A non-interventional, post-authorization safety study (PASS) to evaluate long-term safety of anakinra (Kineret®) in patients with systemic juvenile idiopathic arthritis

PASS information

Title	A non-interventional, post-authorization safety study (PASS) to evaluate long-term safety of anakinra (Kineret®) in patients with systemic juvenile idiopathic arthritis
Version identifier of the final study report	1
Date of last version of the final study report	15 November 2019
EU PAS register number	ENCEPP/SDPP/28378
Active substance	Pharmacotherapeutic group: Immunosuppressants, Interleukin inhibitors, ATC code: L04AC03 anakinra
Medicinal product	Kineret® 100 mg/0.67 ml solution for injection in pre-filled syringe
Product reference	EU/1/02/203/001 - 100 mg - 1-pack EU/1/02/203/002 - 100 mg - 7-pack EU/1/02/203/003 - 100 mg - 28-pack EU/1/02/203/005 - 100 mg/0.67 ml - 1-pack EU/1/02/203/006 - 100 mg/0.67 ml - 7-pack EU/1/02/203/007 - 100 mg/0.67 ml - 28-pack
Procedure number	EMEA/H/C/000363/II/0056
Marketing authorization holder(s)	Swedish Orphan Biovitrum AB (publ), SE-112 76 Stockholm, Sweden
Joint PASS	No
Research question and objectives	Evaluate and characterize long-term safety of Kineret when used in standard clinical practice to treat patients with systemic juvenile idiopathic arthritis (SJIA), including the occurrence of macrophage activation syndrome (MAS) as an event of special interest (ESI).

Country(-ies) of study	Secondary use of data collected by the Paediatric Rheumatology International Trials Organisation (PRINTO) in the Pharmachild JIA registry in 15 countries: Croatia, Denmark, France, Germany, Greece, Hungary, Israel, Italy, Latvia, Netherlands, Norway, Romania, Saudi Arabia, Spain and Switzerland.
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1 Abstract

Title

A non-interventional, post-authorization safety study (PASS) to evaluate long-term safety of anakinra (Kineret®) in patients with systemic juvenile idiopathic arthritis.

Keywords

Kineret, systemic juvenile idiopathic arthritis (SJIA), long-term safety, macrophage activation syndrome (MAS)

Rationale and background

SJIA is the most severe form of juvenile idiopathic arthritis (JIA).

Kineret® is a recombinant human IL-1 receptor antagonist and was first approved in the US in 2001. In the EU/EEA it is approved for rheumatoid arthritis, Cryopyrin-Associated Periodic Syndromes and, since 2018, Still's disease, including SJIA and adult-onset Still's disease.

This study was designed to further investigate long-term safety in SJIA patients treated with Kineret.

Research question and objectives

To evaluate and characterize long-term safety of Kineret, including MAS when used in standard clinical practice to treat patients with SJIA.

Study design

An international, non-interventional, single-armed, pharmacovigilance registry study on long-term safety of Kineret utilizing already available data from the ENCePP certified Pharmachild JIA registry.

Setting

Secondary use of data from the Pharmachild JIA registry.

Subjects and study size, including dropouts

All patients with SJIA as per the ILAR classification criteria enrolled in the registry before 30 September 2018, ever treated with Kineret.

Variables and data sources

The study endpoints were the occurrence of non-serious adverse events (AEs) of at least moderate severity and serious AEs (SAEs), including MAS; the duration of Kineret treatment and reasons for discontinuation.

Results

306 patients were enrolled with both genders equally represented. The median time from the disease onset to the first visit at the treating center and to the first dose of Kineret were 0.2 and 0.3 years, respectively. The median age at Kineret start was 8.0 years. 46.1% of the patients were

continuously treated with Kineret for at least 12 months, 34.0% for at least 18 months and 28.1% for at least 24 months.

201 AEs were reported with an overall IR of 39.5 (95% CI 30.8-50.6) per 100 patient years (py). The most frequently reported MedDRA SOC was “Infections and Infestations” (52 AEs, IR=10.2 per 100 py). There was a total of 56 SAEs (IR 11.0 per 100 py; 95% CI 7.9-15.2) with the most frequent MedDRA SOC being “Infections and Infestations” (13 SAEs, IR=2.6 per 100 py), followed by “Immune system disorders” (11 SAEs as MAS, IR=2.2 per 100 py). The rate of AEs was higher during the first 6 months of treatment compared to later treatment periods. Few AEs led to discontinuation of therapy. Discontinuation of Kineret occurred mostly during the first 6 months of treatment and mainly due to inefficacy (43.1% of all reasons for discontinuation) and remission (30.6%). No deaths occurred.

Ten patients (3.3%) had a history of MAS at baseline. Nine of these patients did not experience any new episodes while on Kineret. In total, 11 patients experienced 12 events (11 SAEs and 1 non-serious AE) of MAS on Kineret treatment. After stopping Kineret, MAS was reported in 8 patients several months after Kineret discontinuation.

Discussion

The results of the present study confirm the long-term safety profile of Kineret in SJIA patients without any new safety findings. The pattern of AEs, including SAEs, was in line with the known safety profile with frequency generally higher during the first 6 months of treatment. Few AEs led to discontinuation. There was no indication that long-term treatment with Kineret increased the risk for MAS and no indication of a rebound effect after Kineret discontinuation.

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2 List of abbreviations

Abbreviation	Term
AE	Adverse event
AOSD	Adult-Onset Still's Disease
bDMARD	Biologic Disease-modifying antirheumatic drug
CAPS	Cryopyrin associated periodic syndromes
CRF	Case report form
CSR	Clinical study report
DMARD	Disease-modifying antirheumatic drug
EMA	European Medicines Agency
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
ESI	Events of special interest
EU/EEA	European Union/ European Economic Area
HLH	Haemophagocytic lymphohistiocytosis (Interchangeable with MAS)
IL-1	Interleukin-1
IL-6	Interleukin-6
ILAR	International League of Associations for Rheumatology
IR	Incidence rate
IRCCS	Istituto di Ricerca e Cura a Carattere Scientifico (Institute for treatment and research)
JIA	Juvenile idiopathic arthritis
LLT	Lowest level term
MAS	Macrophage activation syndrome (Interchangeable with HLH)
NA	Not applicable
NSAID	Non-steroidal anti-inflammatory drug

PASS	Post authorization safety study
PRINTO	Paediatric Rheumatology International Trials Organization
PSUR	Periodic safety update report
PT	Preferred Term
py	Patient-year
RMP	Risk management plan
SAE	Serious adverse event
SAP	Statistical analysis plan
sDMARD	Synthetic Disease-modifying antirheumatic drug
SJIA	Systemic juvenile idiopathic arthritis
Sobi	Swedish Orphan Biovitrum
SOC	System organ class
SmPCs	Summary of Product Characteristics

3 Investigators

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4 Other responsible parties

NA.

5 Milestones

Milestone	Planned date	Actual date	Comments
Start of study data collection	March 2019	10 April 2019	Start of data retrieval and analysis
End of study data collection	April 2019	31 August 2019	End of data collection
Registration in the EU PAS register	March 2019	March 2019	
Final report of study results	October 2019	15 November 2019	Final clinical study report (CSR)

This PASS is based on secondary use of data, utilizing already available data from the Pharmachild JIA registry. In the Pharmachild JIA registry data has been collected since 2011.

Registry data collected up until 30 September 2018 were used in this study.

6 Rationale and background

SJIA is an autoinflammatory disease, characterized by chronic arthritis/arthralgias, high spiking intermittent fever, maculopapular rash, hepatosplenomegaly, lymphadenopathy, serositis, and marked increase in acute-phase reactants (1-3). SJIA is associated with complications, including joint damage, growth impairment, osteoporosis, amyloidosis and, potentially fatal, MAS (4-8). Laboratory and clinical observations suggest an inappropriate activation of the innate immune system, with hypersecretion of the proinflammatory cytokines, such as interleukin-1 (IL-1) and 6 (IL-6).

Anakinra is a human IL-1 receptor antagonist that blocks the biological activity of cytokine IL-1 (IL-1α and IL-1β) by competitively inhibiting its binding to the IL-1 receptor type 1, thereby controlling active inflammation.

Kineret® was first approved in the US in 2001 for treatment of rheumatoid arthritis and subsequently in the EU/EEA in 2002. Kineret has since then also been granted Marketing Authorization for rheumatoid arthritis in Canada, Australia, and Israel. Kineret is also approved for all forms of Cryopyrin-Associated Periodic Syndromes (CAPS) in the EU/EEA, Israel, and Australia, and for the most severe form of CAPS, i.e., NOMID, in the US and Canada. In addition, Kineret is approved for the treatment of SJIA in Australia. In 2018, Kineret was approved in the EU/EEA in adult and pediatric patients for the treatment of Still's disease, including SJIA and AOSD, with active systemic features of moderate to high disease activity, or in patients with continued disease activity after treatment with NSAIDs or glucocorticoids. Kineret can be given as monotherapy or in combination with other anti-inflammatory drugs and DMARDs as per the SmPCs in Europe.

This study was designed to further investigate long-term safety and potential risk for MAS in patients with SJIA treated with Kineret. This non-interventional PASS was included in section III.2-3 of the EU RMP version 4.9 as a category 3 activity (Annex 3).

The protocol for this study was developed in accordance with the EMA guidance for the format and content of the protocol of a non-interventional PASS (9). The study has been registered in the public EU PAS register and on clinicaltrials.gov. The collected safety data will be reported in PSUR and RMP updates as applicable.

7 Research question and objectives

The objective of the study was to evaluate and characterize the long-term safety profile of Kineret treatment when used in standard clinical practice to treat patients with SJIA, including the occurrence of MAS as an ESI.

8 Amendments and updates

None.

9 Research methods

9.1 Study design

This was an international, non-interventional, single-armed, pharmacovigilance registry study of long-term safety utilizing already available data from the ENCePP certified Pharmachild JIA registry.

The study endpoints were the occurrence of non-serious AEs of at least moderate severity and SAEs, including MAS as an ESI, as well as the duration of the Kineret treatment and reasons for Kineret discontinuation.

The chosen design was suitable for a study with the primary objective of assessing long-term safety of Kineret when used in patients with SJIA under standard clinical care.

9.2 Setting

This study was based on secondary use of data from the Pharmachild JIA registry. Data were extracted and analyzed for all male and female patients classified as SJIA, as per the ILAR classification criteria (10,11), included in the Pharmachild JIA registry, who were ever treated with Kineret subsequently to SJIA diagnosis.

No treatment assignment or randomization was applicable.

The Pharmachild JIA registry was set up in December 2011. Both retrospective and prospective data has been collected within the registry. The first Kineret treatment, retrospectively collected in the registry, occurred in 2004. Data collected in the registry up until 30 September 2018 were used in this study.

9.3 Subjects

Male and female patients with a diagnosis of SJIA as per the ILAR classification criteria included in the Pharmachild JIA registry study and who were ever treated with Kineret subsequently to SJIA diagnosis were included in the study.

9.4 Variables

The endpoints to support the objective for the study were:

- The occurrence of non-serious AEs of at least moderate severity and SAEs, including MAS as an ESI.
- The duration of Kineret treatment in a real-world setting.
- The reasons for Kineret treatment discontinuation.

The MedDRA dictionary SOC Immune system disorders includes a specific PT called Haemophagocytic lymphohistiocytosis (HLH), which in the literature and in current clinical practice is referred to as Macrophage Activation Syndrome (MAS) when occurring in patients with SJIA, as per the recent ACR/EULAR classification criteria (7,8). In this report these terms are used as synonymous interchangeably.

The Pharmachild JIA registry CRF collected variables were used in the endpoint analysis of this study as follows:

- Demographics (date of birth, sex, ethnicity, country).
- Date of disease onset, i.e. ‘occurrence of the first clinical manifestation consistent with the disease’, and date of diagnosis.

- Start and stop date of Kineret treatment.
- Start and stop dates of all other SJIA related medications, i.e. sDMARDs or bDMARDs, and systemic glucocorticoids.
- AE SOC/LLT term as per MedDRA dictionary.
- Start date of non-serious AEs of at least moderate severity.
- Start date of all SAEs.
- Report type for AEs: initial or follow-up.
- Date of death.
- Specification of trigger event for incident MAS cases: disease flare, infection, changes of treatment and other.
- Reasons for discontinuation of Kineret treatment: adverse event (moderate/severe/serious event or mild event), intolerance, dose change, inefficacy, remission, surgery, pregnancy or other reason.

9.5 Data sources and measurement

PRINTO (www.printo.it) is a non-profit, non-governmental, international research network founded by Alberto Martini and Nicolino Ruperto in 1996. PRINTO initially included 14 European countries (now 88 countries, 640 centers worldwide with 1348 members today), with the goal to foster, facilitate and co-ordinate the development, conduct, analysis, and reporting of international, multi-center, clinical trials and/or outcome standardization studies in children with paediatric rheumatic diseases.

The Pharmachild JIA registry, which was set up in December 2011 with a 3-year grant from the EU and is maintained by PRINTO, is a registry collecting data from patients with JIA including patients with SJIA.

The Pharmachild JIA registry study has obtained the ENCePP Study Seal awarded on 25 November 2011. ENCePP is a collaborative scientific network coordinated by the European Medicines Agency (EMA) and developed in collaboration with European experts in the fields of pharmacoepidemiology and pharmacovigilance. The ENCePP Study Seal means that a study upholds high standards throughout the research process based on the principles of transparency and scientific independence.

The data source contained both retrospectively and prospectively collected data.

The retrospectively collected data were the data collected from the medical records prior to enrollment in the Pharmachild JIA registry. The prospectively collected data were data collected after enrollment in the registry. For this study retrospectively and prospectively collected data were treated equally.

This study was based on secondary use of data already available in the Pharmchild registry. The source for all data in the registry was the patients' medical records. In the registry both the retrospective and prospective part contained demographics, concomitant medications since onset of disease until last available follow up, AEs that were of at least moderate severity and events of special interest (e.g. MAS). AEs were coded in MedDRA version 21.1. A medical monitor

evaluated all reported AEs. This person was able to raise queries to the centers and request further clarifications.

9.6 Bias

Pharmachild is an observational JIA registry with retrospectively collected and prospectively observed data involving potentially all countries and centers connected to PRINTO.

From a time perspective the data collected in the retrospective components envisioned two steps (12):

- **Step 1:** A census (e.g. collection of patient identification number, age, JIA type and type of treatment) was required from each center before retrospective chart review of safety data initiated to avoid selection biases (e.g. to have the proper denominator against which evaluating the successful data collection).
- **Step 2:** Retrospective chart revision for the collection of moderate/severe non-serious AEs and SAEs until the time of the last available visit. This retrospective chart review was considered successful if at least 70% of the patients listed in the census would have been retrieved.

The study design carries the general limitations inherent in an uncontrolled design regarding statistical analyses, interpretation, generalizability and conclusiveness. The IRs for AEs while exposed to Kineret may be under or overestimated because of exposure-related misclassification of patient-time. The direction of the bias will depend on the direction of the difference in true incidence in the non-exposed (all other treatment options) group vs. Kineret exposed group (e.g. a higher incidence in non-exposed vs. exposed will over-estimate the IRs for the Kineret treatment). The non-exposed patient-time will likely be a mixture of other SJIA-related medications. Misclassification of exposure is likely during non-registered short interruptions of Kineret treatment. Nevertheless, by using a validly conducted register study with the primary objective to research the adverse effects of JIA related medications and with granular recording of exposure time, will alleviate the magnitude of the potential exposure misclassification bias.

The use of sub-populations with patients treated for a certain time may bias the comparisons since the studied patients may have been selected because of a relatively low incidence of adverse events before selection into the sub-population. The probability of experiencing an adverse event by chance may be increased following selection into the sub-population. A comparison with the IR for the respective time window in the total population (the complete set) and not only the sub-population specific IR will likely alleviate a more unbiased conclusion.

All patients in the Pharmachild JIA registry with a diagnosis of SJIA (as per ILAR classification criteria) who were ever treated with Kineret following the SJIA diagnosis were included in this study. No other criteria were used to select patients. In the Pharmachild JIA study a census (e.g. collection of patient identification number, age, JIA type and type of treatment) is required from each center before retrospective chart review of safety data initiation to avoid selection biases (e.g. to have the proper denominator against which evaluating the successful data collection).

9.7 Study size

The sample size was not based on any formal calculation. All 306 patients enrolled in the Pharmachild JIA registry study before 30 September 2018 meeting the criteria defined for the study population were included in the study.

9.8 Data transformation

In the Pharmachild JIA registry data have been collected on-line via the secured PRINTO website. The web system is accessible only to authorized personnel through unique individual usernames and passwords.

Data are cleaned and remotely monitored by designated PRINTO personnel on an ongoing basis to check the accuracy of data. If necessary, additional and more precise information can be requested by the PRINTO personnel.

Technical management of the database is handled by PRINTO.

No individual patient listings were obtained for this study, only summary outputs were reported.

The following variables were derived for this study:

- Time since disease onset was calculated as the difference between ‘start date’ of Kineret treatment and ‘Disease onset’.
- Time from disease onset to first center visit was calculated as the difference between first date center visit and ‘Disease onset’.
- Time since SJIA diagnosis was calculated as the difference between ‘start date’ of Kineret treatment and ‘JIA diagnosis date’.
- Age at start of treatment with Kineret was calculated as the difference between ‘Birth date’ and start date of Kineret treatment.
- Age categories at baseline as follows,
    - Infant (< 2 years).
    - Child (2 years - <12 years).
    - Adolescent (12 years - <18 years).
    - Adult (≥ 18 years).
    - Unknown.
- Ethnicity classification with categories ‘Caucasian, ‘Other’.
- History of MAS (Yes/No). Derived by identifying any known or recorded episodes of MAS prior to baseline.

Each period of Kineret treatment exposure duration was derived as the duration from the start date of Kineret until (and including) the stop date of Kineret plus two (2) days. The two days addition was to account for approximately five (5) half lifes of anakinra. The stop date was substituted with the end of the time window, date of discontinuation of the Kineret treatment exposure, last visit or death where applicable. In case of death or of last visit, the 2 days were not to be added to the duration.

Calendar time windows for Kineret treatment were derived for this study. The time windows were defined as follows: 1-6 months, 7-12 months, 13-18 months, 19-24 months and >24 months of calendar time. For the complete set and the MAS-1 set, time windows were defined in relation to the baseline date. For the long-term treatment set-12, the long-term treatment set-18 and the long-term treatment set-24 respectively, time windows were defined in relation to the index date. In the derivation of number of months, one month will correspond to 30.43 days.

9.9 Statistical methods

9.9.1 Main summary measures

Results were presented descriptively with corresponding two-sided 95% confidence interval, when relevant. Confidence intervals were presented to one more decimal places than the raw data.

Continuous data were summarized using descriptive statistics: n, mean, standard deviation (SD), median, minimum and maximum, 1^{th} and 3^{rd} quartiles, unless otherwise indicated. Minimum and maximum were presented to the same number of decimal places as the raw data and mean, standard deviation and median were presented to one more decimal place than the raw data.

Categorical data were summarized using counts and percentages. Percentages were suppressed when the count is zero, however the category was still displayed. The denominator for all percentages was the number of patients within the population of interest, unless otherwise indicated. Percentages were presented to one decimal place.

IR of events (calculated as the number of the incident events and dividing by the sum of patient years under risk) was expressed as IR per 100 patient years. The IR was derived by a Poisson regression model (with only intercept) and the 95% CI was estimated using the Poisson estimator with a cluster-robust estimate of variance to control for both overdispersion and intracluster correlation.

Statistical analyses were performed using SAS software Version 9.3 or later (SAS Institute Inc, Cary, North Carolina, United States).

9.9.2 Main statistical methods

There were five main analysis sets:

- The complete set, including all patients with SJIA in the registry who have received Kineret at least once following a diagnosis of SJIA as per investigator judgement and enrolled before the cut-off date for the current study (30 September 2018).
- The long-term treatment set-12, including those patients from the complete set with 12 months or more of continuous Kineret treatment*.
- The long-term treatment set-18, including those patients from the complete set with 18 months or more of continuous Kineret treatment*.
- The long-term treatment set-24, including those patients from the complete set with 24 months or more of continuous Kineret treatment*.

- The MAS-1 set, including patients with SJIA who have been diagnosed a first time with MAS following start of Kineret treatment.

*Continuous treatment was defined as ongoing treatment with no more than 30 consecutive days of unexposed duration in between treatment periods. The definition of 'continuous treatment' affected the selection of patients into the long-term treatment set-12, the long-term treatment set-18 and the long-term treatment set-24 as well as the presentation of Kineret treatment exposure and Kineret discontinuation.

For the long-term treatment set-12, 18 and 24 the longest continuous treatment period for each patient was considered for inclusion in the sub-population. For the complete set and the MAS-1 set, the baseline date for each patient was defined as the date of the first dose of Kineret registered following a diagnosis of SJIA as per investigator judgement. For the long-term treatment set-12, 18 and 24, the start date of the most extended treatment period with Kineret was considered as index date.

Calculation of unique IRs of each reported term of non-serious AE, SAE and MAS as an event of special interest (ESI) respectively was performed. A patient was allowed to contribute with multiple events of the same AE term. Therefore, the patient-time did not cease with the occurrence of an event. In addition, mortality rates of all SAEs leading to death were calculated.

Number of years with Kineret treatment, i.e. patient time under risk, was calculated as: the sum of all unique Kineret treatment periods ($\sum$((stop date-start date) +1d +2d) / 365.25) within each time window and for the total duration respectively.

The IR per 100 patient-years was calculated by taking the number of the specific incident event and dividing by the sum of patient years under risk, i.e. exposed to Kineret, multiplied by 100. The following rules were applied:

- AEs occurring outside Kineret treatment exposure, i.e. before, and when Kineret treatment was paused or stopped were not counted.
- The exposure to Kineret treatment was calculated from baseline until the end of the time window, date of discontinuation of the Kineret treatment exposure, last visit or death.
- The periods outside Kineret treatment exposure were excluded from the patient-time.

The IR was derived by a Poisson regression model (with only intercept) and the 95% CI was estimated using the Poisson estimator with a cluster-robust estimate of variance to control for both overdispersion and intracluster correlation.

AE specific IRs was presented overall for the complete study period and also by 6-month calendar time windows defined with reference to the first dose of Kineret.

In a sub-population constituting those with more than 12 months of continuous treatment with Kineret, IRs of non-serious AEs of at least moderate severity, SAEs and MAS were calculated for the time after 12 months and in addition IRs were retrospectively derived for each preceding time window (i.e. 1-6, 7-12 months). Similarly, the analysis was also performed for the subgroup of patients that had more than 18 months (preceding windows to present: 1-6, 7-12 and 13-18 months) and 24 months (preceding windows to present: 1-6, 7-12, 13-18 and 19-24 months) of continuous treatment with Kineret respectively. For patients who were included in the long-term treatment sets, only the patient's longest treatment period was of interest for analysis. The

analyses enabled descriptive comparisons of incidence early in the treatment cycle and incidence resulting from long-term treatment in the same patients.

In the interpretation of the IRs calculated for the sub-populations, i.e. the long-term treatment set-12, the long-term treatment set-18 and the long-term treatment set-24, respective IR for the total study population (the complete set) has been taken into account. Interruptions of treatment, e.g. treatment holidays, were allowed for up to 30 days with respect to the definition of continuous treatment. Neither AEs nor patient-time was counted during the interruption. The following summaries of adverse events were presented:

- Number of AEs (non-serious AEs of at least moderate intensity and serious AEs) and IRs (95% CI) by SOC, PT and time window (the complete set).
- Number of SAEs and IRs (95% CI) by SOC, PT and time window (the complete set).
- Number of SAEs leading to death and mortality rates (95% CI), by SOC, PT and time window (the complete set).
- Number of AEs (non-serious AEs of at least moderate intensity and serious AEs) and IRs (95% CI) by SOC, PT and time window (the long-term treatment set-12).
- Number of AEs (non-serious AEs of at least moderate intensity and serious AEs) and IRs (95% CI) by SOC, PT and time window (the long-term treatment set-18).
- Number of AEs (non-serious AEs of at least moderate intensity and serious AEs) and IRs (95% CI) by SOC, PT and time window (the long-term treatment set-24).
- Number of SAEs and IRs (95% CI) by SOC, PT and time window (the long-term treatment set-12).
- Number of SAEs and IRs (95% CI) by SOC, PT and time window (the long-term treatment set-18).
- Number of SAEs and IRs (95% CI) by SOC, PT and time window (The long-term treatment set-24)

The incidence proportion for each reported AE term was calculated overall and within time windows by counting the number of patients experiencing the event at or after baseline divided with the number of patients treated with Kineret during the respective period. Only events that occur when patients were on Kineret treatment exposure were counted.

