Protocol I4V-GH-B021(a)
Post-Marketing Safety Study on Olumiant® (Baricitinib) Use Among Moderate to Severe Active Rheumatoid Arthritis Patients in China

Confidential Information

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2. List of Abbreviations

Term	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
bDMARD	biologic disease modifying anti-rheumatic drug
BMI	body mass index
CDAI	Clinical Disease Activity Index
cDMARD	conventional disease modifying anti-rheumatic drug
CI	confidence interval
CPK	creatine phosphokinase
CREDIT	Chinese registry of rheumatoid arthritis
CRO	clinical research organization
CRP	C-reactive protein
DAS28	Disease Activity Score modified to include the 28 diarthrodial joint count
DMARDs	disease-modifying antirheumatic drug
DVT	deep venous thrombosis
EAIR	exposure adjusted incidence rate
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ERB	ethical review board
HDL-C	high density lipoprotein-cholesterol
JAK	Janus kinase

LDL-C	low density lipoprotein-cholesterol
MACE	Major Adverse Cardiovascular Event
MAH	marketing authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities
MJS	Morning Joint Stiffness
NMPA	National Medical Products Administration
PE	pulmonary embolism
PMSS	post-marketing safety study
RA	rheumatoid arthritis
RMP	Risk Management Plan
SAE	serious adverse event
SAP	statistical analysis plan
SAR	suspected adverse reaction
SAS	statistical application software
SDAI	Simplified Disease Activity Index
SJC	swollen joint count
TEAE	treatment-emergent adverse event
TJC	tender joint count
ULN	upper limit of normal
URTI	upper respiratory tract infections
UTI	urinary tract infections
VAS	Visual Analogue Scale
VTE	venous thromboembolism

wks	weeks

3. Responsible Parties

Not applicable.

4. Abstract

- **Title**: Post-Marketing Safety Study on Olumiant® (Baricitinib) Use Among Moderate to Severe Active Rheumatoid Arthritis Patients in China
  - Version: 1.0
  - Main author: Yan Zhang, Lilly Suzhou Pharmaceutical Co. Ltd.
- **Rationale and background**: The data from clinical trials in patients with rheumatoid arthritis (RA) demonstrate that Olumiant®(baricitinib) is effective and generally well tolerated; however, the safety profile in the wide population in normal clinical practice has not been characterized. Study I4V-GH-B021 will investigate the safety and effectiveness of Olumiant® as a treatment in patients with moderate to severe active RA. This study will be performed as an additional pharmacovigilance activity of the Risk Management Plan (RMP) for Olumiant® in China, which is required by the National Medical Products Administration (NMPA) according to local regulations. Approximately 600 patients will be analyzed for this study.
- **Research question and objectives**: The primary objective of the study is to describe the incidence of adverse events (AEs) and serious adverse events (SAEs) over a period of 12 weeks. Secondary objectives include: describe the incidence of AEs and SAEs over a period of 24 weeks; change of Disease Activity Score modified to include the 28 diarthrodial joint count (DAS28)- C-reactive protein (CRP), Simplified Disease Activity Index (SDAI) score, and Clinical Disease Activity Index (CDAI) score from baseline to Weeks 12 and 24; proportion of patients achieving DAS28-CRP <2.6, DAS28-CRP ≤3.2, SDAI score ≤3.3, SDAI score ≤11, CDAI score ≤2.8, and CDAI score ≤10 at Weeks 12 and 24; and patient-reported outcomes including mean duration of Morning Joint Stiffness (MJS) and mean Visual Analogue Scale (VAS) for pain, assessed in Weeks 12 and 24 as collected in the electronic-diaries.
- **Study design**: This is a single-country, single arm, prospective, non-interventional study designed to collect all AEs, SAEs regardless of their relatedness to Olumiant® and monitor the effectiveness and patient-reported outcomes of Olumiant® at Weeks 12 and 24.
- **Population**: The study population will consist of patients in China who have been diagnosed with moderate to severe active RA who are at least 18 years of age and have been prescribed Olumiant® according to the approved label by the investigator and provide written consent to release of their data after being informed of the study.
- **Variables**: Patient demographics, diagnosis information, initial history and pre-existing conditions, study drug administration, concomitant medications, tender/swollen joint count, patient and physician global assessments, duration of MJS, pain VAS, AEs, SAEs and treatment information will be collected.
- **Data sources**: This study is based on primary data collection through Chinese registry of rheumatoid arthritis (CREDIT) platform, which includes both physician evaluation and patient-reported outcomes records.

- **Study size**: At least 600 patients are required to be analyzed and reported as the safety analysis population for this study. Approximately 667 patients are required to be enrolled given the expected 10% drop-out rate.
- **Data analysis**: The safety analysis population will include all patients who take at least 1 dose of Olumiant® therapy. When analyzing treatment-emergent AEs (TEAEs), the Medical Dictionary for Regulatory Activities (MedDRA) will be used for coding the terms collected on the data forms and the terms used in analysis.
- **Milestones**: Planned data collection starts from 31-Jul-2020 and planned final study report will be completed around 31-Dec-2022.

5. Amendments and Updates

The overall changes and rationale for the changes made to this protocol are described in the table below. Minor typographical corrections not affecting the content have been made in the document.

