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

EU PAS Register No: ENCEPP/SDPP/28378

Protocol version: 1.0 dated 13 Mar 2019

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
Protocol version identifier	1.0
Date of last version of protocol	13 Mar 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 macrophage activation syndrome (MAS) as an event of special interest (ESI).
Country(-ies) of study	Secondary use of data collected in Croatia, Denmark, France, Germany, Greece, Hungary, Israel, Italy, Latvia, Netherlands, Norway, Romania, Saudi Arabia, Spain and Switzerland.

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Marketing authorization holder(s)

MAH	Swedish Orphan Biovitrum AB (publ) SE-112 76 Stockholm T: +46 8 697 20 00

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1 List of abbreviations

Abbreviation	Term
AE	Adverse event
AOSD	Adult-Onset Still's Disease
CAPS	Cryopyrin associated periodic syndromes
CRF	Case report form
DMARD	Disease-modifying antirheumatic drug
EMA	European Medicines Agency
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
ESI	Events of special interest
EU	European Union
EU PAS register	EU electronic register of post-authorization studies
FDA	Food and Drug Administration
GCP	Good clinical practice
GPP	Good pharmacoepidemiologic practices
GVP	Good pharmacovigilance practice
ICF	Informed consent form
IL-1	Interleukin-1
IL-6	Interleukin-6
ILAR	International League of Associations for Rheumatology
IRCCS	Istituto di Ricerca e Cura a Carattere Scientifico (Institute for treatment and research)
JIA	Juvenile idiopathic arthritis
MAS	Macrophage activation syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate
NSAID	Non-steroidal anti-inflammatory drug
PASS	Post authorization safety study

PRINTO	Paediatric Rheumatology International Trials Organization
PSUR	Periodic safety update report
REB	Research ethics board
RMP	Risk management plan
SAE	Serious adverse event
SAP	Statistical analysis plan
SJIA	Systemic juvenile idiopathic arthritis
Sobi	Swedish Orphan Biovitrum

2 Responsible parties

The parties specified below are responsible for the conduct of the study.

Study Contacts	Contact Name/Address	Telephone/Fax Number & Email
Sponsor	Swedish Orphan Biovitrum AB (publ) SE-112 76 Stockholm, Sweden	T: +46 8 697 20 00
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See Annex 3 for further information on responsible parties.

3 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.
Rationale and background	Systemic juvenile idiopathic arthritis (SJIA) is the most severe form of juvenile idiopathic arthritis (JIA), characterized predominantly by systemic symptoms, such as high spiking intermittent fever, maculopapular rash, hepatosplenomegaly, lymphadenopathy, serositis, and marked increase in acute-phase reactants, but also chronic arthritis. SJIA is associated with complications, including joint damage, growth impairment, osteoporosis, amyloidosis and the potentially fatal macrophage activation syndrome (MAS). Although its pathogenesis is still not completely understood, it is believed to be of autoinflammatory nature. Laboratory and clinical observations suggest an inappropriate activation of the innate immune system, with hypersecretion of the proinflammatory cytokines interleukin-1 (IL-1) and 6 (IL-6). Kineret® is a recombinant human IL-1 receptor antagonist that has been approved in the EU for treating signs and symptoms of rheumatoid arthritis since 2002 and cryopyrin associated periodic syndromes (CAPS) since 2013. In 2018 the European Commission approved Kineret in adult and pediatric patients for the treatment of Still's disease, including SJIA and adult-onset Still's disease (AOSD), with active systemic features of moderate to high disease activity, or in patients with continued disease activity after treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and/or glucocorticoids. As agreed with EMA, the study is designed to further investigate long-term safety and potential risk for MAS in patients with SJIA treated with Kineret.
Research question and objectives	The objective of the study is to evaluate and characterize long-term safety of Kineret when used in standard clinical practice to treat patients with SJIA, including MAS as an event of special interest (ESI). The endpoints are: • The occurrence of non-serious AEs of at least moderate severity and serious AEs (SAEs), including MAS as an ESI. • The duration of Kineret treatment in a real-world setting. • The reasons for Kineret treatment discontinuation.
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.