The following summaries of incidence proportions of adverse events were presented:

- Number of patients and incidence proportions of AEs (non-serious AEs of at least moderate intensity and all serious AEs) by SOC, PT and time window (the complete set).
- Number of patients and incidence proportions of SAEs by SOC, PT and time window (the complete set).

The IR of MAS was analyzed with respect to 1st occurrence and recurrence respectively. The rationale for this was to account for a biological distinction in altered risk following a first event. For the analyses, the 1st occurrence of MAS was defined to occur at or after baseline regardless of whether the patient had a history of MAS or not. The patients included in the risk set for a 2nd

occurrence of MAS were only those who had a 1st occurrence of MAS as defined above. MAS events and patient-time were counted during Kineret treatment exposure that included an additional period of 2 days after treatment stop.

The cumulative probability of a first event of MAS over time was estimated for the complete set. Patients were censored at 2 days after discontinuation of Kineret treatment, if they died for other reasons than MAS (no 2 days addition), if they were lost to follow-up, or if they had still not experienced a MAS event at the last visit.

The number of days from baseline until the first occurrence of MAS was presented for the MAS-1 set. The number of MAS events and percentages were presented grouped by simultaneous Kineret treatment (Yes/No) and days since first injection with Kineret treatment (1-30 days, 31-180 days, 181-365 and >365 days). In addition, the time after Kineret was stopped until the first occurrence of MAS was summarized for the MAS-1 set. All MAS events occurring after baseline were counted regardless of whether patients are under simultaneous Kineret treatment exposure or not. Notwithstanding, in reporting it was indicated whether simultaneous Kineret treatment exposure was present at the occurrence of the event.

The duration of Kineret treatment exposure was presented with summary statistics (n, mean, SD, median, 1th and 3rd quartiles) overall and by time windows. For this analysis, a patient contributed with multiple Kineret treatment exposure periods if had started a new treatment period after a “treatment holiday” of more than 30 days. Duration of Kineret treatment exposure was presented with total number of patients ever treated in respective time window and number of patients at start of interval (patients who were in treatment at the first day of each time window) and numbers of patients continuously treated at end of interval (patients who had contributed for 6 months to each time window). The total number of patients dosed with Kineret at least once in the study had constituted the denominator for the calculation of percentages.

The reasons for Kineret treatment discontinuation for more than 30 days were summarized with number and percentage, for the complete set. A patient could contribute with multiple discontinuations if she/he had started a new treatment period after a treatment holiday of more than 30 days. Furthermore, multiple reasons could be recorded for one single discontinuation.

9.9.3 Missing values

The analysis and presentation were based on available data, i.e. no imputation of missing data was performed. There was no incomplete information on dates (date of birth, date of SJIA onset, date of SJIA diagnosis, start and stop of Kineret, date of adverse event and date of visit).

9.9.4 Sensitivity analyses

NA

9.9.5 Amendments to the statistical analysis plan

None.

9.10 Quality control

Collection of data has followed standard clinical practice in treatment of the patients. The source for all collected data was the patients' medical records.

It is the responsibility of the Investigators in the Pharmachild JIA registry study to ensure completion and to review all data entered on the PRINTO website. At all times, the Investigators have the final responsibility for the accuracy and authenticity of all patient data entered.

The PRINTO web system is provided with validation control and it is not expected to have missing data related to mandatory questions. All data entered are reviewed by the PRINTO coordinating center for completeness and coherence. If necessary, PRINTO personnel contacts the Investigators to verify correctness and consistency of the data and to retrieve missing data if available. In case of discrepancies, specific queries are issued and resolved through a query ticket system. A medical monitor evaluates all reported AEs. Data can be updated or modified by the Investigator only upon request to the PRINTO helpdesk.

Data are validated on an ongoing basis, and a specific validation process is applied. Pharmachild is a still ongoing JIA registry at the time of the this report.

10 Results

10.1 Participants

As stated in the protocol, 307 patients were preliminary identified for inclusion in the analysis.

On 30 September 2018, the cutoff date for inclusion in the study, a total of 306 patients were identified as meeting all inclusion criteria. These were patients with SJIA as per ILAR classification criteria, who had received Kineret at least once subsequently to disease onset (complete set).

Of the 40 countries participating in the Pharmachild JIA registry, 15 countries (37.5%) have reported data on Kineret treatment. In total 97.7% of the patients were from Europe, and only 2.3% from Asia. Caucasian ethnicity was prevalent (70.6%) (Table 1).

Kineret has been given as monotherapy or in combination with other anti-inflammatory drugs, sDMARDs and bDMARDs as per the local standard of care.

10.2 Descriptive data

As shown in Table 1, among the 306 patients from the complete set, female and male patients were equally represented, with a median age at baseline (first dose of Kineret) of 8.0 years. The patients had their first visit at the treating center after a median time of 0.2 years from onset of the first clinical manifestation consistent with the disease. The median time from SJIA diagnosis to start of Kineret treatment was 0.3 years. Ten (3.3%) patients had history of MAS at start of Kineret treatment.

Among the 306 patients, 141 (46.1%) patients were at some point continuously treated with Kineret for at least 12 months (set-12), 104 (34.0%) patients for at least 18 months (set-18) and 86 (28.1%) patients for at least 24 months (set-24). In the long-term treatment sets there was a numerically higher percentage of males than females (57.4%, 56.7%, and 57.0% in the -12, -18, and -24 months treatment sets, respectively).

10.3 Outcome data

For the 306 patients 201 AEs of at least moderate severity were reported during a total of 509.3 py of treatment, with an overall IR of 39.5 (95% CI 30.8-50.6) per 100 py. Overall IRs were higher in the first time window, 1-6 months, (98.9; 95% CI 75.8-129.0), thereafter decreasing over time (Table 2).

A total of 56 SAEs were reported with an overall IR of 11.0 (95% CI 7.9-15.2) per 100 py. See section 10.6 for main details. Among SAEs, “Infections and Infestations” was the most frequent SOC (total of 13 SAEs, IR=2.6 per 100 py), followed by “Immune system disorders” with a total of 11 SAEs of MAS, IR=2.2 per 100 py (Table 4). The IRs were higher during the first 6 months, 6.0 per 100 py in both SOCs.

10.4 Main results

The duration of Kineret treatment is presented in section 10.4.1. Reasons for Kineret discontinuation are summarized in section 10.4.2. Concomitant medications are summarized in section 10.4.3.

10.4.1 Duration of Kineret treatment

Out of the 306 study patients, 141 (46.1%), 104 (34.0%) and 86 (28.1%) patients were at some point continuously treated with Kineret for at least 12, 18, and 24 months, respectively (Table 1). A continuous treatment was defined as ongoing treatment with no more than 30 consecutive days of unexposed duration in between treatment periods (section 9.9.2).

Overall, the 306 patients had a total of 360 courses of Kineret treatment and the mean duration of a treatment course with Kineret was 17.0 (standard deviation 21.1) months and the median duration was 8.9 (first quartile of 3.1, third quartile of 23.5) months (Table 19). The shortest treatment course was 0.2 months, whereas the longest course was 109.9 months.

Six months after first Kineret dose, a total of 184/306 patients (60.1%) were still continuously exposed. Similarly, after 12, 18 and 24 months, there were 134, 97 and 85 patients respectively still continuously on Kineret treatment.

In total 30.1% of the patients were censored at the last date of visit (i.e. Kineret treatment was ongoing at the last report in the registry).

10.4.2 Reasons for Kineret treatment discontinuation

Out of the 306 patients, 233 patients (76.1%) discontinued Kineret at least once (Table 20, censored patients excluded). In total, there were 268 discontinuations with 281 reasons recorded.

The most frequent reason for Kineret discontinuation were inefficacy with 121 occurrences out of 281 reasons in total (43.1%). Similarly, remission was recorded in 30.6% of all reasons. AEs were represented in 10.0% of all reasons for discontinuations (AEs of at least moderate intensity 8.2% and AEs of mild intensity 1.8%). Intolerance was given as the reason for discontinuation in 5.0% of the cases.

Discontinuations due to AEs and intolerance were more frequently reported during the first 6 months of therapy compared to later time periods. The proportion of discontinuations due to remission increased over time up to 18 months.

10.4.3 Concomitant medications

The latest treatment regimen of sDMARDs, bDMARDs and glucocorticoids received at any time from disease onset to the first dose of Kineret is presented in Table 21. Out of 306 patients, 94 (30.7%) had not been treated with either sDMARDs, bDMARDs or glucocorticoids before starting with Kineret (Table 21). The remaining 212 patients (69.3%, derived from Table 21) had received at least one of these treatments. Among the 212 patients, 78 (36.8%) were treated with various combinations of sDMARDs, bDMARDs and glucocorticoids before starting with Kineret and also continued with those concomitantly with Kineret treatment and 134 (63.2%, derived from Table 21) had stopped treatment before they started with Kineret.

A total of 193 (63.1%) patients received at least 1 concomitant SJIA related medication, other than NSAIDs, at the start of Kineret treatment (Table 22). 161/306 (52.6%, derived from table) patients received glucocorticoids concomitantly with Kineret at treatment start.

10.5 Other analyses

NA

10.6 Adverse events/adverse reactions

10.6.1 Adverse events by PT and SOC

Table 2 reports the number of AEs (non-serious AEs of at least moderate intensity and serious AEs) with the related IRs and 95% CI by MedDRA SOC and PT, overall and according to 5 consecutive time windows for Kineret treatment: 1-6 months, 7-12 months, 13-18 months, 19-24 months, and >24 months after first injection of Kineret. In Table 3 the same data are reported by overall PT by decreasing frequency.

A total of 201 AEs were identified with an overall IR of 39.5 (95% CI 30.8-50.6) per 100 py. The overall incidence of AEs decreased over time with the highest IRs during the first 6 months of Kineret treatment. This was confirmed also by the fact that the 95% CI of the IR (IR=98.9, 95% CI (75.8-129)) during the time window of 1-6 months did not overlap with the 95% CI of any of the following time windows. The MedDRA SOC where AEs were most frequently reported was “Infections and Infestations” (a total of 52 AEs, IR=10.2 per 100 py), followed by “Skin and subcutaneous tissue disorders” (a total of 25 AEs, IR=4.9 per100 py), “General disorders and administration site conditions” (a total of 23 AEs, IR=4.5 per 100 py), and “Gastrointestinal disorders” (a total of 18 AEs, IR=3.5 per 100 py).

The most frequently reported PTs in SOC “Infections and Infestations” were respiratory tract infections, constituting 28 out of 52 events (53.8%) (1 ear infection, 2 influenza, 1 lower respiratory tract infection, 1 otitis media, 3 otitis media acute, 2 Pharyngitis, 1 Pharyngitis bacterial, 4 Pneumonia, 1 Pneumonia viral, 4 Respiratory tract infection, 1 Rhinitis, 1 Sinusitis, 1 Tonsillitis, 2 Tonsillitis streptococcal, 3 Upper respiratory tract infection). There were also 3 varicella infections, and 1 case of herpes zoster.

The most frequently reported PTs in SOC “Skin and subcutaneous tissue disorders” were rash, with 8 occurrences, and urticaria and eczema with 3 occurrences each.

The most frequently reported PTs in SOC “General disorders and administration site conditions” were events related to the injection site, with 15 occurrences (8 classified as “Injection site reaction”, 2 each as “Injection site pain” and “Injection site rash”, and one each for “Injection site hypersensitivity”, “Injection site inflammation” and “Injection site urticarial”). Other PTs included fatigue with 3 occurrences while all other reported PTs occurred only once.

The most frequently reported PTs in SOC “Gastrointestinal disorders” were constipation with 6 occurrences and abdominal pain with 4 occurrences.

The SOC “Immune system disorders” included 12 events of MAS and 1 event of unspecified Autoimmune disorder. For further results concerning MAS (MedDRA PT HLH), see the dedicated paragraphs later in this section. Of the 9 AEs reported in the SOC “Blood and lymphatic system disorders”, there were 4 AEs of neutropenia and 2 AEs of lymphadenopathy.

When analyzing the AEs by overall PT by decreasing frequency of occurrence (Table 3), those which had at least 5 occurrences (and IR greater than 1) included, MAS, n=12, was the most reported event with an IR of 2.4 per 100 py. The most frequently reported PTs thereafter were injection-related reactions with an IR of 2.0 per 100 py, injection site reactions with an IR of 1.6 per 100 py, rash, 1.6 per 100 py, and constipation, 1.2 per 100 py. The remaining AEs showed an IR below 1 per 100 py.

The majority of the “injection site reactions” (ISRs) occurred early after start of Kineret.

The 3 infusion related reactions reported were related to a concomitantly administered drug (tocilizumab).

10.6.2 Serious adverse events by PT and SOC

Table 4 reports the number of SAEs with the related IRs and 95% CI by SOC, PT overall and according to 5 consecutive time windows for Kineret treatment: 1-6 months, 7-12 months, 13-18

months, 19-24 months and >24 months after first injection of Kineret. In Table 5 the same data are reported by overall PT by decreasing frequency of occurrence.

A total of 56 SAEs was observed. Overall the IR was of 11.0 per 100 py (95% CI 7.9-15.2), with events within the SOC “Infections and Infestations” being the most reported (a total of 13 SAEs, IR=2.6 per 100 py), followed by “Immune system disorders” (a total of 11 SAEs, IR=2.2 per 100 py, all describing MAS). “Injury, poisoning and procedural complications” covered 9 events, with an IR of 1.8 per 100 py. The remaining SAEs had an IR below 1.0 per 100 py.

SAEs occurred primarily during the first 6 months of treatment (IR=28.1 per 100 py during the 1-6 month’s time window). After 24 months of Kineret treatment, the IR (IR=4.3 per 100 py) was lower than during the first 6 months of treatment. A tendency towards an increase in the SAE IR (IR=13.8 per 100 py) was observed in the 13-18 months’ time window. However, in this time window, 144 patients contributed only to 58.1 py with 95% CI of IR overlapping with the prior and subsequent time window. Moreover only 8 SAEs in total occurred in 6 patients. Among these 6 patients, 5 had re-started the treatment with Kineret.

Analyzing the SAEs by decreasing frequency of PT occurrence (Table 5), MAS was the most reported event (n=11, IR=2.2 per 100 py) followed by injection-related reactions (n=6, IR=1.2 per 100 py). All remaining PTs had an IR below 1 event per 100 py.

MAS was the most frequently reported PT (Table 3, Table 5). In one patient MAS was considered non-serious by the reporting physician: the event consisted of an isolated increase in ferritin levels (67390 mg/ml), Kineret treatment was not stopped and the physician did not report any MAS specific treatment. Events of MAS occurred primarily during the first 6 months of treatment, IR=6.0 per 100 py; in the time window >24 months, the IR of MAS was of 1.5 events per 100 py (Table 3).

No malignancies or SAEs leading to death occurred during Kineret exposure (Table 4 and Table 6).

10.6.3 AEs (including SAEs) in patients with continuous Kineret treatment

The number of AEs (including non-serious AEs of at least moderate intensity and SAEs) and the related incidence rates in the long-treatment sets -12, -18 and 24 are presented by SOC, PT and time window in Table 9, Table 11 and Table 13, respectively. The number and incidence rates of SAEs in the long-treatment sets -12, -18 and 24 are presented by SOC, PT and time window in Table 10, Table 12 and Table 14, respectively.

An overall IR of 20.9 per 100 py (Table 9) for AEs and 5.1 per 100 py for SAEs (Table 10) were observed for the long-term treatment set-12. Among AEs, Infections and infestations was the most frequent SOC, with the highest incidence during the first 6 months (15.7 per 100 py). The remaining SOCs showed an overall IR ranging between 1.2 and 2.2 per 100 py.

Among SAEs, the SOCs “Infections and infestations”, and “Injury, poisoning and procedural complications” were equally represented with an IR of 1.2 per 100 py (Table 10). The SOC “Immune system disorders” (MAS) had an incidence of 1.0 per 100 py (Table 10).

Similar results were seen in the long-term treatment set-18 and -24, with an overall IR of AEs of 14.3 per 100 py (Table 11) and 13.5 per 100 py (Table 13), respectively. SAEs were represented with an incidence of 3.8 per 100 py (Table 12) and 2.9 per 100 py (Table 14), respectively; also the distribution of AEs and SAEs involved the same categories as in the long-term treatment set-12. In the >24 months treatment window of the long-term treatment set -24, covering 168.8 patient years in 86 patients, there were a total of 22 AEs reported spread over 13 different SOCs (Table 13). Among the 22 AEs, 5 were serious (2 MAS, 1 Humerus fracture, 1 Interstitial lung disease and 1 Hip arthroplasty) (Table 14).

10.6.4 MAS as an event of special interest

In total, 11 patients experienced 12 events (11 SAEs and 1 non-serious AE) of MAS on Kineret treatment. The IR of the first occurrence was 2.2 per 100 py (Table 15).

Ten patients had a previous history of MAS at baseline. Nine of these patients did not experience any new episodes while on Kineret. One patient with history of MAS at baseline had 2 additional episodes of MAS during Kineret treatment.

The IR for first occurrence of MAS while on Kineret was lower in patients without a history of MAS (IR (95% CI) = 2.1 per 100 py (1.1-3.9). The IR for a second occurrence of MAS was higher (IR=16.1 per 100 py) compared to IR of the first occurrence. However, it should be noted that only 1 patient had a second occurrence.

The average time since first injection with Kineret until the first occurrence of MAS during simultaneous Kineret treatment was 9 months (Table 16). During Kineret treatment, 36.4% of MAS events occurred during the first 30 days of treatment and 36.3% occurred 6 months or more after the first injection. The shortest time from baseline to a MAS event was 4 days. The frequency of MAS did not increase during continued treatment ((Table 16).

After stopping Kineret, MAS was reported in 8 patients (Table 17). The earliest recurrence occurred in the time window 90-180 days. There was no indication of a “rebound effect” after discontinuing Kineret, i.e. no indication of an increase in MAS incidence immediately after stopping Kineret. Different triggers have been identified as possible causes of MAS (Table 18), disease flares (4 events, 33.3%), changes of treatments (3 events, 25.0%), and infections (2 events, 16.7%) being the most frequent.

10.6.5 Incidence proportions of AEs (including SAEs)

The number of patients and incidence proportions of AEs (including non-serious AEs of at least moderate intensity and SAEs) in the complete set are presented by MedDRA SOC, PT and time window in Table 7. Table 8 focuses on SAEs.

Among the 306 patients included in the study, 99 patients experienced at least one AE, for an incidence proportion of 32.4% across an average treatment duration of 1.66 years (Table 7). Overall, the total number of AEs was 201 (Table 2), meaning an average of 0.66 AEs per patient. Among the patients who had at least one AE the average was 2 AEs per patient.

Considering the SOC categories, 11.8% of patients experienced events in SOC “Infections and infestations”, 7.5% of patients experienced events in SOC “Skin and subcutaneous tissue disorders”, 6.9% in SOC “General disorders and administration site conditions”, 5.2% in the SOCs “Gastrointestinal disorders” and “Injury, poisoning and procedural complications”, and 3.9% in SOC “Immune system disorders”.

Overall, a higher frequency of patients experiencing AEs was observed during the first 6 months (incidence proportion=23.2%) and after 24 months (incidence proportion=19.2%) compared to other time windows (9.8% for 7-12 months, 7.6% for 13-18 months, 4.7% for 19-24 months). However, the number of patient years was much higher in the >24 month’s time window compared to the other time windows, as described in Table 2. When taking number of patient years into account, there was no increased frequency of AEs in the >24 month’s time window. Among the 306 patients of the study, 44 patients experienced at least one SAE, for an incidence proportion of 14.4% (Table 8). The total number of SAEs was 56, meaning an overall average of 0.18 SAEs per patient. Among patients who had at least one SAE the average was 1.3 SAEs per patient.

The risk of experiencing SAEs was highest during the first 6 months (9.2%). The overall incidence showed that the most frequently reported SAEs were serious infections in 13 patients (4.2%), followed by 10 patients with MAS (3.3%) and 9 patients with events in the SOC “Injury, poisoning and procedural complications” (2.9%). In the >24 months’ time window, 8 patients experienced a total of 9 SAE (1 febrile neutropenia, 2 MAS, 1 Epstein-Barr virus infection, 1 gastroenteritis, 1 tonsillitis, 1 humerus fracture, 1 interstitial lung disease and 1 hip arthroplasty).

11 Discussion

11.1 Key results

In the present report, we evaluate the long-term safety profile of Kineret in the real world setting of 306 patients affected by SJIA enrolled in the Phamarchild JIA registry, with children coming primarily from European countries.

In total, 46.1% of the patients were on continuous Kineret treatment for 1 year or more, and 28.1% had more than 2 years of continuous treatment. Regardless of the age at SJIA disease onset, in clinical practice, patients can be treated for years. Similarly, there is evidence from the literature that after 1 year of therapy approximately half of the patients achieve clinical remission. In remaining patients, the SJIA continues to be active with the clinical need for continuous Kineret treatment (13-15).

The expected duration of Kineret treatment seems not to be related to any specific baseline characteristic.

A much lower overall incidence of AEs compared to the canakinumab phase III prospective long-term extension study can be observed; in the current study the overall incidence of AEs was 39.5 per 100 py while in the long-term extension study with canakinumab it was 796.69 per 100 py (16).

This difference may be at least partially explained by the fact that the prospective canakinumab clinical trial presented a very different study design and, as opposed to the present Pharmachild JIA registry study, mild adverse events were collected in the canakinumab study. However, also the literature confirms that with Kineret treatment less AEs are reported in respect to other anti-IL-1 or other bDMARDs (17). From the German BiKer registry, where all adverse events were collected throughout the observation and specially requested on each routine follow up visit, Horneff et al (17) reported a lower incidence of AEs under IL-1 inhibitors, by collecting 71 AEs during etanercept treatment, corresponding to a rate per 100 py of 20 (16-25), 118 AEs during tocilizumab treatment, corresponding to a rate per 100 py of 106 (88-127) and 81 with anti-IL1, corresponding to a rate per 100 py of 69 (56-86).

In general, the rate of AEs was significantly higher during the first 6 months of Kineret treatment and subsequently decreased over time. This phenomenon, already reported in adult cohorts with rheumatoid arthritis treated with anti-TNF biologics (18,19), could be associated with immune system dysregulation adapting to the new immunomodulatory drug. Higher incidence proportions after 24 months can be explained by the higher number of patient years, compared to the previous time windows. Infections/infestations, skin/subcutaneous tissue disorders, and general disorders/administration site conditions were the most frequently reported AEs in our cohort. Also, SAEs occurred primarily during the first 6 months of treatment with an overall incident rate of 11 events per 100 patient years. Infections and immune system disorders were the most frequently reported SAEs.

In the last decade, rare lung disorders, i.e. pulmonary arterial hypertension, interstitial lung disease, and alveolar proteinosis, have been reported in children with Still's disease (20-22). These disease manifestations have often been associated with MAS and have often been fatal. It has been discussed whether immunosuppressive therapy including IL-1 inhibitors can contribute to the development of these disorders. In this study one patient presented with a pulmonary SAE. This was an unspecified interstitial lung disease that occurred after more than 24 months of treatment (23).

There were no malignancies or SAEs leading to death during Kineret treatment in this study. In the Pharmachild JIA registry, where deaths and malignancies are considered events of special interest (12), there are 3 reports of deaths after discontinuation of Kineret treatment (5 months, 3 years, and 5 years after discontinuation, respectively). In addition, there are no malignancies reported after discontinuation of Kineret.