Amendment No.	Date	Section of study protocol	Amendment	Reason
1	04 Mar 2020	Section 7 Rationale and Background	Text was added to provide additional background on adverse events observed in clinical studies. Text was added to provide rationale for study period.	Background information was added to clarify rationale for collection of adverse events and observation period in study design.
		Section 9.3.2 Data Collection Schedule Table 9.1	Included an additional recommend post-baseline visit at Day 28±14 (4±2 weeks) to collect treatment information, concomitant medications, and safety assessment.	The additional recommend post-baseline visit was added to reduce the potential in missing any quick onset adverse events.
		Section 9.5 Study Size	Sample size estimation was updated with incidence of serious infection, prevalence of rheumatoid arthritis (RA) in China and the market estimation.	Updated to use a calculation method as suggested by the National Medical Products Administration (NMPA).
		Sections 4, 8, 9.1, 9.3.3.2 and 9.7.3.2	Criterion for DAS28-CRP was changed from ≤2.6 to <2.6.	The criterion was updated to align with Olumiant® Phase 3 clinical trials.
		Annex 3	Initial safety evaluation report of Olumiant® was added to briefly summarize the safety information.	It's added as required by NMPA.
		Annex 4	Text was added to clarify that China label of Olumiant® will be attached in the Chinese version protocol.	It's added as required by NMPA.

6. Milestones

Milestone	Planned date
Start of data collection	31-Jul-2020
End of data collection	31-Aug-2022
Study progress report[a]	Annual progress report on 31-Jan-2021 and 31-Jan-2022
Final report of study results submission	31-Dec-2022

[a] Progress reports will include descriptive site information, number of patients who have entered they study, and number of patients presenting the outcomes.

7. Rationale and Background

Baricitinib is an orally available, selective Janus kinase (JAK) inhibitor (JAK1/JAK2) (Fridman et al. 2010) approved in Europe, United States, Japan and in many other countries for the treatment of patients with moderate to severe active rheumatoid arthritis (RA). In June 2019, Olumiant® (baricitinib) was approved in China for the treatment of moderate to severe active RA in adult patients who have responded inadequately to or who are intolerant to one or more disease modifying anti-rheumatic drugs (DMARDs). Olumiant® may be used in combination with methotrexate or other non-biological DMARDs according to approved China label.

In the completed Phase 3 studies, compared to placebo as well as approved oral conventional DMARDs (cDMARDs) and injectable biologic DMARDs (bDMARDs) which represent the established standards of care in RA, Olumiant® demonstrated clear, consistent, and clinically meaningful improvements across all relevant domains of efficacy related disease activity, physical function, radiographic progression of structural joint damage, and relevant patient-reported outcome measures. Treatment effects were robust as measured by sensitivity analyses of primary efficacy endpoints and across subgroups. In addition, the results observed among Chinese patients included in study I4V-CR-JAGS are consistent with those observed in the global Phase 3 study for the majority of efficacy measures and incidence rates of serious adverse events (SAEs), including serious infections were similar among patients receiving either Olumiant® or placebo.

As of 13 February 2019, approximately 548 healthy volunteers/Phase 1 study participants and 6555 patients have received Olumiant® since the start of clinical trials. For the integrated analysis of data from the RA clinical development program, consistent with the immunomodulatory mode of action of Olumiant®, treatment-emergent infections were more commonly observed in Olumiant®-treated patients. The most frequently reported infections were upper respiratory tract infections (URTI), viral URTI, urinary tract infections (UTI), bronchitis, pharyngitis, gastroenteritis, herpes zoster, influenza, sinusitis, and herpes simplex. The majority of the commonly reported adverse events (AEs) were anticipated events in the RA population (for example, infections including upper respiratory tract infections) or laboratory abnormalities consistent with the pharmacology of JAK inhibitors (for example, increases in creatine phosphokinase [CPK] and lipids including total cholesterol, low density lipoprotein-cholesterol [LDL-C], high density lipoprotein-cholesterol [HDL-C] and triglycerides). Of these AEs, URTI (including viral upper respiratory tract infections and bronchitis), herpes zoster, lipid increases, and increased CPK were considered adverse drug reactions (ADRs). In the RA clinical development program, no increased risk for SAEs (including serious infections, malignancies, or major adverse cardiac events [MACE]) was observed for either the Olumiant® 4 mg or Olumiant® 2 mg group compared to placebo control. The safety profile of Olumiant® at both the 2 mg and 4 mg once daily dose has remained consistent with long-term treatment. Deaths have been reported infrequently in patients taking Olumiant®, and are not considered a risk with Olumiant® use. (Investigator's Brochure, Lilly 2019).