Study Population	Male and female patients with a diagnosis of SJIA as per the ILAR classification criteria included in the Pharmachild registry study and who were ever treated with Kineret subsequently to SJIA diagnosis.
Variables	The study endpoints are 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.
Data sources	The Paediatric Rheumatology International Trials Organisation (PRINTO) is a non-profit, non-governmental, international research network with the goal to foster, facilitate and co-ordinate the development, conduct, analysis, and reporting of multi-centers, international clinical trials and/or outcome standardization studies in children with paediatric rheumatic diseases. The Pharmachild JIA registry, maintained by PRINTO, is a registry collecting data from patients with JIA including patients with SJIA. In the Pharmachild JIA registry 40 countries are participating of which 15 countries have collected data on Kineret treatment. This study includes secondary use of data already available in the Pharmachild JIA registry. The source for the data in the registry is the patients' medical records.
Study size	All patients enrolled in the Pharmachild JIA registry before September 30, 2018 (study end date) meeting the criteria defined for the study population will be included in the study. It is estimated that approximately 300 patients will fulfill these criteria.

Data analysis	Patient characteristics at baseline will be summarized and presented. The analysis will include calculation of unique incidence rates (with 95% CI) and incidence proportions of each reported term of non-serious AE (moderate and severe) and SAE. A patient may contribute with multiple events of the same AE term. AE specific incidence rates and proportions will be presented overall for the whole study period and also by time windows defined with reference to the first dose of Kineret following a SJIA diagnosis. Analyses of sub-populations with long-term Kineret treatment will enable descriptive comparisons of incidence early in the treatment cycle and incidence resulting from long-term treatment. This study will pay a special interest to the incidence of MAS. Therefore, the time to event since start of Kineret treatment, in this scenario regardless of whether the patient was on Kineret treatment when the event occurred, and the cumulative probability of a first MAS event over time will be analyzed. Trigger events associated with each MAS episodes will be summarized. Summary statistics for the duration of Kineret treatment will be presented overall and by time window. The reasons for Kineret treatment discontinuation will be summarized with number and percentage. Use of other SJIA related medications at baseline and concomitantly with Kineret treatment will be summarized by treatment patterns.
Milestones	The data extraction from the Pharmachild JIA registry is planned to start in March, 2019 and end in April, 2019. A final study report is planned for October, 2019.

4 Amendments and updates

None.

5 Milestones

This PASS is based on secondary use of data, utilizing already available data from the Pharmachild JIA registry. In the Pharmachild registry data has been collected since 2011. Data collected up until September 30, 2018 will be used in this study. The data extraction from the Pharmachild registry will start as soon as the CSP, SAP and contract with PRINTO have been finalized.

Milestone	Planned date
Start of data collection	March, 2019
End of data collection	April, 2019
Registration in the EU PAS register	March, 2019
Final report of study results	October, 2019

6 Rationale and background

SJIA is an autoinflammatory disease, characterized by chronic arthritis, 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 the potentially fatal MAS (4-8). Laboratory and clinical observations suggest an inappropriate activation of the innate immune system, with hypersecretion of the proinflammatory cytokines interleukin-1 (IL-1) and 6 (IL-6).

Kineret® is a human IL-1 receptor antagonist that has been approved in the EU for treating signs and symptoms of rheumatoid arthritis since 2002 and CAPS since 2013. In 2018 the European Commission approved Kineret 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 agreed with EMA, the study is 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 as a category 3 activity.

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

7 Research question and objectives

The objective of the study is 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.

The endpoints to support the objective for the study are:

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

8 Research methods

8.1 Study design

This is 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 are 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 is 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.

8.2 Setting

Data will be extracted and analyzed for all male and female patients with a diagnosis of SJIA as per the ILAR classification criteria (10, 11) included in the Pharmachild registry and who were ever treated with Kineret subsequently to SJIA diagnosis.

