10 June 2021
EMA/385270/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kineret

International non-proprietary name: anakinra

Procedure No. EMEA/H/C/000363/II/0078

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Comments from PRAC	n/a
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Updated PRAC Rapp AR	n/a
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Opinion	10 June 2021

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Swedish Orphan Biovitrum AB (publ) submitted to the European Medicines Agency on 25 November 2020 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	None

Submission of the final report from study (Sobi-ANAKIN-201) listed as a category 3 study in the RMP. This is a non-interventional post-authorisation safety study to evaluate the safety of Kineret in the treatment of Cryopyrin Associated Periodic Syndromes (CAPS) in routine clinical care with regard to serious infections, malignancies, injection site reactions, allergic reactions and medication errors, including reuse of syringe. The RMP version 5.4 has been submitted to reflect completion of this study. In addition, the RMP is updated to include information about a completed paediatric study (Sobi.ANAKIN-301) assessed as per Article 46 of Reg No 1901/2006 (EMEA/H/C/000363/P46/031). This was a randomised, double-blind, placebo-controlled, multicenter, phase 3 study which evaluated the efficacy, the safety, pharmacokinetics and immunogenicity of anakinra as compared to placebo in newly diagnosed Still's disease patients (including systemic juvenile idiopathic arthritis [SJIA] and adult-onset Still's disease [AOSD]).

The requested variation proposed amendments to the Risk Management Plan (RMP).

2. Overall conclusion and impact on the benefit/risk balance

With this variation the MAH submitted the results of the multicentre, non-interventional, non-controlled, post-authorisation safety study (PASS) (Sobi.ANAKIN-201) that collected prospective data in patients with a diagnosis of CAPS and treated with anakinra syringe according to body weight. This study was listed as a category 3 in the RMP.

The primary objective of the study was to evaluate the safety of Kineret treatment in CAPS patients in routine clinical care with focus on serious infections, malignancies, injection site reactions (ISRs), allergic reactions and medication errors, including re-use of the syringe. These are safety concerns listed in the RMP. The secondary objectives of the study were to evaluate the Kineret dosage over time, the proportions of patients who discontinue Kineret treatment temporarily or permanently and the proportion of patients who are transferred to another IL-1 blocking treatment.

A total of 15 to 20 patients were planned to be enrolled in the study. Patients were identified via the Eurofever Registry, organised and maintained by PRINTO. By September 2013, 225 CAPS patients had been enrolled in the Eurofever Registry. Of these 225 patients, treatment information was available for only 94 patient and of these, 61 patients received treatment with anakinra. Thus, within the Eurofever Registry, a total of 61 patients were potential candidates to be included in the PASS. However, only European patients were to be included and recruitment sites were limited to Germany, France, Italy, Netherlands and United-Kingdom which further limited the total number of potential patients to be included. Despite prolongation of the study and other efforts to reach a higher number of patients to be included, it was decided to close the study when a total of 12 patients were included. EMA was consulted when it was decided to close the study and the EMA agreed to this decision.

The majority (11) of all (12) included patient were already in treatment with Kineret at baseline, and only one patient initiated Kineret treatment at the beginning of this study. This may have affected (lowered) the frequency of ISRs but is not expected to have affected other primary endpoints. Among the primary endpoints only 7 cases of infections were reported. These events were reported in a single patient and were not associated with neutropenia. However, only few results of neutrophil counts were available, but these appeared to be within the range of 'Normal'. While this may be considered reassuring, it is not sufficient to draw any conclusions. Importantly, both 'Serious infections' and 'Neutropenia' are mentioned as common (frequency: ≥1/100 to <1/10) adverse reactions in the tabulated list of adverse reactions in section 4.8 of the SmPC and both 'Serious infections' and 'Neutropenia' are also addressed in the SmPC section 4.4 'Special warning and precautions for use'. Thus, the topics are sufficiently addressed in the product information (SmPC).

There were no reports of the other pre-defined primary outcomes (i.e. malignancies, ISRs, allergic reactions and medication errors, including re-use of the syringe) during the study period. Though reassuring, it is speculated if lack of cases of these other pre-defined primary endpoints may be explained by small number of patients in this study.

With regard to malignancies, this brief study was not designed to investigate induction of malignancies in patients undergoing anakinra treatment. Such events are considered rare, as the overall frequency of malignancies in clinical studies in patients with rheumatoid arthritis, including long-term follow-up data, has not been observed to be higher in anakinra-treated patients. Nevertheless, since most of the patients in study Sobi.ANAKIN-201 had begun anakinra treatment prior to enrolment, the total exposure time and hence the potential for malignancy induction, if any, was in principle longer than the exposure they received during the study. In addition, malignancies in patients with CAPS and other auto-inflammatory disorders receiving anakinra treatment are captured and reported as a consequence of post-marketing pharmacovigilance activities. Malignancies are described as an important potential risk in the RMP and are monitored as a Target medical event.