In order to understand the safety data in the real world and with the aim of identifying, characterizing or quantifying a safety hazard, confirming the safety profile of the medicinal product, study I4V-GH-B021 will investigate the safety and effectiveness of Olumiant® as a treatment in Chinese patients with moderate to severe active RA. This study will be performed as an additional pharmacovigilance activity of the Risk Management Plan (RMP) for Olumiant®, which is required by the National Medical Products Administration (NMPA) according to local regulations. Approximately 600 patients will be analyzed for safety (refer to Section 9.5 for more details). In study I4V-CR-JAGS, 59.5% and 75.9% of Chinese patients reported at least 1 treatment-emergent adverse event (TEAE) through Weeks 12 and 24, respectively (I4V-CR-JAGS Clinical Study Report, Lilly 2018). Thus, it's supposed to capture majority of the events during an observation period of 12 and 24 weeks. In addition, according to a real-world large-scale study in China, short treatment duration (median duration less than 24 weeks) of bDMARD therapies was observed due to possible reasons of poor socioeconomic condition and poor patient compliance (Yuan An et al. 2017). Therefore, in this study, AEs will be collected over a period of 12 and 24 weeks.

This is a single-country, single arm, prospective, non-interventional post-marketing safety study (PMSS) conducted in Chinese RA patients in clinical practice setting to describe the incidence of AEs and SAEs, including the incidence of AE/SAE related to Olumiant® as assessed by investigator, and monitor the effectiveness and patient-reported outcomes of Olumiant® at Weeks 12 and 24.

8. Research Question and Objectives

Primary objective

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

Secondary objectives

The secondary objectives are to describe the incidence of AEs, SAEs over a period of 24 weeks, and to describe the effectiveness and patient-reported outcomes of Olumiant® 2 mg in the study population

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

9. Research Methods

9.1. Study design

This PMSS is a single-country, single arm, prospective, non-interventional study designed to collect all AEs, SAEs regardless of their relatedness to Olumiant® over a period of approximately 12 weeks and 24 weeks. Based on collected AE and SAE data, the incidence of TEAE and SAE, including relatedness to administration of Olumiant®, will be evaluated.

This PMSS is also designed to monitor the effectiveness and patient-reported outcomes of Olumiant® by evaluating change from baseline to Weeks 12 and 24 in DAS28-CRP, SDAI score, CDAI score; proportion of patients achieving DAS28-CRP <2.6 and ≤3.2, SDAI score ≤3.3 and ≤11,and CDAI score ≤2.8 and ≤10 at Weeks 12 and 24 (see Section 9.3.3.2 for more details on the criteria); and mean duration of MJS and mean VAS for pain assessed in Weeks 12 and 24 as collected in the e-diaries, among patients in China with moderate to severe active RA receiving treatment with Olumiant®.

The observation period for each case will be either until 30 days after the last dose, or until patients switch to a new RA medication (in case patients stop taking Olumiant® before 24 weeks), or up to 24 weeks.

At least 600 patients will be analyzed and reported as the safety analysis population (refer to Section 9.5 for more details) in this study, and enrollment will be managed accordingly.

Study completion and analyses for all patients may be completed and reported before the end of the renewal submission period. PMSS clinical study report will be submitted to the NMPA before the first Olumiant® license renewal.

9.2. Setting

9.2.1. Study Population

The patient population for this study will consist of patients who have been diagnosed with moderate to severe active RA and initiate treatment with Olumiant® according to the approved label. There are no other treatment groups for the study.

Enrollment starts after site readiness. The decision to enroll a patient in the study will be at the discretion of the investigator, based on the inclusion/exclusion criteria.

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

9.2.2. Inclusion Criteria

- Are at least 18 years old
- Diagnosed with moderate to severe active RA
- Prescribed with Olumiant® according to the approved label by the investigator in the routine care of the patient

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

9.2.3. Exclusion Criteria

- Are simultaneously participating in a different study that includes a treatment intervention and/or an investigational drug
- Contraindicated for the use of Olumiant® according to the approved label.

9.3. Variables

9.3.1. Study treatment

Olumiant® 2 mg will be prescribed in routine clinical setting and will be administered according to the approved label and investigator's judgment. The treatment and treatment initiation or changes are solely at the discretion of the investigator and the patient. There will be no attempt to influence the prescribing patterns of any individual investigator. Treatment for moderate to severe active RA will be prescribed according to the usual standard of care and will not be provided by Eli Lilly and Company (Lilly). Participation in the study will have no influence on payment or reimbursement for any treatment received by patients during the study.

9.3.2. Data Collection Schedule

Table 9.1 shows data collection schedule

Table 9.1 Data Collection Schedule

Procedure	Baseline Visit 1 Day 0 Pre-dose	Recommend Post-baseline Visit 2 Day 28±14 (4±2 wks)	Recommend Post-baseline Visit 3 Day 84±14 (12±2 wks)	Recommend Post-baseline Visit 4 Day 168±14 (24±2 wks)
Confirmation of eligibility and consent to release information	X			
Demographics[a]	X			
Diagnosis[b]	X			
Initial history/pre-existing conditions[c]	X			
Treatment information[d]	X	X	X	X
Concomitant medications[e]	X	X	X	X

Effectiveness assessment[f]	X		X	X
Safety assessment[g]		X	X	X

Abbreviations: AE = adverse event; BMI = body mass index; CDAI = Clinical Disease Activity Index; DAS28 = Disease Activity Score modified to include the 28 diarthrodial joint count; eCRF = electronic case report form; CRP = C-reactive protein; MJS = morning joint stiffness; RA = rheumatoid arthritis; SAE = serious adverse event; SDAI = Simplified Disease Activity Index; VAS = Visual Analogue Scale; wks = weeks.