That is, all eligible patients participating in the Pharmachild JIA registry study are included in this study. No specific exclusion criteria will be applied.

No treatment assignment or randomization is applicable.

This study is based on secondary use of data from the Pharmachild registry. The Pharmachild 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 September 30, 2018 will be used in this study. The data extraction from the registry will start in March, 2019 and end in April, 2019.

40 countries participate in the Pharmachild JIA registry. 15 of these countries have collected data from patients meeting the above criteria; Croatia, Denmark, France, Germany, Greece, Hungary, Israel, Italy, Latvia, Netherlands, Norway, Romania, Saudi Arabia, Spain and Switzerland.

8.3 Variables

The study endpoints are 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.

Management and reporting of AEs are described in Section 10.

In addition, the following will be captured:

- Demographics (sex, ethnicity, country)
- Characteristics at start of Kineret treatment (baseline), i.e. time since disease onset date, time since SJIA diagnosis, co-morbid conditions, history of MAS, global assessment of overall disease activity, age at start of Kineret treatment, SJIA related concomitant medications
- Reason for discontinuation of Kineret treatment.

8.4 Data sources

PRINTO (www.printo.it) is a non-profit, non-governmental, international research network founded by Alberto Martini and Nicolino Ruperto in 1996 (12). 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. PRINTO governing bodies are the advisory council, the national coordinators and the International coordinating center based in Genoa, Italy at the IRCCS G. Gaslini hospital.

The Pharmachild JIA registry, which was set up in December, 2011 with a 3-year grant from EU and is maintained by PRINTO, is a registry collecting data from patients with JIA including patients with SJIA. In the Pharmachild JIA registry 40 countries are participating of which 15 countries have collected data on Kineret treatment: Croatia, Denmark, France, Germany, Greece, Hungary, Israel, Italy, Latvia, Netherlands, Norway, Romania, Saudi Arabia, Spain and Switzerland. The data used in this study will hence be collected from these countries.

The Pharmachild JIA registry study has obtained the ENCePP Study Seal. 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.

As per August 20, 2018 the data source contains both retrospective and prospective data as follows (Table 1).

Table 1

Data type	Number of JIA patients	Number of SJIA patients	Number of SJIA patients treated with Kineret
Only retrospective data	5208	587	212
Retrospective + Prospective data	3508	352	95
Total	8716	939	307

The retrospective data are the data collected from the medical records prior to enrollment in the Pharmachild registry. The prospective data are data collected after enrollment in the registry. For this study retrospective and prospective data will be treated equally.

This study is based on secondary use of data already available in the Pharmchild registry. The source for all data in the registry is the patients' medical records. In the registry both the retrospective and prospective part contain demographics, concomitant medications since onset of disease until last available follow up, AEs that are of at least moderate severity and events of special interest (e.g. MAS). AEs are coded in MedDRA version 21.1. A medical monitor evaluates all reported AEs. This person can raise queries to the centers and request further clarifications.

8.5 Study size

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

It is estimated that approximately 300 patients may be included.

8.6 Data management

In the Pharmachild 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 will be obtained for this study, only summary output will be reported.

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

8.7 Data analysis

Patient characteristics at start of Kineret treatment will be summarized and presented.

There will be 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 (September 30, 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

*For the long-term treatment set-12, 18 and 24 the longest continuous treatment period will be considered for inclusion in the sub-population. Hence, an index date may be set for patients who stopped Kineret treatment and later restarted and remained on treatment for a longer period than the previous.