The incidence rate of MAS was 2.4 events per 100 patient years, which is in line with what is expected for SJIA patient population (24). One third (36.4%) of the MAS events occurred during the first 30 days of treatment; a possible explanation for this could be that Kineret was started when symptoms of MAS were already present or the clinical conditions were rapidly deteriorating due to a severe SJIA flare onset, leading to MAS. There was no evidence that the frequency of MAS increased during continued treatment with Kineret or during the first 90 days after stopping the therapy. Reported trigger events for MAS in the study population were disease flares (4 events), changes of treatments (3 events) and infections (2 events). In the literature, a frequency of MAS prior to Kineret treatment higher than what we found has been recently reported in the United Kingdom (13); this difference was probably related to a greater severity of the SJIA in the UK population. The demographic and clinical features of the different

populations described in the literature and, in particular, the prior and concomitant treatments should also be considered, as they might influence the frequency of MAS by a long-term or concomitant effect. For example, as reported in Swart et al. (12), 75 (3.7%) MAS events were reported in the Pharmachild JIA registry in a sample of 8274 patients, among 2022 Events of special Interest (ESI). In the German registry, BiKer, 11 (0.6%) MAS events were reported out of 3990 patients, among 1697 ESI. In this report, 10 (3.3%) patients had MAS prior Kineret treatment among 306 patients.

In general, the literature suggests that 7-17% of all patients with SJIA develop full-blown MAS (25). Of 323 patients with SJIA enrolled in the canakinumab trials, including the open-label extension phase (total 669 patient-years of exposure) (24), 17 (5.3%) experienced events classified as probable MAS, whilst treated with canakinumab (2.8 events per 100 patient-years) (26). In the long-term canakinumab extension study, 13 MAS events were reported (16). Regarding the tocilizumab clinical trials, in total 22 events were adjudicated as definite (n=11) or potential (n=11) MAS in 21 (3.3%) of the 627 patients with SJIA included in the entire company database (27-29). On the basis of exposure to tocilizumab, the calculated rates of definite and potential MAS in the three cohorts (27-29) were 1.24, 1.84 and 2.10 events per 100 patient-years, respectively.

In particular, history of previous episodes of MAS appeared to have no effect on whether the patients continued long-term Kineret treatment. On the other side, Kineret was usually started during the first months after the SJIA diagnosis with clinical advantage.

The majority of the patients (63.1%) received at least 1 concomitant SJIA related medication, other than NSAIDs, at start of Kineret, while 36.9% of the patients had no treatment for SJIA. In particular, half of the patients received concomitant glucocorticoids, which likely could explain the occurrence of endocrine and steroid-related disorders, such as Cushing's syndrome and cushingoid effects, infections and infestations, bone fractures, overweight, psychiatric disorders and hypertension, mostly reported as sparse events in the first 6 months of therapy.

The main reason for Kineret discontinuation was inefficacy (43.1% of all reasons), however it should be noted that second most common reason for discontinuation was disease remission (30.6%). Furthermore, the remission proportion increased up to 18 months. Relatively few patients discontinued Kineret due to AEs (10.0% of all reasons) or intolerance (5.0%), and most of these events occurred during the first 6 months of treatment.

In summary:

- The pattern and frequency of AEs, including SAEs, were in line with the established safety profile.
- In general, the rate of AEs was higher during the first 6 months of treatment and was significantly lower in the later time periods.
- There was no indication of an increased risk for MAS during Kineret treatment.
- Approximately half (46.1%) of the patients were continuously treated with Kineret for at least 1 year, and approximately one third (28.1%) of the patients were treated for at least 2 years.

- The main reason for discontinuation was inefficacy (43.1% of all reasons) however, remissions accounted for 30.6%.
- Relatively few patients discontinued due to AEs (10.0% of all reasons) and intolerance (5.0%).

11.2 Limitations

The Pharmachild JIA registry has dealt with selection biases (section 9.6) typical of observation registries, as noted in Swart J et al (12): in the Pharmachild JIA registry a total of 11,796 patients were registered in the census registry as of January 2017 from 86 PRINTO centers in 32 countries. Clinical data, including safety data were provided for 8,274/11,796 (70.1%) patients with 60/86 (69.8%) of the participating centers providing safety data for at least 70% of their local JIA patients with a median of 55 patients per center. Prospective data were collected for a total of 3,315 patients.

As stated in section 9.1, the chosen design is deemed acceptable for a study with the primary objective to assess long-term safety of Kineret in patients with SJIA under standard clinical care.

11.3 Interpretation

The study analyzed the long-term safety of Kineret when used in standard clinical practice to treat patients with SJIA. The long-term treatment with Kineret is well-tolerated. The pattern and frequency of AEs, including SAEs, were in line with the established safety profile of Kineret and decreased across treatment duration. Furthermore, the study showed no increased risk of MAS during or directly after Kineret treatment. Discontinuation of treatment occurred more often during the first 6 months and decreased over time. Main reasons for discontinuation were inefficacy and remission in 43.1 and 30.6% of all reasons respectively. Out of all reasons for discontinuation, AEs and intolerance accounted for 15%. Hence, AEs and SAEs did not seem to significantly influence discontinuation.

11.4 Generalisability

This is an international, non-interventional, single-armed, pharmacovigilance registry study on long-term safety of Kineret in SJIA patients, utilizing already available data from the ENCePP certified Pharmachild JIA registry. The Pharmachild JIA registry is collecting data on patients with JIA from 40 countries, of which 15 have collected data on Kineret treatment in SJIA. In the Pharmachild JIA registry, 11% of patients are affected by SJIA (12), confirming the ILAR distribution of this JIA category, which should be around 10% of the JIA population. Moreover, the origin from different geographical areas, as opposed to national registries or single center experiences, provides an overview of the European SJIA patients, which may be generalized to the general population of patients with Still’s disease.

12 Other information

NA

13 Conclusion

The results of the present study confirm the long-term safety profile of Kineret in SJIA patients without any new safety findings. Approximately half (46.1%) of the patients were continuously treated with Kineret for at least 1 year, and 28.1% for at least 2 years.

The pattern and frequency of AEs, including SAEs, were in line with the known safety profile of Kineret. In general, the rate of AEs was highest during the first 6 months of treatment and considerably lower during later time periods. There were no deaths during Kineret treatment. Few patients discontinued due to AEs. The main reason for Kineret discontinuation was inefficacy however, the second most common reason for discontinuation was disease remission. There was no indication that long-term treatment with Kineret increased the risk for MAS, and no indication of a rebound effect after Kineret discontinuation.

Thus, long-term treatment with Kineret in SJIA patients was well tolerated, with no overall increase in incidence rate of AEs, including MAS, over time.

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15 Tables and figures

Table 1. Demographics of the study patient population at baseline[a] (start of Kineret treatment)

	Complete set	**Long-term treatment set-12**	**Long-term treatment set-18**	**Long-term treatment set-24**
N, (%)	**306**	**141 (46.1)**	**104 (34.0)**	**86 (28.1)**
Female, n (%)	154 (50.3)	60 (42.6)	45 (43.3)	37 (43.0)
Male, n (%)	152 (49.7)	81 (57.4)	59 (56.7)	49 (57.0)
Age (years)[b], mean (sd, min, max) median (q1,q3)	8.2 (4.7, 0.8, 20.3) 8.0 (4.0, 11.8)	8.5 (4.6, 0.8, 20.3) 8.5 (4.6, 11.9)	8.6 (4.2, 0.8, 19.3) 8.5 (4.9, 11.4)	8.6 (4.1, 1.0, 19.3) 8.5 (4.9, 11.1)
Age groups, n (%)				
Infant (< 2 years)	22 (7.2)	7 (5.0)	2 (1.9)	1 (1.2)
Child (2 years - <12 years)	210 (68.6)	100 (70.9)	81 (77.9)	68 (79.1)
Adolescent (12 years - <18 years)	69 (22.6)	31 (22.0)	19 (18.3)	16 (18.6)
Adult (≥ 18 years)	5 (1.6)	3 (2.1)	2 (1.9)	1 (1.2)
Time since SJIA onset (years), mean (sd, min, max) median (q1,q3)	2.0 (3.0, 0.0, 16.0) 0.6 (0.2, 2.2)	2.3 (2.8, 0.0, 15.6) 1.1 (0.4, 3.4)	2.7 (2.9, 0.0, 15.6) 1.5 (0.6, 4.3)	2.8 (3.0, 0.0, 15.6) 1.5 (0.6, 4.3)
Time since SJIA diagnosis (years), mean (sd, min, max) median (q1,q3)	1.7 (2.9, 0.0, 15.0) 0.3 (0.0, 1.9)	2.0 (2.7, 0.0, 15.0) 0.8 (0.1, 3.0)	2.4 (2.8, 0.0, 15.0) 1.1 (0.2, 3.8)	2.5 (2.9, 0.0, 15.0) 1.3 (0.2, 4.0)
Time from SJIA onset to first visit (years)[c], mean (sd, min, max) median (q1,q3)	0.9 (1.9, 0.0, 14.9) 0.2 (0.0, 0.8)	0.9 (2.0, 0.0, 14.9) 0.2 (0.1, 0.8)	1.0 (2.2, 0.0, 14.9) 0.2 (0.1, 0.9)	1.1 (2.4, 0.0, 14.9) 0.2 (0.1, 0.8)
Patients with History of MAS, n (%)	10 (3.3)	6 (4.2)	5 (4.8)	4 (4.6)

Table 1. Demographics of the study patient population at baseline[a] (start of Kineret treatment)

	Complete set	**Long-term treatment set-12**	**Long-term treatment set-18**	**Long-term treatment set-24**
N, (%)	**306**	**141 (46.1)**	**104 (34.0)**	**86 (28.1)**
Country of clinic, n (%)				
Croatia	1 (0.3)	0	0	0
Denmark	19 (6.2)	9 (6.4)	6 (5.8)	4 (4.6)
France	49 (16.0)	18 (12.8)	11 (10.6)	9 (10.5)
Germany	1 (0.3)	1 (0.7)	1 (1.0)	1 (1.2)
Greece	11 (3.6)	3 (2.1)	3 (2.9)	3 (3.5)
Hungary	2 (0.6)	0	0	0
Israel	3 (1.0)	1 (0.7)	1 (1.0)	1 (1.2)
Italy	57 (18.6)	33 (23.4)	27 (26.0)	20 (23.3)
Latvia	1 (0.3)	1 (0.7)	1 (1.0)	1 (1.2)
Netherlands	77 (25.2)	26 (18.4)	16 (15.4)	14 (16.3)
Norway	12 (3.9)	7 (5.0)	6 (5.8)	5 (5.8)
Romania	1 (0.3)	1 (0.7)	1 (1.0)	1 (1.2)
Saudi Arabia	4 (1.3)	2 (1.4)	2 (1.9)	2 (2.3)
Spain	46 (15.0)	23 (16.3)	17 (16.3)	14 (16.3)
Switzerland	22 (7.2)	16 (11.3)	12 (11.5)	11 (12.8)

Table 1. Demographics of the study patient population at baseline[a] (start of Kineret treatment)

	Complete set	Long-term treatment set-12	Long-term treatment set-18	Long-term treatment set-24
N, (%)	**306**	**141 (46.1)**	**104 (34.0)**	**86 (28.1)**
Ethnicity, n (%)				
Caucasian	216 (70.6)	97 (68.8)	75 (72.1)	60 (69.8)
Other	90 (29.4)	44 (31.2)	29 (27.9)	26 (30.2)

Abbreviations: SD, Standard deviation; N, number of patients; min, minimum value; max, maximum value; q1, the first quartile; q3, the third quartile.

[a] Baseline date may be postponed for the long-term treatment set 12, 18 and 24.

[b]Age at baseline for the complete set. Age at baseline or at index date for the long-term treatment set 12,18 and 24.

[c]First visit in the clinic center.

Table 2. Number of AEs (non-serious AEs of at least moderate intensity and serious AEs) and incidence rates (95% CI) by SOC, PT and time window (The complete set)

	Time window[a]	**1-6 months**		**7-12 months**		**13-18 months**		**19-24 months**		**>24 months**		**Overall**	
	N	306		194		144		106		104		306	
	Patient-time (years)[b]	117.3		80.2		58.1		47.0		206.7		509.3	
SOC	**PT**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**
All	**All**	**116**	**98.9 (75.8-129.0)**	**26**	**32.4 (19.6-53.5)**	**16**	**27.5 (14.5-52.2)**	**7**	**14.9 (6.0-37.1)**	**36**	**17.4 (11.1-27.4)**	**201**	**39.5 (30.8-50.6)**
Blood and lymphatic system disorders	All	3	2.6 (0.8- 7.9)	2	2.5 (0.6- 9.9)	-	-	-	-	4	1.9 (0.6- 6.4)	9	1.8 (0.9- 3.6)
	Febrile neutropenia	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.4)	1	0.2 (0.0- 1.4)
	Lymphadenitis	-	-	1	1.2 (0.2- 8.8)	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Lymphadenopathy	1	0.9 (0.1- 6.1)	-	-	-	-	-	-	1	0.5 (0.1- 3.4)	2	0.4 (0.1- 1.6)
	Neutropenia	2	1.7 (0.4- 6.8)	1	1.2 (0.2- 8.8)	-	-	-	-	1	0.5 (0.1- 3.4)	4	0.8 (0.3- 2.1)
	Pancytopenia	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.4)	1	0.2 (0.0- 1.4)
Ear and labyrinth disorders	All	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Ear pain	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Endocrine disorders	All	5	4.3 (1.8- 10.2)	-	-	-	-	-	-	-	-	5	1.0 (0.4- 2.4)
	Cushing's syndrome	2	1.7 (0.4- 6.8)	-	-	-	-	-	-	-	-	2	0.4 (0.1- 1.6)
	Cushingoid	2	1.7 (0.4- 6.8)	-	-	-	-	-	-	-	-	2	0.4 (0.1- 1.6)
	Hypothyroidism	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Eye disorders	All	-	-	1	1.2 (0.2- 8.8)	1	1.7 (0.2- 12.2)	-	-	1	0.5 (0.1- 3.3)	3	0.6 (0.2- 1.8)
	Conjunctivitis allergic	-	-	-	-	1	1.7 (0.2- 12.2)	-	-	-	-	1	0.2 (0.0- 1.4)
	Dry eye	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	1	0.2 (0.0- 1.4)
	Eyelid ptosis	-	-	1	1.2 (0.2- 8.8)	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Gastrointestinal disorders	All	13	11.1 (6.0-20.4)	1	1.2 (0.2- 8.8)	-	-	1	2.1 (0.3- 14.9)	3	1.5 (0.5- 4.3)	18	3.5 (2.1- 5.9)
	Abdominal pain	3	2.6 (0.8- 7.9)	1	1.2 (0.2- 8.8)	-	-	-	-	-	-	4	0.8 (0.3- 2.1)

Table 2. Number of AEs (non-serious AEs of at least moderate intensity and serious AEs) and incidence rates (95% CI) by SOC, PT and time window (The complete set)

	Time window[a]	**1-6 months**		**7-12 months**		**13-18 months**		**19-24 months**		**>24 months**		**Overall**	
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SOC	**PT**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**
	Anal pruritus	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Constipation	5	4.3 (1.8- 10.2)	-	-	-	-	-	-	1	0.5 (0.1- 3.5)	6	1.2 (0.5- 2.7)
	Gastritis	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	1	0.2 (0.0- 1.4)
	Nausea	1	0.9 (0.1- 6.0)	-	-	-	-	1	2.1 (0.3- 14.9)	-	-	2	0.4 (0.1- 1.6)
	Odynophagia	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	1	0.2 (0.0- 1.4)
	Pneumatosis intestinalis	1	0.9 (0.1- 6.1)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Stomatitis	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Vomiting	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
General disorders and administration site conditions	All	16	13.6 (8.2- 22.7)	3	3.7 (1.2- 11.5)	1	1.7 (0.2- 12.2)	1	2.1 (0.3- 15.1)	2	1.0 (0.2- 3.8)	23	4.5 (2.9- 7.0)
	Chest pain	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Fatigue	3	2.6 (0.8- 7.9)	-	-	-	-	-	-	-	-	3	0.6 (0.2- 1.8)
	Injection site hypersensitivity	1	0.9 (0.1- 6.1)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Injection site inflammation	-	-	-	-	1	1.7 (0.2- 12.2)	-	-	-	-	1	0.2 (0.0- 1.4)
	Injection site pain	-	-	2	2.5 (0.6- 9.9)	-	-	-	-	-	-	2	0.4 (0.1- 1.6)
	Injection site rash	2	1.7 (0.4- 6.8)	-	-	-	-	-	-	-	-	2	0.4 (0.1- 1.6)
	Injection site reaction	7	6.0 (2.9- 12.4)	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	8	1.6 (0.8- 3.1)
	Injection site urticaria	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Local reaction	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Mucosal erosion	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.4)	1	0.2 (0.0- 1.4)
	Pain	-	-	-	-	-	-	1	2.1 (0.3- 15.1)	-	-	1	0.2 (0.0- 1.4)

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	Pyrexia	-	-	1	1.2 (0.2- 8.8)	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Hepatobiliary disorders	All	3	2.6 (0.8- 7.9)	-	-	-	-	-	-	1	0.5 (0.1- 3.4)	4	0.8 (0.3- 2.1)
	Hepatotoxicity	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.4)	1	0.2 (0.0- 1.4)
	Hypertransaminasaemia	3	2.6 (0.8- 7.9)	-	-	-	-	-	-	-	-	3	0.6 (0.2- 1.8)
Immune system disorders	All	7	6.0 (2.8- 12.5)	1	1.2 (0.2- 8.8)	2	3.4 (0.9- 13.6)	-	-	3	1.5 (0.5- 4.4)	13	2.6 (1.4- 4.6)
	Autoimmune disorder	-	-	-	-	1	1.7 (0.2- 12.1)	-	-	-	-	1	0.2 (0.0- 1.4)
	Haemophagocytic lymphohistiocytosis	7	6.0 (2.8- 12.5)	1	1.2 (0.2- 8.8)	1	1.7 (0.2- 12.2)	-	-	3	1.5 (0.5- 4.4)	12	2.4 (1.3- 4.3)
Infections and infestations	All	23	19.6 (12.4- 31.0)	12	15.0 (6.8- 32.9)	5	8.6 (3.6- 20.7)	-	-	12	5.8 (2.4- 14.1)	52	10.2 (6.7- 15.6)
	Conjunctivitis	-	-	1	1.2 (0.2- 8.8)	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Cystitis	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.5)	1	0.2 (0.0- 1.4)
	Ear infection	-	-	1	1.2 (0.2- 8.8)	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Epstein-Barr viraemia	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Epstein-Barr virus infection	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.5)	1	0.2 (0.0- 1.4)
	Folliculitis	-	-	1	1.2 (0.2- 8.8)	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Fungal skin infection	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Gastroenteritis	-	-	1	1.2 (0.2- 8.8)	-	-	-	-	2	1.0 (0.2- 3.9)	3	0.6 (0.2- 1.8)
	Gastroenteritis rotavirus	1	0.9 (0.1- 6.1)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Gastroenteritis viral	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Herpes zoster	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.4)	1	0.2 (0.0- 1.4)
	Impetigo	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)

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	Infection	1	0.9 (0.1- 6.0)	-	-	1	1.7 (0.2- 12.2)	-	-	-	-	2	0.4 (0.1- 1.6)
	Influenza	2	1.7 (0.4- 6.8)	-	-	-	-	-	-	-	-	2	0.4 (0.1- 1.6)
	Lower respiratory tract infection	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Otitis media	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Otitis media acute	1	0.9 (0.1- 6.0)	2	2.5 (0.6- 9.9)	-	-	-	-	-	-	3	0.6 (0.1- 2.6)
	Parasitic gastroenteritis	-	-	1	1.2 (0.2- 8.8)	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Parvovirus B19 infection	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Pharyngitis	1	0.9 (0.1- 6.0)	-	-	1	1.7 (0.2- 12.3)	-	-	-	-	2	0.4 (0.1- 1.6)
	Pharyngitis bacterial	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.5)	1	0.2 (0.0- 1.4)
	Pneumonia	2	1.7 (0.4- 6.8)	1	1.2 (0.2- 8.8)	1	1.7 (0.2- 12.2)	-	-	-	-	4	0.8 (0.3- 2.1)
	Pneumonia viral	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Pyelonephritis	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Respiratory tract infection	2	1.7 (0.4- 6.8)	-	-	2	3.4 (0.9- 13.7)	-	-	-	-	4	0.8 (0.3- 2.1)
	Rhinitis	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	1	0.2 (0.0- 1.4)
	Sinusitis	-	-	1	1.2 (0.2- 8.8)	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Subcutaneous abscess	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Tonsillitis	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.5)	1	0.2 (0.0- 1.4)
	Tonsillitis streptococcal	-	-	-	-	-	-	-	-	2	1.0 (0.1- 6.8)	2	0.4 (0.1- 2.8)
	Upper respiratory tract infection	2	1.7 (0.4- 6.8)	1	1.2 (0.2- 8.8)	-	-	-	-	-	-	3	0.6 (0.1- 2.6)
	Varicella	-	-	2	2.5 (0.6- 9.9)	-	-	-	-	-	-	2	0.4 (0.1- 1.6)

Table 2. Number of AEs (non-serious AEs of at least moderate intensity and serious AEs) and incidence rates (95% CI) by SOC, PT and time window (The complete set)

	Time window[a]	**1-6 months**		**7-12 months**		**13-18 months**		**19-24 months**		**>24 months**		**Overall**	
	N	306		194		144		106		104		306	
	Patient-time (years)[b]	117.3		80.2		58.1		47.0		206.7		509.3	
SOC	**PT**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**
	Varicella zoster virus infection	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	1	0.2 (0.0- 1.4)
	Viral infection	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	1	0.5 (0.1- 3.5)	2	0.4 (0.1- 1.6)
Injury, poisoning and procedural complications	All	10	8.5 (4.6- 15.8)	1	1.2 (0.2- 8.8)	2	3.4 (0.9- 13.6)	1	2.1 (0.3- 15.1)	2	1.0 (0.3- 3.7)	16	3.1 (1.9- 5.2)
	Hand fracture	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Humerus fracture	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	1	0.2 (0.0- 1.4)
	Infusion related reaction	2	1.7 (0.4- 6.8)	-	-	-	-	1	2.1 (0.3- 15.1)	-	-	3	0.6 (0.2- 1.8)
	Injection related reaction	6	5.1 (2.3- 11.4)	1	1.2 (0.2- 8.8)	2	3.4 (0.9- 13.6)	-	-	1	0.5 (0.1- 3.3)	10	2.0 (1.1- 3.7)
	Joint injury	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Investigations	All	6	5.1 (2.3- 11.3)	1	1.2 (0.2- 8.8)	-	-	-	-	1	0.5 (0.1- 3.3)	8	1.6 (0.7- 3.4)
	Biopsy bone marrow	2	1.7 (0.4- 6.8)	-	-	-	-	-	-	-	-	2	0.4 (0.1- 1.6)
	Hepatic enzyme increased	2	1.7 (0.4- 6.8)	1	1.2 (0.2- 8.8)	-	-	-	-	-	-	3	0.6 (0.1- 2.5)
	Transaminases increased	2	1.7 (0.4- 6.8)	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	3	0.6 (0.2- 1.8)
Metabolism and nutrition disorders	All	3	2.6 (0.8- 7.9)	-	-	1	1.7 (0.2- 12.1)	-	-	-	-	4	0.8 (0.3- 2.1)
	Dehydration	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Hyperuricaemia	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Metabolic acidosis	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Overweight	-	-	-	-	1	1.7 (0.2- 12.1)	-	-	-	-	1	0.2 (0.0- 1.4)
Musculoskeletal and connective tissue disorders	All	1	0.9 (0.1- 6.0)	1	1.2 (0.2- 8.8)	1	1.7 (0.2- 12.3)	-	-	1	0.5 (0.1- 3.3)	4	0.8 (0.3- 2.1)
	Arthritis	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	1	0.2 (0.0- 1.4)

Table 2. Number of AEs (non-serious AEs of at least moderate intensity and serious AEs) and incidence rates (95% CI) by SOC, PT and time window (The complete set)