Note:

- Baseline is the visit where the patient's data is collected prior to the administration of first dose of study drug.
- SAEs should be reported by the investigator to Lilly China or its designee within 24 hours of awareness of the event by completing the Lilly SAE Report Form.
- If patients discontinue Olumiant® before Week 24, safety follow-up will be conducted to confirm any AEs until 30 days after discontinuation, or patients switch to a new RA medication, whichever is earlier.
- Name of the investigational institute and investigator, contract date with the investigator, and patient identification number will be recorded in each eCRF.

[a]Demographics information includes, but is not limited to:

- Initials
- Year of birth/Age
- Sex (female/male)
- BMI: derived from weight and height

[b]Diagnosis information includes, but is not limited to:

- Date of initial diagnosis of moderate to severe active RA
- Rheumatoid factor (from the medical record at the time of enrollment)

[c]Initial history/pre-existing conditions information includes, but is not limited to:

- Previous history of disease-modifying antirheumatic drugs for RA (name of treatment, start date and stop date)
- Other comorbidities (diagnosis, start date and end date) including cardiovascular disease, recent or active infections, fragility fracture and malignancy
- Renal impairment and hepatic impairment (severity [mild, moderate, severe] will be recorded)
- Allergy
- Prior venous thromboembolism (VTE) history

[d]Olumiant® treatment information includes, but not limited to:

- Dose and frequency
- Start date and Stop date

- Reason for dose change or discontinuation

[e]Concomitant medication information includes, but not limited to:

- Medication name
- Dose and frequency
- Indication for use
- Start date and Stop date

[f]Effectiveness assessment (for DAS28-CRP, SDAI, CDAI, duration of MJS, pain VAS) information includes, but not limited to:

- Tender/swollen joint count (28 joints)
- Patient global assessment of disease activity on VAS (0 to 10.0)
- Physician global assessment of disease activity on VAS (0 to 10.0)
- CRP
- Duration of MJS as collected in e-diaries
- Pain on VAS (0 to 10.0) as collected in e-diaries

[g]Safety assessment information will be continually collected during the whole study period, includes, but not limited to:

- AE terms
- Seriousness
- Severity (mild, moderate, severe)
- AE period
- Action taken
- AE outcomes
- Relatedness to Olumiant® administration (Yes/No/Unknown)
- Relevant factors other than Olumiant®
- Laboratory test (if available)

9.3.3. Outcome Variables

Patients will be observed for approximately 24 ± 2 weeks after enrolled with 1 baseline visit and will be recommended to have 2 or 3 post-baseline visits during the study. Data will be collected through an electronic data capture system and reported to the authority per China regulation.

9.3.3.1. Safety Outcomes

Adverse events are any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. For the purpose of this study, all AEs will be collected. These include suspected drug interactions, and events associated with other drugs that are suspected of significantly affecting a patient's management, including those that could cause death, danger to life, admission to hospital, prolongation of hospitalization, persistent or significant disability/incapacity, and birth defects. The Medical Dictionary for Regulatory Activities

(MedDRA) system organ class and preferred term, classified from verbatim terms, will be used for coding the AE terms whether serious or non-serious.

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

Regardless of their severity or relatedness to Olumiant®, any AEs and SAEs (see Section 11.1.1 for SAE definition) arising in temporal association with Olumiant® will be collected and recorded by the investigators using the Safety Assessment Section in the electronic case report form (eCRF) throughout the whole observation period.

As defined in the China RMP (version 1.0), important identified/potential risk include serious infections, hepatotoxicity, foetal malformation following exposure in utero and VTE. Consistent with RMP, the followings will be considered as AEs of special interest:

- Serious infection
- Hepatotoxicity
- VTE including deep venous thrombosis (DVT) and pulmonary embolism (PE)

9.3.3.2. Effectiveness Outcomes

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

Remission is defined as a DAS28-CRP score of <2.6. Low disease activity is defined as a DAS28-CRP score of ≥2.6 to ≤3.2 (Singh et al. 2016).

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

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

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

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

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

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

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

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

9.3.4. Other Variables

Other variables will include patient demographics, diagnosis information, initial history and pre-existing conditions, study drug administration, concomitant medications and treatment information.

9.4. Data Sources

This is a site-based prospective study, which will analyze identified patient-level data. All patients are collected from hospitals and will be followed based on protocol requirements. All variables will be collected through a data platform named "Chinese registry of rheumatoid arthritis (CREDIT)" as a part of routine clinical data collection. The CREDIT was set up as a registry and has been installed on the investigators' clinical computers. Safety and effectiveness data will be recorded by investigators in the CREDIT. Patient-reported outcomes data will be collected in e-diaries through an application installed on patients' smartphones and automatically transferred into CREDIT.

