	1	1 (0.18%)
Weight increased	1	1 (0.18%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

Table ANN. 307 AEs over a Period of 24 Weeks — MedDRA Preferred Term by Decreasing Frequency (≥65 and <75 Years, Safety Analyses Population)

	Safety Analyses Population (N=106)	
PT	*Event*	*n (%)*
AE	79	45 (42.45%)
Urinary tract infection	4	4 (3.77%)
Abdominal pain upper	3	3 (2.83%)
Decreased appetite	3	3 (2.83%)
Pneumonia	4	3 (2.83%)
White blood cell count increased	3	3 (2.83%)
Anaemia	2	2 (1.89%)
Hepatic function abnormal	2	2 (1.89%)
Hyperlipidaemia	2	2 (1.89%)
Hypertension	2	2 (1.89%)
Hyperuricaemia	2	2 (1.89%)
Hypocalcaemia	2	2 (1.89%)
Hypokalaemia	2	2 (1.89%)
Lymphocyte count decreased	2	2 (1.89%)
Thrombocytosis	2	2 (1.89%)
Abdominal discomfort	1	1 (0.94%)
Arthralgia	1	1 (0.94%)
Blood albumin decreased	1	1 (0.94%)
Blood pressure increased	1	1 (0.94%)
Bronchitis	1	1 (0.94%)
Cataract	1	1 (0.94%)
Cerumen impaction	1	1 (0.94%)
Chest pain	1	1 (0.94%)
Cough	1	1 (0.94%)
Death	1	1 (0.94%)
Diabetes mellitus	1	1 (0.94%)
Diarrhoea	1	1 (0.94%)
Dry mouth	1	1 (0.94%)
Eyelid oedema	1	1 (0.94%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

	Safety Analyses Population (N=106)	
PT	*Event*	*n (%)*
Gingivitis	1	1 (0.94%)
Hyperkalaemia	1	1 (0.94%)
Hypoalbuminaemia	1	1 (0.94%)
Hypoglycaemia	1	1 (0.94%)
Ileus paralytic	1	1 (0.94%)
Intervertebral disc protrusion	1	1 (0.94%)
Lumbar vertebral fracture	1	1 (0.94%)
Lymphocyte count increased	1	1 (0.94%)
Lymphocyte percentage increased	1	1 (0.94%)
Mouth ulceration	2	1 (0.94%)
Myelosuppression	1	1 (0.94%)
Nausea	1	1 (0.94%)
Neuropathy peripheral	1	1 (0.94%)
Neutrophil count increased	1	1 (0.94%)
Neutrophil percentage increased	1	1 (0.94%)
Night sweats	1	1 (0.94%)
Oedema peripheral	1	1 (0.94%)
Optic neuritis	1	1 (0.94%)
Otitis externa	1	1 (0.94%)
Palindromic rheumatism	1	1 (0.94%)
Pancreatitis acute	1	1 (0.94%)
Periodontal disease	1	1 (0.94%)
Pharyngitis	1	1 (0.94%)
Platelet count increased	1	1 (0.94%)
Renal failure	1	1 (0.94%)
Renal impairment	1	1 (0.94%)
Rheumatoid arthritis	1	1 (0.94%)
Stomatitis	1	1 (0.94%)
Upper respiratory tract infection	1	1 (0.94%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

Table ANN. 308 AEs over a Period of 24 weeks — MedDRA Preferred Term by Decreasing Frequency (≥75 Years, Safety Analyses Population)

	Safety Analyses Population (N=19)	
PT	*Event*	*n (%)*
AE	21	9 (47.37%)
Anaemia	2	2 (10.53%)
Electrolyte imbalance	3	2 (10.53%)
Hepatic function abnormal	2	2 (10.53%)
Urinary tract infection	2	2 (10.53%)
Arteriosclerosis	1	1 (5.26%)
Gastrooesophageal reflux disease	1	1 (5.26%)
Herpes zoster	1	1 (5.26%)
Hyperlipidaemia	1	1 (5.26%)
Hypertension	1	1 (5.26%)
Intervertebral disc protrusion	1	1 (5.26%)
Lumbar spinal stenosis	1	1 (5.26%)
Lymphocyte count decreased	1	1 (5.26%)
Pneumonia	1	1 (5.26%)
Rash	1	1 (5.26%)
Rheumatoid arthritis	1	1 (5.26%)
Spinal osteoarthritis	1	1 (5.26%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

Table ANN. 309 SAEs over a Period of 12 Weeks— MedDRA Preferred Term by Decreasing Frequency, within System Organ Class (<65 years, Safety Analyses Population)

SOC	*Safety Analyses Population (N=542)*		
PT	*Event*	*n (%)*	*EAIR and 95% CI*
SAE	11	10 (1.85%)	8.31 (3.99, 15.29)
Infections and infestations	3	3 (0.55%)	2.48 (0.51, 7.26)
Otitis media	1	1 (0.18%)	0.83 (0.02, 4.61)
Pneumonia	1	1 (0.18%)	0.83 (0.02, 4.61)
Tonsillitis	1	1 (0.18%)	0.83 (0.02, 4.60)
Musculoskeletal and connective tissue disorders	3	3 (0.55%)	2.48 (0.51, 7.25)
Rheumatoid arthritis	2	2 (0.37%)	1.65 (0.20, 5.97)
Arthralgia	1	1 (0.18%)	0.83 (0.02, 4.60)
Ear and labyrinth disorders	1	1 (0.18%)	0.83 (0.02, 4.60)
Otolithiasis	1	1 (0.18%)	0.83 (0.02, 4.60)
Endocrine disorders	1	1 (0.18%)	0.83 (0.02, 4.61)

Footnote:CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; PT, preferred term; SAE, serious adverse event; SOC, system organ class
n is the number of patients and % is the percentage.
The SOCs are sorted by decreasing number of patients, while the PTs are sorted by decreasing number of patients within SOC.
MedDRA English version 25.1

SOC	*Safety Analyses Population (N=542)*		
PT	*Event*	*n (%)*	*EAIR and 95% CI*
Thyroid mass	1	1 (0.18%)	0.83 (0.02, 4.61)
Hepatobiliary disorders	1	1 (0.18%)	0.83 (0.02, 4.61)
Drug-induced liver injury	1	1 (0.18%)	0.83 (0.02, 4.61)
Nervous system disorders	1	1 (0.18%)	0.83 (0.02, 4.60)
Carotid artery aneurysm	1	1 (0.18%)	0.83 (0.02, 4.60)
Respiratory, thoracic and mediastinal disorders	1	1 (0.18%)	0.83 (0.02, 4.61)
Chronic obstructive pulmonary disease	1	1 (0.18%)	0.83 (0.02, 4.61)

Footnote:CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; PT, preferred term; SAE, serious adverse event; SOC, system organ class
n is the number of patients and % is the percentage.
The SOCs are sorted by decreasing number of patients, while the PTs are sorted by decreasing number of patients within SOC.
MedDRA English version 25.1

Table ANN. 310 SAEs over a Period of 12 Weeks— MedDRA Preferred Term by Decreasing Frequency, within System Organ Class (≥65 and <75 years, Safety Analyses Population)

SOC	*Safety Analyses Population (N=106)*		
PT	*Event*	*n (%)*	*EAIR and 95% CI*
SAE	11	11 (10.38%)	49.24 (24.58, 88.10)
Infections and infestations	3	3 (2.83%)	12.99 (2.68, 37.95)
Pneumonia	3	3 (2.83%)	12.99 (2.68, 37.95)
Gastrointestinal disorders	2	2 (1.89%)	8.65 (1.05, 31.25)
Ileus paralytic	1	1 (0.94%)	4.33 (0.11, 24.10)
Pancreatitis acute	1	1 (0.94%)	4.33 (0.11, 24.10)
Musculoskeletal and connective tissue disorders	2	2 (1.89%)	8.76 (1.06, 31.63)
Intervertebral disc protrusion	1	1 (0.94%)	4.37 (0.11, 24.33)
Rheumatoid arthritis	1	1 (0.94%)	4.34 (0.11, 24.16)
General disorders and administration site conditions	1	1 (0.94%)	4.33 (0.11, 24.10)
Death	1	1 (0.94%)	4.33 (0.11, 24.10)

Footnote:CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; PT, preferred term; SAE, serious adverse event; SOC, system organ class
n is the number of patients and % is the percentage.
The SOCs are sorted by decreasing number of patients, while the PTs are sorted by decreasing number of patients within SOC.
MedDRA English version 25.1

SOC / *PT*	*Safety Analyses Population (N=106)*		
	Event	*n (%)*	*EAIR and 95% CI*
Injury, poisoning and procedural complications	1	1 (0.94%)	4.35 (0.11, 24.25)
Lumbar vertebral fracture	1	1 (0.94%)	4.35 (0.11, 24.25)
Metabolism and nutrition disorders	1	1 (0.94%)	4.34 (0.11, 24.16)
Hyperkalaemia	1	1 (0.94%)	4.34 (0.11, 24.16)
Nervous system disorders	1	1 (0.94%)	4.38 (0.11, 24.38)
Optic neuritis	1	1 (0.94%)	4.38 (0.11, 24.38)

Footnote:CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; PT, preferred term; SAE, serious adverse event; SOC, system organ class
n is the number of patients and % is the percentage.
The SOCs are sorted by decreasing number of patients, while the PTs are sorted by decreasing number of patients within SOC.
MedDRA English version 25.1

Table ANN. 311 SAEs over a Period of 12 Weeks— MedDRA Preferred Term by Decreasing Frequency, within System Organ Class (≥75 years, Safety Analyses Population)

SOC / *PT*	*Safety Analyses Population (N=19)*		
	Event	*n (%)*	*EAIR and 95% CI*
SAE	1	1 (5.26%)	22.78 (0.58, 126.92)
Musculoskeletal and connective tissue disorders	1	1 (5.26%)	22.78 (0.58, 126.92)
Lumbar spinal stenosis	1	1 (5.26%)	22.78 (0.58, 126.92)

Footnote:CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; PT, preferred term; SAE, serious adverse event; SOC, system organ class
n is the number of patients and % is the percentage.
The SOCs are sorted by decreasing number of patients, while the PTs are sorted by decreasing number of patients within SOC.
MedDRA English version 25.1

Table ANN. 312 SAEs over a Period of 24 Weeks— MedDRA Preferred Term by Decreasing Frequency, within System Organ Class (<65 years, Safety Analyses Population)

SOC	*Safety Analyses Population (N=542)*		
PT	*Event*	*n (%)*	*EAIR and 95% CI*
SAE	19	16 (2.95%)	7.60 (4.34, 12.34)
Infections and infestations	5	5 (0.92%)	2.35 (0.76, 5.49)
Appendicitis	1	1 (0.18%)	0.47 (0.01, 2.62)
Influenza	1	1 (0.18%)	0.47 (0.01, 2.61)
Otitis media	1	1 (0.18%)	0.47 (0.01, 2.62)
Pneumonia	1	1 (0.18%)	0.47 (0.01, 2.62)
Tonsillitis	1	1 (0.18%)	0.47 (0.01, 2.61)
Musculoskeletal and connective tissue disorders	5	5 (0.92%)	2.35 (0.76, 5.49)
Arthralgia	2	2 (0.37%)	0.94 (0.11, 3.39)
Rheumatoid arthritis	2	2 (0.37%)	0.94 (0.11, 3.40)
Osteonecrosis	1	1 (0.18%)	0.47 (0.01, 2.62)
Ear and labyrinth disorders	1	1 (0.18%)	0.47 (0.01, 2.61)

Footnote:CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; PT, preferred term; SAE, serious adverse event; SOC, system organ class
n is the number of patients and % is the percentage.
The SOCs are sorted by decreasing number of patients, while the PTs are sorted by decreasing number of patients within SOC.
MedDRA English version 25.1

SOC	*Safety Analyses Population (N=542)*		
PT	*Event*	*n (%)*	*EAIR and 95% CI*
Otolithiasis	1	1 (0.18%)	0.47 (0.01, 2.61)
Endocrine disorders	1	1 (0.18%)	0.47 (0.01, 2.62)
Thyroid mass	1	1 (0.18%)	0.47 (0.01, 2.62)
Eye disorders	2	1 (0.18%)	0.47 (0.01, 2.62)
Cataract	2	1 (0.18%)	0.47 (0.01, 2.62)
Gastrointestinal disorders	1	1 (0.18%)	0.47 (0.01, 2.62)
Gastritis erosive	1	1 (0.18%)	0.47 (0.01, 2.62)
Hepatobiliary disorders	1	1 (0.18%)	0.47 (0.01, 2.62)
Drug-induced liver injury	1	1 (0.18%)	0.47 (0.01, 2.62)
Nervous system disorders	1	1 (0.18%)	0.47 (0.01, 2.61)

Footnote:CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; PT, preferred term; SAE, serious adverse event; SOC, system organ class
n is the number of patients and % is the percentage.
The SOCs are sorted by decreasing number of patients, while the PTs are sorted by decreasing number of patients within SOC.
MedDRA English version 25.1

SOC	*Safety Analyses Population (N=542)*		
PT	*Event*	*n (%)*	*EAIR and 95% CI*
Carotid artery aneurysm	1	1 (0.18%)	0.47 (0.01, 2.61)
Pregnancy, puerperium and perinatal conditions	1	1 (0.18%)	0.47 (0.01, 2.61)
Abortion threatened	1	1 (0.18%)	0.47 (0.01, 2.61)
Respiratory, thoracic and mediastinal disorders	1	1 (0.18%)	0.47 (0.01, 2.62)
Chronic obstructive pulmonary disease	1	1 (0.18%)	0.47 (0.01, 2.62)

Footnote:CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; PT, preferred term; SAE, serious adverse event; SOC, system organ class
n is the number of patients and % is the percentage.
The SOCs are sorted by decreasing number of patients, while the PTs are sorted by decreasing number of patients within SOC.
MedDRA English version 25.1

Table ANN. 313 SAEs over a Period of 24 Weeks— MedDRA Preferred Term by Decreasing Frequency, within System Organ Class (≥65 and <75 years, Safety Analyses Population)

SOC / *PT*	*Safety Analyses Population (N=106)*		
	Event	*n (%)*	*EAIR and 95% CI*
SAE	11	11 (10.38%)	28.06 (14.01, 50.21)
Infections and infestations	3	3 (2.83%)	7.37 (1.52, 21.54)
Pneumonia	3	3 (2.83%)	7.37 (1.52, 21.54)
Gastrointestinal disorders	2	2 (1.89%)	4.89 (0.59, 17.66)
Ileus paralytic	1	1 (0.94%)	2.44 (0.06, 13.62)
Pancreatitis acute	1	1 (0.94%)	2.44 (0.06, 13.62)
Musculoskeletal and connective tissue disorders	2	2 (1.89%)	4.95 (0.60, 17.87)
Intervertebral disc protrusion	1	1 (0.94%)	2.47 (0.06, 13.76)
Rheumatoid arthritis	1	1 (0.94%)	2.45 (0.06, 13.64)
General disorders and administration site conditions	1	1 (0.94%)	2.44 (0.06, 13.62)
Death	1	1 (0.94%)	2.44 (0.06, 13.62)

Footnote:CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; PT, preferred term; SAE, serious adverse event; SOC, system organ class
n is the number of patients and % is the percentage.
The SOCs are sorted by decreasing number of patients, while the PTs are sorted by decreasing number of patients within SOC.
MedDRA English version 25.1

SOC / *PT*	*Safety Analyses Population (N=106)*		
	Event	*n (%)*	*EAIR and 95% CI*
Injury, poisoning and procedural complications	1	1 (0.94%)	2.46 (0.06, 13.70)
Lumbar vertebral fracture	1	1 (0.94%)	2.46 (0.06, 13.70)
Metabolism and nutrition disorders	1	1 (0.94%)	2.46 (0.06, 13.73)
Hyperkalaemia	1	1 (0.94%)	2.46 (0.06, 13.73)
Nervous system disorders	1	1 (0.94%)	2.47 (0.06, 13.76)
Optic neuritis	1	1 (0.94%)	2.47 (0.06, 13.76)

Footnote:CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; PT, preferred term; SAE, serious adverse event; SOC, system organ class
n is the number of patients and % is the percentage.
The SOCs are sorted by decreasing number of patients, while the PTs are sorted by decreasing number of patients within SOC.
MedDRA English version 25.1

Table ANN. 314 SAEs over a Period of 24 Weeks— MedDRA Preferred Term by Decreasing Frequency, within System Organ Class (≥75 years, Safety Analyses Population)

SOC PT	Safety Analyses Population (N=19) Event	 n (%)	 EAIR and 95% CI
SAE	1	1 (5.26%)	14.51 (0.37, 80.87)
Musculoskeletal and connective tissue disorders	1	1 (5.26%)	14.51 (0.37, 80.87)
Lumbar spinal stenosis	1	1 (5.26%)	14.51 (0.37, 80.87)

Footnote:CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; PT, preferred term; SAE, serious adverse event; SOC, system organ class
n is the number of patients and % is the percentage.
The SOCs are sorted by decreasing number of patients, while the PTs are sorted by decreasing number of patients within SOC.
MedDRA English version 25.1

Table ANN. 315 Demographics (1st dosage subgroups, Safety Analyses Population)

		Safety Analyses Population			
		2 mg only (N=580)	*4 mg only (N=53)*	*both dosages (N=34)*	*P value*
Age (years)	n (nmiss)	580 (0)	53 (0)	34 (0)	0.0793
	Mean (Std)	53.66 (12.47)	50.49 (11.01)	50.47 (14.69)	
	Median	55.00	52.00	53.00	
	Q1, Q3	46.50, 63.00	41.00, 59.00	40.00, 58.00	
	Min, Max	20, 85	29, 74	21, 84	
	18-34	50 (8.62%)	5 (9.43%)	6 (17.65%)	0.2288[a]
	35-44	75 (12.93%)	11 (20.75%)	6 (17.65%)	
	45-64	340 (58.62%)	33 (62.26%)	16 (47.06%)	
	65-74	97 (16.72%)	4 (7.55%)	5 (14.71%)	
	>=75	18 (3.10%)	0	1 (2.94%)	
	Total	580 (100.00%)	53 (100.00%)	34 (100.00%)	
Sex	Male	99 (17.07%)	13 (24.53%)	6 (17.65%)	0.3923[b]
	Female	481 (82.93%)	40 (75.47%)	28 (82.35%)	
	Total	580 (100.00%)	53 (100.00%)	34 (100.00%)	
Height (cm)	n (nmiss)	579 (1)	53 (0)	34 (0)	0.0513
	Mean (Std)	160.15 (6.89)	161.24 (6.47)	162.12 (5.96)	
	Median	160.00	160.00	161.50	
	Q1, Q3	156.00, 163.00	157.00, 166.00	158.00, 166.00	
	Min, Max	142, 198	148, 178	150, 175	
Weight (kg)	n (nmiss)	579 (1)	53 (0)	34 (0)	0.2321
	Mean (Std)	57.21 (9.94)	59.02 (10.65)	59.69 (11.27)	
	Median	56.00	58.00	60.00	
	Q1, Q3	50.00, 64.00	50.00, 66.00	50.00, 64.00	
	Min, Max	27.0, 101.0	39.0, 90.0	42.0, 90.0	
BMI (kg/m^2)	n (nmiss)	579 (1)	53 (0)	34 (0)	0.7076
	Mean (Std)	22.27 (3.38)	22.66 (3.60)	22.65 (3.75)	
	Median	21.76	22.60	22.40	
	Q1, Q3	19.84, 24.22	19.53, 25.10	19.61, 24.97	
	Min, Max	12.84, 39.45	17.54, 31.14	18.18, 34.77	
	<18.5	61 (10.54%)	10 (18.87%)	5 (14.71%)	0.2904[a]
	>=18.5-<24	357 (61.66%)	24 (45.28%)	18 (52.94%)	
	>=24-<28	128 (22.11%)	15 (28.30%)	8 (23.53%)	
	>=28	33 (5.70%)	4 (7.55%)	3 (8.82%)	
	Total	579 (100.00%)	53 (100.00%)	34 (100.00%)	
	Missing	1	0	0	
Smoking history	Never smoking	515 (88.79%)	42 (79.25%)	28 (82.35%)	0.1223[b]
	Used to smoke, given up now	22 (3.79%)	5 (9.43%)	2 (5.88%)	
	Still smoking	43 (7.41%)	6 (11.32%)	4 (11.76%)	
	Total	580 (100.00%)	53 (100.00%)	34 (100.00%)	

Footnote: The smoking history information were from 'Life History' page in CRF.

N, number of patients in population; nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.
The percentage denominator is the number of patients with non-missing value.
P values for continuous values were from Wilcoxon rank sum test.
a:P values for categorical values were from Chi-squared test. b:P values for categorical values were from Fisher exact tests.
Both dosages subgroup includes 2 mg to 4 mg and other mixed dosage subgroups.

Table ANN. 316 Demographics (2nd dosage subgroups, Safety Analyses Population)

		Safety Analyses Population				
		2 mg only (N=580)	*4 mg only (N=53)*	*2mg to 4mg (N=14)*	*other mixed dosage (N=20)*	*P value*
Age (years)	n (nmiss)	580 (0)	53 (0)	14 (0)	20 (0)	0.0603
	Mean (Std)	53.66 (12.47)	50.49 (11.01)	47.29 (15.36)	52.70 (14.16)	
	Median	55.00	52.00	49.00	55.00	
	Q1, Q3	46.50, 63.00	41.00, 59.00	40.00, 55.00	40.50, 65.50	
	Min, Max	20, 85	29, 74	21, 84	25, 71	
	18-34	50 (8.62%)	5 (9.43%)	3 (21.43%)	3 (15.00%)	0.1952[a]
	35-44	75 (12.93%)	11 (20.75%)	3 (21.43%)	3 (15.00%)	
	45-64	340 (58.62%)	33 (62.26%)	7 (50.00%)	9 (45.00%)	
	65-74	97 (16.72%)	4 (7.55%)	0	5 (25.00%)	
	>=75	18 (3.10%)	0	1 (7.14%)	0	
	Total	580 (100.00%)	53 (100.00%)	14 (100.00%)	20 (100.00%)	
Sex	Male	99 (17.07%)	13 (24.53%)	2 (14.29%)	4 (20.00%)	0.5356[b]
	Female	481 (82.93%)	40 (75.47%)	12 (85.71%)	16 (80.00%)	
	Total	580 (100.00%)	53 (100.00%)	14 (100.00%)	20 (100.00%)	
Height (cm)	n (nmiss)	579 (1)	53 (0)	14 (0)	20 (0)	0.1005
	Mean (Std)	160.15 (6.89)	161.24 (6.47)	162.86 (5.80)	161.60 (6.17)	
	Median	160.00	160.00	163.00	160.50	
	Q1, Q3	156.00, 163.00	157.00, 166.00	159.00, 167.00	158.00, 165.50	
	Min, Max	142, 198	148, 178	152, 173	150, 175	
Weight (kg)	n (nmiss)	579 (1)	53 (0)	14 (0)	20 (0)	0.3333
	Mean (Std)	57.21 (9.94)	59.02 (10.65)	59.07 (13.09)	60.13 (10.16)	
	Median	56.00	58.00	57.00	60.00	
	Q1, Q3	50.00, 64.00	50.00, 66.00	49.00, 65.00	53.00, 63.25	
	Min, Max	27.0, 101.0	39.0, 90.0	42.0, 90.0	46.5, 89.0	
BMI (kg/m^2)	n (nmiss)	579 (1)	53 (0)	14 (0)	20 (0)	0.6731
	Mean (Std)	22.27 (3.38)	22.66 (3.60)	22.15 (4.01)	23.00 (3.61)	
	Median	21.76	22.60	21.31	22.40	
	Q1, Q3	19.84, 24.22	19.53, 25.10	18.36, 24.13	20.88, 24.99	
	Min, Max	12.84, 39.45	17.54, 31.14	18.18, 30.07	18.29, 34.77	
	<18.5	61 (10.54%)	10 (18.87%)	4 (28.57%)	1 (5.00%)	0.1312[a]
	>=18.5-<24	357 (61.66%)	24 (45.28%)	5 (35.71%)	13 (65.00%)	
	>=24-<28	128 (22.11%)	15 (28.30%)	3 (21.43%)	5 (25.00%)	
	>=28	33 (5.70%)	4 (7.55%)	2 (14.29%)	1 (5.00%)	
	Total	579 (100.00%)	53 (100.00%)	14 (100.00%)	20 (100.00%)	
	Missing	1	0	0	0	
Smoking history	Never smoking	515 (88.79%)	42 (79.25%)	12 (85.71%)	16 (80.00%)	0.1574[b]

Used to smoke, given up now	22 (3.79%)	5 (9.43%)	1 (7.14%)	1 (5.00%)
Still smoking	43 (7.41%)	6 (11.32%)	1 (7.14%)	3 (15.00%)
Total	580 (100.00%)	53 (100.00%)	14 (100.00%)	20 (100.00%)

Footnote: The smoking history information were from 'Life History' page in CRF.
N, number of patients in population; nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.
The percentage denominator is the number of patients with non-missing value.
P values for continuous values were from Wilcoxon rank sum test.
a:P values for categorical values were from Chi-squared test. b:P values for categorical values were from Fisher exact tests.