	Time window[a]	**1-6 months**		**7-12 months**		**13-18 months**		**19-24 months**		**>24 months**		**Overall**	
	N	306		194		144		106		104		306	
	Patient-time (years)[b]	117.3		80.2		58.1		47.0		206.7		509.3	
SOC	**PT**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**
	Back pain	-	-	1	1.2 (0.2- 8.8)	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Rheumatoid arthritis	-	-	-	-	1	1.7 (0.2- 12.3)	-	-	-	-	1	0.2 (0.0- 1.4)
	Still's disease	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Nervous system disorders	All	2	1.7 (0.4- 6.8)	-	-	-	-	3	6.4 (2.1- 19.5)	-	-	5	1.0 (0.4- 2.7)
	Amnesia	-	-	-	-	-	-	1	2.1 (0.3- 14.9)	-	-	1	0.2 (0.0- 1.4)
	Headache	1	0.9 (0.1- 6.0)	-	-	-	-	1	2.1 (0.3- 15.1)	-	-	2	0.4 (0.1- 2.8)
	Petit mal epilepsy	1	0.9 (0.1- 6.0)	-	-	-	-	1	2.1 (0.3- 14.9)	-	-	2	0.4 (0.1- 1.6)
Psychiatric disorders	All	-	-	-	-	2	3.4 (0.9- 13.6)	-	-	1	0.5 (0.1- 3.3)	3	0.6 (0.2- 1.8)
	Attention deficit/hyperactivity disorder	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	1	0.2 (0.0- 1.4)
	Persistent depressive disorder	-	-	-	-	1	1.7 (0.2- 12.1)	-	-	-	-	1	0.2 (0.0- 1.4)
	Psychotic disorder	-	-	-	-	1	1.7 (0.2- 12.1)	-	-	-	-	1	0.2 (0.0- 1.4)
Renal and urinary disorders	All	1	0.9 (0.1- 6.1)	-	-	-	-	1	2.1 (0.3- 14.9)	-	-	2	0.4 (0.1- 1.6)
	Urethral meatus stenosis	1	0.9 (0.1- 6.1)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Urinary incontinence	-	-	-	-	-	-	1	2.1 (0.3- 14.9)	-	-	1	0.2 (0.0- 1.4)
Reproductive system and breast disorders	All	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Balanoposthitis	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Respiratory, thoracic and mediastinal disorders	All	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	1	0.5 (0.1- 3.5)	2	0.4 (0.1- 1.6)
	Asthma	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Interstitial lung disease	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.5)	1	0.2 (0.0- 1.4)

Table 2. Number of AEs (non-serious AEs of at least moderate intensity and serious AEs) and incidence rates (95% CI) by SOC, PT and time window (The complete set)

	Time window[a]	**1-6 months**		**7-12 months**		**13-18 months**		**19-24 months**		**>24 months**		**Overall**	
	N	306		194		144		106		104		306	
	Patient-time (years)[b]	117.3		80.2		58.1		47.0		206.7		509.3	
SOC	**PT**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**
Skin and subcutaneous tissue disorders	All	18	15.3 (9.5- 24.7)	3	3.7 (1.2- 11.5)	1	1.7 (0.2- 12.2)	-	-	3	1.5 (0.5- 4.4)	25	4.9 (3.2- 7.5)
	Dermatitis atopic	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Drug eruption	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Eczema	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	2	1.0 (0.3- 3.7)	3	0.6 (0.2- 1.8)
	Erythema	2	1.7 (0.4- 6.8)	-	-	-	-	-	-	-	-	2	0.4 (0.1- 1.6)
	Mucocutaneous rash	1	0.9 (0.1- 6.1)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Onychomadesis	-	-	-	-	1	1.7 (0.2- 12.2)	-	-	-	-	1	0.2 (0.0- 1.4)
	Pityriasis rosea	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Pruritus	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Pseudocellulitis	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Psoriasis	-	-	1	1.2 (0.2- 8.8)	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Rash	6	5.1 (2.0- 12.8)	1	1.2 (0.2- 8.8)	-	-	-	-	1	0.5 (0.1- 3.5)	8	1.6 (0.7- 3.4)
	Urticaria	3	2.6 (0.8- 8.0)	-	-	-	-	-	-	-	-	3	0.6 (0.2- 1.8)
	Vitiligo	-	-	1	1.2 (0.2- 8.8)	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Surgical and medical procedures	All	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	2	0.4 (0.1- 1.5)
	Hip arthroplasty	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	1	0.2 (0.0- 1.4)
	Lymphadenectomy	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Vascular disorders	All	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Hypertension	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)

Abbreviations: AE, adverse event; SOC, system organ class; PT, preferred term, MedDRA version 21.1; N, number of patients ever treated with Kineret during the time window irrespectively of the length of any unexposed periods; 95% CI, 95% Confidence Interval.

A patient can contribute with multiple AEs of same PT overall and within respective time window.

[a] in relation to baseline (start of Kineret treatment).

[b] only time during periods with Kineret treatment (incl. 2 days post stop) counted.

[c] number of events. Only AEs occurring during Kineret exposed periods (incl. 2 days post stop) are counted.

[d] incidence rate per 100 patient years; number of events/∑patient time.

Table 3. Number of AEs (non-serious AEs of at least moderate intensity and serious AEs) and incidence rates (95% CI) by overall PT decreasing order and time window (The complete set)

Time window[a]	**1-6 months**		**7-12 months**		**13-18 months**		**19-24 months**		**>24 months**		**Overall**	
N	306		194		144		106		104		306	
Patient-time (years)[b]	117.3		80.2		58.1		47.0		206.7		509.3	
PT	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**
All	**116**	**98.9 (75.8-129)**	**26**	**32.4 (19.6-53.5)**	**16**	**27.5 (14.5-52.2)**	**7**	**14.9 (6.0-37.1)**	**36**	**17.4 (11.1-27.4)**	**201**	**39.5 (30.8-50.6)**
Haemophagocytic lymphohistiocytosis	7	6.0 (2.8- 12.5)	1	1.2 (0.2- 8.8)	1	1.7 (0.2- 12.2)	-	-	3	1.5 (0.5- 4.4)	12	2.4 (1.3- 4.3)
Injection related reaction	6	5.1 (2.3- 11.4)	1	1.2 (0.2- 8.8)	2	3.4 (0.9- 13.6)	-	-	1	0.5 (0.1- 3.3)	10	2.0 (1.1- 3.7)
Injection site reaction	7	6.0 (2.9- 12.4)	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	8	1.6 (0.8- 3.1)
Rash	6	5.1 (2.0- 12.8)	1	1.2 (0.2- 8.8)	-	-	-	-	1	0.5 (0.1- 3.5)	8	1.6 (0.7- 3.4)
Constipation	5	4.3 (1.8- 10.2)	-	-	-	-	-	-	1	0.5 (0.1- 3.5)	6	1.2 (0.5- 2.7)
Abdominal pain	3	2.6 (0.8- 7.9)	1	1.2 (0.2- 8.8)	-	-	-	-	-	-	4	0.8 (0.3- 2.1)
Neutropenia	2	1.7 (0.4- 6.8)	1	1.2 (0.2- 8.8)	-	-	-	-	1	0.5 (0.1- 3.4)	4	0.8 (0.3- 2.1)
Pneumonia	2	1.7 (0.4- 6.8)	1	1.2 (0.2- 8.8)	1	1.7 (0.2- 12.2)	-	-	-	-	4	0.8 (0.3- 2.1)
Respiratory tract infection	2	1.7 (0.4- 6.8)	-	-	2	3.4 (0.9- 13.7)	-	-	-	-	4	0.8 (0.3- 2.1)
Eczema	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	2	1.0 (0.3- 3.7)	3	0.6 (0.2- 1.8)
Fatigue	3	2.6 (0.8- 7.9)	-	-	-	-	-	-	-	-	3	0.6 (0.2- 1.8)
Gastroenteritis	-	-	1	1.2 (0.2- 8.8)	-	-	-	-	2	1.0 (0.2- 3.9)	3	0.6 (0.2- 1.8)
Hepatic enzyme increased	2	1.7 (0.4- 6.8)	1	1.2 (0.2- 8.8)	-	-	-	-	-	-	3	0.6 (0.1- 2.5)
Hypertransaminasaemia	3	2.6 (0.8- 7.9)	-	-	-	-	-	-	-	-	3	0.6 (0.2- 1.8)
Infusion related reaction	2	1.7 (0.4- 6.8)	-	-	-	-	1	2.1 (0.3- 15.1)	-	-	3	0.6 (0.2- 1.8)
Otitis media acute	1	0.9 (0.1- 6.0)	2	2.5 (0.6- 9.9)	-	-	-	-	-	-	3	0.6 (0.1- 2.6)
Transaminases increased	2	1.7 (0.4- 6.8)	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	3	0.6 (0.2- 1.8)
Upper respiratory tract infection	2	1.7 (0.4- 6.8)	1	1.2 (0.2- 8.8)	-	-	-	-	-	-	3	0.6 (0.1- 2.6)
Urticaria	3	2.6 (0.8- 8.0)	-	-	-	-	-	-	-	-	3	0.6 (0.2- 1.8)
Biopsy bone marrow	2	1.7 (0.4- 6.8)	-	-	-	-	-	-	-	-	2	0.4 (0.1- 1.6)

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Cushingoid	2	1.7 (0.4- 6.8)	-	-	-	-	-	-	-	-	2	0.4 (0.1- 1.6)
Cushing's syndrome	2	1.7 (0.4- 6.8)	-	-	-	-	-	-	-	-	2	0.4 (0.1- 1.6)
Erythema	2	1.7 (0.4- 6.8)	-	-	-	-	-	-	-	-	2	0.4 (0.1- 1.6)
Headache	1	0.9 (0.1- 6.0)	-	-	-	-	1	2.1 (0.3- 15.1)	-	-	2	0.4 (0.1- 2.8)
Infection	1	0.9 (0.1- 6.0)	-	-	1	1.7 (0.2- 12.2)	-	-	-	-	2	0.4 (0.1- 1.6)
Influenza	2	1.7 (0.4- 6.8)	-	-	-	-	-	-	-	-	2	0.4 (0.1- 1.6)
Injection site pain	-	-	2	2.5 (0.6- 9.9)	-	-	-	-	-	-	2	0.4 (0.1- 1.6)
Injection site rash	2	1.7 (0.4- 6.8)	-	-	-	-	-	-	-	-	2	0.4 (0.1- 1.6)
Lymphadenopathy	1	0.9 (0.1- 6.1)	-	-	-	-	-	-	1	0.5 (0.1- 3.4)	2	0.4 (0.1- 1.6)
Nausea	1	0.9 (0.1- 6.0)	-	-	-	-	1	2.1 (0.3- 14.9)	-	-	2	0.4 (0.1- 1.6)
Petit mal epilepsy	1	0.9 (0.1- 6.0)	-	-	-	-	1	2.1 (0.3- 14.9)	-	-	2	0.4 (0.1- 1.6)
Pharyngitis	1	0.9 (0.1- 6.0)	-	-	1	1.7 (0.2- 12.3)	-	-	-	-	2	0.4 (0.1- 1.6)
Tonsillitis streptococcal	-	-	-	-	-	-	-	-	2	1.0 (0.1- 6.8)	2	0.4 (0.1- 2.8)
Varicella	-	-	2	2.5 (0.6- 9.9)	-	-	-	-	-	-	2	0.4 (0.1- 1.6)
Viral infection	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	1	0.5 (0.1- 3.5)	2	0.4 (0.1- 1.6)
Amnesia	-	-	-	-	-	-	1	2.1 (0.3- 14.9)	-	-	1	0.2 (0.0- 1.4)
Anal pruritus	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Arthritis	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	1	0.2 (0.0- 1.4)
Asthma	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Attention deficit/hyperactivity disorder	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	1	0.2 (0.0- 1.4)
Autoimmune disorder	-	-	-	-	1	1.7 (0.2- 12.1)	-	-	-	-	1	0.2 (0.0- 1.4)

Table 3. Number of AEs (non-serious AEs of at least moderate intensity and serious AEs) and incidence rates (95% CI) by overall PT decreasing order and time window (The complete set)

Time window[a]	**1-6 months**		**7-12 months**		**13-18 months**		**19-24 months**		**>24 months**		**Overall**	
N	306		194		144		106		104		306	
Patient-time (years)[b]	117.3		80.2		58.1		47.0		206.7		509.3	
PT	**n**[c]	**Rate (95% CI)**[d]	**n**[c]	**Rate (95% CI)**[d]	**n**[c]	**Rate (95% CI)**[d]	**n**[c]	**Rate (95% CI)**[d]	**n**[c]	**Rate (95% CI)**[d]	**n**[c]	**Rate (95% CI)**[d]
Back pain	-	-	1	1.2 (0.2- 8.8)	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Balanoposthitis	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Chest pain	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Conjunctivitis	-	-	1	1.2 (0.2- 8.8)	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Conjunctivitis allergic	-	-	-	-	1	1.7 (0.2- 12.2)	-	-	-	-	1	0.2 (0.0- 1.4)
Cystitis	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.5)	1	0.2 (0.0- 1.4)
Dehydration	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Dermatitis atopic	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Drug eruption	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Dry eye	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	1	0.2 (0.0- 1.4)
Ear infection	-	-	1	1.2 (0.2- 8.8)	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Ear pain	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Epstein-Barr viraemia	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Epstein-Barr virus infection	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.5)	1	0.2 (0.0- 1.4)
Eyelid ptosis	-	-	1	1.2 (0.2- 8.8)	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Febrile neutropenia	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.4)	1	0.2 (0.0- 1.4)
Folliculitis	-	-	1	1.2 (0.2- 8.8)	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Fungal skin infection	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Gastritis	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	1	0.2 (0.0- 1.4)
Gastroenteritis rotavirus	1	0.9 (0.1- 6.1)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Gastroenteritis viral	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)

Table 3. Number of AEs (non-serious AEs of at least moderate intensity and serious AEs) and incidence rates (95% CI) by overall PT decreasing order and time window (The complete set)

Time window[a]	**1-6 months**		**7-12 months**		**13-18 months**		**19-24 months**		**>24 months**		**Overall**	
N	306		194		144		106		104		306	
Patient-time (years)[b]	117.3		80.2		58.1		47.0		206.7		509.3	
PT	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**
Hand fracture	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Hepatotoxicity	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.4)	1	0.2 (0.0- 1.4)
Herpes zoster	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.4)	1	0.2 (0.0- 1.4)
Hip arthroplasty	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	1	0.2 (0.0- 1.4)
Humerus fracture	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	1	0.2 (0.0- 1.4)
Hypertension	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Hyperuricaemia	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Hypothyroidism	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Impetigo	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Injection site hypersensitivity	1	0.9 (0.1- 6.1)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Injection site inflammation	-	-	-	-	1	1.7 (0.2- 12.2)	-	-	-	-	1	0.2 (0.0- 1.4)
Injection site urticaria	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Interstitial lung disease	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.5)	1	0.2 (0.0- 1.4)
Joint injury	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Local reaction	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Lower respiratory tract infection	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Lymphadenectomy	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Lymphadenitis	-	-	1	1.2 (0.2- 8.8)	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Metabolic acidosis	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Mucocutaneous rash	1	0.9 (0.1- 6.1)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Mucosal erosion	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.4)	1	0.2 (0.0- 1.4)

Table 3. Number of AEs (non-serious AEs of at least moderate intensity and serious AEs) and incidence rates (95% CI) by overall PT decreasing order and time window (The complete set)

Time window[a]	1-6 months		7-12 months		13-18 months		19-24 months		>24 months		Overall	
N	306		194		144		106		104		306	
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PT	n[c]	Rate (95% CI)[d]	n[c]	Rate (95% CI)[d]	n[c]	Rate (95% CI)[d]	n[c]	Rate (95% CI)[d]	n[c]	Rate (95% CI)[d]	n[c]	Rate (95% CI)[d]
Odynophagia	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	1	0.2 (0.0- 1.4)
Onychomadesis	-	-	-	-	1	1.7 (0.2- 12.2)	-	-	-	-	1	0.2 (0.0- 1.4)
Otitis media	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Overweight	-	-	-	-	1	1.7 (0.2- 12.1)	-	-	-	-	1	0.2 (0.0- 1.4)
Pain	-	-	-	-	-	-	1	2.1 (0.3- 15.1)	-	-	1	0.2 (0.0- 1.4)
Pancytopenia	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.4)	1	0.2 (0.0- 1.4)
Parasitic gastroenteritis	-	-	1	1.2 (0.2- 8.8)	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Parvovirus B19 infection	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Persistent depressive disorder	-	-	-	-	1	1.7 (0.2- 12.1)	-	-	-	-	1	0.2 (0.0- 1.4)
Pharyngitis bacterial	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.5)	1	0.2 (0.0- 1.4)
Pityriasis rosea	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Pneumatosis intestinalis	1	0.9 (0.1- 6.1)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Pneumonia viral	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Pruritus	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Pseudocellulitis	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Psoriasis	-	-	1	1.2 (0.2- 8.8)	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Psychotic disorder	-	-	-	-	1	1.7 (0.2- 12.1)	-	-	-	-	1	0.2 (0.0- 1.4)
Pyelonephritis	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Pyrexia	-	-	1	1.2 (0.2- 8.8)	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Rheumatoid arthritis	-	-	-	-	1	1.7 (0.2- 12.3)	-	-	-	-	1	0.2 (0.0- 1.4)
Rhinitis	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	1	0.2 (0.0- 1.4)

Table 3. Number of AEs (non-serious AEs of at least moderate intensity and serious AEs) and incidence rates (95% CI) by overall PT decreasing order and time window (The complete set)

Time window[a]	**1-6 months**		**7-12 months**		**13-18 months**		**19-24 months**		**>24 months**		**Overall**	
N	306		194		144		106		104		306	
Patient-time (years)[b]	117.3		80.2		58.1		47.0		206.7		509.3	
PT	**n**[c]	**Rate (95% CI)**[d]	**n**[c]	**Rate (95% CI)**[d]	**n**[c]	**Rate (95% CI)**[d]	**n**[c]	**Rate (95% CI)**[d]	**n**[c]	**Rate (95% CI)**[d]	**n**[c]	**Rate (95% CI)**[d]
Sinusitis	-	-	1	1.2 (0.2- 8.8)	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Still's disease	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Stomatitis	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Subcutaneous abscess	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Tonsillitis	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.5)	1	0.2 (0.0- 1.4)
Urethral meatus stenosis	1	0.9 (0.1- 6.1)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Urinary incontinence	-	-	-	-	-	-	1	2.1 (0.3- 14.9)	-	-	1	0.2 (0.0- 1.4)
Varicella zoster virus infection	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	1	0.2 (0.0- 1.4)
Vitiligo	-	-	1	1.2 (0.2- 8.8)	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Vomiting	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)

Abbreviations: AE, adverse event; PT, preferred term, MedDRA version 21.1; N, number of patients ever treated with Kineret during the time window irrespectively of the length of any unexposed periods;

95% CI, 95% Confidence Interval.

[a] in relation to baseline (start of Kineret treatment).

[b] only time during periods with Kineret treatment (incl. 2 days post stop) counted.

[c] number of events. Only AEs occurring during Kineret exposed periods (incl. 2 days post stop) are counted.

[d] incidence rate per 100 patient years; number of events/∑patient time.

Table 4. Number of SAEs and incidence rates (95% CI) by SOC, PT and time window (The complete set)

	Time window[a]	**1-6 months**		**7-12 months**		**13-18 months**		**19-24 months**		**>24 months**		**Overall**	
	N	306		194		144		106		104		306	
	Patient-time (years)[b]	117.3		80.2		58.1		47.0		206.7		509.3	
SOC	**PT**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**
All	**All**	**33**	**28.1 (19.1-41.5)**	**4**	**5.0 (1.9-13.2)**	**8**	**13.8 (5.9-31.9)**	**2**	**4.3 (1.1-16.9)**	**9**	**4.3 (2.2-8.8)**	**56**	**11.0 (7.9-15.2)**
Blood and lymphatic system disorders	All	1	0.9 (0.1- 6.1)	-	-	-	-	-	-	1	0.5 (0.1-3.4)	2	0.4 (0.1-1.6)
	Febrile neutropenia	-	-	-	-	-	-	-	-	1	0.5 (0.1-3.4)	1	0.2 (0.0-1.4)
	Lymphadenopathy	1	0.9 (0.1- 6.1)	-	-	-	-	-	-	-	-	1	0.2 (0.0-1.4)
Gastrointestinal disorders	All	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0-1.4)
	Abdominal pain	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0-1.4)
General disorders and administration site conditions	All	1	0.9 (0.1- 6.1)	1	1.2 (0.2-8.8)	-	-	-	-	-	-	2	0.4 (0.1-1.6)
	Injection site pain	-	-	1	1.2 (0.2-8.8)	-	-	-	-	-	-	1	0.2 (0.0-1.4)
	Injection site reaction	1	0.9 (0.1- 6.1)	-	-	-	-	-	-	-	-	1	0.2 (0.0-1.4)
Hepatobiliary disorders	All	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0-1.4)
	Hypertransaminasaemia	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0-1.4)
Immune system disorders	All	7	6.0 (2.8-12.5)	1	1.2 (0.2-8.8)	1	1.7 (0.2-12.2)	-	-	2	1.0 (0.2-3.8)	11	2.2 (1.1-4.1)
	Haemophagocytic lymphohistiocytosis	7	6.0 (2.8-12.5)	1	1.2 (0.2-8.8)	1	1.7 (0.2-12.2)	-	-	2	1.0 (0.2-3.8)	11	2.2 (1.1-4.1)
Infections and infestations	All	7	6.0 (2.9-12.4)	1	1.2 (0.2-8.8)	2	3.4 (0.9-13.8)	-	-	3	1.5 (0.3-6.3)	13	2.6 (1.4-4.8)

Table 4. Number of SAEs and incidence rates (95% CI) by SOC, PT and time window (The complete set)

	Time window[a]	**1-6 months**		**7-12 months**		**13-18 months**		**19-24 months**		**>24 months**		**Overall**	
	N	306		194		144		106		104		306	
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SOC	**PT**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**
	Epstein-Barr virus infection	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.5)	1	0.2 (0.0- 1.4)
	Gastroenteritis	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.5)	1	0.2 (0.0- 1.4)
	Otitis media	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Parvovirus B19 infection	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Pharyngitis	-	-	-	-	1	1.7 (0.2- 12.3)	-	-	-	-	1	0.2 (0.0- 1.4)
	Pneumonia	2	1.7 (0.4- 6.8)	1	1.2 (0.2- 8.8)	1	1.7 (0.2- 12.2)	-	-	-	-	4	0.8 (0.3- 2.1)
	Pneumonia viral	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Pyelonephritis	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Tonsillitis	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.5)	1	0.2 (0.0- 1.4)
	Viral infection	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Injury, poisoning and procedural complications	All	5	4.3 (1.8- 10.2)	-	-	2	3.4 (0.9- 13.6)	1	2.1 (0.3- 15.1)	1	0.5 (0.1- 3.3)	9	1.8 (0.9- 3.4)
	Humerus fracture	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	1	0.2 (0.0- 1.4)
	Infusion related reaction	1	0.9 (0.1- 6.0)	-	-	-	-	1	2.1 (0.3- 15.1)	-	-	2	0.4 (0.1- 1.6)
	Injection related reaction	4	3.4 (1.3- 9.1)	-	-	2	3.4 (0.9- 13.6)	-	-	-	-	6	1.2 (0.5- 2.6)
Investigations	All	2	1.7 (0.4- 6.8)	-	-	-	-	-	-	-	-	2	0.4 (0.1- 1.6)

Table 4. Number of SAEs and incidence rates (95% CI) by SOC, PT and time window (The complete set)

	Time window[a]	**1-6 months**		**7-12 months**		**13-18 months**		**19-24 months**		**>24 months**		**Overall**	
	N	306		194		144		106		104		306	
	Patient-time (years)[b]	117.3		80.2		58.1		47.0		206.7		509.3	
SOC	**PT**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**
	Biopsy bone marrow	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Hepatic enzyme increased	1	0.9 (0.1- 6.1)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Metabolism and nutrition disorders	All	3	2.6 (0.8- 7.9)	-	-	1	1.7 (0.2- 12.1)	-	-	-	-	4	0.8 (0.3- 2.1)
	Dehydration	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Hyperuricaemia	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Metabolic acidosis	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Overweight	-	-	-	-	1	1.7 (0.2- 12.1)	-	-	-	-	1	0.2 (0.0- 1.4)
Musculoskeletal and connective tissue disorders	All	-	-	-	-	1	1.7 (0.2- 12.3)	-	-	-	-	1	0.2 (0.0- 1.4)
	Rheumatoid arthritis	-	-	-	-	1	1.7 (0.2- 12.3)	-	-	-	-	1	0.2 (0.0- 1.4)
Nervous system disorders	All	1	0.9 (0.1- 6.0)	-	-	-	-	1	2.1 (0.3- 14.9)	-	-	2	0.4 (0.1- 1.6)
	Amnesia	-	-	-	-	-	-	1	2.1 (0.3- 14.9)	-	-	1	0.2 (0.0- 1.4)
	Petit mal epilepsy	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Psychiatric disorders	All	-	-	-	-	1	1.7 (0.2- 12.1)	-	-	-	-	1	0.2 (0.0- 1.4)
	Psychotic disorder	-	-	-	-	1	1.7 (0.2- 12.1)	-	-	-	-	1	0.2 (0.0- 1.4)
Respiratory, thoracic and mediastinal disorders	All	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.5)	1	0.2 (0.0- 1.4)

Table 4. Number of SAEs and incidence rates (95% CI) by SOC, PT and time window (The complete set)

	Time window[a]	**1-6 months**		**7-12 months**		**13-18 months**		**19-24 months**		**>24 months**		**Overall**	
	N	306		194		144		106		104		306	
	Patient-time (years)[b]	117.3		80.2		58.1		47.0		206.7		509.3	
SOC	**PT**	**n**[c]	**Rate (95% CI)**[d]	**n**[c]	**Rate (95% CI)**[d]	**n**[c]	**Rate (95% CI)**[d]	**n**[c]	**Rate (95% CI)**[d]	**n**[c]	**Rate (95% CI)**[d]	**n**[c]	**Rate (95% CI)**[d]
	Interstitial lung disease	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.5)	1	0.2 (0.0- 1.4)
Skin and subcutaneous tissue disorders	All	3	2.6 (0.8- 7.9)	1	1.2 (0.2- 8.8)	-	-	-	-	-	-	4	0.8 (0.3- 2.1)
	Drug eruption	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Pityriasis rosea	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Psoriasis	-	-	1	1.2 (0.2- 8.8)	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
	Urticaria	1	0.9 (0.1- 6.1)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Surgical and medical procedures	All	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	2	0.4 (0.1- 1.5)
	Hip arthroplasty	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	1	0.2 (0.0- 1.4)
	Lymphadenectomy	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)

Abbreviations: SAE, serious adverse event; SOC, system organ class; PT, preferred term, MedDRA version 21.1; N, number of patients ever treated with Kineret during the time window irrespectively of the length of any unexposed periods; 95% CI, 95% Confidence Interval.