8.7.1 Incidence rates of Adverse events

The analyses will include calculation of unique incidence rates (with 95% CI) of each reported non-serious AE (moderate and severe), SAE and MAS as an ESI respectively. A patient may contribute with multiple events of the same AE term. Incidence rate of events (calculated as the number of the incident events divided by the sum of patient years under risk) will be expressed

as incidence rate per 100 patient years. The incidence rate will be derived by a Poisson regression model (with only intercept) and the 95% CI will be estimated using the Poisson estimator with a cluster-robust estimate of variance to control for both overdispersion and intracluster correlation. AE specific incidence rates will be presented overall for the complete study period and by time windows defined with reference to baseline. The time windows will be defined as follows: 1-6 months, 7-12 months, 13-18 months, 19-24 months and >24 months of calendar time. AEs and patient-time will only be counted during Kineret treatment exposure that includes an additional period of 2 days (i.e. slightly longer than 5 half-lives in patients without renal impairment after treatment stop).

8.7.2 Additional analyses of the incidence of MAS

8.7.2.1 Analysis of first occurrence and recurrence of MAS

The incidence rate of MAS will also be analyzed with respect to 1st occurrence and recurrence respectively. The rationale for this is to account for a biological distinction in altered risk following a first event. For the analyses, 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. 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. Likewize, the patients included in the risk set for a 3rd occurrence of MAS are only those who had a 2nd occurrence of MAS etc. MAS events and patient-time will only be counted during Kineret treatment exposure that includes an additional period of 2 days after treatment stop.

8.7.2.2 Analysis of the duration until the incidence of MAS

The number of days from first injection with Kineret (baseline) until the first occurrence of MAS will be presented for the MAS-1 set. The number of MAS events and percentages will be presented grouped by simultaneous Kineret treatment (Yes/No) and days since first injection with Kineret treament (1-30 days, 31-180 days, 181-365 and >365 days).

In addition, the time from discontinuation of Kineret until the first occurrence of MAS will be summarized for the MAS-1 set. The number of events and percentages will be presented grouped by “still treated” and subsequently 10 day intervals since discontinuation of Kineret.

In the time to event analyses, all MAS events occurring after baseline will be counted regardless of whether patients are under simultaneous Kineret treatment exposure or not. Notwithstanding, in reporting it will be indicated whether simultaneous Kineret treatment exposure was present at the occurrence of the event.

8.7.2.3 Kaplan-Meier cumulative probability curve of MAS

The cumulative probability of a first event of MAS over time will be estimated for the complete set and graphically presented as a Kaplan-Meier curve.

In addition, a Kaplan-Meier cumulative probability curve stratified by history of MAS at baseline (Yes/No) will be presented. In the case of too few patients in either of the subgroups (number of patients ≤ 10), the stratified analysis should be dismissed from the CSR.

Patients should be censored at 2 days after discontinuation of Kineret treatment, if they die for other reasons than MAS (no 2 days addition), if they are lost to follow-up, or if they have still not experienced a MAS event at the last visit.

8.7.2.4 Trigger events of MAS

For each event of MAS collected as an ESI, a trigger event is recorded in the CRF. The following categories are possible to record: 'Disease flare', 'infection', 'changes of treatment' and 'other'. The 'other' field is supplemented with a free-text field. For the MAS-1 set, a summary table will present the number of MAS events and percentages per category. Depending on available data recorded in the free-text field for the "other" category, more categories may be added to the summary table. Reasons will only be presented for MAS events that occur when patients are on Kineret treatment exposure (including an additional period of 2 days after treatment stop.

8.7.3 Incidence proportions of Adverse events

The incidence proportion (i.e. risk) for each reported AE term will be 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. As regards to the calculation of time window specific incidence proportions, the start date will be set to equal the start date of the time window or when the patient start Kineret treatment within the time window. Only events that occur when patients are on Kineret treatment exposure (including an additional period of 2 days after treatment stop will be counted.