Table ANN. 317 **Rheumatoid Arthritis Diagnosis (1st Dosage Subgroups, Safety Analyses Population)**

		Safety Analyses Population			
		2 mg only (N=580)	*4 mg only (N=53)*	*both dosages (N=34)*	*P value*
Months from the onset date of RA to ICF (months)	n (nmiss)	580 (0)	53 (0)	34 (0)	0.9399
	Mean (Std)	102.97 (105.75)	98.80 (98.35)	89.79 (88.47)	
	Median	63.13	67.61	47.10	
	Q1, Q3	23.54, 145.61	18.40, 145.58	24.80, 148.96	
	Min, Max	0, 623.67	0.95, 360.48	3.22, 360.15	
Duration of RA (months)	n (nmiss)	580 (0)	53 (0)	34 (0)	0.8062
	Mean (Std)	88.01 (101.35)	81.71 (93.40)	76.30 (86.05)	
	Median	48.25	43.56	41.40	
	Q1, Q3	14.25, 128.89	12.02, 116.80	14.19, 131.19	
	Min, Max	0, 623.67	0, 360.48	0, 360.15	
	<=1 year	124 (21.38%)	13 (24.53%)	7 (20.59%)	0.9726[a]
	>1-<=3 years	119 (20.52%)	12 (22.64%)	9 (26.47%)	
	>3-<=10 years	179 (30.86%)	15 (28.30%)	9 (26.47%)	
	>10 years	158 (27.24%)	13 (24.53%)	9 (26.47%)	
	Total	580 (100.00%)	53 (100.00%)	34 (100.00%)	
Meet the ACR/EULAR 2010 criteria and number of points	Yes	580 (100.00%)	53 (100.00%)	34 (100.00%)	NA[b]
	n (nmiss)	580 (0)	53 (0)	34 (0)	
	Mean (Std)	8.38 (1.49)	7.94 (1.57)	8.41 (1.58)	
	Median	8.00	8.00	8.00	
	Q1, Q3	7.00, 10.00	6.00, 10.00	7.00, 10.00	
	Min, Max	6, 10	6, 10	6, 10	
	Total	580 (100.00%)	53 (100.00%)	34 (100.00%)	

Footnote: The duration of RA (months) = (Date of informed consent – date of diagnosis of RA) / 30.4375, round to 2 decimal place. Months from the onset date of RA to ICF (months) = (Date of informed consent – the onset date of RA) / 30.4375, round to 2 decimal place.
N, number of patients in population; nmiss, no. of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range. The percentage denominator is the number of patients with non-missing value.
P values for continuous values were from Wilcoxon rank sum test.
a:P values for categorical values were from Chi-squared test. b:P values for categorical values were from Fisher exact tests.
Both dosages subgroup includes 2 mg to 4 mg and other mixed dosage subgroups.

Table ANN. 318 Rheumatoid Arthritis Diagnosis (2nd Dosage Subgroups, Safety Analyses Population)

		Safety Analyses Population				
		2 mg only (N=580)	*4 mg only (N=53)*	*2mg to 4mg (N=14)*	*other mixed dosage (N=20)*	*P value*
Months from the onset date of RA to ICF (months)	n (nmiss)	580 (0)	53 (0)	14 (0)	20 (0)	0.9839
	Mean (Std)	102.97 (105.75)	98.80 (98.35)	86.53 (78.83)	92.07 (96.59)	
	Median	63.13	67.61	65.41	37.97	
	Q1, Q3	23.54, 145.61	18.40, 145.58	30.88, 110.78	22.95, 155.76	
	Min, Max	0, 623.67	0.95, 360.48	6.24, 277.68	3.22, 360.15	
Duration of RA (months)	n (nmiss)	580 (0)	53 (0)	14 (0)	20 (0)	0.8457
	Mean (Std)	88.01 (101.35)	81.71 (93.40)	80.52 (79.20)	73.35 (92.44)	
	Median	48.25	43.56	54.53	32.27	
	Q1, Q3	14.25, 128.89	12.02, 116.80	24.54, 110.78	13.68, 140.08	
	Min, Max	0, 623.67	0, 360.48	3.12, 262.70	0, 360.15	
	<=1 year	124 (21.38%)	13 (24.53%)	3 (21.43%)	4 (20.00%)	0.8076[a]
	>1-<=3 years	119 (20.52%)	12 (22.64%)	2 (14.29%)	7 (35.00%)	
	>3-<=10 years	179 (30.86%)	15 (28.30%)	6 (42.86%)	3 (15.00%)	
	>10 years	158 (27.24%)	13 (24.53%)	3 (21.43%)	6 (30.00%)	
	Total	580 (100.00%)	53 (100.00%)	14 (100.00%)	20 (100.00%)	
Meet the ACR/EULAR 2010 criteria and number of points	Yes	580 (100.00%)	53 (100.00%)	14 (100.00%)	20 (100.00%)	NA[b]
	n (nmiss)	580 (0)	53 (0)	14 (0)	20 (0)	
	Mean (Std)	8.38 (1.49)	7.94 (1.57)	8.50 (1.45)	8.35 (1.69)	
	Median	8.00	8.00	8.00	8.50	
	Q1, Q3	7.00, 10.00	6.00, 10.00	7.00, 10.00	7.00, 10.00	
	Min, Max	6, 10	6, 10	6, 10	6, 10	
	Total	580 (100.00%)	53 (100.00%)	14 (100.00%)	20 (100.00%)	

Footnote: The duration of RA (months) = (Date of informed consent – date of diagnosis of RA) / 30.4375, round to 2 decimal place. Months from the onset date of RA to ICF (months) = (Date of informed consent – the onset date of RA) / 30.4375, round to 2 decimal place.
N, number of patients in population; nmiss, no. of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range. The percentage denominator is the number of patients with non-missing value.
P values for continuous values were from Wilcoxon rank sum test.
a:P values for categorical values were from Chi-squared test. b:P values for categorical values were from Fisher exact tests.

Table ANN. 319 **Drug Exposure (1st Dosage Subgroups, Safety Analyses Population)**

		Safety Analyses Population			
		2 mg only (N=580)	*4 mg only years (N=53)*	*Both dosages (N=34)*	*P value*
Overall Olumiant exposure (days)	n (nmiss)	578 (2)	53 (0)	34 (0)	0.3958
	Mean (Std)	144.94 (56.36)	128.92 (64.47)	150.44 (42.96)	
	Median	168.00	156.00	165.50	
	Q1, Q3	128.00, 179.00	70.00, 181.00	140.00, 172.00	
	Min, Max	1, 314	5, 252	55, 203	
Olumiant exposure (days)	n (nmiss)	578 (2)	53 (0)	34 (0)	0.4354
	Mean (Std)	143.10 (56.53)	128.00 (64.27)	148.71 (42.40)	
	Median	167.00	156.00	165.00	
	Q1, Q3	121.00, 177.00	70.00, 181.00	140.00, 172.00	
	Min, Max	1, 314	5, 249	55, 203	
Total patient year exposure		229.4	18.7	14.0	
Number of patients administered only 2mg Olumiant	n (%)	580 (100.00%)	0	0	<.0001
Number of patients administered only 4mg Olumiant	n (%)	0	53 (100.00%)	0	<.0001
Number of patients administered mixed dosage of Olumiant	n (%)	0	0	34 (100.00%)	<.0001

Footnote: N, number of patients in population; nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.
Overall Olumiant exposure (days) = Olumiant discontinue date in study termination page – the earliest start date of treatment in treatment information page +1.
Olumiant exposure (days) = sum of (end date of treatment - start date of treatment +1). The start and end date of treatment are from the same record in treatment information page.
The sum are based on all records in this page.
Total patient year exposure = sum of all patients' year exposure. Patient year exposure = overall Olumiant exposure in days for the patient / 365.25, keep 1 decimal place.
P values for continuous values were from Wilcoxon rank sum test. P values for categorical values were from Fisher exact tests.
Both dosages subgroup includes 2 mg to 4 mg and other mixed dosage subgroups.

Table ANN. 320 **Drug Exposure (2nd Dosage Subgroups, Safety Analyses Population)**

		Safety Analyses Population				
		2 mg only (N=580)	*4 mg only (N=53)*	*2mg to 4mg (N=14)*	*other mixed dosage (N=20)*	*P value*
Overall Olumiant exposure (days)	n (nmiss)	578 (2)	53 (0)	14 (0)	20 (0)	0.5472
	Mean (Std)	144.94 (56.36)	128.92 (64.47)	142.79 (48.82)	155.80 (38.74)	
	Median	168.00	156.00	163.50	165.50	
	Q1, Q3	128.00, 179.00	70.00, 181.00	85.00, 171.00	155.00, 175.00	
	Min, Max	1, 314	5, 252	61, 203	55, 202	
Olumiant exposure (days)	n (nmiss)	578 (2)	53 (0)	14 (0)	20 (0)	0.6188
	Mean (Std)	143.10 (56.53)	128.00 (64.27)	141.50 (48.06)	153.75 (38.43)	
	Median	167.00	156.00	163.50	165.00	
	Q1, Q3	121.00, 177.00	70.00, 181.00	85.00, 172.00	146.00, 170.50	
	Min, Max	1, 314	5, 249	58, 203	55, 203	
Total patient year exposure		229.4	18.7	5.5	8.5	
Number of patients administered only 2mg Olumiant	n (%)	580 (100.00%)	0	0	0	<.0001
Number of patients administered only 4mg Olumiant	n (%)	0	53 (100.00%)	0	0	<.0001
Number of patients administered mixed dosage of Olumiant	n (%)	0	0	14 (100.00%)	20 (100.00%)	<.0001

Footnote: N, number of patients in population; nmiss, number of data missing patients; Std, standard deviation, Q1 and Q3, interquartile range.
Overall Olumiant exposure (days) = Olumiant discontinue date in study termination page – the earliest start date of treatment in treatment information page +1.
Olumiant exposure (days) = sum of (end date of treatment - start date of treatment +1). The start and end date of treatment are from the same record in treatment information page.
The sum are based on all records in this page.
Total patient year exposure = sum of all patients' year exposure. Patient year exposure = overall Olumiant exposure in days for the patient / 365.25, keep 1 decimal place.
P values for continuous values were from Wilcoxon rank sum test. P values for categorical values were from Fisher exact tests.

Table ANN. 321 AE Summary (1st Dosage Subgroups, Safety Analyses Population)

		Safety Analyses Population (N=667)						
	Dosage subgroup	*Event*	*n*	*Patient-year of observation time*	*Patient-year of exposure time*	*Percentage and 95% CI*	*Incidence rate and 95% CI*	*EAIR and 95% CI*
AEs over a period of 12 weeks	2 mg only (Nx=580)	272	187	112.69	108.11	32.24% (28.45%, 36.21%)	165.94 (143.01, 191.51)	172.97 (149.07, 199.62)
	4 mg only (Nx=53)	24	14	10.62	9.83	26.42% (15.26%, 40.33%)	131.83 (72.07, 221.18)	142.42 (77.86, 238.96)
	both dosages (Nx=34)	33	13	6.25	6.09	38.24% (22.17%, 56.44%)	208.00 (110.75, 355.69)	213.46 (113.66, 365.03)
AEs over a period of 24 weeks	2 mg only (Nx=580)	357	221	181.91	173.71	38.10% (34.13%, 42.19%)	121.49 (106.00, 138.61)	127.22 (111.00, 145.15)
	4 mg only (Nx=53)	28	14	16.60	15.45	26.42% (15.26%, 40.33%)	84.34 (46.11, 141.50)	90.61 (49.54, 152.04)
	both dosages (Nx=34)	43	15	10.04	9.42	44.12% (27.19%, 62.11%)	149.40 (83.62, 246.42)	159.24 (89.12, 262.64)
AEs related to study treatment as judged by the investigator over a period of 12 weeks	2 mg only (Nx=580)	98	84	127.59	121.79	14.48% (11.72%, 17.61%)	65.84 (52.51, 81.51)	68.97 (55.01, 85.39)
	4 mg only (Nx=53)	5	3	12.01	11.09	5.66% (1.18%, 15.66%)	24.98 (5.15, 73.00)	27.05 (5.58, 79.06)
	both dosages (Nx=34)	8	8	7.27	7.11	23.53% (10.75%, 41.17%)	110.04 (47.51, 216.83)	112.52 (48.58, 221.70)

Footnote: The number of event for each patient counts the event which happened during the 12-weeks/ 24-weeks observation time. The percentage denominator is the number of analyses population and the numerator is the number of patients with corresponding events.

AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; n, the number of patients with events; SAE, serious adverse event.

The percentage of AEs/SAEs over a period of 12/24 weeks = Number of patients with at least one AE/SAE over a period of 12/24 weeks ÷number of patients in safety analyses population ×100, results round to 2 decimal places.

The incidence rates of AEs/SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ observation time

of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places. The EAIR of AEs /SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at

least one AE/SAE over an observation period of 12/24 weeks ÷ overall exposure time of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.

The calculation of observation time and exposure time could refer to definition in the main body of SAP.

AEs related to study treatment as judged by the investigator are the AEs whose relationship with olumiant are not 'No'. Drug adjustment includes dose increase, dose reduce and temporary discontinuation.

Death is from SAE which the reason is death or AE whose outcome is fatal or death recorded in the page of study termination. Both dosages subgroup includes 2 mg to 4 mg and other mixed dosage subgroups.

		Safety Analyses Population (N=667)						
	Dosage subgroup	*Event*	*n*	*Patient-year of observation time*	*Patient-year of exposure time*	*Percentage and 95% CI*	*Incidence rate and 95% CI*	*EAIR and 95% CI*
AEs related to study treatment as judged by the investigator over a period of 24 weeks	2 mg only (Nx=580)	130	108	217.24	206.58	18.62% (15.53%, 22.03%)	49.71 (40.78, 60.02)	52.28 (42.89, 63.12)
	4 mg only (Nx=53)	6	4	19.58	18.26	7.55% (2.09%, 18.21%)	20.43 (5.57, 52.31)	21.91 (5.97, 56.09)
	both dosages (Nx=34)	11	8	12.43	11.81	23.53% (10.75%, 41.17%)	64.36 (27.79, 126.82)	67.74 (29.24, 133.47)
Death	2 mg only (Nx=580)	2	2	241.47	228.59	0.34% (0.04%, 1.24%)	0.83 (0.10, 2.99)	0.87 (0.11, 3.16)
	4 mg only (Nx=53)	0	0	20.27	18.71	0.00% (0%, 6.72%)	0.00 (NA, 18.20)	0.00 (NA, 19.72)
	both dosages (Nx=34)	0	0	14.70	14.00	0.00% (0%, 10.28%)	0.00 (NA, 25.09)	0.00 (NA, 26.35)
SAEs over a period of 12 weeks	2 mg only (Nx=580)	18	17	135.13	128.62	2.93% (1.72%, 4.65%)	12.58 (7.33, 20.14)	13.22 (7.70, 21.16)
	4 mg only (Nx=53)	3	3	11.91	10.87	5.66% (1.18%, 15.66%)	25.19 (5.19, 73.61)	27.60 (5.69, 80.66)

Footnote: The number of event for each patient counts the event which happened during the 12-weeks/ 24-weeks observation time. The percentage denominator is the number of analyses population and the numerator is the number of patients with corresponding events.
AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; n, the number of patients with events; SAE, serious adverse event.
The percentage of AEs/SAEs over a period of 12/24 weeks = Number of patients with at least one AE/SAE over a period of 12/24 weeks ÷number of patients in safety analyses population ×100, results round to 2 decimal places.
The incidence rates of AEs/SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ observation time
of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places. The EAIR of AEs /SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at
least one AE/SAE over an observation period of 12/24 weeks ÷ overall exposure time of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The calculation of observation time and exposure time could refer to definition in the main body of SAP.
AEs related to study treatment as judged by the investigator are the AEs whose relationship with olumiant are not 'No'. Drug adjustment includes dose increase, dose reduce and temporary discontinuation.
Death is from SAE which the reason is death or AE whose outcome is fatal or death recorded in the page of study termination. Both dosages subgroup includes 2 mg to 4 mg and other mixed dosage subgroups.

		Safety Analyses Population (N=667)						
	Dosage subgroup	*Event*	*n*	*Patient-year of observation time*	*Patient-year of exposure time*	*Percentage and 95% CI*	*Incidence rate and 95% CI*	*EAIR and 95% CI*
	both dosages (Nx=34)	2	2	7.70	7.54	5.88% (0.72%, 19.68%)	25.97 (3.15, 93.83)	26.53 (3.21, 95.82)
SAEs over a period of 24 weeks	2 mg only (Nx=580)	24	23	237.58	225.52	3.97% (2.53%, 5.89%)	9.68 (6.14, 14.53)	10.20 (6.47, 15.30)
	4 mg only (Nx=53)	5	3	19.23	17.69	5.66% (1.18%, 15.66%)	15.60 (3.22, 45.59)	16.96 (3.50, 49.56)
	both dosages (Nx=34)	2	2	14.13	13.51	5.88% (0.72%, 19.68%)	14.15 (1.71, 51.13)	14.80 (1.79, 53.48)
SAEs related to study treatment as judged by the investigator over a period of 12 weeks	2 mg only (Nx=580)	6	6	136.22	129.37	1.03% (0.38%, 2.24%)	4.40 (1.62, 9.59)	4.64 (1.70, 10.09)
	4 mg only (Nx=53)	1	1	12.30	11.25	1.89% (0.05%, 10.07%)	8.13 (0.21, 45.30)	8.89 (0.23, 49.53)
	both dosages (Nx=34)	1	1	7.86	7.70	2.94% (0.07%, 15.33%)	12.72 (0.32, 70.89)	12.99 (0.33, 72.36)
SAEs related to study treatment as judged by the investigator over a period of 24 weeks	2 mg only (Nx=580)	8	8	240.40	227.69	1.38% (0.60%, 2.70%)	3.33 (1.44, 6.56)	3.51 (1.52, 6.92)

Footnote: The number of event for each patient counts the event which happened during the 12-weeks/ 24-weeks observation time. The percentage denominator is the number of analyses population and the numerator is the number of patients with corresponding events.

AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; n, the number of patients with events; SAE, serious adverse event.

The percentage of AEs/SAEs over a period of 12/24 weeks = Number of patients with at least one AE/SAE over a period of 12/24 weeks ÷number of patients in safety analyses population ×100, results round to 2 decimal places.

The incidence rates of AEs/SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ observation time

of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places. The EAIR of AEs /SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at

least one AE/SAE over an observation period of 12/24 weeks ÷ overall exposure time of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.

The calculation of observation time and exposure time could refer to definition in the main body of SAP.

AEs related to study treatment as judged by the investigator are the AEs whose relationship with olumiant are not 'No'. Drug adjustment includes dose increase, dose reduce and temporary discontinuation.

Death is from SAE which the reason is death or AE whose outcome is fatal or death recorded in the page of study termination. Both dosages subgroup includes 2 mg to 4 mg and other mixed dosage subgroups.

		Safety Analyses Population (N=667)						
	Dosage subgroup	*Event*	*n*	*Patient-year of observation time*	*Patient-year of exposure time*	*Percentage and 95% CI*	*Incidence rate and 95% CI*	*EAIR and 95% CI*
	4 mg only (Nx=53)	1	1	20.25	18.71	1.89% (0.05%, 10.07%)	4.94 (0.13, 27.51)	5.34 (0.14, 29.78)
	both dosages (Nx=34)	1	1	14.52	13.91	2.94% (0.07%, 15.33%)	6.89 (0.17, 38.37)	7.19 (0.18, 40.05)
AEs leading to drug adjustment over a period of 12 weeks	2 mg only (Nx=580)	31	26	132.98	126.45	4.48% (2.95%, 6.50%)	19.55 (12.77, 28.65)	20.56 (13.43, 30.13)
	4 mg only (Nx=53)	2	1	12.21	11.21	1.89% (0.05%, 10.07%)	8.19 (0.21, 45.63)	8.92 (0.23, 49.70)
	both dosages (Nx=34)	3	3	7.79	7.55	8.82% (1.86%, 23.68%)	38.51 (7.94, 112.55)	39.74 (8.19, 116.12)
AEs leading to drug adjustment over a period of 24 weeks	2 mg only (Nx=580)	39	34	233.67	221.80	5.86% (4.09%, 8.10%)	14.55 (10.08, 20.33)	15.33 (10.62, 21.42)
	4 mg only (Nx=53)	3	2	19.98	18.58	3.77% (0.46%, 12.98%)	10.01 (1.21, 36.16)	10.76 (1.30, 38.88)
	both dosages (Nx=34)	3	3	13.78	13.08	8.82% (1.86%, 23.68%)	21.77 (4.49, 63.62)	22.94 (4.73, 67.03)

Footnote: The number of event for each patient counts the event which happened during the 12-weeks/ 24-weeks observation time. The percentage denominator is the number of analyses population and the numerator is the number of patients with corresponding events.
AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; n, the number of patients with events; SAE, serious adverse event.
The percentage of AEs/SAEs over a period of 12/24 weeks = Number of patients with at least one AE/SAE over a period of 12/24 weeks ÷number of patients in safety analyses population ×100, results round to 2 decimal places.
The incidence rates of AEs/SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ observation time
of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places. The EAIR of AEs /SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at
least one AE/SAE over an observation period of 12/24 weeks ÷ overall exposure time of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The calculation of observation time and exposure time could refer to definition in the main body of SAP.
AEs related to study treatment as judged by the investigator are the AEs whose relationship with olumiant are not 'No'. Drug adjustment includes dose increase, dose reduce and temporary discontinuation.
Death is from SAE which the reason is death or AE whose outcome is fatal or death recorded in the page of study termination. Both dosages subgroup includes 2 mg to 4 mg and other mixed dosage subgroups.

		Safety Analyses Population (N=667)						
	Dosage subgroup	*Event*	*n*	*Patient-year of observation time*	*Patient-year of exposure time*	*Percentage and 95% CI*	*Incidence rate and 95% CI*	*EAIR and 95% CI*
AEs leading to drug permanent discontinuation over a period of 12 weeks	2 mg only (Nx=580)	18	16	135.21	129.15	2.76% (1.58%, 4.44%)	11.83 (6.76, 19.22)	12.39 (7.08, 20.12)
	4 mg only (Nx=53)	4	4	12.12	11.24	7.55% (2.09%, 18.21%)	33.00 (8.99, 84.50)	35.59 (9.70, 91.12)
	both dosages (Nx=34)	0	0	8.04	7.80	0.00% (0%, 10.28%)	0.00 (NA, 45.88)	0.00 (NA, 47.29)
AEs leading to drug permanent discontinuation over a period of 24 weeks	2 mg only (Nx=580)	22	20	239.67	228.09	3.45% (2.12%, 5.28%)	8.34 (5.10, 12.89)	8.77 (5.36, 13.54)
	4 mg only (Nx=53)	4	4	20.07	18.69	7.55% (2.09%, 18.21%)	19.93 (5.43, 51.03)	21.40 (5.83, 54.80)
	both dosages (Nx=34)	0	0	14.70	14.00	0.00% (0%, 10.28%)	0.00 (NA, 25.09)	0.00 (NA, 26.35)

Footnote: The number of event for each patient counts the event which happened during the 12-weeks/ 24-weeks observation time. The percentage denominator is the number of analyses population and the numerator is the number of patients with corresponding events.
AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; n, the number of patients with events; SAE, serious adverse event.
The percentage of AEs/SAEs over a period of 12/24 weeks = Number of patients with at least one AE/SAE over a period of 12/24 weeks ÷number of patients in safety analyses population ×100, results round to 2 decimal places.
The incidence rates of AEs/SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ observation time
of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places. The EAIR of AEs /SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at
least one AE/SAE over an observation period of 12/24 weeks ÷ overall exposure time of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The calculation of observation time and exposure time could refer to definition in the main body of SAP.
AEs related to study treatment as judged by the investigator are the AEs whose relationship with olumiant are not 'No'. Drug adjustment includes dose increase, dose reduce and temporary discontinuation.
Death is from SAE which the reason is death or AE whose outcome is fatal or death recorded in the page of study termination. Both dosages subgroup includes 2 mg to 4 mg and other mixed dosage subgroups.

Table ANN. 322 AE Summary (2nd Dosage Subgroups, Safety Analyses Population)

		Safety Analyses Population (N=667)						
	Dosage subgroup	*Event*	*n*	*Patient-year of observation time*	*Patient-year of exposure time*	*Percentage and 95% CI*	*Incidence rate and 95% CI*	*EAIR and 95% CI*
AEs over a period of 12 weeks	2 mg only (Nx=580)	272	187	112.69	108.11	32.24% (28.45%, 36.21%)	165.94 (143.01, 191.51)	172.97 (149.07, 199.62)
	4 mg only (Nx=53)	24	14	10.62	9.83	26.42% (15.26%, 40.33%)	131.83 (72.07, 221.18)	142.42 (77.86, 238.96)
	2 mg to 4 mg (Nx=14)	17	6	2.06	2.02	42.86% (17.66%, 71.14%)	291.26 (106.89, 633.96)	297.03 (109.00, 646.51)
	other mixed dosage (Nx=20)	16	7	4.19	4.07	35.00% (15.39%, 59.22%)	167.06 (67.17, 344.22)	171.99 (69.15, 354.37)
AEs over a period of 24 weeks	2 mg only (Nx=580)	357	221	181.91	173.71	38.10% (34.13%, 42.19%)	121.49 (106.00, 138.61)	127.22 (111.00, 145.15)
	4 mg only (Nx=53)	28	14	16.60	15.45	26.42% (15.26%, 40.33%)	84.34 (46.11, 141.50)	90.61 (49.54, 152.04)
	2 mg to 4 mg (Nx=14)	21	6	3.69	3.36	42.86% (17.66%, 71.14%)	162.60 (59.67, 353.92)	178.57 (65.53, 388.67)
	other mixed dosage (Nx=20)	22	9	6.35	6.06	45.00% (23.06%, 68.47%)	141.73 (64.81, 269.05)	148.51 (67.91, 281.93)
AEs related to study treatment as judged by the investigator over a period of 12 weeks	2 mg only (Nx=580)	98	84	127.59	121.79	14.48% (11.72%, 17.61%)	65.84 (52.51, 81.51)	68.97 (55.01, 85.39)

Footnote: The number of event for each patient counts the event which happened during the 12-weeks/ 24-weeks observation time. The percentage denominator is the number of analyses population and the numerator is the number of patients with corresponding events.
AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; n, the number of patients with events; SAE, serious adverse event.
The percentage of AEs/SAEs over a period of 12/24 weeks = Number of patients with at least one AE/SAE over a period of 12/24 weeks ÷number of patients in safety analyses population ×100, results round to 2 decimal places.
The incidence rates of AEs/SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ observation time
of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places. The EAIR of AEs /SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at
least one AE/SAE over an observation period of 12/24 weeks ÷ overall exposure time of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The calculation of observation time and exposure time could refer to definition in the main body of SAP.