A patient can contribute with multiple SAEs of same PT overall and within respective time window.

[a] in relation to baseline (start of Kineret treatment).

[b] only time during periods with Kineret treatment (incl. 2 days post stop) counted.

[c] number of events. Only SAEs occurring during Kineret exposed periods (incl. 2 days post stop) are counted.

[d] incidence rate per 100 patient years; number of events/∑patient time.

Table 5. Number of SAEs and incidence rates (95% CI) by overall PT decreasing order and time window (The complete set)

Time window[a]	**1-6 months**		**7-12 months**		**13-18 months**		**19-24 months**		**>24 months**		**Overall**	
N	306		194		144		106		104		306	
Patient-time (years)[b]	117.3		80.2		58.1		47.0		206.7		509.3	
PT	**n**[c]	**Rate (95% CI)**[d]	**n**[c]	**Rate (95% CI)**[d]	**n**[c]	**Rate (95% CI)**[d]	**n**[c]	**Rate (95% CI)**[d]	**n**[c]	**Rate (95% CI)**[d]	**n**[c]	**Rate (95% CI)**[d]
All	**33**	**28.1 (19.1-41.5)**	**4**	**5.0 (1.9-13.2)**	**8**	**13.8 (5.9-31.9)**	**2**	**4.3 (1.1-16.9)**	**9**	**4.3 (2.2-8.8)**	**56**	**11.0 (7.9-15.2)**
Haemophagocytic lymphohistiocytosis	7	6.0 (2.8- 12.5)	1	1.2 (0.2- 8.8)	1	1.7 (0.2- 12.2)	-	-	2	1.0 (0.2- 3.8)	11	2.2 (1.1- 4.1)
Injection related reaction	4	3.4 (1.3- 9.1)	-	-	2	3.4 (0.9- 13.6)	-	-	-	-	6	1.2 (0.5- 2.6)
Pneumonia	2	1.7 (0.4- 6.8)	1	1.2 (0.2- 8.8)	1	1.7 (0.2- 12.2)	-	-	-	-	4	0.8 (0.3- 2.1)
Infusion related reaction	1	0.9 (0.1- 6.0)	-	-	-	-	1	2.1 (0.3- 15.1)	-	-	2	0.4 (0.1- 1.6)
Abdominal pain	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Amnesia	-	-	-	-	-	-	1	2.1 (0.3- 14.9)	-	-	1	0.2 (0.0- 1.4)
Biopsy bone marrow	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Dehydration	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Drug eruption	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Epstein-Barr virus infection	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.5)	1	0.2 (0.0- 1.4)
Febrile neutropenia	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.4)	1	0.2 (0.0- 1.4)
Gastroenteritis	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.5)	1	0.2 (0.0- 1.4)
Hepatic enzyme increased	1	0.9 (0.1- 6.1)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Hip arthroplasty	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	1	0.2 (0.0- 1.4)
Humerus fracture	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	1	0.2 (0.0- 1.4)
Hypertransaminasaemia	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Hyperuricaemia	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Injection site pain	-	-	1	1.2 (0.2- 8.8)	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Injection site reaction	1	0.9 (0.1- 6.1)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Interstitial lung disease	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.5)	1	0.2 (0.0- 1.4)
Lymphadenectomy	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)

Table 5. Number of SAEs and incidence rates (95% CI) by overall PT decreasing order and time window (The complete set)

Time window[a]	**1-6 months**		**7-12 months**		**13-18 months**		**19-24 months**		**>24 months**		**Overall**	
N	306		194		144		106		104		306	
Patient-time (years)[b]	117.3		80.2		58.1		47.0		206.7		509.3	
PT	**n**[c]	**Rate (95% CI)**[d]	**n**[c]	**Rate (95% CI)**[d]	**n**[c]	**Rate (95% CI)**[d]	**n**[c]	**Rate (95% CI)**[d]	**n**[c]	**Rate (95% CI)**[d]	**n**[c]	**Rate (95% CI)**[d]
Lymphadenopathy	1	0.9 (0.1- 6.1)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Metabolic acidosis	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Otitis media	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Overweight	-	-	-	-	1	1.7 (0.2- 12.1)	-	-	-	-	1	0.2 (0.0- 1.4)
Parvovirus B19 infection	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Petit mal epilepsy	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Pharyngitis	-	-	-	-	1	1.7 (0.2- 12.3)	-	-	-	-	1	0.2 (0.0- 1.4)
Pityriasis rosea	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Pneumonia viral	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Psoriasis	-	-	1	1.2 (0.2- 8.8)	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Psychotic disorder	-	-	-	-	1	1.7 (0.2- 12.1)	-	-	-	-	1	0.2 (0.0- 1.4)
Pyelonephritis	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Rheumatoid arthritis	-	-	-	-	1	1.7 (0.2- 12.3)	-	-	-	-	1	0.2 (0.0- 1.4)
Tonsillitis	-	-	-	-	-	-	-	-	1	0.5 (0.1- 3.5)	1	0.2 (0.0- 1.4)
Urticaria	1	0.9 (0.1- 6.1)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)
Viral infection	1	0.9 (0.1- 6.0)	-	-	-	-	-	-	-	-	1	0.2 (0.0- 1.4)

Abbreviations: SAE, serious adverse event; PT, preferred term, MedDRA version 21.1; N, number of patients ever treated with Kineret during the time window irrespectively of the length of any unexposed periods; 95% CI, 95% Confidence Interval.

A patient can contribute with multiple SAEs of same PT overall and within respective time window.

[a] in relation to baseline (start of Kineret treatment).

[b] only time during periods with Kineret treatment (incl. 2 days post stop) counted.

[c] number of events. Only SAEs occurring during Kineret exposed periods (incl. 2 days post stop) are counted.

[d] incidence rate per 100 patient years; number of events/∑patient time.

Table 6. Number of SAEs leading to death and mortality rates (95% CI) by SOC, PT and time window (The complete set)

	Time window[a]	**1-6 months**		**7-12 months**		**13-18 months**		**19-24 months**		**>24 months**		**Overall**	
	N	306		194		144		106		104		306	
	Patient-time (years)[b]	117.3		80.2		58.1		47.0		206.7		509.3	
SOC	**PT**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**
All	**All**	**0**	**0.0**	**0**	**0.0**	**0**	**0.0**	**0**	**0.0**	**0**	**0.0**	**0**	**0.0**

Abbreviations: SAE, serious adverse event; SOC, system organ class, PT, preferred term, MedDRA version 21.1; N, number of patients ever treated with Kineret during the time window irrespectively of the length of any unexposed periods; 95% CI, 95% Confidence Interval.

[a] in relation to baseline (start of Kineret treatment).

[b] only time during periods with Kineret treatment (incl. 2 days post stop) counted.

[c] number of deaths. Only deaths occurring during Kineret exposed periods (incl. 2 days post stop) are counted.

[d] mortality rate per 100 patient years; number of deaths/∑patient time.

Table 7. Number of patients and incidence proportions of AEs (non-serious AEs of at least moderate intensity and all serious AEs) by SOC, PT and time window (The complete set)

	Time window[a]	**1-6 months**		**7-12 months**		**13-18 months**		**19-24 months**		**>24 months**		**Overall**	
	N[b]	**306**		**194**		**144**		**106**		**104**		**306**	
	Patient-time (years)	**117.3**		**80.2**		**58.1**		**47.0**		**206.7**		**509.3**	
SOC	**PT**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**
All	**All**	**71**	**23.2**	**19**	**9.8**	**11**	**7.6**	**5**	**4.7**	**20**	**19.2**	**99**	**32.4**
Blood and lymphatic system disorders	All	3	1.0	2	1.0	-	-	-	-	3	2.9	8	2.6
	Febrile neutropenia	-	-	-	-	-	-	-	-	1	1.0	1	0.3
	Lymphadenitis	-	-	1	0.5	-	-	-	-	-	-	1	0.3
	Lymphadenopathy	1	0.3	-	-	-	-	-	-	1	1.0	2	0.7
	Neutropenia	2	0.7	1	0.5	-	-	-	-	1	1.0	4	1.3
	Pancytopenia	-	-	-	-	-	-	-	-	1	1.0	1	0.3
Ear and labyrinth disorders	All	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Ear pain	1	0.3	-	-	-	-	-	-	-	-	1	0.3
Endocrine disorders	All	5	1.6	-	-	-	-	-	-	-	-	5	1.6
	Cushing's syndrome	2	0.7	-	-	-	-	-	-	-	-	2	0.7
	Cushingoid	2	0.7	-	-	-	-	-	-	-	-	2	0.7
	Hypothyroidism	1	0.3	-	-	-	-	-	-	-	-	1	0.3
Eye disorders	All	-	-	1	0.5	1	0.7	-	-	1	1.0	3	1.0
	Conjunctivitis allergic	-	-	-	-	1	0.7	-	-	-	-	1	0.3
	Dry eye	-	-	-	-	-	-	-	-	1	1.0	1	0.3
	Eyelid ptosis	-	-	1	0.5	-	-	-	-	-	-	1	0.3
Gastrointestinal disorders	All	11	3.6	1	0.5	-	-	1	0.9	3	2.9	16	5.2
	Abdominal pain	3	1.0	1	0.5	-	-	-	-	-	-	4	1.3
	Anal pruritus	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Constipation	5	1.6	-	-	-	-	-	-	1	1.0	6	2.0

Table 7. Number of patients and incidence proportions of AEs (non-serious AEs of at least moderate intensity and all serious AEs) by SOC, PT and time window (The complete set)

	Time window[a]	**1-6 months**		**7-12 months**		**13-18 months**		**19-24 months**		**>24 months**		**Overall**	
	N[b]	**306**		**194**		**144**		**106**		**104**		**306**	
	Patient-time (years)	**117.3**		**80.2**		**58.1**		**47.0**		**206.7**		**509.3**	
SOC	**PT**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**
	Gastritis	-	-	-	-	-	-	-	-	1	1.0	1	0.3
	Nausea	1	0.3	-	-	-	-	1	0.9	-	-	2	0.7
	Odynophagia	-	-	-	-	-	-	-	-	1	1.0	1	0.3
	Pneumatosis intestinalis	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Stomatitis	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Vomiting	1	0.3	-	-	-	-	-	-	-	-	1	0.3
General disorders and administration site conditions	All	15	4.9	3	1.5	1	0.7	1	0.9	2	1.9	21	6.9
	Chest pain	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Fatigue	3	1.0	-	-	-	-	-	-	-	-	3	1.0
	Injection site hypersensitivity	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Injection site inflammation	-	-	-	-	1	0.7	-	-	-	-	1	0.3
	Injection site pain	-	-	2	1.0	-	-	-	-	-	-	2	0.7
	Injection site rash	2	0.7	-	-	-	-	-	-	-	-	2	0.7
	Injection site reaction	7	2.3	-	-	-	-	-	-	1	1.0	8	2.6
	Injection site urticaria	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Local reaction	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Mucosal erosion	-	-	-	-	-	-	-	-	1	1.0	1	0.3
	Pain	-	-	-	-	-	-	1	0.9	-	-	1	0.3
	Pyrexia	-	-	1	0.5	-	-	-	-	-	-	1	0.3

Table 7. Number of patients and incidence proportions of AEs (non-serious AEs of at least moderate intensity and all serious AEs) by SOC, PT and time window (The complete set)

	Time window[a]	**1-6 months**		**7-12 months**		**13-18 months**		**19-24 months**		**>24 months**		**Overall**	
	N[b]	**306**		**194**		**144**		**106**		**104**		**306**	
	Patient-time (years)	**117.3**		**80.2**		**58.1**		**47.0**		**206.7**		**509.3**	
SOC	**PT**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**
Hepatobiliary disorders	All	3	1.0	-	-	-	-	-	-	1	1.0	4	1.3
	Hepatotoxicity	-	-	-	-	-	-	-	-	1	1.0	1	0.3
	Hypertransaminasaemia	3	1.0	-	-	-	-	-	-	-	-	3	1.0
Immune system disorders	All	7	2.3	1	0.5	2	1.4	-	-	3	2.9	12	3.9
	Autoimmune disorder	-	-	-	-	1	0.7	-	-	-	-	1	0.3
	Haemophagocytic lymphohistiocytosis	7	2.3	1	0.5	1	0.7	-	-	3	2.9	11	3.6
Infections and infestations	All	20	6.5	9	4.6	5	3.5	-	-	7	6.7	36	11.8
	Conjunctivitis	-	-	1	0.5	-	-	-	-	-	-	1	0.3
	Cystitis	-	-	-	-	-	-	-	-	1	1.0	1	0.3
	Ear infection	-	-	1	0.5	-	-	-	-	-	-	1	0.3
	Epstein-Barr viraemia	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Epstein-Barr virus infection	-	-	-	-	-	-	-	-	1	1.0	1	0.3
	Folliculitis	-	-	1	0.5	-	-	-	-	-	-	1	0.3
	Fungal skin infection	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Gastroenteritis	-	-	1	0.5	-	-	-	-	2	1.9	3	1.0
	Gastroenteritis rotavirus	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Gastroenteritis viral	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Herpes zoster	-	-	-	-	-	-	-	-	1	1.0	1	0.3
	Impetigo	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Infection	1	0.3	-	-	1	0.7	-	-	-	-	2	0.7

Table 7. Number of patients and incidence proportions of AEs (non-serious AEs of at least moderate intensity and all serious AEs) by SOC, PT and time window (The complete set)

	Time window[a]	**1-6 months**		**7-12 months**		**13-18 months**		**19-24 months**		**>24 months**		**Overall**	
	N[b]	**306**		**194**		**144**		**106**		**104**		**306**	
	Patient-time (years)	**117.3**		**80.2**		**58.1**		**47.0**		**206.7**		**509.3**	
SOC	**PT**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**
	Influenza	2	0.7	-	-	-	-	-	-	-	-	2	0.7
	Lower respiratory tract infection	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Otitis media	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Otitis media acute	1	0.3	2	1.0	-	-	-	-	-	-	2	0.7
	Parasitic gastroenteritis	-	-	1	0.5	-	-	-	-	-	-	1	0.3
	Parvovirus B19 infection	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Pharyngitis	1	0.3	-	-	1	0.7	-	-	-	-	2	0.7
	Pharyngitis bacterial	-	-	-	-	-	-	-	-	1	1.0	1	0.3
	Pneumonia	2	0.7	1	0.5	1	0.7	-	-	-	-	4	1.3
	Pneumonia viral	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Pyelonephritis	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Respiratory tract infection	2	0.7	-	-	2	1.4	-	-	-	-	4	1.3
	Rhinitis	-	-	-	-	-	-	-	-	1	1.0	1	0.3
	Sinusitis	-	-	1	0.5	-	-	-	-	-	-	1	0.3
	Subcutaneous abscess	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Tonsillitis	-	-	-	-	-	-	-	-	1	1.0	1	0.3
	Tonsillitis streptococcal	-	-	-	-	-	-	-	-	1	1.0	1	0.3
	Upper respiratory tract infection	2	0.7	1	0.5	-	-	-	-	-	-	2	0.7
	Varicella	-	-	2	1.0	-	-	-	-	-	-	2	0.7

Table 7. Number of patients and incidence proportions of AEs (non-serious AEs of at least moderate intensity and all serious AEs) by SOC, PT and time window (The complete set)

	Time window[a]	**1-6 months**		**7-12 months**		**13-18 months**		**19-24 months**		**>24 months**		**Overall**	
	N[b]	**306**		**194**		**144**		**106**		**104**		**306**	
	Patient-time (years)	**117.3**		**80.2**		**58.1**		**47.0**		**206.7**		**509.3**	
SOC	**PT**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**
	Varicella zoster virus infection	-	-	-	-	-	-	-	-	1	1.0	1	0.3
	Viral infection	1	0.3	-	-	-	-	-	-	1	1.0	2	0.7
Injury, poisoning and procedural complications	All	10	3.3	1	0.5	2	1.4	1	0.9	2	1.9	16	5.2
	Hand fracture	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Humerus fracture	-	-	-	-	-	-	-	-	1	1.0	1	0.3
	Infusion related reaction	2	0.7	-	-	-	-	1	0.9	-	-	3	1.0
	Injection related reaction	6	2.0	1	0.5	2	1.4	-	-	1	1.0	10	3.3
	Joint injury	1	0.3	-	-	-	-	-	-	-	-	1	0.3
Investigations	All	6	2.0	1	0.5	-	-	-	-	1	1.0	7	2.3
	Biopsy bone marrow	2	0.7	-	-	-	-	-	-	-	-	2	0.7
	Hepatic enzyme increased	2	0.7	1	0.5	-	-	-	-	-	-	2	0.7
	Transaminases increased	2	0.7	-	-	-	-	-	-	1	1.0	3	1.0
Metabolism and nutrition disorders	All	3	1.0	-	-	1	0.7	-	-	-	-	4	1.3
	Dehydration	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Hyperuricaemia	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Metabolic acidosis	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Overweight	-	-	-	-	1	0.7	-	-	-	-	1	0.3

Table 7. Number of patients and incidence proportions of AEs (non-serious AEs of at least moderate intensity and all serious AEs) by SOC, PT and time window (The complete set)

	Time window[a]	**1-6 months**		**7-12 months**		**13-18 months**		**19-24 months**		**>24 months**		**Overall**	
	N[b]	**306**		**194**		**144**		**106**		**104**		**306**	
	Patient-time (years)	**117.3**		**80.2**		**58.1**		**47.0**		**206.7**		**509.3**	
SOC	**PT**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**
Musculoskeletal and connective tissue disorders	All	1	0.3	1	0.5	1	0.7	-	-	1	1.0	4	1.3
	Arthritis	-	-	-	-	-	-	-	-	1	1.0	1	0.3
	Back pain	-	-	1	0.5	-	-	-	-	-	-	1	0.3
	Rheumatoid arthritis	-	-	-	-	1	0.7	-	-	-	-	1	0.3
	Still's disease	1	0.3	-	-	-	-	-	-	-	-	1	0.3
Nervous system disorders	All	2	0.7	-	-	-	-	3	2.8	-	-	4	1.3
	Amnesia	-	-	-	-	-	-	1	0.9	-	-	1	0.3
	Headache	1	0.3	-	-	-	-	1	0.9	-	-	1	0.3
	Petit mal epilepsy	1	0.3	-	-	-	-	1	0.9	-	-	2	0.7
Psychiatric disorders	All	-	-	-	-	2	1.4	-	-	1	1.0	3	1.0
	Attention deficit/hyperactivity disorder	-	-	-	-	-	-	-	-	1	1.0	1	0.3
	Persistent depressive disorder	-	-	-	-	1	0.7	-	-	-	-	1	0.3
	Psychotic disorder	-	-	-	-	1	0.7	-	-	-	-	1	0.3
Renal and urinary disorders	All	1	0.3	-	-	-	-	1	0.9	-	-	2	0.7
	Urethral meatus stenosis	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Urinary incontinence	-	-	-	-	-	-	1	0.9	-	-	1	0.3
Reproductive system and breast disorders	All	1	0.3	-	-	-	-	-	-	-	-	1	0.3

Table 7. Number of patients and incidence proportions of AEs (non-serious AEs of at least moderate intensity and all serious AEs) by SOC, PT and time window (The complete set)

	Time window[a]	**1-6 months**		**7-12 months**		**13-18 months**		**19-24 months**		**>24 months**		**Overall**	
	N[b]	**306**		**194**		**144**		**106**		**104**		**306**	
	Patient-time (years)	**117.3**		**80.2**		**58.1**		**47.0**		**206.7**		**509.3**	
SOC	**PT**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**
	Balanoposthitis	1	0.3	-	-	-	-	-	-	-	-	1	0.3
Respiratory, thoracic and mediastinal disorders	All	1	0.3	-	-	-	-	-	-	1	1.0	2	0.7
	Asthma	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Interstitial lung disease	-	-	-	-	-	-	-	-	1	1.0	1	0.3
Skin and subcutaneous tissue disorders	All	17	5.6	3	1.5	1	0.7	-	-	3	2.9	23	7.5
	Dermatitis atopic	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Drug eruption	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Eczema	1	0.3	-	-	-	-	-	-	2	1.9	3	1.0
	Erythema	2	0.7	-	-	-	-	-	-	-	-	2	0.7
	Mucocutaneous rash	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Onychomadesis	-	-	-	-	1	0.7	-	-	-	-	1	0.3
	Pityriasis rosea	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Pruritus	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Pseudocellulitis	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Psoriasis	-	-	1	0.5	-	-	-	-	-	-	1	0.3
	Rash	5	1.6	1	0.5	-	-	-	-	1	1.0	7	2.3
	Urticaria	3	1.0	-	-	-	-	-	-	-	-	3	1.0
	Vitiligo	-	-	1	0.5	-	-	-	-	-	-	1	0.3
Surgical and medical procedures	All	1	0.3	-	-	-	-	-	-	1	1.0	2	0.7

Table 7. Number of patients and incidence proportions of AEs (non-serious AEs of at least moderate intensity and all serious AEs) by SOC, PT and time window (The complete set)

	Time window[a]	**1-6 months**		**7-12 months**		**13-18 months**		**19-24 months**		**>24 months**		**Overall**	
	N[b]	**306**		**194**		**144**		**106**		**104**		**306**	
	Patient-time (years)	**117.3**		**80.2**		**58.1**		**47.0**		**206.7**		**509.3**	
SOC	**PT**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**
	Hip arthroplasty	-	-	-	-	-	-	-	-	1	1.0	1	0.3
	Lymphadenectomy	1	0.3	-	-	-	-	-	-	-	-	1	0.3
Vascular disorders	All	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Hypertension	1	0.3	-	-	-	-	-	-	-	-	1	0.3

Abbreviations: AE, adverse event; SOC, system organ class, PT, preferred term, MedDRA version 21.1.