9.5. Study Size

This study will be conducted based on CREDIT, which currently include around 80,000 registered RA patients. And an estimate of 20,000 more RA patients will be enrolled during this study period. Moreover, around 75% RA patients in China is reported as moderate to severe in severity (C. Yu et al. 2018). Considering the proportion of patients applicable to JAK inhibitors, the number of potential users of Olumiant®, which are the target population of this study, is estimated at approximately 562. The sample size was considered focusing on serious infection. The incidence of serious infection of 24 week was 1.6% in clinical trial JAGS (I4V-CR-JAGS

Clinical Study Report, Lilly 2018). Assuming that the incidence of the study is the same of 1.6% based on the trial finding, a sample size of 530 patients would provide the width of 95% confidence interval (CI) with 0.02, such as 95%CI (0.4%, 2.4%). The narrow width of 95% CI could be used to estimate incidence of AE of total population with an accurate statistical judge. Therefore, Lilly considers that 600 patients are needed for a final sample size of safety analysis for this PMSS. This will require enrolling 667 patients considering an assumptive safety follow-up drop-out rate of 10%.

9.6. Data Management

Patient data are recorded on data forms. Investigators/study personnel are responsible for the integrity of the data (that is, accuracy, completeness, legibility, and timeliness) reported to Lilly.

The names of investigational institutes and investigators, and patient identification numbers will be collected in the eCRF. Data collected in CREDIT platform will be transferred into the eCRF. A log that matches a patient's medical chart number and patient identification number will be maintained by the investigator. The date of reporting and name and signature of the reporting investigator will be electronically recorded in the eCRF when the patient's study participation is completed or permanently discontinued. The patient information is only available to the investigators but will be deidentified to Lilly.

9.6.1. Data to be Collected

Safety data will be collected by investigators (see Section 11.1 for details). Effectiveness data including DAS28-CRP, SDAI and CDAI, will be collected at baseline and post-baseline visits. Investigators are responsible for recording those data in CREDIT platform. Patient-reported outcomes including duration of MJS and pain VAS will be collected through e-diaries. Only e-diaries recorded at the timepoint nearest to Weeks 12 and 24 will be captured.

Refer to Section 9.3 for more information about data to be collected.

9.6.2. Missing Data

If data are missing or if a patient decides to discontinue from the study, there will be no imputation applied.

All patients who provide consent to release information and who fulfil study entry criteria will be included in the analyses. Patients may withdraw consent and discontinue participation in the study at any time, with no effect on their medical care or access to treatment. If a patient is withdrawn prior to completing the study follow-up period, any known reason for withdrawal should be documented in the database. All information already collected as part of the study will be retained for analysis; however, no further efforts will be made to obtain or record additional information regarding the patient.

The participating physician or site personnel should make every effort to contact the patients who are lost to follow-up in order to identify the reason for not continuing participating in the study within legal and ethical boundaries. All available information in the patient's file through the date of last contact or visit should be entered in the eCRF for the lost to follow-up patients.

The statistical analysis plan (SAP) will specify how such patients will be considered for purposes of endpoint assessment.

9.6.3. File Retention and Archiving

To enable evaluations and/or audits from regulatory authorities or the study sponsor, the physician agrees to keep records, including the identity of all participating patients, all original signed consent-to-release information, copies of all eCRFs, SAE forms, source documents, and adequate documentation of relevant correspondence. The records should be retained by the physician according to local regulations or as specified in the study specific site contract, whichever is longer.

9.7. Data Analysis

9.7.1. Analyses Overview

All data will be entered, verified, and archived by a contract research organization (CRO) external to Lilly and/or at Lilly. Statistical analyses will be contracted out to a CRO or an independent statistician that possesses the specific training, expertise, and experience relevant to the services being considered and will perform under the guidance and approval of statisticians at Lilly.

Any change to the data analysis methods described in this study protocol will require an amendment ONLY if it changes a principal feature of the study protocol. Any other change to the data analysis methods described in the study protocol and the justification for making the change will be described in the abbreviated PMSS Final Report.

In general, descriptive summary statistics will include the followings:

- For categorical variables: number, number missing, frequency, and percentage (with the percentage excluding the number missing in the denominator)
- For continuous variables: number, number missing, mean, median, standard deviation, minimum, maximum

All calculated values should be reported with at least 2 decimal places. If the calculated value is greater than or equal to 0.01, 2 decimal places will be retained. Otherwise, 3 decimal places will be retained. Two-sided significance level of 0.05 will be used. For p-values, 4 decimals will be retained.

The disposition of all patients who enter the study will be summarized. Patient demographics and baseline characteristics will be summarized with descriptive statistics. Concomitant drug therapy will be provided as a listing by all patients and as a summary.

Subgroup analyses may be performed for AEs, SAEs and effectiveness. No adjustment for multiplicity will be performed. Analysis will be conducted using Statistical Application Software (SAS), Version 9.2 or higher.

More detailed analysis information will be described in the SAP.

9.7.2. Analyses Population

All patients who provide consent to release information and who fulfil the study entry criteria will be included in the analyses. For those patients who are lost to follow-up, or who drop out of the study, the analyses will include all data up to the point of their last data collection.

A detailed description of patient disposition will be provided. It will include a summary of the number and percentage of patients enrolled in the study and treated, as well as number and percentage of patients completing the study or discontinuing (overall and by reason for discontinuation).