AEs related to study treatment as judged by the investigator are the AEs whose relationship with olumiant are not 'No'. Drug adjustment includes dose increase, dose reduce and temporary discontinuation.
Death is from SAE which the reason is death or AE whose outcome is fatal or death recorded in the page of study termination.

		Safety Analyses Population (N=667)						
	Dosage subgroup	*Event*	*n*	*Patient-year of observation time*	*Patient-year of exposure time*	*Percentage and 95% CI*	*Incidence rate and 95% CI*	*EAIR and 95% CI*
	4 mg only (Nx=53)	5	3	12.01	11.09	5.66% (1.18%, 15.66%)	24.98 (5.15, 73.00)	27.05 (5.58, 79.06)
	2 mg to 4 mg (Nx=14)	4	4	2.66	2.62	28.57% (8.39%, 58.10%)	150.38 (40.97, 385.02)	152.67 (41.60, 390.90)
	other mixed dosage (Nx=20)	4	4	4.61	4.49	20.00% (5.73%, 43.66%)	86.77 (23.64, 222.16)	89.09 (24.27, 228.10)
AEs related to study treatment as judged by the investigator over a period of 24 weeks	2 mg only (Nx=580)	130	108	217.24	206.58	18.62% (15.53%, 22.03%)	49.71 (40.78, 60.02)	52.28 (42.89, 63.12)
	4 mg only (Nx=53)	6	4	19.58	18.26	7.55% (2.09%, 18.21%)	20.43 (5.57, 52.31)	21.91 (5.97, 56.09)
	2 mg to 4 mg (Nx=14)	7	4	4.74	4.41	28.57% (8.39%, 58.10%)	84.39 (22.99, 216.07)	90.70 (24.71, 232.24)
	other mixed dosage (Nx=20)	4	4	7.69	7.40	20.00% (5.73%, 43.66%)	52.02 (14.17, 133.18)	54.05 (14.73, 138.40)
Death	2 mg only (Nx=580)	2	2	241.47	228.59	0.34% (0.04%, 1.24%)	0.83 (0.10, 2.99)	0.87 (0.11, 3.16)
	4 mg only (Nx=53)	0	0	20.27	18.71	0.00% (0%, 6.72%)	0.00 (NA, 18.20)	0.00 (NA, 19.72)

Footnote: The number of event for each patient counts the event which happened during the 12-weeks/ 24-weeks observation time. The percentage denominator is the number of analyses population and the numerator is the number of patients with corresponding events.
AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; n, the number of patients with events; SAE, serious adverse event.
The percentage of AEs/SAEs over a period of 12/24 weeks = Number of patients with at least one AE/SAE over a period of 12/24 weeks ÷number of patients in safety analyses population ×100, results round to 2 decimal places.
The incidence rates of AEs/SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ observation time
of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places. The EAIR of AEs /SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at
least one AE/SAE over an observation period of 12/24 weeks ÷ overall exposure time of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The calculation of observation time and exposure time could refer to definition in the main body of SAP.
AEs related to study treatment as judged by the investigator are the AEs whose relationship with olumiant are not 'No'. Drug adjustment includes dose increase, dose reduce and temporary discontinuation.
Death is from SAE which the reason is death or AE whose outcome is fatal or death recorded in the page of study termination.

		Safety Analyses Population (N=667)						
	Dosage subgroup	*Event*	*n*	*Patient-year of observation time*	*Patient-year of exposure time*	*Percentage and 95% CI*	*Incidence rate and 95% CI*	*EAIR and 95% CI*
	2 mg to 4 mg (Nx=14)	0	0	5.88	5.47	0.00% (0%, 23.16%)	0.00 (NA, 62.74)	0.00 (NA, 67.44)
	other mixed dosage (Nx=20)	0	0	8.82	8.53	0.00% (0%, 16.84%)	0.00 (NA, 41.82)	0.00 (NA, 43.25)
SAEs over a period of 12 weeks	2 mg only (Nx=580)	18	17	135.13	128.62	2.93% (1.72%, 4.65%)	12.58 (7.33, 20.14)	13.22 (7.70, 21.16)
	4 mg only (Nx=53)	3	3	11.91	10.87	5.66% (1.18%, 15.66%)	25.19 (5.19, 73.61)	27.60 (5.69, 80.66)
	2 mg to 4 mg (Nx=14)	1	1	2.93	2.89	7.14% (0.18%, 33.87%)	34.13 (0.86, 190.16)	34.60 (0.88, 192.79)
	other mixed dosage (Nx=20)	1	1	4.77	4.65	5.00% (0.13%, 24.87%)	20.96 (0.53, 116.81)	21.51 (0.54, 119.82)
SAEs over a period of 24 weeks	2 mg only (Nx=580)	24	23	237.58	225.52	3.97% (2.53%, 5.89%)	9.68 (6.14, 14.53)	10.20 (6.47, 15.30)
	4 mg only (Nx=53)	5	3	19.23	17.69	5.66% (1.18%, 15.66%)	15.60 (3.22, 45.59)	16.96 (3.50, 49.56)
	2 mg to 4 mg (Nx=14)	1	1	5.70	5.37	7.14% (0.18%, 33.87%)	17.54 (0.44, 97.75)	18.62 (0.47, 103.75)

Footnote: The number of event for each patient counts the event which happened during the 12-weeks/ 24-weeks observation time. The percentage denominator is the number of analyses population and the numerator is the number of patients with corresponding events.
AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; n, the number of patients with events; SAE, serious adverse event.
The percentage of AEs/SAEs over a period of 12/24 weeks = Number of patients with at least one AE/SAE over a period of 12/24 weeks ÷number of patients in safety analyses population ×100, results round to 2 decimal places.
The incidence rates of AEs/SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ observation time
of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places. The EAIR of AEs /SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at
least one AE/SAE over an observation period of 12/24 weeks ÷ overall exposure time of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The calculation of observation time and exposure time could refer to definition in the main body of SAP.
AEs related to study treatment as judged by the investigator are the AEs whose relationship with olumiant are not 'No'. Drug adjustment includes dose increase, dose reduce and temporary discontinuation.
Death is from SAE which the reason is death or AE whose outcome is fatal or death recorded in the page of study termination.

		Safety Analyses Population (N=667)						
	Dosage subgroup	*Event n*		*Patient-year of observation time*	*Patient-year of exposure time*	*Percentage and 95% CI*	*Incidence rate and 95% CI*	*EAIR and 95% CI*
	other mixed dosage (Nx=20)	1	1	8.43	8.14	5.00% (0.13%, 24.87%)	11.86 (0.30, 66.09)	12.29 (0.31, 68.45)
SAEs related to study treatment as judged by the investigator over a period of 12 weeks	2 mg only (Nx=580)	6	6	136.22	129.37	1.03% (0.38%, 2.24%)	4.40 (1.62, 9.59)	4.64 (1.70, 10.09)
	4 mg only (Nx=53)	1	1	12.30	11.25	1.89% (0.05%, 10.07%)	8.13 (0.21, 45.30)	8.89 (0.23, 49.53)
	2 mg to 4 mg (Nx=14)	1	1	2.93	2.89	7.14% (0.18%, 33.87%)	34.13 (0.86, 190.16)	34.60 (0.88, 192.79)
	other mixed dosage (Nx=20)	0	0	4.93	4.81	0.00% (0%, 16.84%)	0.00 (NA, 74.83)	0.00 (NA, 76.69)
SAEs related to study treatment as judged by the investigator over a period of 24 weeks	2 mg only (Nx=580)	8	8	240.40	227.69	1.38% (0.60%, 2.70%)	3.33 (1.44, 6.56)	3.51 (1.52, 6.92)
	4 mg only (Nx=53)	1	1	20.25	18.71	1.89% (0.05%, 10.07%)	4.94 (0.13, 27.51)	5.34 (0.14, 29.78)
	2 mg to 4 mg (Nx=14)	1	1	5.70	5.37	7.14% (0.18%, 33.87%)	17.54 (0.44, 97.75)	18.62 (0.47, 103.75)
	other mixed dosage (Nx=20)	0	0	8.82	8.53	0.00% (0%, 16.84%)	0.00 (NA, 41.82)	0.00 (NA, 43.25)

Footnote: The number of event for each patient counts the event which happened during the 12-weeks/ 24-weeks observation time. The percentage denominator is the number of analyses population and the numerator is the number of patients with corresponding events.
AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; n, the number of patients with events; SAE, serious adverse event.
The percentage of AEs/SAEs over a period of 12/24 weeks = Number of patients with at least one AE/SAE over a period of 12/24 weeks ÷number of patients in safety analyses population ×100, results round to 2 decimal places.
The incidence rates of AEs/SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ observation time
of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places. The EAIR of AEs /SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at

least one AE/SAE over an observation period of 12/24 weeks ÷ overall exposure time of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The calculation of observation time and exposure time could refer to definition in the main body of SAP.
AEs related to study treatment as judged by the investigator are the AEs whose relationship with olumiant are not 'No'. Drug adjustment includes dose increase, dose reduce and temporary discontinuation.
Death is from SAE which the reason is death or AE whose outcome is fatal or death recorded in the page of study termination.

		Safety Analyses Population (N=667)						
	Dosage subgroup	*Event*	*n*	*Patient-year of observation time*	*Patient-year of exposure time*	*Percentage and 95% CI*	*Incidence rate and 95% CI*	*EAIR and 95% CI*
AEs leading to drug adjustment over a period of 12 weeks	2 mg only (Nx=580)	31	26	132.98	126.45	4.48% (2.95%, 6.50%)	19.55 (12.77, 28.65)	20.56 (13.43, 30.13)
	4 mg only (Nx=53)	2	1	12.21	11.21	1.89% (0.05%, 10.07%)	8.19 (0.21, 45.63)	8.92 (0.23, 49.70)
	2 mg to 4 mg (Nx=14)	0	0	3.11	2.99	0.00% (0%, 23.16%)	0.00 (NA, 118.61)	0.00 (NA, 123.37)
	other mixed dosage (Nx=20)	3	3	4.68	4.56	15.00% (3.21%, 37.89%)	64.10 (13.22, 187.33)	65.79 (13.57, 192.26)
AEs leading to drug adjustment over a period of 24 weeks	2 mg only (Nx=580)	39	34	233.67	221.80	5.86% (4.09%, 8.10%)	14.55 (10.08, 20.33)	15.33 (10.62, 21.42)
	4 mg only (Nx=53)	3	2	19.98	18.58	3.77% (0.46%, 12.98%)	10.01 (1.21, 36.16)	10.76 (1.30, 38.88)
	2 mg to 4 mg (Nx=14)	0	0	5.88	5.47	0.00% (0%, 23.16%)	0.00 (NA, 62.74)	0.00 (NA, 67.44)
	other mixed dosage (Nx=20)	3	3	7.90	7.61	15.00% (3.21%, 37.89%)	37.97 (7.83, 110.98)	39.42 (8.13, 115.21)

Footnote: The number of event for each patient counts the event which happened during the 12-weeks/ 24-weeks observation time. The percentage denominator is the number of analyses population and the numerator is the number of patients with corresponding events.
AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; n, the number of patients with events; SAE, serious adverse event.
The percentage of AEs/SAEs over a period of 12/24 weeks = Number of patients with at least one AE/SAE over a period of 12/24 weeks ÷number of patients in safety analyses population ×100, results round to 2 decimal places.
The incidence rates of AEs/SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ observation time
of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places. The EAIR of AEs /SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at
least one AE/SAE over an observation period of 12/24 weeks ÷ overall exposure time of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The calculation of observation time and exposure time could refer to definition in the main body of SAP.
AEs related to study treatment as judged by the investigator are the AEs whose relationship with olumiant are not 'No'. Drug adjustment includes dose increase, dose reduce and temporary discontinuation.
Death is from SAE which the reason is death or AE whose outcome is fatal or death recorded in the page of study termination.

		Safety Analyses Population (N=667)						
	Dosage subgroup	*Event*	*n*	*Patient-year of observation time*	*Patient-year of exposure time*	*Percentage and 95% CI*	*Incidence rate and 95% CI*	*EAIR and 95% CI*
AEs leading to drug permanent discontinuation over a period of 12 weeks	2 mg only (Nx=580)	18	16	135.21	129.15	2.76% (1.58%, 4.44%)	11.83 (6.76, 19.22)	12.39 (7.08, 20.12)
	4 mg only (Nx=53)	4	4	12.12	11.24	7.55% (2.09%, 18.21%)	33.00 (8.99, 84.50)	35.59 (9.70, 91.12)
	2 mg to 4 mg (Nx=14)	0	0	3.11	2.99	0.00% (0%, 23.16%)	0.00 (NA, 118.61)	0.00 (NA, 123.37)
	other mixed dosage (Nx=20)	0	0	4.93	4.81	0.00% (0%, 16.84%)	0.00 (NA, 74.83)	0.00 (NA, 76.69)
AEs leading to drug permanent discontinuation over a period of 24 weeks	2 mg only (Nx=580)	22	20	239.67	228.09	3.45% (2.12%, 5.28%)	8.34 (5.10, 12.89)	8.77 (5.36, 13.54)
	4 mg only (Nx=53)	4	4	20.07	18.69	7.55% (2.09%, 18.21%)	19.93 (5.43, 51.03)	21.40 (5.83, 54.80)
	2 mg to 4 mg (Nx=14)	0	0	5.88	5.47	0.00% (0%, 23.16%)	0.00 (NA, 62.74)	0.00 (NA, 67.44)
	other mixed dosage (Nx=20)	0	0	8.82	8.53	0.00% (0%, 16.84%)	0.00 (NA, 41.82)	0.00 (NA, 43.25)

Footnote: The number of event for each patient counts the event which happened during the 12-weeks/ 24-weeks observation time. The percentage denominator is the number of analyses population and the numerator is the number of patients with corresponding events.
AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; n, the number of patients with events; SAE, serious adverse event.
The percentage of AEs/SAEs over a period of 12/24 weeks = Number of patients with at least one AE/SAE over a period of 12/24 weeks ÷number of patients in safety analyses population ×100, results round to 2 decimal places.
The incidence rates of AEs/SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ observation time
of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places. The EAIR of AEs /SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at
least one AE/SAE over an observation period of 12/24 weeks ÷ overall exposure time of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The calculation of observation time and exposure time could refer to definition in the main body of SAP.
AEs related to study treatment as judged by the investigator are the AEs whose relationship with olumiant are not 'No'. Drug adjustment includes dose increase, dose reduce and temporary discontinuation.
Death is from SAE which the reason is death or AE whose outcome is fatal or death recorded in the page of study termination.

Table ANN. 323 **Summary of AE with Special Interest Based on the Judgement of Investigator (2 mg Only, Safety Analyses Population)**

	Safety Analyses Population (N=580)						
	Event	*n*	*Patient-year of observation time*	*Patient-year of exposure time*	*Percentage and 95% CI*	*Incidence rate and 95% CI*	*EAIR and 95% CI*
AEs with special interest over a period of 12 weeks	17	15	135.20	128.29	2.59% (1.45%, 4.23%)	11.09 (6.21, 18.30)	11.69 (6.54, 19.28)
Serious infection	3	2	136.56	129.57	0.34% (0.04%, 1.24%)	1.46 (0.18, 5.29)	1.54 (0.19, 5.58)
Hepatotoxicity	14	13	135.30	128.30	2.24% (1.20%, 3.80%)	9.61 (5.12, 16.43)	10.13 (5.40, 17.33)
VTE	0	0	136.66	129.58	0.00% (0%, 0.63%)	0.00 (NA, 2.70)	0.00 (NA, 2.85)
AEs with special interest over a period of 24 weeks	27	22	237.31	224.71	3.79% (2.39%, 5.69%)	9.27 (5.81, 14.04)	9.79 (6.14, 14.82)
Serious infection	4	3	241.23	228.37	0.52% (0.11%, 1.50%)	1.24 (0.26, 3.63)	1.31 (0.27, 3.84)
Hepatotoxicity	23	20	237.48	224.72	3.45% (2.12%, 5.28%)	8.42 (5.14, 13.01)	8.90 (5.44, 13.75)
VTE	0	0	241.60	228.59	0.00% (0%, 0.63%)	0.00 (NA, 1.53)	0.00 (NA, 1.61)
AEs with special interest related to study treatment as judged by the investigator over a period of 12 weeks	13	11	135.56	128.65	1.90% (0.95%, 3.37%)	8.11 (4.05, 14.52)	8.55 (4.27, 15.30)
Serious infection	3	2	136.56	129.57	0.34% (0.04%, 1.24%)	1.46 (0.18, 5.29)	1.54 (0.19, 5.58)
Hepatotoxicity	10	9	135.67	128.67	1.55% (0.71%, 2.93%)	6.63 (3.03, 12.59)	6.99 (3.20, 13.28)
VTE	0	0	136.66	129.58	0.00% (0%, 0.63%)	0.00 (NA, 2.70)	0.00 (NA, 2.85)
AEs with special interest related to study treatment as judged by the investigator over a period of 24 weeks	21	17	238.43	225.66	2.93% (1.72%, 4.65%)	7.13 (4.15, 11.42)	7.53 (4.39, 12.06)
Serious infection	4	3	241.23	228.37	0.52% (0.11%, 1.50%)	1.24 (0.26, 3.63)	1.31 (0.27, 3.84)
Hepatotoxicity	17	15	238.61	225.68	2.59% (1.45%, 4.23%)	6.29 (3.52, 10.37)	6.65 (3.72, 10.96)
VTE	0	0	241.60	228.59	0.00% (0%, 0.63%)	0.00 (NA, 1.53)	0.00 (NA, 1.61)

Footnote: The percentage denominator is the number of analyses population and the numerator is the number of patients with corresponding events.

AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; n, the number of patients with events; SAE, serious adverse event; VTE, venous thromboembolism.
The percentage of AEs/SAEs over a period of 12/24 weeks = Number of patients with at least one AE/SAE over a period of 12/24 weeks ÷number of patients in safety analyses population ×100, results round to 2 decimal places.
The incidence rates of AEs/SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ observation time
of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The EAIR of AEs /SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ overall exposure time of
AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The calculation of observation time and exposure time could refer to definition in the main body of SAP.
AEs related to study treatment as judged by the investigator are the AEs whose relationship with olumiant are not 'No'.
AE with special interest is based on the judgement of investigator recorded in EDC.

	Safety Analyses Population (N=580)						
	Event	*n*	*Patient-year of observation time*	*Patient-year of exposure time*	*Percentage and 95% CI*	*Incidence rate and 95% CI*	*EAIR and 95% CI*
SAEs with special interest over a period of 12 weeks	3	3	136.41	129.50	0.52% (0.11%, 1.50%)	2.20 (0.45, 6.43)	2.32 (0.48, 6.77)
Serious infection	2	2	136.57	129.58	0.34% (0.04%, 1.24%)	1.46 (0.18, 5.29)	1.54 (0.19, 5.58)
Hepatotoxicity	1	1	136.50	129.50	0.17% (0.004%, 0.96%)	0.73 (0.02, 4.08)	0.77 (0.02, 4.30)
VTE	0	0	136.66	129.58	0.00% (0%, 0.63%)	0.00 (NA, 2.70)	0.00 (NA, 2.85)
SAEs with special interest over a period of 24 weeks	4	4	241.08	228.31	0.69% (0.19%, 1.76%)	1.66 (0.45, 4.25)	1.75 (0.48, 4.49)
Serious infection	3	3	241.24	228.39	0.52% (0.11%, 1.50%)	1.24 (0.26, 3.63)	1.31 (0.27, 3.84)
Hepatotoxicity	1	1	241.45	228.51	0.17% (0.004%, 0.96%)	0.41 (0.01, 2.31)	0.44 (0.01, 2.44)
VTE	0	0	241.60	228.59	0.00% (0%, 0.63%)	0.00 (NA, 1.53)	0.00 (NA, 1.61)

Footnote: The percentage denominator is the number of analyses population and the numerator is the number of patients with corresponding events.
AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; n, the number of patients with events; SAE, serious adverse event; VTE, venous thromboembolism.
The percentage of AEs/SAEs over a period of 12/24 weeks = Number of patients with at least one AE/SAE over a period of 12/24 weeks ÷number of patients in safety analyses population ×100, results round to 2 decimal places.
The incidence rates of AEs/SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ observation time
of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The EAIR of AEs /SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ overall exposure time of
AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The calculation of observation time and exposure time could refer to definition in the main body of SAP.
AEs related to study treatment as judged by the investigator are the AEs whose relationship with olumiant are not 'No'.
AE with special interest is based on the judgement of investigator recorded in EDC.

Table ANN. 324 Summary of AE with Special Interest Based on the Judgement of Investigator (4 mg Only, Safety Analyses Population)

	Safety Analyses Population (N=53)						
	Event	*n*	*Patient-year of observation time*	*Patient-year of exposure time*	*Percentage and 95% CI*	*Incidence rate and 95% CI*	*EAIR and 95% CI*
AEs with special interest over a period of 12 weeks	1	1	12.24	11.25	1.89% (0.05%, 10.07%)	8.17 (0.21, 45.52)	8.89 (0.23, 49.53)
Serious infection	0	0	12.32	11.25	0.00% (0%, 6.72%)	0.00 (NA, 29.94)	0.00 (NA, 32.79)
Hepatotoxicity	1	1	12.24	11.25	1.89% (0.05%, 10.07%)	8.17 (0.21, 45.52)	8.89 (0.23, 49.53)
VTE	0	0	12.32	11.25	0.00% (0%, 6.72%)	0.00 (NA, 29.94)	0.00 (NA, 32.79)
AEs with special interest over a period of 24 weeks	1	1	20.19	18.71	1.89% (0.05%, 10.07%)	4.95 (0.13, 27.60)	5.34 (0.14, 29.78)
Serious infection	0	0	20.27	18.71	0.00% (0%, 6.72%)	0.00 (NA, 18.20)	0.00 (NA, 19.72)
Hepatotoxicity	1	1	20.19	18.71	1.89% (0.05%, 10.07%)	4.95 (0.13, 27.60)	5.34 (0.14, 29.78)
VTE	0	0	20.27	18.71	0.00% (0%, 6.72%)	0.00 (NA, 18.20)	0.00 (NA, 19.72)
AEs with special interest related to study treatment as judged by the investigator over a period of 12 weeks	1	1	12.24	11.25	1.89% (0.05%, 10.07%)	8.17 (0.21, 45.52)	8.89 (0.23, 49.53)
Serious infection	0	0	12.32	11.25	0.00% (0%, 6.72%)	0.00 (NA, 29.94)	0.00 (NA, 32.79)
Hepatotoxicity	1	1	12.24	11.25	1.89% (0.05%, 10.07%)	8.17 (0.21, 45.52)	8.89 (0.23, 49.53)
VTE	0	0	12.32	11.25	0.00% (0%, 6.72%)	0.00 (NA, 29.94)	0.00 (NA, 32.79)
AEs with special interest related to study treatment as judged by the investigator over a period of 24 weeks	1	1	20.19	18.71	1.89% (0.05%, 10.07%)	4.95 (0.13, 27.60)	5.34 (0.14, 29.78)
Serious infection	0	0	20.27	18.71	0.00% (0%, 6.72%)	0.00 (NA, 18.20)	0.00 (NA, 19.72)
Hepatotoxicity	1	1	20.19	18.71	1.89% (0.05%, 10.07%)	4.95 (0.13, 27.60)	5.34 (0.14, 29.78)
VTE	0	0	20.27	18.71	0.00% (0%, 6.72%)	0.00 (NA, 18.20)	0.00 (NA, 19.72)

Footnote: The percentage denominator is the number of analyses population and the numerator is the number of patients with corresponding events.

AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; n, the number of patients with events; SAE, serious adverse event; VTE, venous thromboembolism.
The percentage of AEs/SAEs over a period of 12/24 weeks = Number of patients with at least one AE/SAE over a period of 12/24 weeks ÷number of patients in safety analyses population ×100, results round to 2 decimal places.
The incidence rates of AEs/SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ observation time
of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The EAIR of AEs /SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ overall exposure time of
AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The calculation of observation time and exposure time could refer to definition in the main body of SAP.
AEs related to study treatment as judged by the investigator are the AEs whose relationship with olumiant are not 'No'.
AE with special interest is based on the judgement of investigator recorded in EDC.