[a] in relation to baseline (start of Kineret treatment).

[b] number of patients ever treated with Kineret in respective time window.

[c] number of patients experiencing the event. Only AEs occurring during Kineret exposed periods (incl. 2 days post stop) are counted.

[d] incidence proportion (%), n/N.

Table 8. Number of patients and incidence proportions of SAEs by SOC, PT and time window (The complete set)

	Time window[a]	**1-6 months**		**7-12 months**		**13-18 months**		**19-24 months**		**>24 months**		**Overall**	
	N[b]	**306**		**194**		**144**		**106**		**104**		**306**	
	Patient-time (years)	**117.3**		**80.2**		**58.1**		**47.0**		**206.7**		**509.3**	
SOC	**PT**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**
All	**All**	**28**	**9.2**	**4**	**2.1**	**6**	**4.2**	**2**	**1.9**	**8**	**7.7**	**44**	**14.4**
Blood and lymphatic system disorders	All	1	0.3	-	-	-	-	-	-	1	1.0	2	0.7
	Febrile neutropenia	-	-	-	-	-	-	-	-	1	1.0	1	0.3
	Lymphadenopathy	1	0.3	-	-	-	-	-	-	-	-	1	0.3
Gastrointestinal disorders	All	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Abdominal pain	1	0.3	-	-	-	-	-	-	-	-	1	0.3
General disorders and administration site conditions	All	1	0.3	1	0.5	-	-	-	-	-	-	2	0.7
	Injection site pain	-	-	1	0.5	-	-	-	-	-	-	1	0.3
	Injection site reaction	1	0.3	-	-	-	-	-	-	-	-	1	0.3
Hepatobiliary disorders	All	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Hypertransaminasaemia	1	0.3	-	-	-	-	-	-	-	-	1	0.3
Immune system disorders	All	7	2.3	1	0.5	1	0.7	-	-	2	1.9	10	3.3
	Haemophagocytic lymphohistiocytosis	7	2.3	1	0.5	1	0.7	-	-	2	1.9	10	3.3
Infections and infestations	All	7	2.3	1	0.5	2	1.4	-	-	3	2.9	13	4.2
	Epstein-Barr virus infection	-	-	-	-	-	-	-	-	1	1.0	1	0.3
	Gastroenteritis	-	-	-	-	-	-	-	-	1	1.0	1	0.3
	Otitis media	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Parvovirus B19 infection	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Pharyngitis	-	-	-	-	1	0.7	-	-	-	-	1	0.3
	Pneumonia	2	0.7	1	0.5	1	0.7	-	-	-	-	4	1.3
	Pneumonia viral	1	0.3	-	-	-	-	-	-	-	-	1	0.3

Table 8. Number of patients and incidence proportions of SAEs by SOC, PT and time window (The complete set)

	Time window[a]	**1-6 months**		**7-12 months**		**13-18 months**		**19-24 months**		**>24 months**		**Overall**	
	N[b]	**306**		**194**		**144**		**106**		**104**		**306**	
	Patient-time (years)	**117.3**		**80.2**		**58.1**		**47.0**		**206.7**		**509.3**	
SOC	**PT**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**
	Pyelonephritis	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Tonsillitis	-	-	-	-	-	-	-	-	1	1.0	1	0.3
	Viral infection	1	0.3	-	-	-	-	-	-	-	-	1	0.3
Injury, poisoning and procedural complications	All	5	1.6	-	-	2	1.4	1	0.9	1	1.0	9	2.9
	Humerus fracture	-	-	-	-	-	-	-	-	1	1.0	1	0.3
	Infusion related reaction	1	0.3	-	-	-	-	1	0.9	-	-	2	0.7
	Injection related reaction	4	1.3	-	-	2	1.4	-	-	-	-	6	2.0
Investigations	All	2	0.7	-	-	-	-	-	-	-	-	2	0.7
	Biopsy bone marrow	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Hepatic enzyme increased	1	0.3	-	-	-	-	-	-	-	-	1	0.3
Metabolism and nutrition disorders	All	3	1.0	-	-	1	0.7	-	-	-	-	4	1.3
	Dehydration	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Hyperuricaemia	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Metabolic acidosis	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Overweight	-	-	-	-	1	0.7	-	-	-	-	1	0.3
Musculoskeletal and connective tissue disorders	All	-	-	-	-	1	0.7	-	-	-	-	1	0.3
	Rheumatoid arthritis	-	-	-	-	1	0.7	-	-	-	-	1	0.3
Nervous system disorders	All	1	0.3	-	-	-	-	1	0.9	-	-	2	0.7
	Amnesia	-	-	-	-	-	-	1	0.9	-	-	1	0.3
	Petit mal epilepsy	1	0.3	-	-	-	-	-	-	-	-	1	0.3
Psychiatric disorders	All	-	-	-	-	1	0.7	-	-	-	-	1	0.3

Table 8. Number of patients and incidence proportions of SAEs by SOC, PT and time window (The complete set)

	Time window[a]	**1-6 months**		**7-12 months**		**13-18 months**		**19-24 months**		**>24 months**		**Overall**	
	N[b]	**306**		**194**		**144**		**106**		**104**		**306**	
	Patient-time (years)	**117.3**		**80.2**		**58.1**		**47.0**		**206.7**		**509.3**	
SOC	**PT**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**	**n[c]**	**Incidence proportion[d]**
	Psychotic disorder	-	-	-	-	1	0.7	-	-	-	-	1	0.3
Respiratory, thoracic and mediastinal disorders	All	-	-	-	-	-	-	-	-	1	1.0	1	0.3
	Interstitial lung disease	-	-	-	-	-	-	-	-	1	1.0	1	0.3
Skin and subcutaneous tissue disorders	All	3	1.0	1	0.5	-	-	-	-	-	-	4	1.3
	Drug eruption	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Pityriasis rosea	1	0.3	-	-	-	-	-	-	-	-	1	0.3
	Psoriasis	-	-	1	0.5	-	-	-	-	-	-	1	0.3
	Urticaria	1	0.3	-	-	-	-	-	-	-	-	1	0.3
Surgical and medical procedures	All	1	0.3	-	-	-	-	-	-	1	1.0	2	0.7
	Hip arthroplasty	-	-	-	-	-	-	-	-	1	1.0	1	0.3
	Lymphadenectomy	1	0.3	-	-	-	-	-	-	-	-	1	0.3

Abbreviations: SAE, serious adverse event; SOC, system organ class; PT, preferred term, MedDRA version 21.1.

[a] in relation to baseline (start of Kineret treatment).

[b] number of patients ever treated with Kineret in respective time window.

[c] number of patients experiencing the event. Only SAEs occurring during Kineret exposed periods (incl. 2 days post stop) are counted.

[d] incidence proportion (%), n/N.

Table 9. Number of AEs (non-serious AEs of at least moderate intensity and all serious AEs) and incidence rates (95% CI) by SOC, PT and time window (The long-term treatment set-12)

	Time window[a]	**1-6 months**		**7-12 months**		**>12 months**		**Overall**	
	N	**141**		**141**		**141**		**141**	
	Patient time (years)[b]	**70.1**		**70.0**		**275.5**		**415.6**	
SOC	**PT**	**n[c]**	**Rate (95% CI) [d]**	**n[c]**	**Rate (95% CI) [d]**	**n[c]**	**Rate (95% CI) [d]**	**n[c]**	**Rate (95% CI) [d]**
All	**All**	**30**	**42.8 (27.2-67.2)**	**18**	**25.7 (13.4-49.3)**	**39**	**14.2 (9.6-20.8)**	**87**	**20.9 (14.6-30.1)**
Blood and lymphatic system disorders	All	-	-	2	2.9 (0.7- 11.3)	3	1.1 (0.4- 3.3)	5	1.2 (0.5 - 2.8)
	Lymphadenitis	-	-	1	1.4 (0.2- 10.1)	-	-	1	0.2 (0.0 - 1.7)
	Lymphadenopathy	-	-	-	-	1	0.4 (0.1- 2.6)	1	0.2 (0.0 - 1.7)
	Neutropenia	-	-	1	1.4 (0.2- 10.1)	1	0.4 (0.1- 2.6)	2	0.5 (0.1 - 1.9)
	Pancytopenia	-	-	-	-	1	0.4 (0.1- 2.5)	1	0.2 (0.0 - 1.7)
Ear and labyrinth disorders	All	1	1.4 (0.2- 10.1)	-	-	-	-	1	0.2 (0.0 - 1.7)
	Ear pain	1	1.4 (0.2- 10.1)	-	-	-	-	1	0.2 (0.0 - 1.7)
Eye disorders	All	-	-	1	1.4 (0.2- 10.1)	2	0.7 (0.2- 2.9)	3	0.7 (0.2 - 2.2)
	Conjunctivitis allergic	-	-	-	-	1	0.4 (0.1- 2.6)	1	0.2 (0.0 - 1.7)
	Dry eye	-	-	-	-	1	0.4 (0.1- 2.5)	1	0.2 (0.0 - 1.7)
	Eyelid ptosis	-	-	1	1.4 (0.2- 10.1)	-	-	1	0.2 (0.0 - 1.7)
Gastrointestinal disorders	All	1	1.4 (0.2- 10.1)	1	1.4 (0.2- 10.1)	3	1.1 (0.4- 3.2)	5	1.2 (0.5 - 2.8)
	Abdominal pain	-	-	1	1.4 (0.2- 10.1)	-	-	1	0.2 (0.0 - 1.7)
	Gastritis	-	-	-	-	1	0.4 (0.1- 2.5)	1	0.2 (0.0 - 1.7)
	Nausea	-	-	-	-	1	0.4 (0.1- 2.5)	1	0.2 (0.0 - 1.7)
	Odynophagia	-	-	-	-	1	0.4 (0.1- 2.5)	1	0.2 (0.0 - 1.7)
	Stomatitis	1	1.4 (0.2- 10.1)	-	-	-	-	1	0.2 (0.0 - 1.7)
General disorders and administration site conditions	All	5	7.1 (2.6- 19.9)	1	1.4 (0.2- 10.1)	3	1.1 (0.4- 3.3)	9	2.2 (1.1 - 4.4)
	Fatigue	1	1.4 (0.2- 10.1)	-	-	-	-	1	0.2 (0.0 - 1.7)
	Injection site inflammation	-	-	-	-	1	0.4 (0.1- 2.6)	1	0.2 (0.0 - 1.7)
	Injection site pain	-	-	1	1.4 (0.2- 10.1)	-	-	1	0.2 (0.0 - 1.7)
	Injection site rash	1	1.4 (0.2- 10.1)	-	-	-	-	1	0.2 (0.0 - 1.7)
	Injection site reaction	3	4.3 (1.4- 13.1)	-	-	1	0.4 (0.1- 2.5)	4	1.0 (0.4 - 2.5)

Table 9. Number of AEs (non-serious AEs of at least moderate intensity and all serious AEs) and incidence rates (95% CI) by SOC, PT and time window (The long-term treatment set-12)

	Time window[a]	**1-6 months**		**7-12 months**		**>12 months**		**Overall**	
	N	**141**		**141**		**141**		**141**	
	Patient time (years)[b]	**70.1**		**70.0**		**275.5**		**415.6**	
SOC	**PT**	**n[c]**	**Rate (95% CI) [d]**	**n[c]**	**Rate (95% CI) [d]**	**n[c]**	**Rate (95% CI) [d]**	**n[c]**	**Rate (95% CI) [d]**
	Mucosal erosion	-	-	-	-	1	0.4 (0.1- 2.6)	1	0.2 (0.0 - 1.7)
Hepatobiliary disorders	All	-	-	-	-	1	0.4 (0.1- 2.6)	1	0.2 (0.0 - 1.7)
	Hepatotoxicity	-	-	-	-	1	0.4 (0.1- 2.6)	1	0.2 (0.0 - 1.7)
Immune system disorders	All	1	1.4 (0.2- 10.1)	1	1.4 (0.2- 10.1)	3	1.1 (0.4- 3.3)	5	1.2 (0.4 - 3.3)
	Autoimmune disorder	1	1.4 (0.2- 10.1)	-	-	-	-	1	0.2 (0.0 - 1.7)
	Haemophagocytic lymphohistiocytosis	-	-	1	1.4 (0.2- 10.1)	3	1.1 (0.4- 3.3)	4	1.0 (0.3 - 3.1)
Infections and infestations	All	11	15.7 (7.7- 32.1)	7	10.0 (3.0- 33.5)	8	2.9 (1.2- 7.3)	26	6.3 (3.2- 12.2)
	Conjunctivitis	-	-	1	1.4 (0.2- 10.1)	-	-	1	0.2 (0.0 - 1.7)
	Ear infection	-	-	1	1.4 (0.2- 10.1)	-	-	1	0.2 (0.0 - 1.7)
	Gastroenteritis	-	-	-	-	1	0.4 (0.1- 2.6)	1	0.2 (0.0 - 1.7)
	Herpes zoster	-	-	-	-	1	0.4 (0.1- 2.5)	1	0.2 (0.0 - 1.7)
	Infection	-	-	-	-	1	0.4 (0.1- 2.6)	1	0.2 (0.0 - 1.7)
	Influenza	1	1.4 (0.2- 10.1)	-	-	-	-	1	0.2 (0.0 - 1.7)
	Lower respiratory tract infection	1	1.4 (0.2- 10.1)	-	-	-	-	1	0.2 (0.0 - 1.7)
	Otitis media	1	1.4 (0.2- 10.1)	-	-	-	-	1	0.2 (0.0 - 1.7)
	Otitis media acute	1	1.4 (0.2- 10.1)	1	1.4 (0.2- 10.1)	-	-	2	0.5 (0. 1- 3.4)
	Parasitic gastroenteritis	-	-	1	1.4 (0.2- 10.1)	-	-	1	0.2 (0.0 - 1.7)
	Parvovirus B19 infection	1	1.4 (0.2- 10.1)	-	-	-	-	1	0.2 (0.0 - 1.7)
	Pharyngitis bacterial	-	-	-	-	1	0.4 (0.1- 2.6)	1	0.2 (0.0 - 1.7)
	Pneumonia	2	2.9 (0.7- 11.3)	-	-	1	0.4 (0.1- 2.6)	3	0.7 (0.2 - 2.2)
	Respiratory tract infection	1	1.4 (0.2- 10.1)	-	-	1	0.4 (0.1- 2.6)	2	0.5 (0.1 - 1.9)
	Sinusitis	-	-	1	1.4 (0.2- 10.1)	-	-	1	0.2 (0.0 - 1.7)
	Subcutaneous abscess	1	1.4 (0.2- 10.1)	-	-	-	-	1	0.2 (0.0 - 1.7)
	Tonsillitis streptococcal	-	-	-	-	2	0.7 (0.1- 5.1)	2	0.5 (0.1 - 3.4)

Table 9. Number of AEs (non-serious AEs of at least moderate intensity and all serious AEs) and incidence rates (95% CI) by SOC, PT and time window (The long-term treatment set-12)

	Time window[a]	**1-6 months**		**7-12 months**		**>12 months**		**Overall**	
	N	**141**		**141**		**141**		**141**	
	Patient time (years)[b]	**70.1**		**70.0**		**275.5**		**415.6**	
SOC	**PT**	**n[c]**	**Rate (95% CI) [d]**	**n[c]**	**Rate (95% CI) [d]**	**n[c]**	**Rate (95% CI) [d]**	**n[c]**	**Rate (95% CI) [d]**
	Upper respiratory tract infection	1	1.4 (0.2- 10.1)	1	1.4 (0.2- 10.1)	-	-	2	0.5 (0.1 - 3.4)
	Varicella	-	-	1	1.4 (0.2- 10.1)	-	-	1	0.2 (0.0 - 1.7)
	Varicella zoster virus infection	1	1.4 (0.2- 10.1)	-	-	-	-	1	0.2 (0.0 - 1.7)
Injury, poisoning and procedural complications	All	1	1.4 (0.2- 10.1)	2	2.9 (0.7- 11.3)	3	1.1 (0.4- 3.3)	6	1.4 (0.7 - 3.2)
	Humerus fracture	-	-	-	-	1	0.4 (0.1- 2.5)	1	0.2 (0.0 - 1.7)
	Infusion related reaction	-	-	-	-	1	0.4 (0.1- 2.6)	1	0.2 (0.0 - 1.7)
	Injection related reaction	1	1.4 (0.2- 10.1)	2	2.9 (0.7- 11.3)	1	0.4 (0.1- 2.6)	4	1.0 (0.4 - 2.6)
Investigations	All	2	2.9 (0.7- 11.3)	1	1.4 (0.2- 10.1)	1	0.4 (0.1- 2.5)	4	1.0 (0. 3- 3.1)
	Hepatic enzyme increased	1	1.4 (0.2- 10.1)	1	1.4 (0.2- 10.1)	-	-	2	0.5 (0.1 - 3.4)
	Transaminases increased	1	1.4 (0.2- 10.1)	-	-	1	0.4 (0.1- 2.5)	2	0.5 (0.1 - 1.9)
Metabolism and nutrition disorders	All	2	2.9 (0.7- 11.3)	-	-	-	-	2	0.5 (0.1 - 1.9)
	Dehydration	1	1.4 (0.2- 10.1)	-	-	-	-	1	0.2 (0.0 - 1.7)
	Hyperuricaemia	1	1.4 (0.2- 10.1)	-	-	-	-	1	0.2 (0.0 - 1.7)
Musculoskeletal and connective tissue disorders	All	-	-	-	-	1	0.4 (0.1- 2.5)	1	0.2 (0.0 - 1.7)
	Arthritis	-	-	-	-	1	0.4 (0.1- 2.5)	1	0.2 (0.0 - 1.7)
Nervous system disorders	All	-	-	-	-	2	0.7 (0.2- 2.9)	2	0.5 (0.1 - 1.9)
	Amnesia	-	-	-	-	1	0.4 (0.1- 2.6)	1	0.2 (0.0 - 1.7)
	Petit mal epilepsy	-	-	-	-	1	0.4 (0.1- 2.5)	1	0.2 (0.0 - 1.7)
Psychiatric disorders	All	-	-	-	-	3	1.1 (0.4- 3.3)	3	0.7 (0.2 - 2.2)
	Attention deficit/hyperactivity disorder	-	-	-	-	1	0.4 (0.1- 2.5)	1	0.2 (0.0 - 1.7)
	Persistent depressive disorder	-	-	-	-	1	0.4 (0.1- 2.6)	1	0.2 (0.0 - 1.7)
	Psychotic disorder	-	-	-	-	1	0.4 (0.1- 2.6)	1	0.2 (0.0 - 1.7)
Renal and urinary disorders	All	-	-	-	-	1	0.4 (0.1- 2.6)	1	0.2 (0.0 - 1.7)
	Urinary incontinence	-	-	-	-	1	0.4 (0.1- 2.6)	1	0.2 (0.0 - 1.7)

Table 9. Number of AEs (non-serious AEs of at least moderate intensity and all serious AEs) and incidence rates (95% CI) by SOC, PT and time window (The long-term treatment set-12)

	Time window[a]	**1-6 months**		**7-12 months**		**>12 months**		**Overall**	
	N	**141**		**141**		**141**		**141**	
	Patient time (years)[b]	**70.1**		**70.0**		**275.5**		**415.6**	
SOC	**PT**	**n[c]**	**Rate (95% CI) [d]**	**n[c]**	**Rate (95% CI) [d]**	**n[c]**	**Rate (95% CI) [d]**	**n[c]**	**Rate (95% CI) [d]**
Reproductive system and breast disorders	All	1	1.4 (0.2- 10.1)	-	-	-	-	1	0.2 (0.0 - 1.7)
	Balanoposthitis	1	1.4 (0.2- 10.1)	-	-	-	-	1	0.2 (0.0 - 1.7)
Respiratory, thoracic and mediastinal disorders	All	1	1.4 (0.2- 10.1)	-	-	1	0.4 (0.1- 2.6)	2	0.5 (0.1- 1.9)
	Asthma	1	1.4 (0.2- 10.1)	-	-	-	-	1	0.2 (0.0 - 1.7)
	Interstitial lung disease	-	-	-	-	1	0.4 (0.1- 2.6)	1	0.2 (0.0 - 1.7)
Skin and subcutaneous tissue disorders	All	2	2.9 (0.7- 11.3)	2	2.9 (0.7- 11.3)	3	1.1 (0.4- 3.4)	7	1.7 (0.7 - 3.9)
	Dermatitis atopic	1	1.4 (0.2- 10.1)	-	-	-	-	1	0.2 (0.0 - 1.7)
	Eczema	-	-	-	-	1	0.4 (0.1- 2.5)	1	0.2 (0.0 - 1.7)
	Onychomadesis	-	-	-	-	1	0.4 (0.1- 2.6)	1	0.2 (0.0 - 1.7)
	Rash	1	1.4 (0.2- 10.1)	1	1.4 (0.2- 10.1)	1	0.4 (0.1- 2.6)	3	0.7 (0.2 - 2.2)
	Vitiligo	-	-	1	1.4 (0.2- 10.1)	-	-	1	0.2 (0.0 - 1.7)
Surgical and medical procedures	All	1	1.4 (0.2- 10.1)	-	-	1	0.4 (0.1- 2.5)	2	0.5 (0.1 - 1.9)
	Hip arthroplasty	-	-	-	-	1	0.4 (0.1- 2.5)	1	0.2 (0.0 - 1.7)
	Lymphadenectomy	1	1.4 (0.2- 10.1)	-	-	-	-	1	0.2 (0.0 - 1.7)
Vascular disorders	All	1	1.4 (0.2- 10.1)	-	-	-	-	1	0.2 (0.0 - 1.7)
	Hypertension	1	1.4 (0.2- 10.1)	-	-	-	-	1	0.2 (0.0 - 1.7)

Abbreviations: AE, adverse event; SOC, system organ class; PT, preferred term, MedDRA version 21.1; N, number of patients continuously treated with Kineret during the time window**;** 95% CI, 95% Confidence Interval.

A patient can contribute with multiple AEs of same PT overall and within respective time window.

The long-term treatment set-12 includes patients with any period of continuous Kineret treatment (up to 30 days interruption is allowed) for 12 months or more.

[a] in relation to start of the longest Kineret treatment period.

[b] only time during periods with Kineret treatment (incl. 2 days post stop) counted.

[c] number of events. Only AEs occurring during Kineret exposed periods (incl. 2 days post stop) are counted.

[d] incidence rate per 100 patient years; number of events/∑patient time.