8.7.4 Incidence rates of Adverse events in sub-population

In a sub-population constituting those with more than 12 months of continuous treatment with Kineret, incidence rates of non-serious AEs of at least moderate severity, all serious AEs and MAS will be calculated for the time after 12 months and in addition incidence rates will be retrospectively derived for each preceding time window (i.e. 1-6, 7-12 months). Similarly, the analysis will also be performed for the subgroup of patients that have more than 18 (preceding windows to present: 1-6, 7-12 and 13-18 months) and 24 (preceding windows to present: 1-6, 7-12, 13-18 and 19-24 months) months of continuous treatment with Kineret respectively. These analyses will enable descriptive comparisons of incidence early in the treatment cycle and incidence resulting from long-term treatment. In the interpretation of the incidence rates calculated for the sub-populations, respective incidence rate for the total study population (the complete set) will also be taken into account. Interruptions of treatment, e.g. treatment holidays, will be allowed for up to 30 days with respect to the definition of continuous treatment. Neither AEs nor patient-time will be counted during the interruption.

Only events that occur when patients are on Kineret treatment exposure (including an additional period of 2 days after treatment stop will be counted.

8.7.5 Duration of treatment and reasons for discontinuation

Summary statistics for the duration of Kineret treatment will be presented overall and by time window.

The reasons for Kineret treatment discontinuation for more than 30 days will be summarized with number and percentage. The reasons for discontinuation will be collected as per the Pharmachild CRF: adverse event (moderate/severe/serious event or mild event), intolerance, dose change, inefficacy, remission, surgery, pregnancy or other reason. A patient can contribute with multiple discontinuations if starting a new treatment period after a treatment holiday of more than 30 days. Furthermore, multiple reasons can be recorded for one single discontinuation

8.7.6 Concomitant medications

Treatment regimens of DMARDs, biologics and systemic glucocorticoids concomitantly with first dose of Kineret will be summarized by dividing patients in groups of treatment patterns, i.e.

- Kineret only.
- Kineret+MTX.
- Kineret+glucocorticoids.
- Kineret+MTX+glucocorticoids.
- Kineret+other biologics.
- Kineret+other biologics+MTX.
- Kineret+other biologics+MTX+glucocorticoids.
- Kineret+other biologics+glucocorticoids.

In addition, treatment patterns (prescribed treatments) prior to initiating Kineret will also be presented. Categories to present are:

- None.
- MTX only.
- Glucocorticoids only.
- Biologic agents only (other than Kineret).
- Biologic agents other than Kineret+glucocorticoids.
- MTX+glucocorticoids.
- MTX+biologic agents other than Kineret.
- MTX+biologics other than Kineret+glucocorticoids.

Number and percentage of patients within each category of treatment pattern will be presented.

8.8 Quality control

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

It is the responsibility of the Investigators in the Pharmachild 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 is 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 is validated on an ongoing basis, and a specific validation process is applied.

8.9 Limitations of the research methods

An uncontrolled single-armed study design is the only feasible design in this non-interventional study since a fair comparator group would be difficult to introduce given the real-world practice of treatment regimen. Accordingly, the study design carries the general limitations inherent in an uncontrolled design regarding statistical analyses, interpretation, generalizability and conclusiveness. The incidence rates 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 incidence rates 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 selected 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 incidence rate for the respective time window in the total population (the complete set) and not only the sub-population specific incidence rate will likely alleviate a more unbiased conclusion.

All patients in the Pharmachild registry with a diagnosis of SJIA (as per ILAR classification criteria) and who were ever treated with Kineret following the SJIA diagnosis will be included in

this study. No other criteria will be used to select patients. In the Pharmachild study a census (e.g. collection of patient identification number, age, JIA type and type of treatment) is required from each centre 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).

Altogether, 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.

8.10 Other aspects

The relevant aspects of the study are covered in previous sections.

9 Protection of human subjects

This study will comply with the definition of the non-interventional (observational) study provided in Article 2(c) of Directive 2001/20/EC (13), the definition for Post-Authorization Safety Studies in Directive 2001/83/EC Art 1 (14), and its refinement provided in the Guideline of Good Pharmacovigilance Practices (GVP) Module VIII – Post-Authorization Safety Studies (15) . This study will conducted in compliance with the code of Good Pharmacoepidemiology Practices (GPP) (16) and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) standards.