	Safety Analyses Population (N=53)						
	Event	*n*	*Patient-year of observation time*	*Patient-year of exposure time*	*Percentage and 95% CI*	*Incidence rate and 95% CI*	*EAIR and 95% CI*
SAEs with special interest over a period of 12 weeks	0	0	12.32	11.25	0.00% (0%, 6.72%)	0.00 (NA, 29.94)	0.00 (NA, 32.79)
Serious infection	0	0	12.32	11.25	0.00% (0%, 6.72%)	0.00 (NA, 29.94)	0.00 (NA, 32.79)
Hepatotoxicity	0	0	12.32	11.25	0.00% (0%, 6.72%)	0.00 (NA, 29.94)	0.00 (NA, 32.79)
VTE	0	0	12.32	11.25	0.00% (0%, 6.72%)	0.00 (NA, 29.94)	0.00 (NA, 32.79)
SAEs with special interest over a period of 24 weeks	0	0	20.27	18.71	0.00% (0%, 6.72%)	0.00 (NA, 18.20)	0.00 (NA, 19.72)
Serious infection	0	0	20.27	18.71	0.00% (0%, 6.72%)	0.00 (NA, 18.20)	0.00 (NA, 19.72)
Hepatotoxicity	0	0	20.27	18.71	0.00% (0%, 6.72%)	0.00 (NA, 18.20)	0.00 (NA, 19.72)
VTE	0	0	20.27	18.71	0.00% (0%, 6.72%)	0.00 (NA, 18.20)	0.00 (NA, 19.72)

Footnote: The percentage denominator is the number of analyses population and the numerator is the number of patients with corresponding events.
AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; n, the number of patients with events; SAE, serious adverse event; VTE, venous thromboembolism.
The percentage of AEs/SAEs over a period of 12/24 weeks = Number of patients with at least one AE/SAE over a period of 12/24 weeks ÷number of patients in safety analyses population ×100, results round to 2 decimal places.
The incidence rates of AEs/SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ observation time
of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The EAIR of AEs /SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ overall exposure time of
AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The calculation of observation time and exposure time could refer to definition in the main body of SAP.
AEs related to study treatment as judged by the investigator are the AEs whose relationship with olumiant are not 'No'.
AE with special interest is based on the judgement of investigator recorded in EDC.

Table ANN. 325 **Summary of AE with Special Interest Based on the Judgement of Investigator (Both Dosages, Safety Analyses Population)**

	Safety Analyses Population (N=34)						
	Event	*n*	*Patient-year of observation time*	*Patient-year of exposure time*	*Percentage and 95% CI*	*Incidence rate and 95% CI*	*EAIR and 95% CI*
AEs with special interest over a period of 12 weeks	3	3	7.64	7.48	8.82% (1.86%, 23.68%)	39.27 (8.10, 114.75)	40.11 (8.27, 117.21)
Serious infection	1	1	7.86	7.70	2.94% (0.07%, 15.33%)	12.72 (0.32, 70.89)	12.99 (0.33, 72.36)
Hepatotoxicity	2	2	7.82	7.58	5.88% (0.72%, 19.68%)	25.58 (3.10, 92.39)	26.39 (3.20, 95.31)
VTE	0	0	8.04	7.80	0.00% (0%, 10.28%)	0.00 (NA, 45.88)	0.00 (NA, 47.29)
AEs with special interest over a period of 24 weeks	3	3	13.85	13.23	8.82% (1.86%, 23.68%)	21.66 (4.47, 63.30)	22.68 (4.68, 66.27)
Serious infection	1	1	14.52	13.91	2.94% (0.07%, 15.33%)	6.89 (0.17, 38.37)	7.19 (0.18, 40.05)
Hepatotoxicity	2	2	14.03	13.33	5.88% (0.72%, 19.68%)	14.26 (1.73, 51.49)	15.00 (1.82, 54.20)
VTE	0	0	14.70	14.00	0.00% (0%, 10.28%)	0.00 (NA, 25.09)	0.00 (NA, 26.35)
AEs with special interest related to study treatment as judged by the investigator over a period of 12 weeks	3	3	7.64	7.48	8.82% (1.86%, 23.68%)	39.27 (8.10, 114.75)	40.11 (8.27, 117.21)
Serious infection	1	1	7.86	7.70	2.94% (0.07%, 15.33%)	12.72 (0.32, 70.89)	12.99 (0.33, 72.36)
Hepatotoxicity	2	2	7.82	7.58	5.88% (0.72%, 19.68%)	25.58 (3.10, 92.39)	26.39 (3.20, 95.31)
VTE	0	0	8.04	7.80	0.00% (0%, 10.28%)	0.00 (NA, 45.88)	0.00 (NA, 47.29)
AEs with special interest related to study treatment as judged by the investigator over a period of 24 weeks	3	3	13.85	13.23	8.82% (1.86%, 23.68%)	21.66 (4.47, 63.30)	22.68 (4.68, 66.27)
Serious infection	1	1	14.52	13.91	2.94% (0.07%, 15.33%)	6.89 (0.17, 38.37)	7.19 (0.18, 40.05)
Hepatotoxicity	2	2	14.03	13.33	5.88% (0.72%, 19.68%)	14.26 (1.73, 51.49)	15.00 (1.82, 54.20)
VTE	0	0	14.70	14.00	0.00% (0%, 10.28%)	0.00 (NA, 25.09)	0.00 (NA, 26.35)

Footnote: The percentage denominator is the number of analyses population and the numerator is the number of patients with corresponding events.

AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; n, the number of patients with events; SAE, serious adverse event; VTE, venous thromboembolism.
The percentage of AEs/SAEs over a period of 12/24 weeks = Number of patients with at least one AE/SAE over a period of 12/24 weeks ÷number of patients in safety analyses population ×100, results round to 2 decimal places.
The incidence rates of AEs/SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ observation time
of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The EAIR of AEs /SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ overall exposure time of
AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The calculation of observation time and exposure time could refer to definition in the main body of SAP.
AEs related to study treatment as judged by the investigator are the AEs whose relationship with olumiant are not 'No'.
AE with special interest is based on the judgement of investigator recorded in EDC. Both dosages subgroup includes 2 mg to 4 mg and other mixed dosage subgroups.

	Safety Analyses Population (N=34)						
	Event	*n*	*Patient-year of observation time*	*Patient-year of exposure time*	*Percentage and 95% CI*	*Incidence rate and 95% CI*	*EAIR and 95% CI*
SAEs with special interest over a period of 12 weeks	1	1	7.86	7.70	2.94% (0.07%, 15.33%)	12.72 (0.32, 70.89)	12.99 (0.33, 72.36)
Serious infection	1	1	7.86	7.70	2.94% (0.07%, 15.33%)	12.72 (0.32, 70.89)	12.99 (0.33, 72.36)
Hepatotoxicity	0	0	8.04	7.80	0.00% (0%, 10.28%)	0.00 (NA, 45.88)	0.00 (NA, 47.29)
VTE	0	0	8.04	7.80	0.00% (0%, 10.28%)	0.00 (NA, 45.88)	0.00 (NA, 47.29)
SAEs with special interest over a period of 24 weeks	1	1	14.52	13.91	2.94% (0.07%, 15.33%)	6.89 (0.17, 38.37)	7.19 (0.18, 40.05)
Serious infection	1	1	14.52	13.91	2.94% (0.07%, 15.33%)	6.89 (0.17, 38.37)	7.19 (0.18, 40.05)
Hepatotoxicity	0	0	14.70	14.00	0.00% (0%, 10.28%)	0.00 (NA, 25.09)	0.00 (NA, 26.35)
VTE	0	0	14.70	14.00	0.00% (0%, 10.28%)	0.00 (NA, 25.09)	0.00 (NA, 26.35)

Footnote: The percentage denominator is the number of analyses population and the numerator is the number of patients with corresponding events.
AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; n, the number of patients with events; SAE, serious adverse event; VTE, venous thromboembolism.
The percentage of AEs/SAEs over a period of 12/24 weeks = Number of patients with at least one AE/SAE over a period of 12/24 weeks ÷number of patients in safety analyses population ×100, results round to 2 decimal places.
The incidence rates of AEs/SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ observation time
of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The EAIR of AEs /SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ overall exposure time of
AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The calculation of observation time and exposure time could refer to definition in the main body of SAP.
AEs related to study treatment as judged by the investigator are the AEs whose relationship with olumiant are not 'No'.
AE with special interest is based on the judgement of investigator recorded in EDC. Both dosages subgroup includes 2 mg to 4 mg and other mixed dosage subgroups.

Table ANN. 326 **Summary of AE with Special Interest Based on Judgment of Investigator (2 mg to 4 mg, Safety Analyses Population)**

	Safety Analyses Population (N=14)						
	Event	*n*	*Patient-year of observation time*	*Patient-year of exposure time*	*Percentage and 95% CI*	*Incidence rate and 95% CI*	*EAIR and 95% CI*
AEs with special interest over a period of 12 weeks	2	2	2.80	2.76	14.29% (1.78%, 42.81%)	71.43 (8.65, 258.02)	72.46 (8.78, 261.76)
Serious infection	1	1	2.93	2.89	7.14% (0.18%, 33.87%)	34.13 (0.86, 190.16)	34.60 (0.88, 192.79)
Hepatotoxicity	1	1	2.98	2.86	7.14% (0.18%, 33.87%)	33.56 (0.85, 186.97)	34.97 (0.89, 194.81)
VTE	0	0	3.11	2.99	0.00% (0%, 23.16%)	0.00 (NA, 118.61)	0.00 (NA, 123.37)
AEs with special interest over a period of 24 weeks	2	2	5.34	5.01	14.29% (1.78%, 42.81%)	37.45 (4.54, 135.29)	39.92 (4.83, 144.21)
Serious infection	1	1	5.70	5.37	7.14% (0.18%, 33.87%)	17.54 (0.44, 97.75)	18.62 (0.47, 103.75)
Hepatotoxicity	1	1	5.52	5.11	7.14% (0.18%, 33.87%)	18.12 (0.46, 100.94)	19.57 (0.50, 109.03)
VTE	0	0	5.88	5.47	0.00% (0%, 23.16%)	0.00 (NA, 62.74)	0.00 (NA, 67.44)
AEs with special interest related to study treatment as judged by the investigator over a period of 12 weeks	2	2	2.80	2.76	14.29% (1.78%, 42.81%)	71.43 (8.65, 258.02)	72.46 (8.78, 261.76)
Serious infection	1	1	2.93	2.89	7.14% (0.18%, 33.87%)	34.13 (0.86, 190.16)	34.60 (0.88, 192.79)
Hepatotoxicity	1	1	2.98	2.86	7.14% (0.18%, 33.87%)	33.56 (0.85, 186.97)	34.97 (0.89, 194.81)
VTE	0	0	3.11	2.99	0.00% (0%, 23.16%)	0.00 (NA, 118.61)	0.00 (NA, 123.37)
AEs with special interest related to study treatment as judged by the investigator over a period of 24 weeks	2	2	5.34	5.01	14.29% (1.78%, 42.81%)	37.45 (4.54, 135.29)	39.92 (4.83, 144.21)
Serious infection	1	1	5.70	5.37	7.14% (0.18%, 33.87%)	17.54 (0.44, 97.75)	18.62 (0.47, 103.75)
Hepatotoxicity	1	1	5.52	5.11	7.14% (0.18%, 33.87%)	18.12 (0.46, 100.94)	19.57 (0.50, 109.03)
VTE	0	0	5.88	5.47	0.00% (0%, 23.16%)	0.00 (NA, 62.74)	0.00 (NA, 67.44)

Footnote: The percentage denominator is the number of analyses population and the numerator is the number of patients with corresponding events.

AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; n, the number of patients with events; SAE, serious adverse event; VTE, venous thromboembolism.
The percentage of AEs/SAEs over a period of 12/24 weeks = Number of patients with at least one AE/SAE over a period of 12/24 weeks ÷number of patients in safety analyses population ×100, results round to 2 decimal places.
The incidence rates of AEs/SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ observation time
of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The EAIR of AEs /SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ overall exposure time of
AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The calculation of observation time and exposure time could refer to definition in the main body of SAP.
AEs related to study treatment as judged by the investigator are the AEs whose relationship with olumiant are not 'No'.
AE with special interest is based on the judgement of investigator recorded in EDC.

	Safety Analyses Population (N=14)						
	Event	*n*	*Patient-year of observation time*	*Patient-year of exposure time*	*Percentage and 95% CI*	*Incidence rate and 95% CI*	*EAIR and 95% CI*
SAEs with special interest over a period of 12 weeks	1	1	2.93	2.89	7.14% (0.18%, 33.87%)	34.13 (0.86, 190.16)	34.60 (0.88, 192.79)
Serious infection	1	1	2.93	2.89	7.14% (0.18%, 33.87%)	34.13 (0.86, 190.16)	34.60 (0.88, 192.79)
Hepatotoxicity	0	0	3.11	2.99	0.00% (0%, 23.16%)	0.00 (NA, 118.61)	0.00 (NA, 123.37)
VTE	0	0	3.11	2.99	0.00% (0%, 23.16%)	0.00 (NA, 118.61)	0.00 (NA, 123.37)
SAEs with special interest over a period of 24 weeks	1	1	5.70	5.37	7.14% (0.18%, 33.87%)	17.54 (0.44, 97.75)	18.62 (0.47, 103.75)
Serious infection	1	1	5.70	5.37	7.14% (0.18%, 33.87%)	17.54 (0.44, 97.75)	18.62 (0.47, 103.75)
Hepatotoxicity	0	0	5.88	5.47	0.00% (0%, 23.16%)	0.00 (NA, 62.74)	0.00 (NA, 67.44)
VTE	0	0	5.88	5.47	0.00% (0%, 23.16%)	0.00 (NA, 62.74)	0.00 (NA, 67.44)

Footnote: The percentage denominator is the number of analyses population and the numerator is the number of patients with corresponding events.
AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; n, the number of patients with events; SAE, serious adverse event; VTE, venous thromboembolism.
The percentage of AEs/SAEs over a period of 12/24 weeks = Number of patients with at least one AE/SAE over a period of 12/24 weeks ÷number of patients in safety analyses population ×100, results round to 2 decimal places.
The incidence rates of AEs/SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ observation time
of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The EAIR of AEs /SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ overall exposure time of
AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The calculation of observation time and exposure time could refer to definition in the main body of SAP.
AEs related to study treatment as judged by the investigator are the AEs whose relationship with olumiant are not 'No'.
AE with special interest is based on the judgement of investigator recorded in EDC.

Table ANN. 327 **Summary of AE with Special Interest Based on the Judgement of Investigator (Other mixed dosage, Safety Analyses Population)**

	Safety Analyses Population (N=20)						
	Event	*n*	*Patient-year of observation time*	*Patient-year of exposure time*	*Percentage and 95% CI*	*Incidence rate and 95% CI*	*EAIR and 95% CI*
AEs with special interest over a period of 12 weeks	1	1	4.84	4.72	5.00% (0.13%, 24.87%)	20.66 (0.52, 115.12)	21.19 (0.54, 118.04)
Serious infection	0	0	4.93	4.81	0.00% (0%, 16.84%)	0.00 (NA, 74.83)	0.00 (NA, 76.69)
Hepatotoxicity	1	1	4.84	4.72	5.00% (0.13%, 24.87%)	20.66 (0.52, 115.12)	21.19 (0.54, 118.04)
VTE	0	0	4.93	4.81	0.00% (0%, 16.84%)	0.00 (NA, 74.83)	0.00 (NA, 76.69)
AEs with special interest over a period of 24 weeks	1	1	8.51	8.22	5.00% (0.13%, 24.87%)	11.75 (0.30, 65.47)	12.17 (0.31, 67.78)
Serious infection	0	0	8.82	8.53	0.00% (0%, 16.84%)	0.00 (NA, 41.82)	0.00 (NA, 43.25)
Hepatotoxicity	1	1	8.51	8.22	5.00% (0.13%, 24.87%)	11.75 (0.30, 65.47)	12.17 (0.31, 67.78)
VTE	0	0	8.82	8.53	0.00% (0%, 16.84%)	0.00 (NA, 41.82)	0.00 (NA, 43.25)
AEs with special interest related to study treatment as judged by the investigator over a period of 12 weeks	1	1	4.84	4.72	5.00% (0.13%, 24.87%)	20.66 (0.52, 115.12)	21.19 (0.54, 118.04)
Serious infection	0	0	4.93	4.81	0.00% (0%, 16.84%)	0.00 (NA, 74.83)	0.00 (NA, 76.69)
Hepatotoxicity	1	1	4.84	4.72	5.00% (0.13%, 24.87%)	20.66 (0.52, 115.12)	21.19 (0.54, 118.04)
VTE	0	0	4.93	4.81	0.00% (0%, 16.84%)	0.00 (NA, 74.83)	0.00 (NA, 76.69)
AEs with special interest related to study treatment as judged by the investigator over a period of 24 weeks	1	1	8.51	8.22	5.00% (0.13%, 24.87%)	11.75 (0.30, 65.47)	12.17 (0.31, 67.78)
Serious infection	0	0	8.82	8.53	0.00% (0%, 16.84%)	0.00 (NA, 41.82)	0.00 (NA, 43.25)
Hepatotoxicity	1	1	8.51	8.22	5.00% (0.13%, 24.87%)	11.75 (0.30, 65.47)	12.17 (0.31, 67.78)
VTE	0	0	8.82	8.53	0.00% (0%, 16.84%)	0.00 (NA, 41.82)	0.00 (NA, 43.25)

Footnote: The percentage denominator is the number of analyses population and the numerator is the number of patients with corresponding events.

AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; n, the number of patients with events; SAE, serious adverse event; VTE, venous thromboembolism.
The percentage of AEs/SAEs over a period of 12/24 weeks = Number of patients with at least one AE/SAE over a period of 12/24 weeks ÷number of patients in safety analyses population ×100, results round to 2 decimal places.
The incidence rates of AEs/SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ observation time
of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The EAIR of AEs /SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ overall exposure time of
AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The calculation of observation time and exposure time could refer to definition in the main body of SAP.
AEs related to study treatment as judged by the investigator are the AEs whose relationship with olumiant are not 'No'.
AE with special interest is based on the judgement of investigator recorded in EDC.

	Safety Analyses Population (N=20)						
	Event	*n*	*Patient-year of observation time*	*Patient-year of exposure time*	*Percentage and 95% CI*	*Incidence rate and 95% CI*	*EAIR and 95% CI*
SAEs with special interest over a period of 12 weeks	0	0	4.93	4.81	0.00% (0%, 16.84%)	0.00 (NA, 74.83)	0.00 (NA, 76.69)
Serious infection	0	0	4.93	4.81	0.00% (0%, 16.84%)	0.00 (NA, 74.83)	0.00 (NA, 76.69)
Hepatotoxicity	0	0	4.93	4.81	0.00% (0%, 16.84%)	0.00 (NA, 74.83)	0.00 (NA, 76.69)
VTE	0	0	4.93	4.81	0.00% (0%, 16.84%)	0.00 (NA, 74.83)	0.00 (NA, 76.69)
SAEs with special interest over a period of 24 weeks	0	0	8.82	8.53	0.00% (0%, 16.84%)	0.00 (NA, 41.82)	0.00 (NA, 43.25)
Serious infection	0	0	8.82	8.53	0.00% (0%, 16.84%)	0.00 (NA, 41.82)	0.00 (NA, 43.25)
Hepatotoxicity	0	0	8.82	8.53	0.00% (0%, 16.84%)	0.00 (NA, 41.82)	0.00 (NA, 43.25)
VTE	0	0	8.82	8.53	0.00% (0%, 16.84%)	0.00 (NA, 41.82)	0.00 (NA, 43.25)

Footnote: The percentage denominator is the number of analyses population and the numerator is the number of patients with corresponding events.
AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; n, the number of patients with events; SAE, serious adverse event; VTE, venous thromboembolism.
The percentage of AEs/SAEs over a period of 12/24 weeks = Number of patients with at least one AE/SAE over a period of 12/24 weeks ÷number of patients in safety analyses population ×100, results round to 2 decimal places.
The incidence rates of AEs/SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ observation time
of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The EAIR of AEs /SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ overall exposure time of
AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The calculation of observation time and exposure time could refer to definition in the main body of SAP.
AEs related to study treatment as judged by the investigator are the AEs whose relationship with olumiant are not 'No'.
AE with special interest is based on the judgement of investigator recorded in EDC.

Table ANN. 328 **AEs over a Period of 12 Weeks by Maximum Severity — MedDRA Preferred Term by Decreasing Frequency, Within System Organ Class (2 mg Only, Safety Analyses Population)**

	Safety Analyses Population (N=580)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
AE	272	187 (32.24%)	193	122 (21.03%)	62	50 (8.62%)	17	15 (2.59%)
Infections and infestations	55	47 (8.10%)	33	26 (4.48%)	19	18 (3.10%)	3	3 (0.52%)
Upper respiratory tract infection	18	17 (2.93%)	13	12 (2.07%)	5	5 (0.86%)	0	0
Urinary tract infection	10	10 (1.72%)	6	6 (1.03%)	4	4 (0.69%)	0	0
Pneumonia	6	5 (0.86%)	0	0	4	3 (0.52%)	2	2 (0.34%)
Herpes zoster	3	3 (0.52%)	0	0	3	3 (0.52%)	0	0
Pharyngitis	3	3 (0.52%)	1	1 (0.17%)	2	2 (0.34%)	0	0
Bronchitis	1	1 (0.17%)	0	0	1	1 (0.17%)	0	0
Enterovirus infection	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Gingivitis	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Herpes ophthalmic	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Herpes simplex	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Herpes virus infection	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Otitis externa	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Otitis media	1	1 (0.17%)	0	0	0	0	1	1 (0.17%)
Periodontitis	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Pulmonary tuberculosis	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Pulpitis dental	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Streptococcal infection	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=580)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Tonsillitis	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Urethritis	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Vulvovaginal mycotic infection	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Investigations	51	43 (7.41%)	50	42 (7.24%)	1	1 (0.17%)	0	0
Platelet count increased	14	14 (2.41%)	14	14 (2.41%)	0	0	0	0
Lymphocyte count decreased	7	7 (1.21%)	7	7 (1.21%)	0	0	0	0
White blood cell count decreased	5	5 (0.86%)	5	5 (0.86%)	0	0	0	0
White blood cell count increased	5	5 (0.86%)	5	5 (0.86%)	0	0	0	0
Alanine aminotransferase increased	3	3 (0.52%)	3	3 (0.52%)	0	0	0	0
Neutrophil count increased	3	3 (0.52%)	3	3 (0.52%)	0	0	0	0
Aspartate aminotransferase increased	2	2 (0.34%)	2	2 (0.34%)	0	0	0	0
Blood pressure increased	2	2 (0.34%)	1	1 (0.17%)	1	1 (0.17%)	0	0
Fibrin D dimer increased	2	2 (0.34%)	2	2 (0.34%)	0	0	0	0
Blood creatine phosphokinase increased	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Blood triglycerides increased	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Coagulation test abnormal	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Lipids increased	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Lymphocyte count increased	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Lymphocyte percentage increased	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0