9.7.2.1. Safety Analyses Population

The safety population consists of all patients who take at least 1 dose of Olumiant® according to the approved label as prescribed by the investigator in the routine care of the patient and provide safety information. Safety follow-up will be conducted for confirming any occurrence of AE either until 30 days after the last dose, or until patients switch to a new RA medication (in case patients stop taking Olumiant® before 24 weeks), or up to 24 weeks.

9.7.2.2. Effectiveness Analyses Population

The effectiveness analysis population consists of all patients included in the safety analyses population, who participate in the follow-up visit within the protocol-defined visit window, thus having a baseline and at least 1 post-baseline effectiveness observation. If data are missing or if a patient discontinues from the study, there will be no imputation applied.

Patients who have been administered Olumiant® for less than 10 weeks should be excluded from the effectiveness analysis set.

9.7.2.3. Early Discontinuation

Patients' participation in the study may be discontinued before observation period for reasons including the followings:

- AE
- Lost to follow-up (any patients who repeatedly fail to return for scheduled visits and are unable to be contacted by the study site)
- Patient's decision (including withdrawal of consent to release information, etc.)
- Investigator's decision (including lack of effectiveness, etc.)
- Death
- Others

If a patient discontinues Olumiant® during the study and does not return for any post-baseline visits, the patient will be contacted through methods including but not limited to phone call, text message, or mail for collection of AE information and reasons for discontinuation of the treatment. All relevant information will be captured on the eCRF. Patients who are discontinued from the study will be included in the safety analyses population if they take at least 1 dose of

Olumiant® and provide safety follow-up information. If data cannot be collected at the discontinuation visit or contact, the data will be considered as missing data.

9.7.3. Treatment Outcome Analyses

9.7.3.1. Safety Analyses

Based on collected safety data, TEAE and SAE, AE of special interest, incidence rate and exposure adjusted incidence rate (EAIR), and the corresponding 95% CI will be calculated.

For AE percentage, the denominator is the total number of patients in the safety analysis population. Incidence rates will be calculated as the number of patients with an event per 100 patient-years of observation time, including any post-drug follow-up time, with observation time censored at event start date. The EAIR will be calculated as the number of patients with an event per 100 patient-years of overall Olumiant® exposure time.

The incidence of AEs (95% CI) will be summarized by their maximum severity. The maximum severity of an event will be defined as the maximum among all severities reported for that particular event during treatment. And the incidence of AEs (95% CI) will also be summarized by the relatedness to administration of Olumiant®.

The incidence of AEs (95% CI) and the number of events will be summarized by patient demographics, baseline characteristics, and other important factors.

The AEs reported as reasons for discontinuation will be summarized.

When analyzing AEs, the MedDRA system organ class and preferred term, classified from verbatim terms, will be used for coding the terms collected on the data forms, and the terms used in the analysis. The most updated version of MedDRA at the time of database lock will be used.

Further details will be described in the SAP.

9.7.3.2. Effectiveness Analyses

Presentation of outcome measures will be summarized by descriptive statistics from the data recorded at all visits.

Summary statistics such as the mean, standard deviation, minimum, maximum (for continuous variable) and the frequency, percentage (for categorical variable) will be presented for the effectiveness measures, including the changes from baseline to Weeks 12 and 24 in DAS28-CRP, SDAI score, CDAI score and proportions of patients achieving DAS28-CRP <2.6 and ≤ 3.2, SDAI ≤ 3.3 and ≤ 11, and CDAI score ≤ 2.8 and ≤ 10 at Weeks 12 and 24. Patient-reported outcomes include mean duration of MJS and mean VAS for pain, all these measures are assessed in Weeks 12 and 24 as collected in the e-diaries.

The changes from baseline to Weeks 12 and 24 in DAS28-CRP, SDAI score, CDAI score, MJS, VAS, and proportions of patients achieving DAS28-CRP <2.6 and ≤ 3.2, SDAI ≤ 3.3 and ≤ 11, and CDAI score ≤ 2.8 and ≤ 10 at Weeks 12 and 24 will be further analyzed by patient demographics and baseline characteristics.

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

Further details will be described in the SAP.

9.7.4. Subgroup Analyses

Subgroup analyses may be performed for the incidence of AEs and effectiveness at Week 12 and/or Week 24.

Details of subgroup analyses will be described in the SAP.

9.7.5. Interim Analyses

The interim analyses for safety and effectiveness will be evaluated once 300 patients have completed regular surveillance period of 12 weeks.

9.8. Quality Control

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

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the followings:

- Provide instructional material to the study sites, as appropriate.
- Sponsor a start-up training session to instruct the investigators and study coordinators. This session will give instructions on the protocol, the completion of the eCRFs, and study procedures.
- Make periodic visits to the study site.
- Be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax.
- Review and evaluate eCRF data and use standard computer edits to detect errors in data collection.
- Conduct a quality review of the database.

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

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the investigator will keep records of clinical notes and patient medical records as original

source documents for the study. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ethical review boards (ERBs) with direct access to original source documents.

9.9. Limitations of the Research Methods

In order to reduce potential bias in patient selection, participating physicians located in different cities will be asked to invite all patients from CREDIT platform, regardless of disease severity, who meet the study criteria to participate in the study.

Since this is an observational study that patients' treatments are not intervened, it is highly possible that comparatively higher rate of loss-of-follow-up will be observed than in clinical trials.