Table 10. Number of SAEs and incidence rates (95% CI) by SOC, PT and time window (The long-term treatment set-12)

	Time window[a]	**1-6 months**		**7-12 months**		**>12 months**		**Overall**	
	N	**141**		**141**		**141**		**141**	
	Patient time (years)[b]	**70.1**		**70.0**		**275.5**		**415.6**	
SOC	**PT**	**n[c]**	**Rate (95% CI) [d]**	**n[c]**	**Rate (95% CI) [d]**	**n[c]**	**Rate (95% CI) [d]**	**n[c]**	**Rate (95% CI) [d]**
All	**All**	**8**	**11.4 (5.0-26.2)**	**2**	**2.9 (0.7-11.3)**	**11**	**4.0 (2.1-7.5)**	**21**	**5.1 (3.1-8.3)**
Immune system disorders	All	-	-	1	1.4 (0.2-10.1)	3	1.1 (0.4-3.3)	4	1.0 (0.3- 3.1)
	Haemophagocytic lymphohistiocytosis	-	-	1	1.4 (0.2-10.1)	3	1.1 (0.4-3.3)	4	1.0 (0.3- 3.1)
Infections and infestations	All	4	5.7 (2.2-15.0)	-	-	1	0.4 (0.1-2.6)	5	1.2 (0.5- 2.9)
	Otitis media	1	1.4 (0.2-10.1)	-	-	-	-	1	0.2 (0.0- 1.7)
	Parvovirus B19 infection	1	1.4 (0.2-10.1)	-	-	-	-	1	0.2 (0.0- 1.7)
	Pneumonia	2	2.9 (0.7-11.3)	-	-	1	0.4 (0.1-2.6)	3	0.7 (0.2- 2.2)
Injury, poisoning and procedural complications	All	1	1.4 (0.2-10.1)	1	1.4 (0.2-10.1)	3	1.1 (0.4-3.3)	5	1.2 (0.5- 2.9)
	Humerus fracture	-	-	-	-	1	0.4 (0.1-2.5)	1	0.2 (0.0- 1.7)
	Infusion related reaction	-	-	-	-	1	0.4 (0.1-2.6)	1	0.2 (0.0- 1.7)
	Injection related reaction	1	1.4 (0.2-10.1)	1	1.4 (0.2-10.1)	1	0.4 (0.1-2.6)	3	0.7 (0.2- 2.3)
Metabolism and nutrition disorders	All	2	2.9 (0.7-11.3)	-	-	-	-	2	0.5 (0.1- 1.9)
	Dehydration	1	1.4 (0.2-10.1)	-	-	-	-	1	0.2 (0.0- 1.7)
	Hyperuricaemia	1	1.4 (0.2-10.1)	-	-	-	-	1	0.2 (0.0- 1.7)
Nervous system disorders	All	-	-	-	-	1	0.4 (0.1-2.6)	1	0.2 (0.0- 1.7)
	Amnesia	-	-	-	-	1	0.4 (0.1-2.6)	1	0.2 (0.0- 1.7)
Psychiatric disorders	All	-	-	-	-	1	0.4 (0.1-2.6)	1	0.2 (0.0- 1.7)
	Psychotic disorder	-	-	-	-	1	0.4 (0.1-2.6)	1	0.2 (0.0- 1.7)
Respiratory, thoracic and mediastinal disorders	All	-	-	-	-	1	0.4 (0.1-2.6)	1	0.2 (0.0- 1.7)
	Interstitial lung disease	-	-	-	-	1	0.4 (0.1-2.6)	1	0.2 (0.0- 1.7)
Surgical and medical procedures	All	1	1.4 (0.2-10.1)	-	-	1	0.4 (0.1-2.5)	2	0.5 (0.1- 1.9)
	Hip arthroplasty	-	-	-	-	1	0.4 (0.1-2.5)	1	0.2 (0.0- 1.7)
	Lymphadenectomy	1	1.4 (0.2-10.1)	-	-	-	-	1	0.2 (0.0- 1.7)

Abbreviations: SAE, serious adverse event; SOC, system organ class; PT, preferred term, MedDRA version 21.1; N, number of patients continuously treated with Kineret during the time window**;** 95% CI, 95% Confidence Interval.

A patient can contribute with multiple SAEs of same PT overall and within respective time window.

The long-term treatment set-12 includes patients with any period of continuous Kineret treatment (up to 30 days interruption is allowed) for 12 months or more.

[a] in relation to start of the longest Kineret treatment period.

[b] only time during periods with Kineret treatment (incl. 2 days post stop) counted.

[c] number of events. Only SAEs occurring during Kineret exposed periods (incl. 2 days post stop) are counted.

[d] incidence rate per 100 patient years; number of events/∑patient time.

Table 11. Number of AEs (non-serious AEs of at least moderate intensity and all serious AEs) and incidence rates (95% CI) by SOC, PT and time window (The long-term treatment set-18)

	Time window[a]	**1-6 months**		**7-12 months**		**13-18 months**		**>18 months**		**Overall**	
	N	**104**		**104**		**104**		**104**		**104**	
	Patient time (years)[b]	**51.8**		**51.6**		**51.8**		**215.8**		**371.0**	
SOC	**PT**	**n[c]**	**Rate (95% CI) [d]**	**n[c]**	**Rate (95% CI) [d]**	**n[c]**	**Rate (95% CI) [d]**	**n[c]**	**Rate (95% CI) [d]**	**n[c]**	**Rate (95% CI) [d]**
All	**All**	**13**	**25.1 (13.9-45.3)**	**9**	**17.4 (8.7-35.0)**	**3**	**5.8 (1.9-17.7)**	**28**	**13.0 (8.5-19.9)**	**53**	**14.3 (9.5-21.4)**
Blood and lymphatic system disorders	All	-	-	2	3.9 (1.0- 15.3)	-	-	3	1.4 (0.5- 4.3)	5	1.3 (0.6- 3.2)
	Lymphadenitis	-	-	1	1.9 (0.3- 13.6)	-	-	-	-	1	0.3 (0.0- 1.9)
	Lymphadenopathy	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	1	0.3 (0.0- 1.9)
	Neutropenia	-	-	1	1.9 (0.3- 13.6)	-	-	1	0.5 (0.1- 3.3)	2	0.5 (0.1- 2.2)
	Pancytopenia	-	-	-	-	-	-	1	0.5 (0.1- 3.2)	1	0.3 (0.0- 1.9)
Eye disorders	All	-	-	1	1.9 (0.3- 13.6)	-	-	1	0.5 (0.1- 3.2)	2	0.5 (0.1- 2.1)
	Dry eye	-	-	-	-	-	-	1	0.5 (0.1- 3.2)	1	0.3 (0.0- 1.9)
	Eyelid ptosis	-	-	1	1.9 (0.3- 13.6)	-	-	-	-	1	0.3 (0.0- 1.9)
Gastrointestinal disorders	All	-	-	-	-	-	-	3	1.4 (0.5- 4.0)	3	0.8 (0.3- 2.4)
	Gastritis	-	-	-	-	-	-	1	0.5 (0.1- 3.2)	1	0.3 (0.0- 1.9)
	Nausea	-	-	-	-	-	-	1	0.5 (0.1- 3.2)	1	0.3 (0.0- 1.9)
	Odynophagia	-	-	-	-	-	-	1	0.5 (0.1- 3.1)	1	0.3 (0.0- 1.8)
General disorders and administration site conditions	All	2	3.9 (1.0- 15.2)	1	1.9 (0.3- 13.7)	-	-	2	0.9 (0.2- 3.6)	5	1.3 (0.6- 3.1)
	Injection site pain	-	-	1	1.9 (0.3- 13.7)	-	-	-	-	1	0.3 (0.0- 1.9)
	Injection site reaction	2	3.9 (1.0- 15.2)	-	-	-	-	1	0.5 (0.1- 3.2)	3	0.8 (0.3- 2.4)
	Mucosal erosion	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	1	0.3 (0.0- 1.9)
Hepatobiliary disorders	All	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	1	0.3 (0.0- 1.9)
	Hepatotoxicity	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	1	0.3 (0.0- 1.9)
Immune system disorders	All	1	1.9 (0.3- 13.6)	1	1.9 (0.3- 13.6)	-	-	2	0.9 (0.2- 3.6)	4	1.1 (0.3- 3.5)
	Autoimmune disorder	1	1.9 (0.3- 13.6)	-	-	-	-	-	-	1	0.3 (0.0- 1.9)
	Haemophagocytic lymphohistiocytosis	-	-	1	1.9 (0.3- 13.6)	-	-	2	0.9 (0.2- 3.6)	3	0.8 (0.2- 3.4)
Infections and infestations	All	4	7.7 (3.0- 20.2)	1	1.9 (0.3- 13.6)	-	-	5	2.3 (0.6- 8.4)	10	2.7 (1.3- 5.8)

Table 11. Number of AEs (non-serious AEs of at least moderate intensity and all serious AEs) and incidence rates (95% CI) by SOC, PT and time window (The long-term treatment set-18)

	Time window[a]	**1-6 months**		**7-12 months**		**13-18 months**		**>18 months**		**Overall**	
	N	**104**		**104**		**104**		**104**		**104**	
	Patient time (years)[b]	**51.8**		**51.6**		**51.8**		**215.8**		**371.0**	
SOC	**PT**	**n[c]**	**Rate (95% CI) [d]**	**n[c]**	**Rate (95% CI) [d]**	**n[c]**	**Rate (95% CI) [d]**	**n[c]**	**Rate (95% CI) [d]**	**n[c]**	**Rate (95% CI) [d]**
	Gastroenteritis	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	1	0.3 (0.0- 1.9)
	Herpes zoster	-	-	-	-	-	-	1	0.5 (0.1- 3.2)	1	0.3 (0.0- 1.9)
	Parvovirus B19 infection	1	1.9 (0.3- 13.6)	-	-	-	-	-	-	1	0.3 (0.0- 1.9)
	Pharyngitis bacterial	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	1	0.3 (0.0- 1.9)
	Pneumonia	1	1.9 (0.3- 13.6)	-	-	-	-	-	-	1	0.3 (0.0- 1.9)
	Respiratory tract infection	1	1.9 (0.3- 13.6)	-	-	-	-	-	-	1	0.3 (0.0- 1.9)
	Sinusitis	-	-	1	1.9 (0.3- 13.6)	-	-	-	-	1	0.3 (0.0- 1.9)
	Tonsillitis streptococcal	-	-	-	-	-	-	2	0.9 (0.1- 6.5)	2	0.5 (0.1- 3.8)
	Varicella zoster virus infection	1	1.9 (0.3- 13.6)	-	-	-	-	-	-	1	0.3 (0.0- 1.9)
Injury, poisoning and procedural complications	All	-	-	1	1.9 (0.3- 13.6)	-	-	2	0.9 (0.2- 3.6)	3	0.8 (0.3- 2.5)
	Humerus fracture	-	-	-	-	-	-	1	0.5 (0.1- 3.1)	1	0.3 (0.0- 1.9)
	Infusion related reaction	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	1	0.3 (0.0- 1.9)
	Injection related reaction	-	-	1	1.9 (0.3- 13.6)	-	-	-	-	1	0.3 (0.0- 1.9)
Investigations	All	2	3.9 (1.0- 15.2)	1	1.9 (0.3- 13.6)	-	-	1	0.5 (0.1- 3.1)	4	1.1 (0.3- 3.5)
	Hepatic enzyme increased	1	1.9 (0.3- 13.6)	1	1.9 (0.3- 13.6)	-	-	-	-	2	0.5 (0.1- 3.8)
	Transaminases increased	1	1.9 (0.3- 13.6)	-	-	-	-	1	0.5 (0.1- 3.1)	2	0.5 (0.1- 2.1)
Metabolism and nutrition disorders	All	1	1.9 (0.3- 13.6)	-	-	-	-	-	-	1	0.3 (0.0- 1.9)
	Hyperuricaemia	1	1.9 (0.3- 13.6)	-	-	-	-	-	-	1	0.3 (0.0- 1.9)
Musculoskeletal and connective tissue disorders	All	-	-	-	-	1	1.9 (0.3- 13.6)	-	-	1	0.3 (0.0- 1.9)
	Arthritis	-	-	-	-	1	1.9 (0.3- 13.6)	-	-	1	0.3 (0.0- 1.9)
Nervous system disorders	All	-	-	-	-	-	-	2	0.9 (0.2- 3.7)	2	0.5 (0.1- 2.1)
	Amnesia	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	1	0.3 (0.0- 1.9)
	Petit mal epilepsy	-	-	-	-	-	-	1	0.5 (0.1- 3.2)	1	0.3 (0.0- 1.9)
Psychiatric disorders	All	-	-	-	-	2	3.9 (1- 15.3)	1	0.5 (0.1- 3.2)	3	0.8 (0.3- 2.5)

Table 11. Number of AEs (non-serious AEs of at least moderate intensity and all serious AEs) and incidence rates (95% CI) by SOC, PT and time window (The long-term treatment set-18)

	Time window[a]	**1-6 months**		**7-12 months**		**13-18 months**		**>18 months**		**Overall**	
	N	**104**		**104**		**104**		**104**		**104**	
	Patient time (years)[b]	**51.8**		**51.6**		**51.8**		**215.8**		**371.0**	
SOC	**PT**	**n[c]**	**Rate (95% CI) [d]**	**n[c]**	**Rate (95% CI) [d]**	**n[c]**	**Rate (95% CI) [d]**	**n[c]**	**Rate (95% CI) [d]**	**n[c]**	**Rate (95% CI) [d]**
	Attention deficit/hyperactivity disorder	-	-	-	-	-	-	1	0.5 (0.1- 3.2)	1	0.3 (0.0- 1.9)
	Persistent depressive disorder	-	-	-	-	1	1.9 (0.3- 13.6)	-	-	1	0.3 (0.0- 1.9)
	Psychotic disorder	-	-	-	-	1	1.9 (0.3- 13.6)	-	-	1	0.3 (0.0- 1.9)
Renal and urinary disorders	All	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	1	0.3 (0.0- 1.9)
	Urinary incontinence	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	1	0.3 (0.0- 1.9)
Respiratory, thoracic and mediastinal disorders	All	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	1	0.3 (0.0- 1.9)
	Interstitial lung disease	-	-	-	-	-	-	1	0.5 (0.1- 3.3)	1	0.3 (0.0- 1.9)
Skin and subcutaneous tissue disorders	All	1	1.9 (0.3- 13.6)	1	1.9 (0.3- 13.6)	-	-	2	0.9 (0.2- 3.7)	4	1.1 (0.4- 2.8)
	Eczema	-	-	-	-	-	-	1	0.5 (0.1- 3.2)	1	0.3 (0.0- 1.9)
	Rash	1	1.9 (0.3- 13.6)	1	1.9 (0.3- 13.6)	-	-	1	0.5 (0.1- 3.3)	3	0.8 (0.3- 2.5)
Surgical and medical procedures	All	1	1.9 (0.3- 13.6)	-	-	-	-	1	0.5 (0.1- 3.2)	2	0.5 (0.1- 2.1)
	Hip arthroplasty	-	-	-	-	-	-	1	0.5 (0.1- 3.2)	1	0.3 (0.0- 1.9)
	Lymphadenectomy	1	1.9 (0.3- 13.6)	-	-	-	-	-	-	1	0.3 (0.0- 1.9)
Vascular disorders	All	1	1.9 (0.3- 13.6)	-	-	-	-	-	-	1	0.3 (0.0- 1.9)
	Hypertension	1	1.9 (0.3- 13.6)	-	-	-	-	-	-	1	0.3 (0.0- 1.9)

Abbreviations: AE, adverse event; SOC, system organ class; PT, preferred term, MedDRA version 21.1; N, number of patients continuously treated with Kineret during the time window; 95% CI, 95% Confidence Interval.

A patient can contribute with multiple AEs of same PT overall and within respective time window.

The long-term treatment set-18 includes patients with any period of continuous Kineret treatment (up to 30 days interruption is allowed) for 18 months or more.

[a] in relation to start of the longest Kineret treatment period.

[b] only time during periods with Kineret treatment (incl. 2 days post stop) counted.

[c] number of events. Only AEs occurring during Kineret exposed periods (incl. 2 days post stop) are counted.

[d] incidence rate per 100 patient years; number of events/∑patient time.

Table 12. Number of SAEs and incidence rates (95% CI) by SOC, PT and time window (The long-term treatment set-18)

	Time window[a]	**1-6 months**		**7-12 months**		**13-18 months**		**>18 months**		**Overall**	
	N	**104**		**104**		**104**		**104**		**104**	
	Patient time (years)[b]	**51.8**		**51.6**		**51.8**		**215.8**		**371.0**	
SOC	**PT**	**n[c]**	**Rate (95% CI) [d]**	**n[c]**	**Rate (95% CI) [d]**	**n[c]**	**Rate (95% CI) [d]**	**n[c]**	**Rate (95% CI) [d]**	**n[c]**	**Rate (95% CI) [d]**
All	**All**	**4**	**7.7 (2.4-25.2)**	**2**	**3.9 (1.0-15.3)**	**1**	**1.9 (0.3-13.6)**	**7**	**3.2 (1.6-6.6)**	**14**	**3.8 (2.1-6.9)**
Immune system disorders	All	-	-	1	1.9 (0.3-13.6)	-	-	2	0.9 (0.2-3.6)	3	0.8 (0.2-3.4)
	Haemophagocytic lymphohistiocytosis	-	-	1	1.9 (0.3-13.6)	-	-	2	0.9 (0.2-3.6)	3	0.8 (0.2-3.4)
Infections and infestations	All	2	3.9 (1-15.2)	-	-	-	-	-	-	2	0.5 (0.1-2.2)
	Parvovirus B19 infection	1	1.9 (0.3-13.6)	-	-	-	-	-	-	1	0.3 (0.0-1.9)
	Pneumonia	1	1.9 (0.3-13.6)	-	-	-	-	-	-	1	0.3 (0.0-1.9)
Injury, poisoning and procedural complications	All	-	-	1	1.9 (0.3-13.6)	-	-	2	0.9 (0.2-3.6)	3	0.8 (0.3-2.5)
	Humerus fracture	-	-	-	-	-	-	1	0.5 (0.1-3.1)	1	0.3 (0.0-1.9)
	Infusion related reaction	-	-	-	-	-	-	1	0.5 (0.1-3.3)	1	0.3 (0.0-1.9)
	Injection related reaction	-	-	1	1.9 (0.3-13.6)	-	-	-	-	1	0.3 (0.0-1.9)
Metabolism and nutrition disorders	All	1	1.9 (0.3-13.6)	-	-	-	-	-	-	1	0.3 (0.0-1.9)
	Hyperuricaemia	1	1.9 (0.3-13.6)	-	-	-	-	-	-	1	0.3 (0.0-1.9)
Nervous system disorders	All	-	-	-	-	-	-	1	0.5 (0.1-3.3)	1	0.3 (0.0-1.9)
	Amnesia	-	-	-	-	-	-	1	0.5 (0.1-3.3)	1	0.3 (0.0-1.9)
Psychiatric disorders	All	-	-	-	-	1	1.9 (0.3-13.6)	-	-	1	0.3 (0.0-1.9)
	Psychotic disorder	-	-	-	-	1	1.9 (0.3-13.6)	-	-	1	0.3 (0.0-1.9)
Respiratory, thoracic and mediastinal disorders	All	-	-	-	-	-	-	1	0.5 (0.1-3.3)	1	0.3 (0.0-1.9)
	Interstitial lung disease	-	-	-	-	-	-	1	0.5 (0.1-3.3)	1	0.3 (0.0-1.9)
Surgical and medical procedures	All	1	1.9 (0.3-13.6)	-	-	-	-	1	0.5 (0.1-3.2)	2	0.5 (0.1-2.1)
	Hip arthroplasty	-	-	-	-	-	-	1	0.5 (0.1-3.2)	1	0.3 (0.0-1.9)
	Lymphadenectomy	1	1.9 (0.3-13.6)	-	-	-	-	-	-	1	0.3 (0.0-1.9)

Abbreviations: SAE, serious adverse event; SOC, system organ class; PT, preferred term, MedDRA version 21.1; N, number of patients continuously treated with Kineret during the time window**;** 95% CI, 95% Confidence Interval.

A patient can contribute with multiple SAEs of same PT overall and within respective time window.

The long-term treatment set-18 includes patients with any period of continuous Kineret treatment (up to 30 days interruption is allowed) for 18 months or more.

[a] in relation to start of the longest Kineret treatment period.

[b] only time during periods with Kineret treatment (incl. 2 days post stop) counted.

[c] number of events. Only SAEs occurring during Kineret exposed periods (incl. 2 days post stop) are counted.

[d] incidence rate per 100 patient years; number of events/∑patient time.

Table 13. Number of AEs (non-serious AEs of at least moderate intensity and all serious AEs) and incidence rates (95% CI) by SOC, PT and time window (The long-term treatment set-24)

	Time window[a]	**1-6 months**		**7-12 months**		**13-18 months**		**19-24 months**		**>24 months**		**Overall**	
	N	**86**		**86**		**86**		**86**		**86**		**86**	
	Patient-time (years)[b]	**42.8**		**42.7**		**42.8**		**42.8**		**168.8**		**340.0**	
SOC	**PT**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**
All	**All**	**9**	**21.1 (10.5-41.9)**	**7**	**16.4 (7.3-37.0)**	**3**	**7.1 (2.3-21.3)**	**5**	**11.7 (4.2-32.2)**	**22**	**13.1 (7.8-21.6)**	**46**	**13.5 (8.7-21.1)**
Blood and lymphatic system disorders	All	-	-	1	2.3 (0.3- 16.4)	-	-	-	-	3	1.8 (0.6- 5.5)	4	1.2 (0.5- 3.0)
	Lymphadenitis	-	-	1	2.3 (0.3- 16.4)	-	-	-	-	-	-	1	0.3 (0.0- 2.0)
	Lymphadenopathy	-	-	-	-	-	-	-	-	1	0.6 (0.1- 4.2)	1	0.3 (0.0- 2.1)
	Neutropenia	-	-	-	-	-	-	-	-	1	0.6 (0.1- 4.2)	1	0.3 (0.0- 2.1)
	Pancytopenia	-	-	-	-	-	-	-	-	1	0.6 (0.1- 4.2)	1	0.3 (0.0- 2.1)
Eye disorders	All	-	-	1	2.3 (0.3- 16.4)	-	-	-	-	1	0.6 (0.1- 4.1)	2	0.6 (0.2- 2.3)
	Dry eye	-	-	-	-	-	-	-	-	1	0.6 (0.1- 4.1)	1	0.3 (0.0- 2.1)
	Eyelid ptosis	-	-	1	2.3 (0.3- 16.4)	-	-	-	-	-	-	1	0.3 (0.0- 2.0)
Gastrointestinal disorders	All	-	-	-	-	-	-	1	2.3 (0.3- 16.4)	2	1.2 (0.3- 4.4)	3	0.9 (0.3- 2.6)
	Gastritis	-	-	-	-	-	-	-	-	1	0.6 (0.1- 4.0)	1	0.3 (0.0- 2.0)
	Nausea	-	-	-	-	-	-	1	2.3 (0.3- 16.4)	-	-	1	0.3 (0.0- 2.0)
	Odynophagia	-	-	-	-	-	-	-	-	1	0.6 (0.1- 4.0)	1	0.3 (0.0- 2.0)
General disorders and administration site conditions	All	2	4.7 (1.2- 18.4)	1	2.3 (0.3- 16.5)	-	-	-	-	2	1.2 (0.3- 4.6)	5	1.5 (0.6- 3.4)
	Injection site pain	-	-	1	2.3 (0.3- 16.5)	-	-	-	-	-	-	1	0.3 (0.0- 2.1)
	Injection site reaction	2	4.7 (1.2- 18.4)	-	-	-	-	-	-	1	0.6 (0.1- 4.0)	3	0.9 (0.3- 2.6)
	Mucosal erosion	-	-	-	-	-	-	-	-	1	0.6 (0.1- 4.2)	1	0.3 (0.0- 2.1)
Hepatobiliary disorders	All	-	-	-	-	-	-	-	-	1	0.6 (0.1- 4.2)	1	0.3 (0.0- 2.1)
	Hepatotoxicity	-	-	-	-	-	-	-	-	1	0.6 (0.1- 4.2)	1	0.3 (0.0- 2.1)
Immune system disorders	All	1	2.3 (0.3- 16.4)	1	2.3 (0.3- 16.4)	-	-	-	-	2	1.2 (0.3- 4.6)	4	1.2 (0.4- 3.8)
	Autoimmune disorder	1	2.3 (0.3- 16.4)	-	-	-	-	-	-	-	-	1	0.3 (0.0- 2.1)
	Haemophagocytic lymphohistiocytosis	-	-	1	2.3 (0.3- 16.4)	-	-	-	-	2	1.2 (0.3- 4.6)	3	0.9 (0.2- 3.7)
Infections and infestations	All	2	4.7 (1.2- 18.4)	1	2.3 (0.3- 16.4)	-	-	1	2.3 (0.3- 16.4)	4	2.4 (0.5- 11.0)	8	2.4 (1.0- 5.8)

Table 13. Number of AEs (non-serious AEs of at least moderate intensity and all serious AEs) and incidence rates (95% CI) by SOC, PT and time window (The long-term treatment set-24)