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MedDRA English version 25.1

	Safety Analyses Population (N=580)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Red blood cells urine positive	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Weight increased	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Gastrointestinal disorders	27	25 (4.31%)	21	19 (3.28%)	4	4 (0.69%)	2	2 (0.34%)
Abdominal pain upper	3	3 (0.52%)	2	2 (0.34%)	1	1 (0.17%)	0	0
Diarrhoea	3	3 (0.52%)	3	3 (0.52%)	0	0	0	0
Gastrointestinal disorder	3	3 (0.52%)	3	3 (0.52%)	0	0	0	0
Nausea	3	3 (0.52%)	3	3 (0.52%)	0	0	0	0
Abdominal discomfort	2	2 (0.34%)	2	2 (0.34%)	0	0	0	0
Mouth ulceration	3	2 (0.34%)	3	2 (0.34%)	0	0	0	0
Abdominal distension	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Dry mouth	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Functional gastrointestinal disorder	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Gastritis	1	1 (0.17%)	0	0	1	1 (0.17%)	0	0
Ileus paralytic	1	1 (0.17%)	0	0	0	0	1	1 (0.17%)
Noninfective gingivitis	1	1 (0.17%)	0	0	1	1 (0.17%)	0	0
Pancreatitis acute	1	1 (0.17%)	0	0	0	0	1	1 (0.17%)
Periodontal disease	1	1 (0.17%)	0	0	1	1 (0.17%)	0	0
Stomatitis	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Toothache	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=580)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Metabolism and nutrition disorders	28	24 (4.14%)	23	20 (3.45%)	4	3 (0.52%)	1	1 (0.17%)
Hyperlipidaemia	6	6 (1.03%)	5	5 (0.86%)	1	1 (0.17%)	0	0
Hyperuricaemia	5	5 (0.86%)	5	5 (0.86%)	0	0	0	0
Decreased appetite	4	4 (0.69%)	4	4 (0.69%)	0	0	0	0
Electrolyte imbalance	3	2 (0.34%)	2	1 (0.17%)	1	1 (0.17%)	0	0
Hypocalcaemia	2	2 (0.34%)	2	2 (0.34%)	0	0	0	0
Hypokalaemia	2	2 (0.34%)	2	2 (0.34%)	0	0	0	0
Diabetes mellitus	1	1 (0.17%)	0	0	1	1 (0.17%)	0	0
Dyslipidaemia	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Hypercholesterolaemia	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Hyperkalaemia	1	1 (0.17%)	0	0	0	0	1	1 (0.17%)
Hypoalbuminaemia	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Hypoglycaemia	1	1 (0.17%)	0	0	1	1 (0.17%)	0	0
Blood and lymphatic system disorders	20	20 (3.45%)	17	17 (2.93%)	3	3 (0.52%)	0	0
Anaemia	9	9 (1.55%)	8	8 (1.38%)	1	1 (0.17%)	0	0
Thrombocytosis	3	3 (0.52%)	3	3 (0.52%)	0	0	0	0
Leukopenia	2	2 (0.34%)	2	2 (0.34%)	0	0	0	0
Myelosuppression	2	2 (0.34%)	0	0	2	2 (0.34%)	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=580)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Coagulopathy	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Eosinophilia	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Monocytosis	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Thrombocytopenia	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Hepatobiliary disorders	17	16 (2.76%)	10	10 (1.72%)	5	5 (0.86%)	2	1 (0.17%)
Hepatic function abnormal	15	15 (2.59%)	10	10 (1.72%)	5	5 (0.86%)	0	0
Drug-induced liver injury	2	1 (0.17%)	0	0	0	0	2	1 (0.17%)
Musculoskeletal and connective tissue disorders	19	15 (2.59%)	6	3 (0.52%)	9	8 (1.38%)	4	4 (0.69%)
Arthralgia	6	6 (1.03%)	2	2 (0.34%)	4	4 (0.69%)	0	0
Rheumatoid arthritis	5	5 (0.86%)	1	1 (0.17%)	2	2 (0.34%)	2	2 (0.34%)
Intervertebral disc protrusion	3	3 (0.52%)	1	1 (0.17%)	1	1 (0.17%)	1	1 (0.17%)
Joint swelling	2	2 (0.34%)	1	1 (0.17%)	1	1 (0.17%)	0	0
Back pain	1	1 (0.17%)	0	0	1	1 (0.17%)	0	0
Lumbar spinal stenosis	1	1 (0.17%)	0	0	0	0	1	1 (0.17%)
Spinal osteoarthritis	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Skin and subcutaneous tissue disorders	10	10 (1.72%)	6	6 (1.03%)	4	4 (0.69%)	0	0
Acne	3	3 (0.52%)	2	2 (0.34%)	1	1 (0.17%)	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=580)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Alopecia	2	2 (0.34%)	1	1 (0.17%)	1	1 (0.17%)	0	0
Dermatitis	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Night sweats	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Rash	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Skin erosion	1	1 (0.17%)	0	0	1	1 (0.17%)	0	0
Skin ulcer	1	1 (0.17%)	0	0	1	1 (0.17%)	0	0
General disorders and administration site conditions	8	7 (1.21%)	6	5 (0.86%)	1	1 (0.17%)	1	1 (0.17%)
Asthenia	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Chest discomfort	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Chest pain	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Chills	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Death	1	1 (0.17%)	0	0	0	0	1	1 (0.17%)
Face oedema	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Oedema peripheral	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Peripheral swelling	1	1 (0.17%)	0	0	1	1 (0.17%)	0	0
Respiratory, thoracic and mediastinal disorders	8	7 (1.21%)	4	3 (0.52%)	4	4 (0.69%)	0	0
Cough	3	3 (0.52%)	1	1 (0.17%)	2	2 (0.34%)	0	0
Bronchiectasis	1	1 (0.17%)	0	0	1	1 (0.17%)	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=580)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Interstitial lung disease	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Laryngeal pain	1	1 (0.17%)	0	0	1	1 (0.17%)	0	0
Oropharyngeal pain	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Productive cough	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Vascular disorders	6	6 (1.03%)	3	3 (0.52%)	3	3 (0.52%)	0	0
Hypertension	5	5 (0.86%)	2	2 (0.34%)	3	3 (0.52%)	0	0
Arteriosclerosis	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Reproductive system and breast disorders	6	5 (0.86%)	5	4 (0.69%)	1	1 (0.17%)	0	0
Abnormal uterine bleeding	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Adenomyosis	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Dysmenorrhoea	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Ectropion of cervix	1	1 (0.17%)	0	0	1	1 (0.17%)	0	0
Menstrual disorder	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Vaginal discharge	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Nervous system disorders	4	4 (0.69%)	2	2 (0.34%)	1	1 (0.17%)	1	1 (0.17%)
Carotid artery aneurysm	1	1 (0.17%)	0	0	0	0	1	1 (0.17%)
Headache	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
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MedDRA English version 25.1

	Safety Analyses Population (N=580)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Neuropathy peripheral	1	1 (0.17%)	0	0	1	1 (0.17%)	0	0
Somnolence	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Ear and labyrinth disorders	3	3 (0.52%)	1	1 (0.17%)	1	1 (0.17%)	1	1 (0.17%)
Cerumen impaction	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Otolithiasis	1	1 (0.17%)	0	0	0	0	1	1 (0.17%)
Vertigo	1	1 (0.17%)	0	0	1	1 (0.17%)	0	0
Endocrine disorders	4	3 (0.52%)	3	2 (0.34%)	0	0	1	1 (0.17%)
Thyroid mass	3	2 (0.34%)	2	1 (0.17%)	0	0	1	1 (0.17%)
Hypothyroidism	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Eye disorders	2	2 (0.34%)	2	2 (0.34%)	0	0	0	0
Cataract	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Eyelid oedema	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Cardiac disorders	1	1 (0.17%)	0	0	1	1 (0.17%)	0	0
Arteriosclerosis coronary artery	1	1 (0.17%)	0	0	1	1 (0.17%)	0	0
Injury, poisoning and procedural complications	1	1 (0.17%)	0	0	0	0	1	1 (0.17%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=580)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Lumbar vertebral fracture	1	1 (0.17%)	0	0	0	0	1	1 (0.17%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Thyroid cancer	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Renal and urinary disorders	1	1 (0.17%)	0	0	1	1 (0.17%)	0	0
Renal failure	1	1 (0.17%)	0	0	1	1 (0.17%)	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

Table ANN. 329 AEs over a Period of 12 Weeks by Maximum Severity — MedDRA Preferred Term by Decreasing Frequency, Within System Organ Class (4 mg Only, Safety Analyses Population)

	Safety Analyses Population (N=53)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
AE	24	14 (26.42%)	17	7 (13.21%)	5	5 (9.43%)	2	2 (3.77%)
Metabolism and nutrition disorders	5	5 (9.43%)	3	3 (5.66%)	2	2 (3.77%)	0	0
Hyperlipidaemia	2	2 (3.77%)	1	1 (1.89%)	1	1 (1.89%)	0	0
Hypertriglyceridaemia	1	1 (1.89%)	0	0	1	1 (1.89%)	0	0
Hypocalcaemia	1	1 (1.89%)	1	1 (1.89%)	0	0	0	0
Vitamin D deficiency	1	1 (1.89%)	1	1 (1.89%)	0	0	0	0
Gastrointestinal disorders	3	3 (5.66%)	3	3 (5.66%)	0	0	0	0
Gastrointestinal disorder	1	1 (1.89%)	1	1 (1.89%)	0	0	0	0
Haemorrhagic erosive gastritis	1	1 (1.89%)	1	1 (1.89%)	0	0	0	0
Oral blood blister	1	1 (1.89%)	1	1 (1.89%)	0	0	0	0
Musculoskeletal and connective tissue disorders	3	3 (5.66%)	0	0	1	1 (1.89%)	2	2 (3.77%)
Rheumatoid arthritis	2	2 (3.77%)	0	0	1	1 (1.89%)	1	1 (1.89%)
Arthralgia	1	1 (1.89%)	0	0	0	0	1	1 (1.89%)
Nervous system disorders	2	2 (3.77%)	1	1 (1.89%)	1	1 (1.89%)	0	0
Dizziness	1	1 (1.89%)	1	1 (1.89%)	0	0	0	0
Optic neuritis	1	1 (1.89%)	0	0	1	1 (1.89%)	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=53)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Skin and subcutaneous tissue disorders	2	2 (3.77%)	2	2 (3.77%)	0	0	0	0
Alopecia	1	1 (1.89%)	1	1 (1.89%)	0	0	0	0
Eczema	1	1 (1.89%)	1	1 (1.89%)	0	0	0	0
Endocrine disorders	1	1 (1.89%)	0	0	1	1 (1.89%)	0	0
Hypothyroidism	1	1 (1.89%)	0	0	1	1 (1.89%)	0	0
Hepatobiliary disorders	1	1 (1.89%)	1	1 (1.89%)	0	0	0	0
Hepatic function abnormal	1	1 (1.89%)	1	1 (1.89%)	0	0	0	0
Infections and infestations	1	1 (1.89%)	1	1 (1.89%)	0	0	0	0
Urinary tract infection	1	1 (1.89%)	1	1 (1.89%)	0	0	0	0
Investigations	3	1 (1.89%)	3	1 (1.89%)	0	0	0	0
Neutrophil count increased	1	1 (1.89%)	1	1 (1.89%)	0	0	0	0
Neutrophil percentage increased	1	1 (1.89%)	1	1 (1.89%)	0	0	0	0
White blood cell count increased	1	1 (1.89%)	1	1 (1.89%)	0	0	0	0
Psychiatric disorders	1	1 (1.89%)	1	1 (1.89%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=53)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Sleep disorder	1	1 (1.89%)	1	1 (1.89%)	0	0	0	0
Vascular disorders	2	1 (1.89%)	2	1 (1.89%)	0	0	0	0
Hypertension	2	1 (1.89%)	2	1 (1.89%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

Table ANN. 330 **AEs Over a Period of 12 Weeks by Maximum Severity — MedDRA Preferred Term by Decreasing Frequency, within System Organ Class (Both dosages, Safety Analyses Population)**

	Safety Analyses Population (N=34)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
AE	33	13 (38.24%)	27	7 (20.59%)	3	3 (8.82%)	3	3 (8.82%)
Investigations	13	5 (14.71%)	13	5 (14.71%)	0	0	0	0
Neutrophil count increased	3	3 (8.82%)	3	3 (8.82%)	0	0	0	0
Neutrophil percentage increased	3	3 (8.82%)	3	3 (8.82%)	0	0	0	0
White blood cell count increased	3	3 (8.82%)	3	3 (8.82%)	0	0	0	0
Alanine aminotransferase increased	2	2 (5.88%)	2	2 (5.88%)	0	0	0	0
Blood albumin decreased	1	1 (2.94%)	1	1 (2.94%)	0	0	0	0
Haemoglobin decreased	1	1 (2.94%)	1	1 (2.94%)	0	0	0	0
Gastrointestinal disorders	3	3 (8.82%)	3	3 (8.82%)	0	0	0	0
Aphthous ulcer	1	1 (2.94%)	1	1 (2.94%)	0	0	0	0
Diarrhoea	1	1 (2.94%)	1	1 (2.94%)	0	0	0	0
Gastrooesophageal reflux disease	1	1 (2.94%)	1	1 (2.94%)	0	0	0	0
Musculoskeletal and connective tissue disorders	3	3 (8.82%)	2	2 (5.88%)	0	0	1	1 (2.94%)
Pain in extremity	1	1 (2.94%)	1	1 (2.94%)	0	0	0	0
Rheumatoid arthritis	1	1 (2.94%)	0	0	0	0	1	1 (2.94%)
Spinal osteoarthritis	1	1 (2.94%)	1	1 (2.94%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
Both dosages subgroup includes 2 mg to 4 mg and other mixed dosage subgroups.
MedDRA English version 25.1

SOC / PT	Safety Analyses Population (N=34) Overall Event	Overall n (%)	Severity Mild Event	Mild n (%)	Moderate Event	Moderate n (%)	Severe Event	Severe n (%)
Blood and lymphatic system disorders	2	2 (5.88%)	2	2 (5.88%)	0	0	0	0
Anaemia	1	1 (2.94%)	1	1 (2.94%)	0	0	0	0
Thrombocytosis	1	1 (2.94%)	1	1 (2.94%)	0	0	0	0
General disorders and administration site conditions	2	2 (5.88%)	1	1 (2.94%)	1	1 (2.94%)	0	0
Chest pain	1	1 (2.94%)	1	1 (2.94%)	0	0	0	0
Oedema peripheral	1	1 (2.94%)	0	0	1	1 (2.94%)	0	0
Hepatobiliary disorders	2	2 (5.88%)	1	1 (2.94%)	1	1 (2.94%)	0	0
Hepatic function abnormal	2	2 (5.88%)	1	1 (2.94%)	1	1 (2.94%)	0	0
Respiratory, thoracic and mediastinal disorders	2	2 (5.88%)	1	1 (2.94%)	0	0	1	1 (2.94%)
Chronic obstructive pulmonary disease	1	1 (2.94%)	0	0	0	0	1	1 (2.94%)
Cough	1	1 (2.94%)	1	1 (2.94%)	0	0	0	0
Ear and labyrinth disorders	1	1 (2.94%)	0	0	1	1 (2.94%)	0	0
Vertigo	1	1 (2.94%)	0	0	1	1 (2.94%)	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
Both dosages subgroup includes 2 mg to 4 mg and other mixed dosage subgroups.
MedDRA English version 25.1

	Safety Analyses Population (N=34)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Infections and infestations	1	1 (2.94%)	0	0	0	0	1	1 (2.94%)
Pneumonia	1	1 (2.94%)	0	0	0	0	1	1 (2.94%)
Nervous system disorders	1	1 (2.94%)	1	1 (2.94%)	0	0	0	0
Headache	1	1 (2.94%)	1	1 (2.94%)	0	0	0	0
Renal and urinary disorders	1	1 (2.94%)	1	1 (2.94%)	0	0	0	0
Renal impairment	1	1 (2.94%)	1	1 (2.94%)	0	0	0	0
Skin and subcutaneous tissue disorders	2	1 (2.94%)	2	1 (2.94%)	0	0	0	0
Alopecia	1	1 (2.94%)	1	1 (2.94%)	0	0	0	0
Pruritus	1	1 (2.94%)	1	1 (2.94%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
Both dosages subgroup includes 2 mg to 4 mg and other mixed dosage subgroups.
MedDRA English version 25.1

Table ANN. 331 AEs over a Period of 12 Weeks by Maximum Severity — MedDRA Preferred Term by Decreasing Frequency, Within System Organ Class (2 mg to 4 mg, Safety Analyses Population)

	Safety Analyses Population (N=14)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
AE	17	6 (42.86%)	13	2 (14.29%)	2	2 (14.29%)	2	2 (14.29%)
Investigations	8	2 (14.29%)	8	2 (14.29%)	0	0	0	0
Alanine aminotransferase increased	2	2 (14.29%)	2	2 (14.29%)	0	0	0	0
Neutrophil count increased	2	2 (14.29%)	2	2 (14.29%)	0	0	0	0
Neutrophil percentage increased	2	2 (14.29%)	2	2 (14.29%)	0	0	0	0
White blood cell count increased	2	2 (14.29%)	2	2 (14.29%)	0	0	0	0
Musculoskeletal and connective tissue disorders	2	2 (14.29%)	1	1 (7.14%)	0	0	1	1 (7.14%)
Rheumatoid arthritis	1	1 (7.14%)	0	0	0	0	1	1 (7.14%)
Spinal osteoarthritis	1	1 (7.14%)	1	1 (7.14%)	0	0	0	0
Blood and lymphatic system disorders	1	1 (7.14%)	1	1 (7.14%)	0	0	0	0
Anaemia	1	1 (7.14%)	1	1 (7.14%)	0	0	0	0
Ear and labyrinth disorders	1	1 (7.14%)	0	0	1	1 (7.14%)	0	0
Vertigo	1	1 (7.14%)	0	0	1	1 (7.14%)	0	0
Gastrointestinal disorders	1	1 (7.14%)	1	1 (7.14%)	0	0	0	0
Gastrooesophageal reflux disease	1	1 (7.14%)	1	1 (7.14%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=14)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Hepatobiliary disorders	1	1 (7.14%)	0	0	1	1 (7.14%)	0	0
Hepatic function abnormal	1	1 (7.14%)	0	0	1	1 (7.14%)	0	0
Infections and infestations	1	1 (7.14%)	0	0	0	0	1	1 (7.14%)
Pneumonia	1	1 (7.14%)	0	0	0	0	1	1 (7.14%)
Skin and subcutaneous tissue disorders	2	1 (7.14%)	2	1 (7.14%)	0	0	0	0
Alopecia	1	1 (7.14%)	1	1 (7.14%)	0	0	0	0
Pruritus	1	1 (7.14%)	1	1 (7.14%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

Table ANN. 332 **AEs over a Period of 12 Weeks — MedDRA Preferred Term by Decreasing Frequency (Other Mixed Dosage, Safety Analyses Population)**

	Safety Analyses Population (N=20)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
AE	16	7 (35.00%)	14	5 (25.00%)	1	1 (5.00%)	1	1 (5.00%)
Investigations	5	3 (15.00%)	5	3 (15.00%)	0	0	0	0
Blood albumin decreased	1	1 (5.00%)	1	1 (5.00%)	0	0	0	0
Haemoglobin decreased	1	1 (5.00%)	1	1 (5.00%)	0	0	0	0
Neutrophil count increased	1	1 (5.00%)	1	1 (5.00%)	0	0	0	0
Neutrophil percentage increased	1	1 (5.00%)	1	1 (5.00%)	0	0	0	0
White blood cell count increased	1	1 (5.00%)	1	1 (5.00%)	0	0	0	0
Gastrointestinal disorders	2	2 (10.00%)	2	2 (10.00%)	0	0	0	0
Aphthous ulcer	1	1 (5.00%)	1	1 (5.00%)	0	0	0	0
Diarrhoea	1	1 (5.00%)	1	1 (5.00%)	0	0	0	0
General disorders and administration site conditions	2	2 (10.00%)	1	1 (5.00%)	1	1 (5.00%)	0	0
Chest pain	1	1 (5.00%)	1	1 (5.00%)	0	0	0	0
Oedema peripheral	1	1 (5.00%)	0	0	1	1 (5.00%)	0	0
Respiratory, thoracic and mediastinal disorders	2	2 (10.00%)	1	1 (5.00%)	0	0	1	1 (5.00%)
Chronic obstructive pulmonary disease	1	1 (5.00%)	0	0	0	0	1	1 (5.00%)
Cough	1	1 (5.00%)	1	1 (5.00%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

SOC / PT	Safety Analyses Population (N=20) Overall Event	Overall n (%)	Severity Mild Event	Mild n (%)	Moderate Event	Moderate n (%)	Severe Event	Severe n (%)
Blood and lymphatic system disorders	1	1 (5.00%)	1	1 (5.00%)	0	0	0	0
Thrombocytosis	1	1 (5.00%)	1	1 (5.00%)	0	0	0	0
Hepatobiliary disorders	1	1 (5.00%)	1	1 (5.00%)	0	0	0	0
Hepatic function abnormal	1	1 (5.00%)	1	1 (5.00%)	0	0	0	0
Musculoskeletal and connective tissue disorders	1	1 (5.00%)	1	1 (5.00%)	0	0	0	0
Pain in extremity	1	1 (5.00%)	1	1 (5.00%)	0	0	0	0
Nervous system disorders	1	1 (5.00%)	1	1 (5.00%)	0	0	0	0
Headache	1	1 (5.00%)	1	1 (5.00%)	0	0	0	0
Renal and urinary disorders	1	1 (5.00%)	1	1 (5.00%)	0	0	0	0
Renal impairment	1	1 (5.00%)	1	1 (5.00%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

Table ANN. 333 **AEs over a Period of 24 Weeks by Maximum Severity — MedDRA Preferred Term by Decreasing Frequency, within System Organ Class (2 mg only, Safety Analyses Population)**

	Safety Analyses Population (N=580)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
AE	357	221 (38.10%)	254	144 (24.83%)	81	57 (9.83%)	22	20 (3.45%)
Infections and infestations	70	60 (10.34%)	41	33 (5.69%)	24	22 (3.79%)	5	5 (0.86%)
Upper respiratory tract infection	21	18 (3.10%)	15	13 (2.24%)	6	5 (0.86%)	0	0
Urinary tract infection	14	14 (2.41%)	10	10 (1.72%)	4	4 (0.69%)	0	0
Pneumonia	9	8 (1.38%)	1	1 (0.17%)	6	5 (0.86%)	2	2 (0.34%)
Herpes zoster	6	6 (1.03%)	1	1 (0.17%)	5	5 (0.86%)	0	0
Pharyngitis	3	3 (0.52%)	1	1 (0.17%)	2	2 (0.34%)	0	0
Appendicitis	1	1 (0.17%)	0	0	0	0	1	1 (0.17%)
Bronchitis	1	1 (0.17%)	0	0	1	1 (0.17%)	0	0
Enterovirus infection	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Gingivitis	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Herpes ophthalmic	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Herpes simplex	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Herpes virus infection	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Influenza	1	1 (0.17%)	0	0	0	0	1	1 (0.17%)
Otitis externa	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Otitis media	1	1 (0.17%)	0	0	0	0	1	1 (0.17%)
Periodontitis	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Pulmonary tuberculosis	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=580)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Pulpitis dental	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Streptococcal infection	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Tonsillitis	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Urethritis	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Vulvovaginal mycotic infection	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Investigations	68	55 (9.48%)	66	53 (9.14%)	2	2 (0.34%)	0	0
Platelet count increased	16	16 (2.76%)	16	16 (2.76%)	0	0	0	0
Lymphocyte count decreased	10	10 (1.72%)	9	9 (1.55%)	1	1 (0.17%)	0	0
White blood cell count decreased	6	6 (1.03%)	6	6 (1.03%)	0	0	0	0
White blood cell count increased	7	6 (1.03%)	7	6 (1.03%)	0	0	0	0
Alanine aminotransferase increased	3	3 (0.52%)	3	3 (0.52%)	0	0	0	0
Aspartate aminotransferase increased	3	3 (0.52%)	3	3 (0.52%)	0	0	0	0
Neutrophil count increased	4	3 (0.52%)	4	3 (0.52%)	0	0	0	0
Blood bilirubin increased	2	2 (0.34%)	2	2 (0.34%)	0	0	0	0
Blood pressure increased	2	2 (0.34%)	1	1 (0.17%)	1	1 (0.17%)	0	0
Fibrin D dimer increased	2	2 (0.34%)	2	2 (0.34%)	0	0	0	0
Blood creatine phosphokinase increased	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Blood triglycerides increased	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Coagulation test abnormal	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
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MedDRA English version 25.1

	Safety Analyses Population (N=580)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Lipids increased	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Liver function test abnormal	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Lymphocyte count increased	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Lymphocyte percentage increased	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Neutrophil count decreased	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Platelet count decreased	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Protein urine present	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Red blood cells urine positive	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Weight decreased	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Weight increased	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Metabolism and nutrition disorders	34	29 (5.00%)	29	25 (4.31%)	4	3 (0.52%)	1	1 (0.17%)
Hyperlipidaemia	8	8 (1.38%)	7	7 (1.21%)	1	1 (0.17%)	0	0
Hyperuricaemia	6	6 (1.03%)	6	6 (1.03%)	0	0	0	0
Decreased appetite	5	5 (0.86%)	5	5 (0.86%)	0	0	0	0
Dyslipidaemia	2	2 (0.34%)	2	2 (0.34%)	0	0	0	0
Electrolyte imbalance	3	2 (0.34%)	2	1 (0.17%)	1	1 (0.17%)	0	0
Hypocalcaemia	2	2 (0.34%)	2	2 (0.34%)	0	0	0	0
Hypokalaemia	2	2 (0.34%)	2	2 (0.34%)	0	0	0	0
Diabetes mellitus	1	1 (0.17%)	0	0	1	1 (0.17%)	0	0

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	Safety Analyses Population (N=580)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Glucose tolerance impaired	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Hypercholesterolaemia	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Hyperkalaemia	1	1 (0.17%)	0	0	0	0	1	1 (0.17%)
Hypoalbuminaemia	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Hypoglycaemia	1	1 (0.17%)	0	0	1	1 (0.17%)	0	0
Gastrointestinal disorders	32	27 (4.66%)	24	21 (3.62%)	6	4 (0.69%)	2	2 (0.34%)
Abdominal pain upper	4	4 (0.69%)	3	3 (0.52%)	1	1 (0.17%)	0	0
Abdominal discomfort	3	3 (0.52%)	3	3 (0.52%)	0	0	0	0
Diarrhoea	3	3 (0.52%)	3	3 (0.52%)	0	0	0	0
Gastrointestinal disorder	3	3 (0.52%)	3	3 (0.52%)	0	0	0	0
Nausea	3	3 (0.52%)	3	3 (0.52%)	0	0	0	0
Mouth ulceration	3	2 (0.34%)	3	2 (0.34%)	0	0	0	0
Abdominal distension	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Dry mouth	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Functional gastrointestinal disorder	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Gastritis	1	1 (0.17%)	0	0	1	1 (0.17%)	0	0
Gastritis erosive	2	1 (0.17%)	0	0	2	1 (0.17%)	0	0
Ileus paralytic	1	1 (0.17%)	0	0	0	0	1	1 (0.17%)
Noninfective gingivitis	1	1 (0.17%)	0	0	1	1 (0.17%)	0	0

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	Safety Analyses Population (N=580)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Oral mucosal eruption	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Pancreatitis acute	1	1 (0.17%)	0	0	0	0	1	1 (0.17%)
Periodontal disease	1	1 (0.17%)	0	0	1	1 (0.17%)	0	0
Stomatitis	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Toothache	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Blood and lymphatic system disorders	26	25 (4.31%)	22	21 (3.62%)	4	4 (0.69%)	0	0
Anaemia	14	13 (2.24%)	12	11 (1.90%)	2	2 (0.34%)	0	0
Thrombocytosis	3	3 (0.52%)	3	3 (0.52%)	0	0	0	0
Coagulopathy	2	2 (0.34%)	2	2 (0.34%)	0	0	0	0
Leukopenia	2	2 (0.34%)	2	2 (0.34%)	0	0	0	0
Myelosuppression	2	2 (0.34%)	0	0	2	2 (0.34%)	0	0
Eosinophilia	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Monocytosis	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Thrombocytopenia	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Musculoskeletal and connective tissue disorders	30	25 (4.31%)	10	7 (1.21%)	14	12 (2.07%)	6	6 (1.03%)
Arthralgia	9	8 (1.38%)	3	3 (0.52%)	5	4 (0.69%)	1	1 (0.17%)
Rheumatoid arthritis	7	7 (1.21%)	2	2 (0.34%)	3	3 (0.52%)	2	2 (0.34%)
Intervertebral disc protrusion	3	3 (0.52%)	1	1 (0.17%)	1	1 (0.17%)	1	1 (0.17%)