Since this is a single-arm study, it is not feasible to assess the safety and effectiveness of Olumiant® compared to other agents.

9.10. Other Aspects

Not applicable.

10. Protection of Human Subjects

Observational studies will be submitted to ERBs for approval whenever required by local law. In addition, regardless of local law, all primary data collected in observational studies will be submitted to at least 1 independent body (for example, ERB) for review to confirm that the study is considered non-interventional in that country. Regulatory authorities will be notified, and approval will be sought as required by local laws and regulations. Annual progress reports will be submitted to ERBs and regulatory authorities as required by local laws and regulations and will be submitted to NMPA annually.

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Chinese good clinical practices and applicable laws and regulations of China.

11. Management and Reporting of Adverse Events/Adverse Reactions

11.1. Primary Data Collection Study

The study personnel will collect via electronic data entry all protocol-defined AEs, including all associated fatal outcomes, occurring in temporal association with Lilly product(s) that are under evaluation as defined in this protocol. The protocol-defined AEs include all AEs in this study.

Adverse events collected will be summarized in the interim safety report (if applicable) and in the final study report.

Study personnel are requested to report any suspected adverse reactions (SARs) with Lilly products not under evaluation in this protocol or SARs with non-Lilly products to the appropriate party (for example, regulators or the marketing authorization holder) as they would in normal practice.

Study personnel are not obligated to actively collect AEs or SAEs in patients once they have discontinued from the study. However, if the study personnel learn of any SAE, including death, at any time after the patient has discontinued from the study and the event is considered reasonably possibly related to the Lilly product under evaluation, the study personnel must promptly notify Lilly.

When patients discontinue from study, the AE reporting should follow the normal practice.

11.1.1. Serious Adverse Events

The study personnel will report to Lilly or its designee any protocol-defined SAE arising in temporal association with the Lilly product(s) under evaluation within 24 hours of awareness of the event via a sponsor-approved method. Reports issued via telephone are to be immediately followed with official notification on study-specific SAE forms. A protocol-defined SAE is any AE from this study that results in one of the following outcomes:

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

11.1.2. Nonserious Adverse Events

The study personnel will record any nonserious protocol-defined AE arising in temporal association with the Lilly product(s) under evaluation within 30 days of awareness of the event via electronic data entry.

11.2. Secondary Data Collection Study (Not Applicable)

11.3. Product Complaints

Lilly collects product complaints on investigational products and drug delivery systems used in medical research studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Complaints related to unblinded comparator drugs or concomitant drugs/drug delivery systems are reported directly to the manufacturers of those drugs/devices in accordance with the approved label.

Investigators are instructed to report product complaints as they would for products in the marketplace.

12. Plans for Disseminating and Communicating Study Results

Final reports will be submitted to regulatory agencies. The study findings may be submitted to a scientific congress and/or to a peer-reviewed journal.

13. References

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Annex 1. List of Standalone Documents

Not applicable.

Annex 2. ENCePP Checklist for Study Protocols

Not applicable.

Annex 3.Initial Safety Evaluation Report

Materials for evaluation include (1) safety data and monitoring data of adverse drug reactions from various studies conducted by the drug manufacturer (pre-clinical and clinical studies); (2) studies and reports in domestic and international science literature with respect to adverse drug reactions, drug-induced injuries, interactions and toxic effects; (3) drug safety information released by domestic and international drug administration authorities; (4) relevant information about reports of severe adverse reactions / events of the same types of products.

The evaluation should include the following content: known adverse reactions and estimated incidence, animal test, potential safety signals discovered in clinical studies, severe adverse reactions occurred to the same type of products (especially types of reactions), severe adverse reactions that need further clarification, special groups for whom pre-marketing studies lack safety data, potential drug interactions, possible factors affecting adverse drug reactions, toxic reactions of drug overdose, as well as other safety issues that need further clarification.

The toxicologic and toxicokinetic profiles of Olumiant® were characterized in oral studies of up to 6 months in rats and 9 months in dogs. Genetic toxicology, safety pharmacology, embryo-fetal toxicology studies in rats and rabbits, a rat fertility study, a rat pre-postnatal study and a phototoxicity study have been conducted to support clinical development. The safety of Olumiant® was also characterized in juvenile rats. Overall, the major cell types affected by Janus kinase (JAK) inhibition in the nonclinical safety studies were lymphocytes and eosinophils. Significant decreases in mean lymphocyte counts are generally not observed clinically. In addition to immunosuppression, evidence of renal tubular toxicity and an exacerbated incidence of age-related cardiomyopathy was seen in rats given high doses (100/60 mg/kg) of Olumiant® for 6 months. Skeletal malformations (bent limbs and rib anomalies) and an increased incidence of skeletal development variations occurred in rat fetuses. Decreased pup weights were the dose-limiting effect in the rat pre-postnatal study. In juvenile rats, like adults, effects on body weight and the immune system were observed. Bone effects observed in the juvenile study included bacterial osteomyelitis with secondary fracture in one high dose animal, and exacerbation of femoral head and neck degeneration/atrophy (Investigator's Brochure, Lilly 2019).