This study will be conducted in compliance with this protocol and in accordance with the ethical principles for Medical Research Involving Human Subjects in the Declaration of Helsinki (17) and will be consistent with the International Ethical Guidelines for Biomedical Research Involving Human Subjects and applicable parts of the ICH GCP (18) (19), as well as all other applicable regulatory requirements. This study will be conducted in compliance with the European data protection regulation, GDPR (20).

Study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s). The investigator will also ensure that this study is conducted in accordance with the local laws and regulations.

9.1 Research Ethics Review (REB)

All necessary approvals for collection of the data in the Pharmachild registry have been obtained by PRINTO.

The PRINTO network is allowed to share summary data with pharmaceutical companies. Additional approval is needed for sharing of raw data. However, no individual patient listings will be obtained for this study, only summary outputs. Hence no additional approvals are required.

9.2 Informed consent

Not applicable. Patients signed an ICF when entering the Pharmachild registry which includes an approval to share data with regulatory authorities (EMA, FDA or national authorities) and pharmaceutical companies, this without collecting additional consent.

In some of the participating countries a signed ICF is not required to collect retrospective data. This is reflected in the Pharmachild registry which contains more retrospective than prospective data as demonstrated in table 1 in section 8.4

9.3 Confidentiality

Patient identity information (i.e. first and last name, date of birth and the national patient unique identifier) is available only for authorized study site personnel. The PRINTO web system will automatically encrypt the patient identity information and only encrypted data will be saved on the PRINTO central database. The web system will automatically assign a PRINTO patient id number.

The PRINTO encryption algorithm is designed in a way by which it is impossible for PRINTO to decrypt the patient identity information. This means that patient identity information is not included in study data sets or any documentation that are transmitted to the Sponsor. The study data sets will include age, which has been calculated from the patient's date of birth.

9.4 De-identification of patient data

Only authorized site personnel will have access to identifiable personal details.

In any presentations or in publications of the results of the study, the patients' identities will remain anonymous and confidential. If any government health agencies should inspect the medical records of the patients, every effort will be made to keep the patients' personal data confidential.

9.5 Sponsor documents

PRINTO agrees that all information received from the Sponsor, including but not limited to this protocol, and any other study information, remain the sole and exclusive property of the Sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the Sponsor. PRINTO further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.6 PRINTO documents

The database remains the sole and exclusive property of the IRCCS Istituto Giannina Gaslini hospital. Data will be shared with the Sponsor for the purpose of reporting to health authorities.

10 Management and reporting of adverse events/adverse reactions

10.1 Definitions

10.1.1 Adverse event

An adverse event (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product; the event does not necessarily have a causal relationship with the treatment or usage. In the Pharmachild registry only moderate, severe and very severe events are collected (mild AEs are not collected, unless they are SAEs).

10.1.2 Serious adverse events (SAE)

An AE that meets one or more of the following criteria/outcomes is classified as serious:

- Death.
- An adverse experience that places the subject at immediate risk of death from the adverse drug experience as it occurred
- In-patient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly or birth defect
- An event that, based on appropriate medical judgement, may jeopardize the subject and may require a medical or surgical intervention to prevent an outcome described above
- Cancer
- Overdose
- Suspected transmission of an infectious agent via the drug (e.g., any organism, virus, or infectious particle, pathogenic or non-pathogenic).
- Other

Although overdose, cancer and suspected transmission of an infectious agent via the drug are not always serious by regulatory definition, these events are handled as SAEs.

10.1.3 Events of special interest (ESI)

For the purpose of this study MAS is considered as an ESI. In the Pharmachild registry several other events are also considered as ESIs, but for the purpose of this study only MAS is considered as an ESI.

10.2 Eliciting and recording adverse event information

All non-serious AEs of at least moderate severity, serious AEs and ESIs (including MAS) related or not related to Kineret, are recorded in the Pharmachild CRF and captured in the database. For each event the following data is collected: description of event, onset date, serious or not, applicable serious criteria, intensity, laboratory tests, other relevant history and outcome. For MAS the following additional data is collected: trigger events, clinical features, laboratory features, tests performed and treatments of MAS.