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	Safety Analyses Population (N=580)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Joint swelling	2	2 (0.34%)	1	1 (0.17%)	1	1 (0.17%)	0	0
Osteonecrosis	2	2 (0.34%)	1	1 (0.17%)	0	0	1	1 (0.17%)
Palindromic rheumatism	2	2 (0.34%)	0	0	2	2 (0.34%)	0	0
Arthropathy	1	1 (0.17%)	0	0	1	1 (0.17%)	0	0
Back pain	1	1 (0.17%)	0	0	1	1 (0.17%)	0	0
Lumbar spinal stenosis	1	1 (0.17%)	0	0	0	0	1	1 (0.17%)
Spinal osteoarthritis	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Synovial cyst	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Hepatobiliary disorders	25	22 (3.79%)	15	14 (2.41%)	8	7 (1.21%)	2	1 (0.17%)
Hepatic function abnormal	21	19 (3.28%)	14	13 (2.24%)	7	6 (1.03%)	0	0
Drug-induced liver injury	3	2 (0.34%)	0	0	1	1 (0.17%)	2	1 (0.17%)
Liver injury	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Skin and subcutaneous tissue disorders	12	12 (2.07%)	7	7 (1.21%)	5	5 (0.86%)	0	0
Acne	3	3 (0.52%)	2	2 (0.34%)	1	1 (0.17%)	0	0
Alopecia	3	3 (0.52%)	1	1 (0.17%)	2	2 (0.34%)	0	0
Rash	2	2 (0.34%)	2	2 (0.34%)	0	0	0	0
Dermatitis	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Night sweats	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0

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All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
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	Safety Analyses Population (N=580)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Skin erosion	1	1 (0.17%)	0	0	1	1 (0.17%)	0	0
Skin ulcer	1	1 (0.17%)	0	0	1	1 (0.17%)	0	0
Respiratory, thoracic and mediastinal disorders	11	10 (1.72%)	7	6 (1.03%)	4	4 (0.69%)	0	0
Cough	5	5 (0.86%)	3	3 (0.52%)	2	2 (0.34%)	0	0
Bronchiectasis	2	2 (0.34%)	1	1 (0.17%)	1	1 (0.17%)	0	0
Interstitial lung disease	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Laryngeal pain	1	1 (0.17%)	0	0	1	1 (0.17%)	0	0
Oropharyngeal pain	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Productive cough	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
General disorders and administration site conditions	10	9 (1.55%)	8	7 (1.21%)	1	1 (0.17%)	1	1 (0.17%)
Asthenia	2	2 (0.34%)	2	2 (0.34%)	0	0	0	0
Chest discomfort	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Chest pain	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Chills	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Death	1	1 (0.17%)	0	0	0	0	1	1 (0.17%)
Face oedema	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Oedema peripheral	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Peripheral swelling	1	1 (0.17%)	0	0	1	1 (0.17%)	0	0

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	Safety Analyses Population (N=580)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Pyrexia	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Reproductive system and breast disorders	7	6 (1.03%)	6	5 (0.86%)	1	1 (0.17%)	0	0
Abnormal uterine bleeding	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Adenomyosis	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Breast mass	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Dysmenorrhoea	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Ectropion of cervix	1	1 (0.17%)	0	0	1	1 (0.17%)	0	0
Menstrual disorder	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Vaginal discharge	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Vascular disorders	6	6 (1.03%)	3	3 (0.52%)	3	3 (0.52%)	0	0
Hypertension	5	5 (0.86%)	2	2 (0.34%)	3	3 (0.52%)	0	0
Arteriosclerosis	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Ear and labyrinth disorders	4	4 (0.69%)	2	2 (0.34%)	1	1 (0.17%)	1	1 (0.17%)
Vertigo	2	2 (0.34%)	1	1 (0.17%)	1	1 (0.17%)	0	0
Cerumen impaction	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Otolithiasis	1	1 (0.17%)	0	0	0	0	1	1 (0.17%)

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	Safety Analyses Population (N=580)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Eye disorders	4	4 (0.69%)	4	4 (0.69%)	0	0	0	0
Cataract	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Dry eye	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Eyelid oedema	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Ocular discomfort	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Nervous system disorders	4	4 (0.69%)	2	2 (0.34%)	1	1 (0.17%)	1	1 (0.17%)
Carotid artery aneurysm	1	1 (0.17%)	0	0	0	0	1	1 (0.17%)
Headache	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Neuropathy peripheral	1	1 (0.17%)	0	0	1	1 (0.17%)	0	0
Somnolence	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Endocrine disorders	4	3 (0.52%)	3	2 (0.34%)	0	0	1	1 (0.17%)
Thyroid mass	3	2 (0.34%)	2	1 (0.17%)	0	0	1	1 (0.17%)
Hypothyroidism	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Injury, poisoning and procedural complications	3	3 (0.52%)	1	1 (0.17%)	1	1 (0.17%)	1	1 (0.17%)
Limb injury	1	1 (0.17%)	0	0	1	1 (0.17%)	0	0
Lumbar vertebral fracture	1	1 (0.17%)	0	0	0	0	1	1 (0.17%)
Tendon injury	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0

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	Safety Analyses Population (N=580)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Psychiatric disorders	3	3 (0.52%)	3	3 (0.52%)	0	0	0	0
Anxiety disorder	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Insomnia	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Sleep disorder	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Cardiac disorders	1	1 (0.17%)	0	0	1	1 (0.17%)	0	0
Arteriosclerosis coronary artery	1	1 (0.17%)	0	0	1	1 (0.17%)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Thyroid cancer	1	1 (0.17%)	1	1 (0.17%)	0	0	0	0
Pregnancy, puerperium and perinatal conditions	1	1 (0.17%)	0	0	0	0	1	1 (0.17%)
Abortion threatened	1	1 (0.17%)	0	0	0	0	1	1 (0.17%)
Renal and urinary disorders	1	1 (0.17%)	0	0	1	1 (0.17%)	0	0
Renal failure	1	1 (0.17%)	0	0	1	1 (0.17%)	0	0

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Table ANN. 334 AEs over a Period of 24 Weeks Maximum Severity— MedDRA Preferred Term by Decreasing Frequency, within System Organ Class (4 mg only, Safety Analyses Population)

	Safety Analyses Population (N=53)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
AE	28	14 (26.42%)	19	7 (13.21%)	5	5 (9.43%)	4	2 (3.77%)
Metabolism and nutrition disorders	5	5 (9.43%)	3	3 (5.66%)	2	2 (3.77%)	0	0
Hyperlipidaemia	2	2 (3.77%)	1	1 (1.89%)	1	1 (1.89%)	0	0
Hypertriglyceridaemia	1	1 (1.89%)	0	0	1	1 (1.89%)	0	0
Hypocalcaemia	1	1 (1.89%)	1	1 (1.89%)	0	0	0	0
Vitamin D deficiency	1	1 (1.89%)	1	1 (1.89%)	0	0	0	0
Gastrointestinal disorders	3	3 (5.66%)	3	3 (5.66%)	0	0	0	0
Gastrointestinal disorder	1	1 (1.89%)	1	1 (1.89%)	0	0	0	0
Haemorrhagic erosive gastritis	1	1 (1.89%)	1	1 (1.89%)	0	0	0	0
Oral blood blister	1	1 (1.89%)	1	1 (1.89%)	0	0	0	0
Musculoskeletal and connective tissue disorders	3	3 (5.66%)	0	0	1	1 (1.89%)	2	2 (3.77%)
Rheumatoid arthritis	2	2 (3.77%)	0	0	1	1 (1.89%)	1	1 (1.89%)
Arthralgia	1	1 (1.89%)	0	0	0	0	1	1 (1.89%)
Infections and infestations	2	2 (3.77%)	2	2 (3.77%)	0	0	0	0
Herpes zoster	1	1 (1.89%)	1	1 (1.89%)	0	0	0	0
Urinary tract infection	1	1 (1.89%)	1	1 (1.89%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
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	Safety Analyses Population (N=53)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Nervous system disorders	2	2 (3.77%)	1	1 (1.89%)	1	1 (1.89%)	0	0
Dizziness	1	1 (1.89%)	1	1 (1.89%)	0	0	0	0
Optic neuritis	1	1 (1.89%)	0	0	1	1 (1.89%)	0	0
Skin and subcutaneous tissue disorders	2	2 (3.77%)	2	2 (3.77%)	0	0	0	0
Alopecia	1	1 (1.89%)	1	1 (1.89%)	0	0	0	0
Eczema	1	1 (1.89%)	1	1 (1.89%)	0	0	0	0
Endocrine disorders	1	1 (1.89%)	0	0	1	1 (1.89%)	0	0
Hypothyroidism	1	1 (1.89%)	0	0	1	1 (1.89%)	0	0
Eye disorders	2	1 (1.89%)	0	0	0	0	2	1 (1.89%)
Cataract	2	1 (1.89%)	0	0	0	0	2	1 (1.89%)
Hepatobiliary disorders	1	1 (1.89%)	1	1 (1.89%)	0	0	0	0
Hepatic function abnormal	1	1 (1.89%)	1	1 (1.89%)	0	0	0	0
Injury, poisoning and procedural complications	1	1 (1.89%)	1	1 (1.89%)	0	0	0	0
Nail injury	1	1 (1.89%)	1	1 (1.89%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=53)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Investigations	3	1 (1.89%)	3	1 (1.89%)	0	0	0	0
Neutrophil count increased	1	1 (1.89%)	1	1 (1.89%)	0	0	0	0
Neutrophil percentage increased	1	1 (1.89%)	1	1 (1.89%)	0	0	0	0
White blood cell count increased	1	1 (1.89%)	1	1 (1.89%)	0	0	0	0
Psychiatric disorders	1	1 (1.89%)	1	1 (1.89%)	0	0	0	0
Sleep disorder	1	1 (1.89%)	1	1 (1.89%)	0	0	0	0
Vascular disorders	2	1 (1.89%)	2	1 (1.89%)	0	0	0	0
Hypertension	2	1 (1.89%)	2	1 (1.89%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

Table ANN. 335 **AEs over a Period of 24 Weeks by Maximum Severity— MedDRA Preferred Term by Decreasing Frequency, within System Organ Class (both dosages, Safety Analyses Population)**

	Safety Analyses Population (N=34)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
AE	43	15 (44.12%)	32	7 (20.59%)	8	5 (14.71%)	3	3 (8.82%)
Investigations	15	6 (17.65%)	15	6 (17.65%)	0	0	0	0
Neutrophil count increased	3	3 (8.82%)	3	3 (8.82%)	0	0	0	0
Neutrophil percentage increased	3	3 (8.82%)	3	3 (8.82%)	0	0	0	0
White blood cell count increased	4	3 (8.82%)	4	3 (8.82%)	0	0	0	0
Alanine aminotransferase increased	2	2 (5.88%)	2	2 (5.88%)	0	0	0	0
Blood albumin decreased	1	1 (2.94%)	1	1 (2.94%)	0	0	0	0
Haemoglobin decreased	1	1 (2.94%)	1	1 (2.94%)	0	0	0	0
Rheumatoid factor increased	1	1 (2.94%)	1	1 (2.94%)	0	0	0	0
Musculoskeletal and connective tissue disorders	8	5 (14.71%)	4	3 (8.82%)	3	1 (2.94%)	1	1 (2.94%)
Rheumatoid arthritis	2	2 (5.88%)	1	1 (2.94%)	0	0	1	1 (2.94%)
Arthralgia	2	1 (2.94%)	0	0	2	1 (2.94%)	0	0
Back pain	1	1 (2.94%)	1	1 (2.94%)	0	0	0	0
Pain in extremity	1	1 (2.94%)	1	1 (2.94%)	0	0	0	0
Spinal osteoarthritis	1	1 (2.94%)	1	1 (2.94%)	0	0	0	0
Synovial cyst	1	1 (2.94%)	0	0	1	1 (2.94%)	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
Both dosages subgroup includes 2 mg to 4 mg and other mixed dosage subgroups.
MedDRA English version 25.1

	Safety Analyses Population (N=34)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Gastrointestinal disorders	3	3 (8.82%)	3	3 (8.82%)	0	0	0	0
Aphthous ulcer	1	1 (2.94%)	1	1 (2.94%)	0	0	0	0
Diarrhoea	1	1 (2.94%)	1	1 (2.94%)	0	0	0	0
Gastrooesophageal reflux disease	1	1 (2.94%)	1	1 (2.94%)	0	0	0	0
Blood and lymphatic system disorders	2	2 (5.88%)	2	2 (5.88%)	0	0	0	0
Anaemia	1	1 (2.94%)	1	1 (2.94%)	0	0	0	0
Thrombocytosis	1	1 (2.94%)	1	1 (2.94%)	0	0	0	0
General disorders and administration site conditions	2	2 (5.88%)	1	1 (2.94%)	1	1 (2.94%)	0	0
Chest pain	1	1 (2.94%)	1	1 (2.94%)	0	0	0	0
Oedema peripheral	1	1 (2.94%)	0	0	1	1 (2.94%)	0	0
Hepatobiliary disorders	2	2 (5.88%)	1	1 (2.94%)	1	1 (2.94%)	0	0
Hepatic function abnormal	2	2 (5.88%)	1	1 (2.94%)	1	1 (2.94%)	0	0
Infections and infestations	2	2 (5.88%)	0	0	1	1 (2.94%)	1	1 (2.94%)
Laryngopharyngitis	1	1 (2.94%)	0	0	1	1 (2.94%)	0	0
Pneumonia	1	1 (2.94%)	0	0	0	0	1	1 (2.94%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
Both dosages subgroup includes 2 mg to 4 mg and other mixed dosage subgroups.
MedDRA English version 25.1

SOC / PT	Safety Analyses Population (N=34) Overall Event	Overall n (%)	Severity Mild Event	Mild n (%)	Moderate Event	Moderate n (%)	Severe Event	Severe n (%)
Nervous system disorders	2	2 (5.88%)	1	1 (2.94%)	1	1 (2.94%)	0	0
Headache	2	2 (5.88%)	1	1 (2.94%)	1	1 (2.94%)	0	0
Respiratory, thoracic and mediastinal disorders	2	2 (5.88%)	1	1 (2.94%)	0	0	1	1 (2.94%)
Chronic obstructive pulmonary disease	1	1 (2.94%)	0	0	0	0	1	1 (2.94%)
Cough	1	1 (2.94%)	1	1 (2.94%)	0	0	0	0
Ear and labyrinth disorders	1	1 (2.94%)	0	0	1	1 (2.94%)	0	0
Vertigo	1	1 (2.94%)	0	0	1	1 (2.94%)	0	0
Metabolism and nutrition disorders	1	1 (2.94%)	1	1 (2.94%)	0	0	0	0
Hyperlipidaemia	1	1 (2.94%)	1	1 (2.94%)	0	0	0	0
Renal and urinary disorders	1	1 (2.94%)	1	1 (2.94%)	0	0	0	0
Renal impairment	1	1 (2.94%)	1	1 (2.94%)	0	0	0	0
Skin and subcutaneous tissue disorders	2	1 (2.94%)	2	1 (2.94%)	0	0	0	0
Alopecia	1	1 (2.94%)	1	1 (2.94%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
Both dosages subgroup includes 2 mg to 4 mg and other mixed dosage subgroups.
MedDRA English version 25.1

	Safety Analyses Population (N=34)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Pruritus	1	1 (2.94%)	1	1 (2.94%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
Both dosages subgroup includes 2 mg to 4 mg and other mixed dosage subgroups.
MedDRA English version 25.1

Table ANN. 336 **AEs over a Period of 24 Weeks by Maximum Severity— MedDRA Preferred Term by Decreasing Frequency, within System Organ Class (2 mg to 4 mg, Safety Analyses Population)**

	Safety Analyses Population (N=14)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
AE	21	6 (42.86%)	15	2 (14.29%)	4	2 (14.29%)	2	2 (14.29%)
Musculoskeletal and connective tissue disorders	4	3 (21.43%)	2	2 (14.29%)	1	0	1	1 (7.14%)
Rheumatoid arthritis	2	2 (14.29%)	1	1 (7.14%)	0	0	1	1 (7.14%)
Spinal osteoarthritis	1	1 (7.14%)	1	1 (7.14%)	0	0	0	0
Synovial cyst	1	1 (7.14%)	0	0	1	1 (7.14%)	0	0
Infections and infestations	2	2 (14.29%)	0	0	1	1 (7.14%)	1	1 (7.14%)
Laryngopharyngitis	1	1 (7.14%)	0	0	1	1 (7.14%)	0	0
Pneumonia	1	1 (7.14%)	0	0	0	0	1	1 (7.14%)
Investigations	9	2 (14.29%)	9	2 (14.29%)	0	0	0	0
Alanine aminotransferase increased	2	2 (14.29%)	2	2 (14.29%)	0	0	0	0
Neutrophil count increased	2	2 (14.29%)	2	2 (14.29%)	0	0	0	0
Neutrophil percentage increased	2	2 (14.29%)	2	2 (14.29%)	0	0	0	0
White blood cell count increased	3	2 (14.29%)	3	2 (14.29%)	0	0	0	0
Blood and lymphatic system disorders	1	1 (7.14%)	1	1 (7.14%)	0	0	0	0
Anaemia	1	1 (7.14%)	1	1 (7.14%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=14)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Ear and labyrinth disorders	1	1 (7.14%)	0	0	1	1 (7.14%)	0	0
Vertigo	1	1 (7.14%)	0	0	1	1 (7.14%)	0	0
Gastrointestinal disorders	1	1 (7.14%)	1	1 (7.14%)	0	0	0	0
Gastrooesophageal reflux disease	1	1 (7.14%)	1	1 (7.14%)	0	0	0	0
Hepatobiliary disorders	1	1 (7.14%)	0	0	1	1 (7.14%)	0	0
Hepatic function abnormal	1	1 (7.14%)	0	0	1	1 (7.14%)	0	0
Skin and subcutaneous tissue disorders	2	1 (7.14%)	2	1 (7.14%)	0	0	0	0
Alopecia	1	1 (7.14%)	1	1 (7.14%)	0	0	0	0
Pruritus	1	1 (7.14%)	1	1 (7.14%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

Table ANN. 337 **AEs over a Period of 24 Weeks by Maximum Severity— MedDRA Preferred Term by Decreasing Frequency, within System Organ Class (Other mixed dosage, Safety Analyses Population)**

	Safety Analyses Population (N=20)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
AE	22	9 (45.00%)	17	5 (25.00%)	4	3 (15.00%)	1	1 (5.00%)
Investigations	6	4 (20.00%)	6	4 (20.00%)	0	0	0	0
Blood albumin decreased	1	1 (5.00%)	1	1 (5.00%)	0	0	0	0
Haemoglobin decreased	1	1 (5.00%)	1	1 (5.00%)	0	0	0	0
Neutrophil count increased	1	1 (5.00%)	1	1 (5.00%)	0	0	0	0
Neutrophil percentage increased	1	1 (5.00%)	1	1 (5.00%)	0	0	0	0
Rheumatoid factor increased	1	1 (5.00%)	1	1 (5.00%)	0	0	0	0
White blood cell count increased	1	1 (5.00%)	1	1 (5.00%)	0	0	0	0
Gastrointestinal disorders	2	2 (10.00%)	2	2 (10.00%)	0	0	0	0
Aphthous ulcer	1	1 (5.00%)	1	1 (5.00%)	0	0	0	0
Diarrhoea	1	1 (5.00%)	1	1 (5.00%)	0	0	0	0
General disorders and administration site conditions	2	2 (10.00%)	1	1 (5.00%)	1	1 (5.00%)	0	0
Chest pain	1	1 (5.00%)	1	1 (5.00%)	0	0	0	0
Oedema peripheral	1	1 (5.00%)	0	0	1	1 (5.00%)	0	0
Musculoskeletal and connective tissue disorders	4	2 (10.00%)	2	1 (5.00%)	2	1 (5.00%)	0	0
Arthralgia	2	1 (5.00%)	0	0	2	1 (5.00%)	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=20)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Back pain	1	1 (5.00%)	1	1 (5.00%)	0	0	0	0
Pain in extremity	1	1 (5.00%)	1	1 (5.00%)	0	0	0	0
Nervous system disorders	2	2 (10.00%)	1	1 (5.00%)	1	1 (5.00%)	0	0
Headache	2	2 (10.00%)	1	1 (5.00%)	1	1 (5.00%)	0	0
Respiratory, thoracic and mediastinal disorders	2	2 (10.00%)	1	1 (5.00%)	0	0	1	1 (5.00%)
Chronic obstructive pulmonary disease	1	1 (5.00%)	0	0	0	0	1	1 (5.00%)
Cough	1	1 (5.00%)	1	1 (5.00%)	0	0	0	0
Blood and lymphatic system disorders	1	1 (5.00%)	1	1 (5.00%)	0	0	0	0
Thrombocytosis	1	1 (5.00%)	1	1 (5.00%)	0	0	0	0
Hepatobiliary disorders	1	1 (5.00%)	1	1 (5.00%)	0	0	0	0
Hepatic function abnormal	1	1 (5.00%)	1	1 (5.00%)	0	0	0	0
Metabolism and nutrition disorders	1	1 (5.00%)	1	1 (5.00%)	0	0	0	0
Hyperlipidaemia	1	1 (5.00%)	1	1 (5.00%)	0	0	0	0
Renal and urinary disorders	1	1 (5.00%)	1	1 (5.00%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

	Safety Analyses Population (N=20)		*Severity*					
SOC	*Overall*		*Mild*		*Moderate*		*Severe*	
PT	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*	*Event*	*n (%)*
Renal impairment	1	1 (5.00%)	1	1 (5.00%)	0	0	0	0

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term; SOC, system organ class
All AEs are summarized for event. n is the number of patients and % is the percentage. For the summary of number of patients, the AE with maximum severity are summarized for patient within the specific SOC and PT of the corresponding row.
The SOCs are sorted by decreasing overall number of patients, while the PTs are sorted by decreasing overall number of patients within SOC.
MedDRA English version 25.1

Table ANN. 338 AEs over a Period of 12 weeks— MedDRA Preferred Term by Decreasing Frequency (2 mg only, Safety Analyses Population)

	Safety Analyses Population (N=580)	
PT	*Event*	*n (%)*
AE	272	187 (32.24%)
Upper respiratory tract infection	18	17 (2.93%)
Hepatic function abnormal	15	15 (2.59%)
Platelet count increased	14	14 (2.41%)
Urinary tract infection	10	10 (1.72%)
Anaemia	9	9 (1.55%)
Lymphocyte count decreased	7	7 (1.21%)
Arthralgia	6	6 (1.03%)
Hyperlipidaemia	6	6 (1.03%)
Hypertension	5	5 (0.86%)
Hyperuricaemia	5	5 (0.86%)
Pneumonia	6	5 (0.86%)
Rheumatoid arthritis	5	5 (0.86%)
White blood cell count decreased	5	5 (0.86%)
White blood cell count increased	5	5 (0.86%)
Decreased appetite	4	4 (0.69%)
Abdominal pain upper	3	3 (0.52%)
Acne	3	3 (0.52%)
Alanine aminotransferase increased	3	3 (0.52%)
Cough	3	3 (0.52%)
Diarrhoea	3	3 (0.52%)
Gastrointestinal disorder	3	3 (0.52%)
Herpes zoster	3	3 (0.52%)
Intervertebral disc protrusion	3	3 (0.52%)
Nausea	3	3 (0.52%)
Neutrophil count increased	3	3 (0.52%)
Pharyngitis	3	3 (0.52%)
Thrombocytosis	3	3 (0.52%)
Abdominal discomfort	2	2 (0.34%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

	Safety Analyses Population (N=580)	
PT	*Event*	*n (%)*
Alopecia	2	2 (0.34%)
Aspartate aminotransferase increased	2	2 (0.34%)
Blood pressure increased	2	2 (0.34%)
Electrolyte imbalance	3	2 (0.34%)
Fibrin D dimer increased	2	2 (0.34%)
Hypocalcaemia	2	2 (0.34%)
Hypokalaemia	2	2 (0.34%)
Joint swelling	2	2 (0.34%)
Leukopenia	2	2 (0.34%)
Mouth ulceration	3	2 (0.34%)
Myelosuppression	2	2 (0.34%)
Thyroid mass	3	2 (0.34%)
Abdominal distension	1	1 (0.17%)
Abnormal uterine bleeding	1	1 (0.17%)
Adenomyosis	1	1 (0.17%)
Arteriosclerosis	1	1 (0.17%)
Arteriosclerosis coronary artery	1	1 (0.17%)
Asthenia	1	1 (0.17%)
Back pain	1	1 (0.17%)
Blood creatine phosphokinase increased	1	1 (0.17%)
Blood triglycerides increased	1	1 (0.17%)
Bronchiectasis	1	1 (0.17%)
Bronchitis	1	1 (0.17%)
Carotid artery aneurysm	1	1 (0.17%)
Cataract	1	1 (0.17%)
Cerumen impaction	1	1 (0.17%)
Chest discomfort	1	1 (0.17%)
Chest pain	1	1 (0.17%)
Chills	1	1 (0.17%)
Coagulation test abnormal	1	1 (0.17%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