As of 13 February 2019, 3 Phase 2 studies (I4V-MC-JADC, I4V-MC-JADA, and I4V-JE-JADN) and 5 Phase 3 (I4V-MC-JADZ [JADZ], I4V-MC-JADV [JADV], I4V-MC-JADX [JADX], I4V-MC-JADW [JADW], and I4V-CR-JAGS [JAGS]) clinical studies have been completed in patients with moderate to severe rheumatoid arthritis (RA), and an extension study to collect long-term data is ongoing (I4VMC-JADY [JADY]). An Olumiant® 4-mg dose was included in all Phase3 studies. An Olumiant® 2-mg dose was included in 2 Phase 3 studies, which incorporated placebo control. No increased risk for serious adverse events (SAEs) (including serious infections, malignancies, or major adverse cardiac events [MACE]) was observed for either the 4-mg or 2-mg group compared to placebo control. In Olumiant®-treated patients, there

were no SAE preferred terms that were reported by >1% of patients. In the 2-mg versus 4-mg comparison, there were no differences in the proportion of patients with SAEs through 16 weeks. In the long-term Olumiant® 2-mg versus 4-mg data, a higher proportion of patients reported SAEs in the 4-mg group compared with patients receiving 2-mg dose. Serious infections were not different from placebo and no differences were noted between doses for serious or opportunistic infections in the placebo-controlled data. The safety profile of Olumiant® at both the 2-mg and 4-mg once daily dose has remained consistent with long-term treatment. Deaths have been reported infrequently in patients taking Olumiant®, and are not considered a risk with Olumiant® use. The most frequently reported SAEs in the placebo-controlled studies in Olumiant® 4-mg treated patients (N=1142) were herpes zoster (n=3), cellulitis (n=2), RA (n=2), pulmonary embolism (n=2), anemia (n=2), and coronary artery disease (n=2). These events occurred in at least 2 patients in 16 weeks of placebo-controlled data (Investigator's Brochure, Lilly 2019).

Adverse drug reactions and risks considered to be associated with Olumiant® are summarized below (Investigator's Brochure, Lilly 2019):

Infections (Including Opportunistic Infections)

As with other immunomodulatory therapies, Olumiant® may increase the risk of developing infections such as upper respiratory tract infections. Events of tuberculosis have been observed in patients taking Olumiant®, including cases of extrapulmonary disease. Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were reported in clinical studies. The majority of infections reported from the Olumiant® clinical trial program has been mild-to-moderate in nature. The risk of infections has not been correlated with neutropenia.

Venous Thromboembolism

Events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving Olumiant®. Data from the placebo-controlled time period from the integrated safety analysis of Phase 2/3 RA studies showed a numerical imbalance in the reports of DVT/PE, with more events reported in the Olumiant® 4-mg group compared to the placebo group. The exposure-adjusted incidence rate (EAIR) of DVT/PE for Olumiant®-treated RA patients over long-term exposures was similar to the background rates published in the literature. There was no pattern of increased or decreased risk in any given 24-week time period including long-term exposures (0.53). Risk factors found more commonly in patients with these events included prior history of DVT/PE, obesity, and older age. Available evidence does not establish a causal association.

Increase in Hepatic Analytes

Increases in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) greater than 3 times upper limit of normal (ULN) were uncommonly seen in patients treated with Olumiant®. Most increases resolved with continued use or temporary discontinuation of Olumiant® and did not recur.

Renal Impairment

Patients with an estimated glomerular filtration rate (eGFR) <40 mL/min/1.73m^2 were excluded from study participation in the Phase 3 RA clinical trials. Renal function was found to significantly affect Olumiant® exposure.

Malignancies

In nonclinical toxicology studies, Olumiant® was not genotoxic, nor was it carcinogenic in rat and mouse studies. The overall incidence rates of malignancies observed in the Olumiant® development program remained stable over time and did not exceed the background rate. The risk of malignancies, including lymphoma, is increased in patients with RA. Immunomodulatory medicinal products may increase the risk of malignancies, including lymphoma. The clinical data are insufficient to assess the potential incidence of malignancies following exposure to Olumiant®. Long-term safety evaluations are ongoing.

Major Adverse Cardiovascular Events (MACE)

While long-term observations are limited, clinical trial data available to date do not suggest an increased risk for MACE. Major adverse cardiovascular event was not associated with hypercholesterolemia or hyperlipidemia, and the incidence rates for MACE were similar to the background rates for the RA population.

Lipids (i.e., High-Density Lipoprotein [HDL], Low-Density Lipoprotein [LDL], Triglycerides)

Treatment with Olumiant® has been associated with dose-related increases in total cholesterol, triglycerides, LDL-cholesterol (C), and HDL-C with stable LDL/HDL ratio. The pattern and incidence of increases in LDL-C and triglycerides stabilized on long-term exposure to Olumiant®. The statistically significant increase in treatment-emergent hyperlipidemia did not lead to serious events or discontinuations of Olumiant®.

In summary, based on these analyses, Olumiant® is safe and generally well tolerated.

Annex 4. Drug Insert Sheet

This annex is added per National Medical Products Administration (NMPA) request. The China label for Olumiant® is attached here in the Chinese version of this protocol.

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