Non-serious mild AEs, e.g. discomfort noticed but no disruption of daily activities, have not been reported in the Pharmachild registry and will hence not be considered in this study either.

10.3 Exposure during pregnancy or via breast feeding

For the purpose of this study pregnancy data will not be collected, unless reported as an AE.

10.4 Follow-up of unresolved adverse events

In the Pharmachild registry AEs have been followed until resolution or until the treating physician has assessed them as chronic or stable, or until the participation in the registry has ended. AEs which are unresolved at the time of the data extraction will not be followed up for the purpose of this study.

10.5 Laboratory safety assessment

Not applicable.

10.6 Monitoring of the benefit-risk balance

Not applicable.

11 Plans for disseminating and communicating study results

After completion of the study, the result should be published in a peer reviewed scientific journal and may be considered for reporting at a scientific meeting. The Sponsor will be responsible for these activities and will work with PRINTO to determine how the publication is written, the

number and order of authors, the journal or scientific meeting to which it will be submitted, and other related issues.

The study will be registered in the public EU PAS register and on clinicaltrials.gov. As agreed with EMA the final study report will be submitted at the latest by the end of 2019. In addition, the collected safety data will be reported in PSUR and in RMP updates where applicable.

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Annex 1. List of stand-alone documents

Number	Document reference number	Date	Title
1	Version 4.9	28 Feb 2019	EU Risk Management Plan
2	Version 1.0	To be finalized prior to the start of data collection.	Statistical Analysis Plan

Annex 2. ENCePP checklist for study protocols

Annex 3. Responsible parties

The parties specified below are responsible for the conduct of the study.

Study Contacts	Contact Name/Address	Telephone/Fax Number & Email
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Annex 4. Approvals

PASS protocol Sobi.Anakin-302

A non-interventional, post-authorization safety study (PASS) to evaluate long-term safety of anakinra (Kineret®) in patients with systemic juvenile idiopathic arthritis Version 1.0

Version: 1.0

Dated Final version: 13 March 2019

Principal Investigator

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Medical Director

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Senior Statistical Scientist

Signature:

Date:

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Clinical Study Manager

Signature:

Date:

[redacted]
Head of Drug Safety, QPPV

Signature:

Date:

Sobi
Product: anakinra/Kineret
Clinical study no: Sobi.Anakin-302

Annex 4. Approvals

PASS protocol Sobi.Anakin-302

A non-interventional, post-authorization safety study (PASS) to evaluate long-term safety of anakinra (Kineret®) in patients with systemic juvenile idiopathic arthritis Version 1.0

Version: 1.0

Dated Final version: 13 March 2019

Principal Investigator

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Date: 14 Mar 2019

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Clinical Study Manager

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Date: 14 Mar 2019

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Signature: [redacted]

Date: 14 Mar 2019

Investigator statement

I have read the protocol entitled "A non-interventional, post-authorization safety study (PASS) to evaluate long-term safety of anakinra (Kineret®) in patients with systemic juvenile idiopathic arthritis". I agree to conduct the study in compliance with the Final Protocol, Version 1.0, March 13, 2019, the International Conference on Harmonisation (ICH) E6, Principles of Good Pharmacoepidemiology Practices (GPP), applicable parts of the Guideline for Good Clinical Practice, the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) standards, GDPR, applicable regulatory/government regulations, and in accordance with the latest revision of the Ethical Principles for Medical Research Involving Human Subjects (the Declaration of Helsinki).

I will not implement any changes to study procedures or conduct without prior approval from the sponsor and, when applicable, the Independent Ethics Committee/Institutional Review Board and Regulatory Authority.

I agree to maintain the confidentiality of this study protocol, as described on the title page. Further, I will not publish results of the study without authorization from Swedish Orphan Biovitrum AB (publ).

15/03/2019

Signature of Principal Investigator | Date

NICOLINO RUPERTO

Printed Name of Principal Investigator