	Safety Analyses Population (N=580)	
PT	*Event*	*n (%)*
Coagulopathy	1	1 (0.17%)
Death	1	1 (0.17%)
Dermatitis	1	1 (0.17%)
Diabetes mellitus	1	1 (0.17%)
Drug-induced liver injury	2	1 (0.17%)
Dry mouth	1	1 (0.17%)
Dyslipidaemia	1	1 (0.17%)
Dysmenorrhoea	1	1 (0.17%)
Ectropion of cervix	1	1 (0.17%)
Enterovirus infection	1	1 (0.17%)
Eosinophilia	1	1 (0.17%)
Eyelid oedema	1	1 (0.17%)
Face oedema	1	1 (0.17%)
Functional gastrointestinal disorder	1	1 (0.17%)
Gastritis	1	1 (0.17%)
Gingivitis	1	1 (0.17%)
Headache	1	1 (0.17%)
Herpes ophthalmic	1	1 (0.17%)
Herpes simplex	1	1 (0.17%)
Herpes virus infection	1	1 (0.17%)
Hypercholesterolaemia	1	1 (0.17%)
Hyperkalaemia	1	1 (0.17%)
Hypoalbuminaemia	1	1 (0.17%)
Hypoglycaemia	1	1 (0.17%)
Hypothyroidism	1	1 (0.17%)
Ileus paralytic	1	1 (0.17%)
Interstitial lung disease	1	1 (0.17%)
Laryngeal pain	1	1 (0.17%)
Lipids increased	1	1 (0.17%)
Lumbar spinal stenosis	1	1 (0.17%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

	Safety Analyses Population (N=580)	
PT	*Event*	*n (%)*
Lumbar vertebral fracture	1	1 (0.17%)
Lymphocyte count increased	1	1 (0.17%)
Lymphocyte percentage increased	1	1 (0.17%)
Menstrual disorder	1	1 (0.17%)
Monocytosis	1	1 (0.17%)
Neuropathy peripheral	1	1 (0.17%)
Night sweats	1	1 (0.17%)
Noninfective gingivitis	1	1 (0.17%)
Oedema peripheral	1	1 (0.17%)
Oropharyngeal pain	1	1 (0.17%)
Otitis externa	1	1 (0.17%)
Otitis media	1	1 (0.17%)
Otolithiasis	1	1 (0.17%)
Pancreatitis acute	1	1 (0.17%)
Periodontal disease	1	1 (0.17%)
Periodontitis	1	1 (0.17%)
Peripheral swelling	1	1 (0.17%)
Productive cough	1	1 (0.17%)
Pulmonary tuberculosis	1	1 (0.17%)
Pulpitis dental	1	1 (0.17%)
Rash	1	1 (0.17%)
Red blood cells urine positive	1	1 (0.17%)
Renal failure	1	1 (0.17%)
Skin erosion	1	1 (0.17%)
Skin ulcer	1	1 (0.17%)
Somnolence	1	1 (0.17%)
Spinal osteoarthritis	1	1 (0.17%)
Stomatitis	1	1 (0.17%)
Streptococcal infection	1	1 (0.17%)
Thrombocytopenia	1	1 (0.17%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

	Safety Analyses Population (N=580)	
PT	*Event*	*n (%)*
Thyroid cancer	1	1 (0.17%)
Tonsillitis	1	1 (0.17%)
Toothache	1	1 (0.17%)
Urethritis	1	1 (0.17%)
Vaginal discharge	1	1 (0.17%)
Vertigo	1	1 (0.17%)
Vulvovaginal mycotic infection	1	1 (0.17%)
Weight increased	1	1 (0.17%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

Table ANN. 339 AEs over a Period of 12 weeks— MedDRA Preferred Term by Decreasing Frequency (4 mg only, Safety Analyses Population)

	Safety Analyses Population (N=53)	
PT	*Event*	*n (%)*
AE	24	14 (26.42%)
Hyperlipidaemia	2	2 (3.77%)
Rheumatoid arthritis	2	2 (3.77%)
Alopecia	1	1 (1.89%)
Arthralgia	1	1 (1.89%)
Dizziness	1	1 (1.89%)
Eczema	1	1 (1.89%)
Gastrointestinal disorder	1	1 (1.89%)
Haemorrhagic erosive gastritis	1	1 (1.89%)
Hepatic function abnormal	1	1 (1.89%)
Hypertension	2	1 (1.89%)
Hypertriglyceridaemia	1	1 (1.89%)
Hypocalcaemia	1	1 (1.89%)
Hypothyroidism	1	1 (1.89%)
Neutrophil count increased	1	1 (1.89%)
Neutrophil percentage increased	1	1 (1.89%)
Optic neuritis	1	1 (1.89%)
Oral blood blister	1	1 (1.89%)
Sleep disorder	1	1 (1.89%)
Urinary tract infection	1	1 (1.89%)
Vitamin D deficiency	1	1 (1.89%)
White blood cell count increased	1	1 (1.89%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

Table ANN. 340 AEs over a Period of 12 weeks— MedDRA Preferred Term by Decreasing Frequency (both dosages, Safety Analyses Population)

	Safety Analyses Population (N=34)	
PT	*Event*	*n (%)*
AE	33	13 (38.24%)
Neutrophil count increased	3	3 (8.82%)
Neutrophil percentage increased	3	3 (8.82%)
White blood cell count increased	3	3 (8.82%)
Alanine aminotransferase increased	2	2 (5.88%)
Hepatic function abnormal	2	2 (5.88%)
Alopecia	1	1 (2.94%)
Anaemia	1	1 (2.94%)
Aphthous ulcer	1	1 (2.94%)
Blood albumin decreased	1	1 (2.94%)
Chest pain	1	1 (2.94%)
Chronic obstructive pulmonary disease	1	1 (2.94%)
Cough	1	1 (2.94%)
Diarrhoea	1	1 (2.94%)
Gastrooesophageal reflux disease	1	1 (2.94%)
Haemoglobin decreased	1	1 (2.94%)
Headache	1	1 (2.94%)
Oedema peripheral	1	1 (2.94%)
Pain in extremity	1	1 (2.94%)
Pneumonia	1	1 (2.94%)
Pruritus	1	1 (2.94%)
Renal impairment	1	1 (2.94%)
Rheumatoid arthritis	1	1 (2.94%)
Spinal osteoarthritis	1	1 (2.94%)
Thrombocytosis	1	1 (2.94%)
Vertigo	1	1 (2.94%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
Both dosages subgroup includes 2 mg to 4 mg and other mixed dosage subgroups.
MedDRA English version 25.1

Table ANN. 341 AEs over a Period of 12 weeks— MedDRA Preferred Term by Decreasing Frequency (2 mg to 4 mg, Safety Analyses Population)

	Safety Analyses Population (N=14)	
PT	*Event*	*n (%)*
AE	17	6 (42.86%)
Alanine aminotransferase increased	2	2 (14.29%)
Neutrophil count increased	2	2 (14.29%)
Neutrophil percentage increased	2	2 (14.29%)
White blood cell count increased	2	2 (14.29%)
Alopecia	1	1 (7.14%)
Anaemia	1	1 (7.14%)
Gastrooesophageal reflux disease	1	1 (7.14%)
Hepatic function abnormal	1	1 (7.14%)
Pneumonia	1	1 (7.14%)
Pruritus	1	1 (7.14%)
Rheumatoid arthritis	1	1 (7.14%)
Spinal osteoarthritis	1	1 (7.14%)
Vertigo	1	1 (7.14%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

Table ANN. 342 AEs over a Period of 12 weeks— MedDRA Preferred Term by Decreasing Frequency (Other mixed dosage, Safety Analyses Population)

	Safety Analyses Population (N=20)	
PT	*Event*	*n (%)*
AE	16	7 (35.00%)
Aphthous ulcer	1	1 (5.00%)
Blood albumin decreased	1	1 (5.00%)
Chest pain	1	1 (5.00%)
Chronic obstructive pulmonary disease	1	1 (5.00%)
Cough	1	1 (5.00%)
Diarrhoea	1	1 (5.00%)
Haemoglobin decreased	1	1 (5.00%)
Headache	1	1 (5.00%)
Hepatic function abnormal	1	1 (5.00%)
Neutrophil count increased	1	1 (5.00%)
Neutrophil percentage increased	1	1 (5.00%)
Oedema peripheral	1	1 (5.00%)
Pain in extremity	1	1 (5.00%)
Renal impairment	1	1 (5.00%)
Thrombocytosis	1	1 (5.00%)
White blood cell count increased	1	1 (5.00%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

Table ANN. 343 AEs over a Period of 24 weeks— MedDRA Preferred Term by Decreasing Frequency (2 mg only, Safety Analyses Population)

	Safety Analyses Population (N=580)	
PT	*Event*	*n (%)*
AE	357	221 (38.10%)
Hepatic function abnormal	21	19 (3.28%)
Upper respiratory tract infection	21	18 (3.10%)
Platelet count increased	16	16 (2.76%)
Urinary tract infection	14	14 (2.41%)
Anaemia	14	13 (2.24%)
Lymphocyte count decreased	10	10 (1.72%)
Arthralgia	9	8 (1.38%)
Hyperlipidaemia	8	8 (1.38%)
Pneumonia	9	8 (1.38%)
Rheumatoid arthritis	7	7 (1.21%)
Herpes zoster	6	6 (1.03%)
Hyperuricaemia	6	6 (1.03%)
White blood cell count decreased	6	6 (1.03%)
White blood cell count increased	7	6 (1.03%)
Cough	5	5 (0.86%)
Decreased appetite	5	5 (0.86%)
Hypertension	5	5 (0.86%)
Abdominal pain upper	4	4 (0.69%)
Abdominal discomfort	3	3 (0.52%)
Acne	3	3 (0.52%)
Alanine aminotransferase increased	3	3 (0.52%)
Alopecia	3	3 (0.52%)
Aspartate aminotransferase increased	3	3 (0.52%)
Diarrhoea	3	3 (0.52%)
Gastrointestinal disorder	3	3 (0.52%)
Intervertebral disc protrusion	3	3 (0.52%)
Nausea	3	3 (0.52%)
Neutrophil count increased	4	3 (0.52%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

	Safety Analyses Population (N=580)	
PT	*Event*	*n (%)*
Pharyngitis	3	3 (0.52%)
Thrombocytosis	3	3 (0.52%)
Asthenia	2	2 (0.34%)
Blood bilirubin increased	2	2 (0.34%)
Blood pressure increased	2	2 (0.34%)
Bronchiectasis	2	2 (0.34%)
Coagulopathy	2	2 (0.34%)
Drug-induced liver injury	3	2 (0.34%)
Dyslipidaemia	2	2 (0.34%)
Electrolyte imbalance	3	2 (0.34%)
Fibrin D dimer increased	2	2 (0.34%)
Hypocalcaemia	2	2 (0.34%)
Hypokalaemia	2	2 (0.34%)
Joint swelling	2	2 (0.34%)
Leukopenia	2	2 (0.34%)
Mouth ulceration	3	2 (0.34%)
Myelosuppression	2	2 (0.34%)
Osteonecrosis	2	2 (0.34%)
Palindromic rheumatism	2	2 (0.34%)
Rash	2	2 (0.34%)
Thyroid mass	3	2 (0.34%)
Vertigo	2	2 (0.34%)
Abdominal distension	1	1 (0.17%)
Abnormal uterine bleeding	1	1 (0.17%)
Abortion threatened	1	1 (0.17%)
Adenomyosis	1	1 (0.17%)
Anxiety disorder	1	1 (0.17%)
Appendicitis	1	1 (0.17%)
Arteriosclerosis	1	1 (0.17%)
Arteriosclerosis coronary artery	1	1 (0.17%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

	Safety Analyses Population (N=580)	
PT	*Event*	*n (%)*
Arthropathy	1	1 (0.17%)
Back pain	1	1 (0.17%)
Blood creatine phosphokinase increased	1	1 (0.17%)
Blood triglycerides increased	1	1 (0.17%)
Breast mass	1	1 (0.17%)
Bronchitis	1	1 (0.17%)
Carotid artery aneurysm	1	1 (0.17%)
Cataract	1	1 (0.17%)
Cerumen impaction	1	1 (0.17%)
Chest discomfort	1	1 (0.17%)
Chest pain	1	1 (0.17%)
Chills	1	1 (0.17%)
Coagulation test abnormal	1	1 (0.17%)
Death	1	1 (0.17%)
Dermatitis	1	1 (0.17%)
Diabetes mellitus	1	1 (0.17%)
Dry eye	1	1 (0.17%)
Dry mouth	1	1 (0.17%)
Dysmenorrhoea	1	1 (0.17%)
Ectropion of cervix	1	1 (0.17%)
Enterovirus infection	1	1 (0.17%)
Eosinophilia	1	1 (0.17%)
Eyelid oedema	1	1 (0.17%)
Face oedema	1	1 (0.17%)
Functional gastrointestinal disorder	1	1 (0.17%)
Gastritis	1	1 (0.17%)
Gastritis erosive	2	1 (0.17%)
Gingivitis	1	1 (0.17%)
Glucose tolerance impaired	1	1 (0.17%)
Headache	1	1 (0.17%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

	Safety Analyses Population (N=580)	
PT	*Event*	*n (%)*
Herpes ophthalmic	1	1 (0.17%)
Herpes simplex	1	1 (0.17%)
Herpes virus infection	1	1 (0.17%)
Hypercholesterolaemia	1	1 (0.17%)
Hyperkalaemia	1	1 (0.17%)
Hypoalbuminaemia	1	1 (0.17%)
Hypoglycaemia	1	1 (0.17%)
Hypothyroidism	1	1 (0.17%)
Ileus paralytic	1	1 (0.17%)
Influenza	1	1 (0.17%)
Insomnia	1	1 (0.17%)
Interstitial lung disease	1	1 (0.17%)
Laryngeal pain	1	1 (0.17%)
Limb injury	1	1 (0.17%)
Lipids increased	1	1 (0.17%)
Liver function test abnormal	1	1 (0.17%)
Liver injury	1	1 (0.17%)
Lumbar spinal stenosis	1	1 (0.17%)
Lumbar vertebral fracture	1	1 (0.17%)
Lymphocyte count increased	1	1 (0.17%)
Lymphocyte percentage increased	1	1 (0.17%)
Menstrual disorder	1	1 (0.17%)
Monocytosis	1	1 (0.17%)
Neuropathy peripheral	1	1 (0.17%)
Neutrophil count decreased	1	1 (0.17%)
Night sweats	1	1 (0.17%)
Noninfective gingivitis	1	1 (0.17%)
Ocular discomfort	1	1 (0.17%)
Oedema peripheral	1	1 (0.17%)
Oral mucosal eruption	1	1 (0.17%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

	Safety Analyses Population (N=580)	
PT	*Event*	*n (%)*
Oropharyngeal pain	1	1 (0.17%)
Otitis externa	1	1 (0.17%)
Otitis media	1	1 (0.17%)
Otolithiasis	1	1 (0.17%)
Pancreatitis acute	1	1 (0.17%)
Periodontal disease	1	1 (0.17%)
Periodontitis	1	1 (0.17%)
Peripheral swelling	1	1 (0.17%)
Platelet count decreased	1	1 (0.17%)
Productive cough	1	1 (0.17%)
Protein urine present	1	1 (0.17%)
Pulmonary tuberculosis	1	1 (0.17%)
Pulpitis dental	1	1 (0.17%)
Pyrexia	1	1 (0.17%)
Red blood cells urine positive	1	1 (0.17%)
Renal failure	1	1 (0.17%)
Skin erosion	1	1 (0.17%)
Skin ulcer	1	1 (0.17%)
Sleep disorder	1	1 (0.17%)
Somnolence	1	1 (0.17%)
Spinal osteoarthritis	1	1 (0.17%)
Stomatitis	1	1 (0.17%)
Streptococcal infection	1	1 (0.17%)
Synovial cyst	1	1 (0.17%)
Tendon injury	1	1 (0.17%)
Thrombocytopenia	1	1 (0.17%)
Thyroid cancer	1	1 (0.17%)
Tonsillitis	1	1 (0.17%)
Toothache	1	1 (0.17%)
Urethritis	1	1 (0.17%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

	Safety Analyses Population (N=580)	
PT	*Event*	*n (%)*
Vaginal discharge	1	1 (0.17%)
Vulvovaginal mycotic infection	1	1 (0.17%)
Weight decreased	1	1 (0.17%)
Weight increased	1	1 (0.17%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

Table ANN. 344 AEs over a Period of 24 weeks— MedDRA Preferred Term by Decreasing Frequency (4 mg only, Safety Analyses Population)

	Safety Analyses Population (N=53)	
PT	*Event*	*n (%)*
AE	28	14 (26.42%)
Hyperlipidaemia	2	2 (3.77%)
Rheumatoid arthritis	2	2 (3.77%)
Alopecia	1	1 (1.89%)
Arthralgia	1	1 (1.89%)
Cataract	2	1 (1.89%)
Dizziness	1	1 (1.89%)
Eczema	1	1 (1.89%)
Gastrointestinal disorder	1	1 (1.89%)
Haemorrhagic erosive gastritis	1	1 (1.89%)
Hepatic function abnormal	1	1 (1.89%)
Herpes zoster	1	1 (1.89%)
Hypertension	2	1 (1.89%)
Hypertriglyceridaemia	1	1 (1.89%)
Hypocalcaemia	1	1 (1.89%)
Hypothyroidism	1	1 (1.89%)
Nail injury	1	1 (1.89%)
Neutrophil count increased	1	1 (1.89%)
Neutrophil percentage increased	1	1 (1.89%)
Optic neuritis	1	1 (1.89%)
Oral blood blister	1	1 (1.89%)
Sleep disorder	1	1 (1.89%)
Urinary tract infection	1	1 (1.89%)
Vitamin D deficiency	1	1 (1.89%)
White blood cell count increased	1	1 (1.89%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

Table ANN. 345 AEs over a Period of 24 weeks— MedDRA Preferred Term by Decreasing Frequency (both dosages, Safety Analyses Population)

	Safety Analyses Population (N=34)	
PT	*Event*	*n (%)*
AE	43	15 (44.12%)
Neutrophil count increased	3	3 (8.82%)
Neutrophil percentage increased	3	3 (8.82%)
White blood cell count increased	4	3 (8.82%)
Alanine aminotransferase increased	2	2 (5.88%)
Headache	2	2 (5.88%)
Hepatic function abnormal	2	2 (5.88%)
Rheumatoid arthritis	2	2 (5.88%)
Alopecia	1	1 (2.94%)
Anaemia	1	1 (2.94%)
Aphthous ulcer	1	1 (2.94%)
Arthralgia	2	1 (2.94%)
Back pain	1	1 (2.94%)
Blood albumin decreased	1	1 (2.94%)
Chest pain	1	1 (2.94%)
Chronic obstructive pulmonary disease	1	1 (2.94%)
Cough	1	1 (2.94%)
Diarrhoea	1	1 (2.94%)
Gastrooesophageal reflux disease	1	1 (2.94%)
Haemoglobin decreased	1	1 (2.94%)
Hyperlipidaemia	1	1 (2.94%)
Laryngopharyngitis	1	1 (2.94%)
Oedema peripheral	1	1 (2.94%)
Pain in extremity	1	1 (2.94%)
Pneumonia	1	1 (2.94%)
Pruritus	1	1 (2.94%)
Renal impairment	1	1 (2.94%)
Rheumatoid factor increased	1	1 (2.94%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
Both dosages subgroup includes 2 mg to 4 mg and other mixed dosage subgroups.
MedDRA English version 25.1

	Safety Analyses Population (N=34)	
PT	*Event*	*n (%)*
Spinal osteoarthritis	1	1 (2.94%)
Synovial cyst	1	1 (2.94%)
Thrombocytosis	1	1 (2.94%)
Vertigo	1	1 (2.94%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
Both dosages subgroup includes 2 mg to 4 mg and other mixed dosage subgroups.
MedDRA English version 25.1

Table ANN. 346 AEs over a Period of 24 weeks— MedDRA Preferred Term by Decreasing Frequency (2 mg to 4 mg, Safety Analyses Population)

	Safety Analyses Population (N=14)	
PT	*Event*	*n (%)*
AE	21	6 (42.86%)
Alanine aminotransferase increased	2	2 (14.29%)
Neutrophil count increased	2	2 (14.29%)
Neutrophil percentage increased	2	2 (14.29%)
Rheumatoid arthritis	2	2 (14.29%)
White blood cell count increased	3	2 (14.29%)
Alopecia	1	1 (7.14%)
Anaemia	1	1 (7.14%)
Gastrooesophageal reflux disease	1	1 (7.14%)
Hepatic function abnormal	1	1 (7.14%)
Laryngopharyngitis	1	1 (7.14%)
Pneumonia	1	1 (7.14%)
Pruritus	1	1 (7.14%)
Spinal osteoarthritis	1	1 (7.14%)
Synovial cyst	1	1 (7.14%)
Vertigo	1	1 (7.14%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

Table ANN. 347 **AEs over a Period of 24 weeks— MedDRA Preferred Term by Decreasing Frequency (Other mixed dosage, Safety Analyses Population)**

	Safety Analyses Population (N=20)	
PT	*Event*	*n (%)*
AE	22	9 (45.00%)
Headache	2	2 (10.00%)
Aphthous ulcer	1	1 (5.00%)
Arthralgia	2	1 (5.00%)
Back pain	1	1 (5.00%)
Blood albumin decreased	1	1 (5.00%)
Chest pain	1	1 (5.00%)
Chronic obstructive pulmonary disease	1	1 (5.00%)
Cough	1	1 (5.00%)
Diarrhoea	1	1 (5.00%)
Haemoglobin decreased	1	1 (5.00%)
Hepatic function abnormal	1	1 (5.00%)
Hyperlipidaemia	1	1 (5.00%)
Neutrophil count increased	1	1 (5.00%)
Neutrophil percentage increased	1	1 (5.00%)
Oedema peripheral	1	1 (5.00%)
Pain in extremity	1	1 (5.00%)
Renal impairment	1	1 (5.00%)
Rheumatoid factor increased	1	1 (5.00%)
Thrombocytosis	1	1 (5.00%)
White blood cell count increased	1	1 (5.00%)

Footnote: AE, adverse event; N, number of patients in population; PT, preferred term
n is the number of patients and % is the percentage.
The PTs are sorted by decreasing number of patients.
MedDRA English version 25.1

Table ANN. 348 **SAEs over a Period of 12 Weeks— MedDRA Preferred Term by Decreasing Frequency, within System Organ Class (2 mg only, Safety Analyses Population)**

SOC	*Safety Analyses Population (N=580)*		
PT	*Event*	*n (%)*	*EAIR and 95% CI*
SAE	18	17 (2.93%)	13.22 (7.70, 21.16)
Infections and infestations	5	5 (0.86%)	3.86 (1.25, 9.01)
Pneumonia	3	3 (0.52%)	2.32 (0.48, 6.77)
Otitis media	1	1 (0.17%)	0.77 (0.02, 4.30)
Tonsillitis	1	1 (0.17%)	0.77 (0.02, 4.30)
Musculoskeletal and connective tissue disorders	4	4 (0.69%)	3.10 (0.84, 7.93)
Rheumatoid arthritis	2	2 (0.34%)	1.54 (0.19, 5.58)
Intervertebral disc protrusion	1	1 (0.17%)	0.77 (0.02, 4.31)
Lumbar spinal stenosis	1	1 (0.17%)	0.77 (0.02, 4.30)
Gastrointestinal disorders	2	2 (0.34%)	1.54 (0.19, 5.58)
Ileus paralytic	1	1 (0.17%)	0.77 (0.02, 4.30)
Pancreatitis acute	1	1 (0.17%)	0.77 (0.02, 4.30)

Footnote: CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; PT, preferred term; SAE, serious adverse event; SOC, system organ class
n is the number of patients and % is the percentage.
The SOCs are sorted by decreasing number of patients, while the PTs are sorted by decreasing number of patients within SOC.
MedDRA English version 25.1

SOC / *PT*	*Safety Analyses Population (N=580)*		
	Event	*n (%)*	*EAIR and 95% CI*
Ear and labyrinth disorders	1	1 (0.17%)	0.77 (0.02, 4.30)
Otolithiasis	1	1 (0.17%)	0.77 (0.02, 4.30)
Endocrine disorders	1	1 (0.17%)	0.77 (0.02, 4.31)
Thyroid mass	1	1 (0.17%)	0.77 (0.02, 4.31)
General disorders and administration site conditions	1	1 (0.17%)	0.77 (0.02, 4.30)
Death	1	1 (0.17%)	0.77 (0.02, 4.30)
Hepatobiliary disorders	1	1 (0.17%)	0.77 (0.02, 4.30)
Drug-induced liver injury	1	1 (0.17%)	0.77 (0.02, 4.30)
Injury, poisoning and procedural complications	1	1 (0.17%)	0.77 (0.02, 4.30)
Lumbar vertebral fracture	1	1 (0.17%)	0.77 (0.02, 4.30)

Footnote: CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; PT, preferred term; SAE, serious adverse event; SOC, system organ class
n is the number of patients and % is the percentage.
The SOCs are sorted by decreasing number of patients, while the PTs are sorted by decreasing number of patients within SOC.
MedDRA English version 25.1

SOC	*Safety Analyses Population (N=580)*		
PT	*Event*	*n (%)*	*EAIR and 95% CI*
Metabolism and nutrition disorders	1	1 (0.17%)	0.77 (0.02, 4.30)
Hyperkalaemia	1	1 (0.17%)	0.77 (0.02, 4.30)
Nervous system disorders	1	1 (0.17%)	0.77 (0.02, 4.30)
Carotid artery aneurysm	1	1 (0.17%)	0.77 (0.02, 4.30)

Footnote: CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; PT, preferred term; SAE, serious adverse event; SOC, system organ class
n is the number of patients and % is the percentage.
The SOCs are sorted by decreasing number of patients, while the PTs are sorted by decreasing number of patients within SOC.
MedDRA English version 25.1

Table ANN. 349 **SAEs over a Period of 12 Weeks— MedDRA Preferred Term by Decreasing Frequency, within System Organ Class (4 mg only, Safety Analyses Population)**