	Time window[a]	**1-6 months**		**7-12 months**		**13-18 months**		**19-24 months**		**>24 months**		**Overall**	
	N	**86**		**86**		**86**		**86**		**86**		**86**	
	Patient-time (years)[b]	**42.8**		**42.7**		**42.8**		**42.8**		**168.8**		**340.0**	
SOC	**PT**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**
	Gastroenteritis	-	-	-	-	-	-	1	2.3 (0.3- 16.4)	-	-	1	0.3 (0.0- 2.1)
	Herpes zoster	-	-	-	-	-	-	-	-	1	0.6 (0.1- 4.1)	1	0.3 (0.0- 2.1)
	Parvovirus B19 infection	1	2.3 (0.3- 16.4)	-	-	-	-	-	-	-	-	1	0.3 (0.0- 2.1)
	Pharyngitis bacterial	-	-	-	-	-	-	-	-	1	0.6 (0.1- 4.3)	1	0.3 (0.0- 2.1)
	Sinusitis	-	-	1	2.3 (0.3- 16.4)	-	-	-	-	-	-	1	0.3 (0.0- 2.1)
	Tonsillitis streptococcal	-	-	-	-	-	-	-	-	2	1.2 (0.2- 8.3)	2	0.6 (0.1- 4.1)
	Varicella zoster virus infection	1	2.3 (0.3- 16.4)	-	-	-	-	-	-	-	-	1	0.3 (0.0- 2.1)
Injury, poisoning and procedural complications	All	-	-	-	-	-	-	-	-	1	0.6 (0.1- 4.0)	1	0.3 (0.0- 2.0)
	Humerus fracture	-	-	-	-	-	-	-	-	1	0.6 (0.1- 4.0)	1	0.3 (0.0- 2.0)
Investigations	All	2	4.7 (1.2- 18.4)	1	2.3 (0.3- 16.4)	-	-	-	-	1	0.6 (0.1- 4.0)	4	1.2 (0.4- 3.8)
	Hepatic enzyme increased	1	2.3 (0.3- 16.4)	1	2.3 (0.3- 16.4)	-	-	-	-	-	-	2	0.6 (0.1- 4.1)
	Transaminases increased	1	2.3 (0.3- 16.4)	-	-	-	-	-	-	1	0.6 (0.1- 4.0)	2	0.6 (0.2- 2.3)
Metabolism and nutrition disorders	All	1	2.3 (0.3- 16.4)	-	-	-	-	-	-	-	-	1	0.3 (0.0- 2.1)
	Hyperuricaemia	1	2.3 (0.3- 16.4)	-	-	-	-	-	-	-	-	1	0.3 (0.0- 2.1)
Musculoskeletal and connective tissue disorders	All	-	-	-	-	1	2.3 (0.3- 16.4)	-	-	-	-	1	0.3 (0.0- 2.1)
	Arthritis	-	-	-	-	1	2.3 (0.3- 16.4)	-	-	-	-	1	0.3 (0.0- 2.1)
Nervous system disorders	All	-	-	-	-	-	-	2	4.7 (1.2- 18.4)	-	-	2	0.6 (0.1- 2.3)
	Amnesia	-	-	-	-	-	-	1	2.3 (0.3- 16.4)	-	-	1	0.3 (0.0- 2.1)
	Petit mal epilepsy	-	-	-	-	-	-	1	2.3 (0.3- 16.4)	-	-	1	0.3 (0.0- 2.0)
Psychiatric disorders	All	-	-	-	-	2	4.7 (1.2- 18.4)	-	-	1	0.6 (0.1- 4.0)	3	0.9 (0.3- 2.7)

Table 13. Number of AEs (non-serious AEs of at least moderate intensity and all serious AEs) and incidence rates (95% CI) by SOC, PT and time window (The long-term treatment set-24)

	Time window[a]	**1-6 months**		**7-12 months**		**13-18 months**		**19-24 months**		**>24 months**		**Overall**	
	N	**86**		**86**		**86**		**86**		**86**		**86**	
	Patient-time (years)[b]	**42.8**		**42.7**		**42.8**		**42.8**		**168.8**		**340.0**	
SOC	**PT**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**
	Attention deficit/hyperactivity disorder	-	-	-	-	-	-	-	-	1	0.6 (0.1- 4.0)	1	0.3 (0.0- 2.0)
	Persistent depressive disorder	-	-	-	-	1	2.3 (0.3- 16.4)	-	-	-	-	1	0.3 (0.0- 2.1)
	Psychotic disorder	-	-	-	-	1	2.3 (0.3- 16.4)	-	-	-	-	1	0.3 (0.0- 2.1)
Renal and urinary disorders	All	-	-	-	-	-	-	1	2.3 (0.3- 16.4)	-	-	1	0.3 (0.0- 2.1)
	Urinary incontinence	-	-	-	-	-	-	1	2.3 (0.3- 16.4)	-	-	1	0.3 (0.0- 2.1)
Respiratory, thoracic and mediastinal disorders	All	-	-	-	-	-	-	-	-	1	0.6 (0.1- 4.2)	1	0.3 (0.0- 2.1)
	Interstitial lung disease	-	-	-	-	-	-	-	-	1	0.6 (0.1- 4.2)	1	0.3 (0.0- 2.1)
Skin and subcutaneous tissue disorders	All	1	2.3 (0.3- 16.4)	1	2.3 (0.3- 16.4)	-	-	-	-	2	1.2 (0.3- 4.7)	4	1.2 (0.5- 3.1)
	Eczema	-	-	-	-	-	-	-	-	1	0.6 (0.1- 4.1)	1	0.3 (0.0- 2.1)
	Rash	1	2.3 (0.3- 16.4)	1	2.3 (0.3- 16.4)	-	-	-	-	1	0.6 (0.1- 4.3)	3	0.9 (0.3- 2.7)
Surgical and medical procedures	All	-	-	-	-	-	-	-	-	1	0.6 (0.1- 4.0)	1	0.3 (0.0- 2.0)
	Hip arthroplasty	-	-	-	-	-	-	-	-	1	0.6 (0.1- 4.0)	1	0.3 (0.0- 2.0)

Abbreviations: AE, adverse event; SOC, system organ class; PT, preferred term, MedDRA version 21.1; N, number of patients continuously treated with Kineret during the time window**;** 95% CI, 95% Confidence Interval.

A patient can contribute with multiple AEs of same PT overall and within respective time window.

The long-term treatment set-24 includes patients with any period of continuous Kineret treatment (up to 30 days interruption is allowed) for 24 months or more.

[a] in relation to start of the longest Kineret treatment period.

[b] only time during periods with Kineret treatment (incl. 2 days post stop) counted.

[c] number of events. Only AEs occurring during Kineret exposed periods (incl. 2 days post stop) are counted.

[d] incidence rate per 100 patient years; number of events/∑patient time.

Table 14. Number of SAEs and incidence rates (95% CI) by SOC, PT and time window (The long-term treatment set-24)

	Time window[a]	**1-6 months**		**7-12 months**		**13-18 months**		**19-24 months**		**>24 months**		**Overall**	
	N	**86**		**86**		**86**		**86**		**86**		**86**	
	Patient-time (years)[b]	**42.8**		**42.7**		**42.8**		**42.8**		**168.8**		**340.0**	
SOC	**PT**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**	**n[c]**	**Rate (95% CI)[d]**
	All	**2**	**4.7 (1.2-18.4)**	**1**	**2.3 (0.3-16.4)**	**1**	**2.3 (0.3-16.4)**	**1**	**2.3 (0.3-16.4)**	**5**	**2.9 (1.3-6.7)**	**10**	**2.9 (1.5-5.9)**
Immune system disorders	All	-	-	1	2.3 (0.3-16.4)	-	-	-	-	2	1.2 (0.3-4.6)	3	0.9 (0.2-3.7)
	Haemophagocytic lymphohistiocytosis	-	-	1	2.3 (0.3-16.4)	-	-	-	-	2	1.2 (0.3-4.6)	3	0.9 (0.2-3.7)
Infections and infestations	All	1	2.3 (0.3-16.4)	-	-	-	-	-	-	-	-	1	0.3 (0.0-2.1)
	Parvovirus B19 infection	1	2.3 (0.3-16.4)	-	-	-	-	-	-	-	-	1	0.3 (0.0-2.1)
Injury, poisoning and procedural complications	All	-	-	-	-	-	-	-	-	1	0.6 (0.1-4.0)	1	0.3 (0.0-2.0)
	Humerus fracture	-	-	-	-	-	-	-	-	1	0.6 (0.1-4.0)	1	0.3 (0.0-2.0)
Metabolism and nutrition disorders	All	1	2.3 (0.3-16.4)	-	-	-	-	-	-	-	-	1	0.3 (0.0-2.1)
	Hyperuricaemia	1	2.3 (0.3-16.4)	-	-	-	-	-	-	-	-	1	0.3 (0.0-2.1)
Nervous system disorders	All	-	-	-	-	-	-	1	2.3 (0.3-16.4)	-	-	1	0.3 (0.0-2.1)
	Amnesia	-	-	-	-	-	-	1	2.3 (0.3-16.4)	-	-	1	0.3 (0.0-2.1)
Psychiatric disorders	All	-	-	-	-	1	2.3 (0.3-16.4)	-	-	-	-	1	0.3 (0.0-2.1)
	Psychotic disorder	-	-	-	-	1	2.3 (0.3-16.4)	-	-	-	-	1	0.3 (0.0-2.1)
Respiratory, thoracic and mediastinal disorders	All	-	-	-	-	-	-	-	-	1	0.6 (0.1-4.2)	1	0.3 (0.0-2.1)
	Interstitial lung disease	-	-	-	-	-	-	-	-	1	0.6 (0.1-4.2)	1	0.3 (0.0-2.1)
Surgical and medical procedures	All	-	-	-	-	-	-	-	-	1	0.6 (0.1-4.0)	1	0.3 (0.0-2.0)
	Hip arthroplasty	-	-	-	-	-	-	-	-	1	0.6 (0.1-4.0)	1	0.3 (0.0-2.0)

Abbreviations: SAE, serious adverse event; SOC, system organ class; PT, preferred term, MedDRA version 21.1; N, number of patients continuously treated with Kineret during the time window**;** 95% CI, 95% Confidence Interval.

A patient can contribute with multiple SAEs of same PT overall and within respective time window.

The long-term treatment set-24 includes patients with any period of continuous Kineret treatment (up to 30 days interruption is allowed) for 24 months or more.

[a] in relation to start of the longest Kineret treatment period.

[b] only time during periods with Kineret treatment (incl. 2 days post stop) counted.

[c] number of events. Only SAEs occurring during Kineret exposed periods (incl. 2 days post stop) are counted.

[d] incidence rate per 100 patient years; number of events/∑patient time.

Table 15. Number of first occurrence and recurrence of MAS events and incidence rates, overall and by history of MAS (The complete set)

History of MAS at baseline	**N**	10		
	MAS event	**n[a]**	**Patient-time (years)[b]**	**Rate (95% CI)[c]**
	1st occurrence[d]	1	18.0	5.6 (0.7-42.9)
	2nd occurrence[e]	1	1.0	100
	3rd occurrence	0	5.6	0
No History of MAS recorded at baseline	**N**	296		
	MAS event	**n[a]**	**Patient-time (years)[b]**	**Rate (95% CI)[c]**
	1st occurrence[d]	10	479.5	2.1 (1.1-3.9)
	2nd occurrence[e]	0	5.2	0
	3rd occurrence	0	-	-
ALL	**N**	306		
	MAS event	**n[a]**	**Patient-time (years)[b]**	**Rate (95% CI)[c]**
	1st occurrence[d]	11	497.5	2.2 (1.2-4.1)
	2nd occurrence[e]	1	6.2	16.1 (2.6-97.7)
	3rd occurrence	0	5.6	0

Abbreviations: MAS, macrophage activation syndrome ('MAS' is equal to MedDRA Preferred Term: Haemophagocytic lymphohistiocytosis, MedDRA version 21.1); N, number of patients starting Kineret treatment; 95% CI, 95% Confidence Interval.

[a]number of MAS events. Only MAS occurring during Kineret exposed periods (incl. 2 days post stop) are counted.

[b]only time during periods with Kineret treatment (incl. 2 days post stop) counted.

[c]incidence rate per 100 patient years; number of events/∑patient time;

[d]the 1st occurrence of MAS is defined to occur at or after baseline regardless of whether the patient had a history of MAS or not; For the 1th occurence: time at risk is calculated from the first dose until the 1st event-MAS, last dose, last follow-up, or data-lock point for the report, whichever occurs first.

[e]the patients included in the risk set for a 2nd occurrence of MAS are only those who had a 1st occurrence of MAS as defined above. Time at risk is calculated from the 1st event of MAS until the 2nd occurrence of MAS, last dose, last follow-up, or data-lock point for the report, whichever occurs first.

Table 16. Number of first occurrence of MAS events by history of MAS and time since first injection with Kineret (The MAS-1 set)

	History of MAS at baseline		No History of MAS recorded at baseline		Total	
N	**1**		**18**		**19**	
Time since first injection with Kineret	**n**	**%**	**n**	**%**	**n**	**%**
MAS during Kineret treatment						
1 -30 days	0	0.0	4	40.0	4	36.4
31-180 days	0	0.0	3	30.0	3	27.3
181-365 days	1	100.0	0	0.0	1	9.0
>365 days	0	0.0	3	30.0	3	27.3
Total	1	100.0	10	55.6	11	57.9
Mean time[a] (sd;min;max)	358		270 (395; 4; 968)		278 (375; 4; 968)	
MAS after Kineret is stopped						
1 -30 days	0	0.0	0	0.0	0	0.0
31-180 days	0	0.0	0	0.0	0	0.0
181-365 days	0	0.0	2	25.0	2	25.0
>365 days	0	0.0	6	75.0	6	75.0
Total	0	0.0	8	44.4	8	42.1
Mean time[a] (sd;min;max)	-		873 (725; 220; 2377)		873 (725; 220; 2377)	
Overall						
1 -30 days	0	0.0	4	22.2	4	21.0
31-180 days	0	0.0	3	16.7	3	15.8
181-365 days	1	100.0	2	11.1	3	15.8

Table 16. Number of first occurrence of MAS events by history of MAS and time since first injection with Kineret (The MAS-1 set)

	History of MAS at baseline		No History of MAS recorded at baseline		Total	
N	**1**		**18**		**19**	
Time since first injection with Kineret	**n**	**%**	**n**	**%**	**n**	**%**
>365 days	0	0.0	9	50.0	9	47.4
Total	1	100.0	18	100.0	19	100.0
Mean time[a] (sd;min;max)	358		538 (628; 4; 2377)		528 (612; 4; 2377)	

Abbreviations: MAS, macrophage activation syndrome ('MAS' is equal to MedDRA Preferred Term: Haemophagocytic lymphohistiocytosis, MedDRA version 21.1); N, number of patients, SD, standard deviation; min, minimum value; max, maximum value; n, number of MAS events.

The MAS-1 set, including patients who have been diagnosed a first time with MAS following start of Kineret treatment. All events following the first dose of Kineret, regardless of whether the patient is on Kineret treatment exposure are counted.

[a] presented in days.

Table 17. Number of first occurrence of MAS events by time since Kineret discontinuation (The MAS-1 set)

	Overall	
N	**19**	
MAS during Kineret treatment	**11**	
MAS after Kineret is stopped	**8**	
Time since Kineret discontinuation	**n**	**%[a]**
1 -90 days	0	0.0
90-180 days	2	25.0
181-270 days	1	12.5
271-365 days	1	12.5
366-548 days	2	25.0
549-730 days	0	0.0
>730 days	2	25.0

Abbreviations: MAS, macrophage activation syndrome ('MAS' is equal to MedDRA Preferred Term: Haemophagocytic lymphohistiocytosis, MedDRA version 21.1); N, number of patients with first occurrence of MAS, n, number of MAS events.

The MAS-1 set, including patients who have been diagnosed a first time with MAS following start of Kineret treatment. All events following the first dose of Kineret, regardless of whether the patient is on Kineret treatment exposure are counted.

[a] percentages are calculated in relation to number of first occurrence of MAS events after kineret is stopped.

Table 18. Trigger events for MAS events during simultaneous Kineret treatment (The MAS-1 set)

	Overall	
N	**19**	
Number of MAS events during Kineret	**12**	
Trigger event	**n**	**%**
Disease flare	4	33.3
Infection	2	16.7
Changes of treatment	3	25.0
Unknown	3	25.0
Total	12	100.0

Abbreviations: MAS, macrophage activation syndrome (‘MAS’ is equal to MedDRA Preferred Term: Haemophagocytic lymphohistiocytosis, MedDRA version 21.1); N, number of patients, n, number of MAS events.

The MAS-1 set, including patients who have been diagnosed a first time with MAS following start of Kineret treatment. All events following the first dose of Kineret, regardless of whether the patient is on Kineret treatment exposure are counted.

Table 19. Duration of treatment with Kineret, overall and by treatment time window (The complete set)

Time window (months) in relation to baseline (start of Kineret treatment)	**N[a]**	**Mean (SD) (months)**	**Median (q1, q3) (months)**	**n[b]**	**n[c]**	**% still continuously treated at end of interval (n[c]/N)**
1-6	312	4.5 (2.0)	6.0 (2.8, 6.0)	306	184	60.1
7-12	194	5.0 (1.7)	6.0 (4.6, 6.0)	194	134	43.8
13-18	146	4.8 (1.9)	6.0 (3.7, 6.0)	144	97	31.7
19-24	107	5.3 (1.5)	6.0 (6.0, 6.0)	106	85	27.8
25-30	95	5.0 (1.8)	6.0 (4.9, 6.0)	93	69	22.5
>30	100	20.1 (20.7)	12.4 (4.8, 29.1)	88	-	-
Total	360	17.0 (21.1)	8.9 (3.1, 23.5)	306	92[*]	30.1

Abbreviations: SD, standard deviation; q1, the first quartile; q3, the third quartile.

Continuos treatment is defined as ongoing treatment with no more than 30 consecutive days of unexposed duration in between treatment periods.

[a]total number of patients treated ever during specified period (total periods), a patient may contribute multiple times if starting a new treatment period after a temporary stop of more than 30 days.

n[b]: numbers of patients at start of interval, patients who are in treatment at the first day of each time window.

n[c]: numbers of patients continuously treated at end of interval, patients who contribute for 6 months to each time window.

[*]Number of patients with the last date of treatment coinciding with the last date of visit (treatment periods censored at the last date of visit).

Table 20. Reasons for discontinuation of Kineret treatment, overall and by time window (The complete set)

Time window[a]	**Overall**		**1-6 months**		**7-12 months**		**13-18 months**		**19-24 months**		**>24 months**	
N-total number of patients	**306**		**306**		**194**		**144**		**106**		**104**	
Total number of reasons for discontinuations	**281**		**109**		**53**		**34**		**13**		**72**	
Reason[b]	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Adverse event at least of moderate intensity	23	8.2	17	15.6	2	3.8	3	8.8	0	0.0	1	1.4
Intolerance	14	5.0	8	7.3	3	5.7	1	2.9	0	0.0	2	2.8
Dose change	2	0.7	1	0.9	1	1.9	0	0.0	0	0.0	0	0.0
Inefficacy	121	43.1	51	46.8	20	37.7	8	23.5	6	46.2	36	50.0
Remission	86	30.6	20	18.3	21	39.6	19	55.9	4	30.8	22	30.6
Surgery	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Pregnancy	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Other reason	23	8.2	7	6.4	5	9.4	3	8.8	2	15.4	6	8.3
Mild adverse event[c]	5	1.8	4	3.7	1	1.9	0	0.0	0	0.0	0	0.0
Change therapy	11	3.9	2	1.8	2	3.8	2	5.9	1	7.7	4	5.6
No compliance	4	1.4	0	0.0	2	3.8	0	0.0	1	7.7	1	1.4
Other	3	1.1	1	0.9	0	0.0	1	2.9	0	0.0	1	1.4

Unknown	12	4.3	5	4.6	1	1.9	0	0.0	1	7.7	5	6.9
Number of patients discontinued[d]	233	76.1	102	33.3	50	25.8	33	22.9	13	12.3	61	58.7
Number of discontinuations[e]	268	87.6	103	33.7	50	25.8	33	22.9	13	12.3	69	66.3

Treatment periods censored at the last date of visit are not to be considered as treatment discontinuations.
A patient can contribute with multiple discontinuations, if starting a new treatment period after a temporary stop of more than 30 days, and multiple reasons for one single discontinuation.
[a]In relation to baseline (start of Kineret treatment).
[b]The denominator for the calculation of percentages is the total number of reasons for discontinuations.
[c]Mild adverse events are not reported anywhere else because the Pharmachild JIA registry decided to collect adverse event at least of moderate intensity.
[d,e] The denominator for the calculation of percentages is the total number of patients (N).

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Table 21. Latest treatment regimen of sDMARDs, bDMARDs and glucocorticoids (by decreasing order) receiving at any time from disease onset to the first dose of Kineret (The complete set).

N	**228**	**78***	**306**
Treatment regimen	**Latest treatment regimen occurring any time before the first dose of Kineret, n(%)**	**Treatment starting before the first dose of Kineret but continuing after starting of Kineret, n(%)**	**Total**
None	94 (41.2)	-	94 (30.7)
Glucocorticoids only	32 (14.0)	42 (53.8)	74 (24.2)
bDMARDs[a] only	24 (10.5)	-	24 (7.8)
bDMARDs[a]+glucocorticoids	13 (5.7)	-	13 (4.2)
MTX+bDMARDs[a]	12 (5.3)	1 (1.3)	13 (4.2)
MTX only	11 (4.8)	8 (10.3)	19 (6.2)
MTX+glucocorticoids	11 (4.8)	25 (32.0)	36 (11.8)
MTX+bDMARDs[a]+glucocorticoids	8 (3.5)	-	8 (2.6)
sDMARDs[b]+bDMARDs[a] +MTX	5 (2.2)	-	5 (1.6)
sDMARDs[b]+bDMARDs[a]+MTX+glucocorticoids	5 (2.2)	-	5 (1.6)
sDMARDs[b]+bDMARDs[a]	3 (1.3)	-	3 (1.0)
sDMARDs[b]+glucocorticoids	3 (1.3)	-	3 (1.0)
sDMARDs[b]+MTX	2 (0.9)	-	2 (0.7)
sDMARDs[b]+bDMARDs[a]+glucocorticoids	2 (0.9)	-	2 (0.7)
sDMARDs[b]+MTX+glucocorticoids	2 (0.9)	2 (2.6)	4 (1.3)
sDMARDs[b] only	1 (0.4)	-	1(0.3)

Abbreviations: MTX: Metothrexate; DMARDs: Disease modifying antirheumatic drugs.
[a] other than Kineret.
[b] other than MTX.

* Among the 306 patients treated with Kineret, 78 patients were treated with concomitant treatment regimens (treatments starting before the first dose of Kineret but continuing after starting of Kineret).

Table 22. Concomitant treatment regimen of sDMARDs, bDMARDs and glucocorticoids (by decreasing order) with the first dose of Kineret (The complete set).

N	**306**
Concomitant treatment regimen	**n (%)**
Kineret only	113 (36.9)
Kineret+glucocorticoids	83 (27.1)
Kineret+MTX+glucocorticoids	63 (20.6)
Kineret+MTX	25 (8.2)
Kineret+MTX+glucocorticoids+sDMARDs[a]	6 (2.0)
Kineret+glucocorticoids+sDMARDs[a]	5 (1.6)
Kineret+sDMARDs[a]	4 (1.3)
Kineret+bDMARDs[b]+MTX+glucocorticoids	3 (1.0)
Kineret+bDMARDs[b]	1 (0.3)
Kineret+bDMARDs[b]+MTX	1 (0.3)
Kineret+bDMARDs[b]+DMARDs[a]	1 (0.3)
Kineret+bDMARDs[b]+glucocorticoids+DMARDs[a]	1 (0.3)
Kineret+bDMARDs[b]+glucocorticoids	0
Kineret+sDMARDs[c]+MTX	0
Kineret+sDMARDs[c]+bDMARDs[b] +MTX	0
Kineret+sDMARDs[c]+bDMARDs[b]+MTX+glucocorticoids	0

Abbreviations: MTX: Metothrexate; DMARDs: Disease modifying antirheumatic drugs.
[a] other than MTX.
[b] other than Kineret.

Annex 1. List of stand-alone documents

Number	Document reference number	Date	Title
1	**Version 1.0**	13 March 2019	Study Protocol Sobi.Anakin-302 CSP
2	**Version 1.0**	14 March 2019	Statistical Analysis Plan Sobi.Anakin-302 SAP
3	**Version 4.9**	28 February 2019	Kineret EU Risk Management Plan
4	**NA**	15 November 2019	Principal Investigator and Sobi CSR signature pages

Annex 2. Additional information

No additional information