SOC	*Safety Analyses Population (N=53)*		
PT	*Event*	*n (%)*	*EAIR and 95% CI*
SAE	3	3 (5.66%)	27.60 (5.69, 80.66)
Musculoskeletal and connective tissue disorders	2	2 (3.77%)	17.95 (2.17, 64.85)
Arthralgia	1	1 (1.89%)	8.89 (0.23, 49.53)
Rheumatoid arthritis	1	1 (1.89%)	8.98 (0.23, 50.01)
Nervous system disorders	1	1 (1.89%)	9.11 (0.23, 50.74)
Optic neuritis	1	1 (1.89%)	9.11 (0.23, 50.74)

Footnote: CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; PT, preferred term; SAE, serious adverse event; SOC, system organ class
n is the number of patients and % is the percentage.
The SOCs are sorted by decreasing number of patients, while the PTs are sorted by decreasing number of patients within SOC.
MedDRA English version 25.1

Table ANN. 350 **SAEs over a Period of 12 Weeks— MedDRA Preferred Term by Decreasing Frequency, within System Organ Class (both dosages, Safety Analyses Population)**

SOC	*Safety Analyses Population (N=34)*		
PT	*Event*	*n (%)*	*EAIR and 95% CI*
SAE	2	2 (5.88%)	26.53 (3.21, 95.82)
Infections and infestations	1	1 (2.94%)	12.99 (0.33, 72.36)
Pneumonia	1	1 (2.94%)	12.99 (0.33, 72.36)
Respiratory, thoracic and mediastinal disorders	1	1 (2.94%)	13.09 (0.33, 72.93)
Chronic obstructive pulmonary disease	1	1 (2.94%)	13.09 (0.33, 72.93)

Footnote: CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; PT, preferred term; SAE, serious adverse event; SOC, system organ class
n is the number of patients and % is the percentage.
The SOCs are sorted by decreasing number of patients, while the PTs are sorted by decreasing number of patients within SOC.
Both dosages subgroup includes 2 mg to 4 mg and other mixed dosage subgroups.
MedDRA English version 25.1

Table ANN. 351 SAEs over a Period of 12 Weeks— MedDRA Preferred Term by Decreasing Frequency, within System Organ Class (2 mg to 4 mg, Safety Analyses Population)

SOC	*Safety Analyses Population (N=14)*		
PT	*Event*	*n (%)*	*EAIR and 95% CI*
SAE	1	1 (7.14%)	34.60 (0.88, 192.79)
Infections and infestations	1	1 (7.14%)	34.60 (0.88, 192.79)
Pneumonia	1	1 (7.14%)	34.60 (0.88, 192.79)

Footnote: CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; PT, preferred term; SAE, serious adverse event; SOC, system organ class
n is the number of patients and % is the percentage.
The SOCs are sorted by decreasing number of patients, while the PTs are sorted by decreasing number of patients within SOC.
MedDRA English version 25.1

Table ANN. 352 **SAEs over a Period of 12 Weeks— MedDRA Preferred Term by Decreasing Frequency, within System Organ Class (Other mixed dosage, Safety Analyses Population)**

SOC	*Safety Analyses Population (N=20)*		
PT	*Event*	*n (%)*	*EAIR and 95% CI*
SAE	1	1 (5.00%)	21.51 (0.54, 119.82)
Respiratory, thoracic and mediastinal disorders	1	1 (5.00%)	21.51 (0.54, 119.82)
Chronic obstructive pulmonary disease	1	1 (5.00%)	21.51 (0.54, 119.82)

Footnote: CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; PT, preferred term; SAE, serious adverse event; SOC, system organ class
n is the number of patients and % is the percentage.
The SOCs are sorted by decreasing number of patients, while the PTs are sorted by decreasing number of patients within SOC.
MedDRA English version 25.1

Table ANN. 353 **SAEs over a Period of 24 Weeks— MedDRA Preferred Term by Decreasing Frequency, within System Organ Class (2 mg only, Safety Analyses Population)**

SOC	*Safety Analyses Population (N=580)*		
PT	*Event*	*n (%)*	*EAIR and 95% CI*
SAE	24	23 (3.97%)	10.20 (6.47, 15.30)
Infections and infestations	7	7 (1.21%)	3.07 (1.24, 6.33)
Pneumonia	3	3 (0.52%)	1.31 (0.27, 3.84)
Appendicitis	1	1 (0.17%)	0.44 (0.01, 2.44)
Influenza	1	1 (0.17%)	0.44 (0.01, 2.44)
Otitis media	1	1 (0.17%)	0.44 (0.01, 2.44)
Tonsillitis	1	1 (0.17%)	0.44 (0.01, 2.44)
Musculoskeletal and connective tissue disorders	6	6 (1.03%)	2.64 (0.97, 5.74)
Rheumatoid arthritis	2	2 (0.34%)	0.88 (0.11, 3.16)
Arthralgia	1	1 (0.17%)	0.44 (0.01, 2.44)
Intervertebral disc protrusion	1	1 (0.17%)	0.44 (0.01, 2.44)
Lumbar spinal stenosis	1	1 (0.17%)	0.44 (0.01, 2.44)
Osteonecrosis	1	1 (0.17%)	0.44 (0.01, 2.44)

Footnote: CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; PT, preferred term; SAE, serious adverse event; SOC, system organ class
n is the number of patients and % is the percentage.
The SOCs are sorted by decreasing number of patients, while the PTs are sorted by decreasing number of patients within SOC.
MedDRA English version 25.1

SOC / *PT*	*Safety Analyses Population (N=580)*		
	Event	*n (%)*	*EAIR and 95% CI*
Gastrointestinal disorders	3	3 (0.52%)	1.31 (0.27, 3.84)
Gastritis erosive	1	1 (0.17%)	0.44 (0.01, 2.44)
Ileus paralytic	1	1 (0.17%)	0.44 (0.01, 2.44)
Pancreatitis acute	1	1 (0.17%)	0.44 (0.01, 2.44)
Ear and labyrinth disorders	1	1 (0.17%)	0.44 (0.01, 2.44)
Otolithiasis	1	1 (0.17%)	0.44 (0.01, 2.44)
Endocrine disorders	1	1 (0.17%)	0.44 (0.01, 2.44)
Thyroid mass	1	1 (0.17%)	0.44 (0.01, 2.44)
General disorders and administration site conditions	1	1 (0.17%)	0.44 (0.01, 2.44)
Death	1	1 (0.17%)	0.44 (0.01, 2.44)

Footnote: CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; PT, preferred term; SAE, serious adverse event; SOC, system organ class
n is the number of patients and % is the percentage.
The SOCs are sorted by decreasing number of patients, while the PTs are sorted by decreasing number of patients within SOC.
MedDRA English version 25.1

SOC	*Safety Analyses Population (N=580)*		
PT	*Event*	*n (%)*	*EAIR and 95% CI*
Hepatobiliary disorders	1	1 (0.17%)	0.44 (0.01, 2.44)
Drug-induced liver injury	1	1 (0.17%)	0.44 (0.01, 2.44)
Injury, poisoning and procedural complications	1	1 (0.17%)	0.44 (0.01, 2.44)
Lumbar vertebral fracture	1	1 (0.17%)	0.44 (0.01, 2.44)
Metabolism and nutrition disorders	1	1 (0.17%)	0.44 (0.01, 2.44)
Hyperkalaemia	1	1 (0.17%)	0.44 (0.01, 2.44)
Nervous system disorders	1	1 (0.17%)	0.44 (0.01, 2.44)
Carotid artery aneurysm	1	1 (0.17%)	0.44 (0.01, 2.44)
Pregnancy, puerperium and perinatal conditions	1	1 (0.17%)	0.44 (0.01, 2.44)
Abortion threatened	1	1 (0.17%)	0.44 (0.01, 2.44)

Footnote: CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; PT, preferred term; SAE, serious adverse event; SOC, system organ class
n is the number of patients and % is the percentage.
The SOCs are sorted by decreasing number of patients, while the PTs are sorted by decreasing number of patients within SOC.
MedDRA English version 25.1

Table ANN. 354 **SAEs over a Period of 24 Weeks— MedDRA Preferred Term by Decreasing Frequency, within System Organ Class (4 mg only, Safety Analyses Population)**

SOC	*Safety Analyses Population (N=53)*		
PT	*Event*	*n (%)*	*EAIR and 95% CI*
SAE	5	3 (5.66%)	16.96 (3.50, 49.56)
Musculoskeletal and connective tissue disorders	2	2 (3.77%)	11.04 (1.34, 39.87)
Arthralgia	1	1 (1.89%)	5.34 (0.14, 29.78)
Rheumatoid arthritis	1	1 (1.89%)	5.52 (0.14, 30.75)
Eye disorders	2	1 (1.89%)	5.46 (0.14, 30.43)
Cataract	2	1 (1.89%)	5.46 (0.14, 30.43)
Nervous system disorders	1	1 (1.89%)	5.47 (0.14, 30.48)
Optic neuritis	1	1 (1.89%)	5.47 (0.14, 30.48)

Footnote: CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; PT, preferred term; SAE, serious adverse event; SOC, system organ class
n is the number of patients and % is the percentage.
The SOCs are sorted by decreasing number of patients, while the PTs are sorted by decreasing number of patients within SOC.
MedDRA English version 25.1

Table ANN. 355 **SAEs over a Period of 24 Weeks— MedDRA Preferred Term by Decreasing Frequency, within System Organ Class (both dosages, Safety Analyses Population)**

SOC	*Safety Analyses Population (N=34)*		
PT	*Event*	*n (%)*	*EAIR and 95% CI*
SAE	2	2 (5.88%)	14.80 (1.79, 53.48)
Infections and infestations	1	1 (2.94%)	7.19 (0.18, 40.05)
Pneumonia	1	1 (2.94%)	7.19 (0.18, 40.05)
Respiratory, thoracic and mediastinal disorders	1	1 (2.94%)	7.35 (0.19, 40.94)
Chronic obstructive pulmonary disease	1	1 (2.94%)	7.35 (0.19, 40.94)

Footnote: CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; PT, preferred term; SAE, serious adverse event; SOC, system organ class
n is the number of patients and % is the percentage.
The SOCs are sorted by decreasing number of patients, while the PTs are sorted by decreasing number of patients within SOC.
Both dosages subgroup includes 2 mg to 4 mg and other mixed dosage subgroups.
MedDRA English version 25.1

Table ANN. 356 **SAEs over a Period of 24 Weeks— MedDRA Preferred Term by Decreasing Frequency, within System Organ Class (2 mg to 4 mg, Safety Analyses Population)**

SOC	*Safety Analyses Population (N=14)*		
PT	*Event*	*n (%)*	*EAIR and 95% CI*
SAE	1	1 (7.14%)	18.62 (0.47, 103.75)
Infections and infestations	1	1 (7.14%)	18.62 (0.47, 103.75)
Pneumonia	1	1 (7.14%)	18.62 (0.47, 103.75)

Footnote: CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; PT, preferred term; SAE, serious adverse event; SOC, system organ class
n is the number of patients and % is the percentage.
The SOCs are sorted by decreasing number of patients, while the PTs are sorted by decreasing number of patients within SOC.
MedDRA English version 25.1

Table ANN. 357 **SAEs over a Period of 24 Weeks— MedDRA Preferred Term by Decreasing Frequency, within System Organ Class (Other mixed dosage, Safety Analyses Population)**

SOC	*Safety Analyses Population (N=20)*		
PT	*Event*	*n (%)*	*EAIR and 95% CI*
SAE	1	1 (5.00%)	12.29 (0.31, 68.45)
Respiratory, thoracic and mediastinal disorders	1	1 (5.00%)	12.29 (0.31, 68.45)
Chronic obstructive pulmonary disease	1	1 (5.00%)	12.29 (0.31, 68.45)

Footnote: CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; PT, preferred term; SAE, serious adverse event; SOC, system organ class
n is the number of patients and % is the percentage.
The SOCs are sorted by decreasing number of patients, while the PTs are sorted by decreasing number of patients within SOC.
MedDRA English version 25.1

Table ANN. 358 **AE Summary (Renal Impairment Subgroups, Safety Analyses Population)**

		Safety Analyses Population (N=667)						
	Renal impairment subgroup	*Event*	*n*	*Patient-year of observation time*	*Patient-year of exposure time*	*Percentage and 95% CI*	*Incidence rate and 95% CI*	*EAIR and 95% CI*
AEs over a period of 12 weeks	yes (Nx=14)	15	7	2.28	2.20	50.00% (23.04%, 76.96%)	307.02 (123.44, 632.57)	318.18 (127.93, 655.58)
	no (Nx=653)	314	207	127.28	121.84	31.70% (28.14%, 35.42%)	162.63 (141.23, 186.36)	169.89 (147.54, 194.68)
AEs over a period of 24 weeks	yes (Nx=14)	16	7	3.78	3.70	50.00% (23.04%, 76.96%)	185.19 (74.45, 381.55)	189.19 (76.06, 389.80)
	no (Nx=653)	412	243	204.77	194.89	37.21% (33.49%, 41.05%)	118.67 (104.22, 134.57)	124.69 (109.50, 141.39)
AEs related to study treatment as judged by the investigator over a period of 12 weeks	yes (Nx=14)	3	2	3.17	3.07	14.29% (1.78%, 42.81%)	63.09 (7.64, 227.91)	65.15 (7.89, 235.33)
	no (Nx=653)	108	93	143.70	136.91	14.24% (11.65%, 17.16%)	64.72 (52.24, 79.28)	67.93 (54.83, 83.22)
AEs related to study treatment as judged by the investigator over a period of 24 weeks	yes (Nx=14)	3	2	5.75	5.67	14.29% (1.78%, 42.81%)	34.78 (4.21, 125.65)	35.27 (4.27, 127.42)
	no (Nx=653)	144	118	243.49	230.98	18.07% (15.19%, 21.24%)	48.46 (40.11, 58.04)	51.09 (42.29, 61.18)

Footnote: The number of event for each patient counts the event which happened during the 12-weeks/ 24-weeks observation time. The percentage denominator is the number of analyses population and the numerator is the number of patients with corresponding events.
AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; n, the number of patients with events; SAE, serious adverse event.
The percentage of AEs/SAEs over a period of 12/24 weeks = Number of patients with at least one AE/SAE over a period of 12/24 weeks ÷number of patients in safety analyses population ×100, results round to 2 decimal places.
The incidence rates of AEs/SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ observation time

of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places. The EAIR of AEs /SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at
least one AE/SAE over an observation period of 12/24 weeks ÷ overall exposure time of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The calculation of observation time and exposure time could refer to definition in the main body of SAP.
AEs related to study treatment as judged by the investigator are the AEs whose relationship with olumiant are not 'No'. Drug adjustment includes dose increase, dose reduce and temporary discontinuation.
Death is from SAE which the reason is death or AE whose outcome is fatal or death recorded in the page of study termination.

	Renal impairment subgroup	*Safety Analyses Population (N=667)*						
		Event	*n*	*Patient-year of observation time*	*Patient-year of exposure time*	*Percentage and 95% CI*	*Incidence rate and 95% CI*	*EAIR and 95% CI*
Death	yes (Nx=14)	0	0	6.25	6.09	0.00% (0%, 23.16%)	0.00 (NA, 59.02)	0.00 (NA, 60.57)
	no (Nx=653)	2	2	270.19	255.21	0.31% (0.04%, 1.10%)	0.74 (0.09, 2.67)	0.78 (0.09, 2.83)
SAEs over a period of 12 weeks	yes (Nx=14)	3	3	3.09	3.00	21.43% (4.66%, 50.80%)	97.09 (20.02, 283.73)	100.00 (20.62, 292.24)
	no (Nx=653)	20	19	151.65	144.02	2.91% (1.76%, 4.51%)	12.53 (7.54, 19.57)	13.19 (7.94, 20.60)
SAEs over a period of 24 weeks	yes (Nx=14)	3	3	5.39	5.31	21.43% (4.66%, 50.80%)	55.66 (11.48, 162.66)	56.50 (11.65, 165.11)
	no (Nx=653)	28	25	265.55	251.41	3.83% (2.49%, 5.60%)	9.41 (6.09, 13.90)	9.94 (6.44, 14.68)
SAEs related to study treatment as judged by the investigator over a period of 12 weeks	yes (Nx=14)	1	1	3.43	3.33	7.14% (0.18%, 33.87%)	29.15 (0.74, 162.44)	30.03 (0.76, 167.32)

Footnote: The number of event for each patient counts the event which happened during the 12-weeks/ 24-weeks observation time. The percentage denominator is the number of analyses population and the numerator is the number of patients with corresponding events.
AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; n, the number of patients with events; SAE, serious adverse event.
The percentage of AEs/SAEs over a period of 12/24 weeks = Number of patients with at least one AE/SAE over a period of 12/24 weeks ÷number of patients in safety analyses population ×100, results round to 2 decimal places.
The incidence rates of AEs/SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ observation time
of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places. The EAIR of AEs /SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at
least one AE/SAE over an observation period of 12/24 weeks ÷ overall exposure time of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The calculation of observation time and exposure time could refer to definition in the main body of SAP.
AEs related to study treatment as judged by the investigator are the AEs whose relationship with olumiant are not 'No'. Drug adjustment includes dose increase, dose reduce and temporary discontinuation.
Death is from SAE which the reason is death or AE whose outcome is fatal or death recorded in the page of study termination.

		Safety Analyses Population (N=667)						
	Renal impairment subgroup	*Event*	*n*	*Patient-year of observation time*	*Patient-year of exposure time*	*Percentage and 95% CI*	*Incidence rate and 95% CI*	*EAIR and 95% CI*
	no (Nx=653)	7	7	152.96	144.99	1.07% (0.43%, 2.20%)	4.58 (1.84, 9.43)	4.83 (1.94, 9.95)
SAEs related to study treatment as judged by the investigator over a period of 24 weeks	yes (Nx=14)	1	1	6.17	6.09	7.14% (0.18%, 33.87%)	16.21 (0.41, 90.30)	16.42 (0.42, 91.49)
	no (Nx=653)	9	9	269.00	254.21	1.38% (0.63%, 2.60%)	3.35 (1.53, 6.35)	3.54 (1.62, 6.72)
AEs leading to drug adjustment over a period of 12 weeks	yes (Nx=14)	4	2	3.35	3.26	14.29% (1.78%, 42.81%)	59.70 (7.23, 215.66)	61.35 (7.43, 221.62)
	no (Nx=653)	32	28	149.62	141.95	4.29% (2.87%, 6.14%)	18.71 (12.44, 27.05)	19.73 (13.11, 28.51)
AEs leading to drug adjustment over a period of 24 weeks	yes (Nx=14)	4	2	5.81	5.73	14.29% (1.78%, 42.81%)	34.42 (4.17, 124.35)	34.90 (4.23, 126.09)
	no (Nx=653)	41	37	261.63	247.74	5.67% (4.02%, 7.73%)	14.14 (9.96, 19.49)	14.94 (10.52, 20.59)

Footnote: The number of event for each patient counts the event which happened during the 12-weeks/ 24-weeks observation time. The percentage denominator is the number of analyses population and the numerator is the number of patients with corresponding events.
AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; n, the number of patients with events; SAE, serious adverse event.
The percentage of AEs/SAEs over a period of 12/24 weeks = Number of patients with at least one AE/SAE over a period of 12/24 weeks ÷number of patients in safety analyses population ×100, results round to 2 decimal places.
The incidence rates of AEs/SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ observation time
of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places. The EAIR of AEs /SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at
least one AE/SAE over an observation period of 12/24 weeks ÷ overall exposure time of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The calculation of observation time and exposure time could refer to definition in the main body of SAP.
AEs related to study treatment as judged by the investigator are the AEs whose relationship with olumiant are not 'No'. Drug adjustment includes dose increase, dose reduce and temporary discontinuation.
Death is from SAE which the reason is death or AE whose outcome is fatal or death recorded in the page of study termination.

		Safety Analyses Population (N=667)						
	Renal impairment subgroup	*Event*	*n*	*Patient-year of observation time*	*Patient-year of exposure time*	*Percentage and 95% CI*	*Incidence rate and 95% CI*	*EAIR and 95% CI*
AEs leading to drug permanent discontinuation over a period of 12 weeks	yes (Nx=14)	0	0	3.43	3.33	0.00% (0%, 23.16%)	0.00 (NA, 107.55)	0.00 (NA, 110.78)
	no (Nx=653)	22	20	151.95	144.85	3.06% (1.88%, 4.69%)	13.16 (8.04, 20.33)	13.81 (8.43, 21.32)
AEs leading to drug permanent discontinuation over a period of 24 weeks	yes (Nx=14)	0	0	6.25	6.09	0.00% (0%, 23.16%)	0.00 (NA, 59.02)	0.00 (NA, 60.57)
	no (Nx=653)	26	24	268.19	254.70	3.68% (2.37%, 5.42%)	8.95 (5.73, 13.32)	9.42 (6.04, 14.02)

Footnote: The number of event for each patient counts the event which happened during the 12-weeks/ 24-weeks observation time. The percentage denominator is the number of analyses population and the numerator is the number of patients with corresponding events.
AE, adverse event; CI, confidence interval; EAIR, exposure adjusted incidence rate; N, number of patients in population; n, the number of patients with events; SAE, serious adverse event.
The percentage of AEs/SAEs over a period of 12/24 weeks = Number of patients with at least one AE/SAE over a period of 12/24 weeks ÷number of patients in safety analyses population ×100, results round to 2 decimal places.
The incidence rates of AEs/SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at least one AE/SAE over an observation period of 12/24 weeks ÷ observation time
of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places. The EAIR of AEs /SAEs over a period of 12/24 weeks (person/100 person-year) = Number of patients with at
least one AE/SAE over an observation period of 12/24 weeks ÷ overall exposure time of AEs/SAEs over a period of 12/24 weeks (years) ×100, results round to 2 decimal places.
The calculation of observation time and exposure time could refer to definition in the main body of SAP.
AEs related to study treatment as judged by the investigator are the AEs whose relationship with olumiant are not 'No'. Drug adjustment includes dose increase, dose reduce and temporary discontinuation.
Death is from SAE which the reason is death or AE whose outcome is fatal or death recorded in the page of study termination.

Annex 3. Listings

Listings are available upon request.

Annex 4. List of investigators

Centre Number	Centre Name	Name	Business Email	City	Number of Patients Entered
0001	Peking Union Medical College Hospital	Xiaofeng Zeng	zengxfpumc@163.com	Beijing	20
0400	The Second Affiliated Hospital of Nanchang University	Xinwang Duan	13970085678@163.com	Nanchang	29
1100	Yiyang Central Hospital	Jian Shi	408739063@qq.com	Yiyang	67
1753	The Third Affiliate Hospital of CQMU	Chongyang Liu	dpyylcy@126.com	Chongqing	34
0021	The Third Affiliated Hospital, Sun Yat-Sen University	Jieruo Gu	gujieruo@163.com	Guangzhou	50
1468	The Sixth Affiliated Hospital of Sun Yat-Sen University	Jianlin Huang	jianlin_h@163.com	Guangzhou	5
0824	Taizhou Central Hospital	Guofen Wang	897809981@qq.com	Taizhou	19
1747	The Second Affiliated Hospital of Guangxi Medical University	Cundong Mi	md-392@126.com	Nanning	11
0121	ZiBo Central Hospital	Xiuying Zhang	zbzhxy@126.com	Zibo	65
0076	First People's Hospital of Yunnan Province	Qin Li	liqinfm@163.com	Kunming	16
0223	Sinopharm Dongfeng General Hospital	Qihuan Liu	liuqihuan-392@163.com	Shiyan	49
0235	Tangshan Workers Hospital	Shengquan Tong	tonnymd@163.com	Tangshan	8
0402	Yuyao People's Hospital	Wei Wei	jiayi435@126.com	Yuyao	19

Centre Number	Centre Name	Name	Business Email	City	Number of Patients Entered
1207	Liuzhou People's Hospital	Yuan Liu	liuyuanem@163.com	Liuzhou	30
0063	Tongji Hospital, Tongji Medical College, Huazhong University of Science & Technology	Shenghao Tu	shtu@tjh.tjmu.edu.cn	Wuhan	22
0029	West China Hospital, Sichuan University	Yi Liu	yi2006liu@163.com	Chengdu	5
0090	Shangdong Provincial Hospital	Hongsheng Sun	13869192509@126.com	Jinan	1
0104	Wuhan Union Hospital, Tongji Medical College, Huazhong University of Science and Technology	Rong Du	283996771@qq.com	Wuhan	60
0151	Weifang People’s Hospital	Yun Zhu	652657655@qq.com	Weifang	15
0030	Affiliated Hospital of North Sichuan Medical College	Jianping Liu	ljpbr@sina.com	Nanchong	3
0082	Zhejiang Provincial People’s Hospital	Yasong Li	lysong2@163.com	Hangzhou	13
1566	Xinxiang Central Hospital	Xiuqin Geng	xiuqinxinxiang@163.com	Xinxiang	2
0058	Hainan General Hospital	Feng Zhan	renal@126.com	Haikou	17
0043	Peking University Shougang Hospital	Kuanting Wang	kuantingwang@163.com	Beijing	11
0066	Affiliated Hospital of Inner Mongolia Medical University	Hongbin Li	Lhbwb73@163.com	Hohhot	23
0073	Wuxi NO.2 People's Hospital	Tianli Ren	rentianliwx@qq.com	Wuxi	7

Centre Number	Centre Name	Name	Business Email	City	Number of Patients Entered
0067	Nanfang Hospital	Min Yang	minyanggz@163.com	Guangzhou	12
1001	Shiyan Renmin Hospital	Hong Tao	63886515@qq.com	Shiyan	6
0977	Anyang District Hospital	Xiaohan Wang	wangxiaohan11@hotmail.com	Puyang	22
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