With regard to the secondary objectives, in total, 6 (50%) patients permanently discontinued treatment with Kineret. Of those, 2 patients discontinued at Year 1; 3 patients at Year 2; and 1 patient at Year >3; there were no permanent discontinuations of Kineret at Year 3. The reason for permanent discontinuation included change to another IL-1 blocking treatment (5 patients), inefficacy (1 patient) and non-compliance (1 patient). All 5 patients that transferred to another IL-1 blocking treatment reported to have switched to canakinumab.

Only 1 patient temporarily discontinued treatment with Kineret; the discontinuation occurred during Year 2, due to non-compliance. The patient discontinued treatment with Kineret after the laboratory results indicated that the patient had developed neutropenia. The AE was assessed as non-serious and the Kineret dose was adjusted. However, after registering the AE the laboratory results were reviewed and the investigator confirmed that the patient did not had neutropenia as previously reported, as consequence the treatment with Kineret was reintroduced in the original dose.

The majority of the patients increased in weight during the anakinra treatment. For the children (n=5), this weight gain is considered to be due to normal growth and is as such not a concern. Among the 7 adult patients (aged >18 years), a total of 6 patients gained weight during the treatment with anakinra as they are expected to have obtained target height and weight according to their age. One (1) patient lost 11 kg during treatment with anakinra, 1 patient increased weight with 19 kg whereas the remaining 4 patients increased weight with 2-5 kg. The patients were treated for 2.5–3.2 years. Of note, in 2016 'Weight gain' was noted as a potential safety issue related to the treatment with IL-1 blocking agents including anakinra. The signal detection was however, closed without confirmation of a causal relationship between increased weight and the IL-1 blocking agents. There was no request of updating the product information and thus, currently there is no information regarding weight gain in

the Kineret SmPC. Based on the few data included in the present PASS and the outcome of the signal detection in 2016, no further action is currently considered necessary.

In conclusion, the present PASS included a total of 12 patients all treated with anakinra due to CAPS. One patient experienced a total of 7 infections (not associated with neutropenia); no other events mentioned as primary endpoints were reported. The majority of patients increased their weight during treatment with anakinra however, it is unclear if it was related to the anakinra treatment. A signal detection of a causal relationship between increased weight and the IL-1 blocking agents raised in 2016 was not confirmed.

Overall, the results from the present PASS does not raise any concerns and no amendments to the product information is considered necessary.

The summary of safety concerns remains unchanged upon completion of the PASS Sobi.ANAKIN-201, since the results of the PASS did not provide significant new information to any of the risks due to the low power of the study.

The RMP version 5.4 has been updated to reflect completion of this study. The Data lock point of the RMP was updated from May 1, 2018 to May 1, 2020.

Furthermore, during this time period the anaSTILLs study (Sobi.ANAKIN-301) was completed and therefore part II and VI of the RMP have been updated with information from this study. In addition, the exposure sections have been updated due to the updated Data lock point as well as the follow-up forms in Annex 4 (minor modifications). This is agreed.

The benefit-risk balance of Kineret remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		**Type**	**Annexes affected**
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	None

Submission of the final report from study (Sobi-ANAKIN-201) listed as a category 3 study in the RMP. This is a non-interventional post-authorisation safety study to evaluate the safety of Kineret in the treatment of Cryopyrin Associated Periodic Syndromes (CAPS) in routine clinical care with regard to serious infections, malignancies, injection site reactions, allergic reactions and medication errors, including reuse of syringe. The RMP version 5.4 has been updated to reflect completion of this study. In addition, the RMP is updated to include information about a completed paediatric study (Sobi.ANAKIN-301) assessed as per Article 46 of Reg No 1901/2006 (EMEA/H/C/000363/P46/031). This was a randomised, double-blind, placebo-controlled, multicenter, phase 3 study which evaluated the efficacy, the safety, pharmacokinetics and immunogenicity of anakinra as compared to placebo in newly diagnosed Still's disease patients (including systemic juvenile idiopathic arthritis [SJIA] and adult-onset Still's disease [AOSD]).

☒is recommended for approval.

Amendments to the marketing authorisation

The variation requires amendments to the Risk Management Plan.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion EMEA/H/C/000363/II/0078.

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

Kineret (anakinra) is indicated for different diseases, including treatment of rheumatoid arthritis, periodic fever syndromes, CAPS, Familial Mediterranean Fever, Still's Disease. Anakinra is a human IL-1 receptor antagonist that blocks the biological activity of cytokine IL-1 (IL-1α and IL-1β) by competitively inhibiting its binding to the IL-1 receptor type 1, thereby controlling active inflammation. Kineret can be given as monotherapy or in combination with other anti-inflammatory drugs and disease-modifying antirheumatic drugs (DMARDs).

Cryopyrin-Associated Periodic Syndromes (CAPS), is a rare disease, caused by an autosomal dominant mutation in the NLRP3 gene, which leads to overproduction of IL-1β, and generates a life-long autoinflammatory syndrome. It consists of three distinct clinical diseases: Familial Cold Autoinflammatory Syndrome (FCAS), Muckle-Wells Syndrome (MWS) and Cutaneous Articular Syndrome/Neonatal-Onset Multisystem Inflammatory Disease (CINCA/NOMID), recognized as a severity spectrum rather than separate entities.

In November 2013 the European Commission approved Kineret in adults, adolescents, children and infants aged 8 months and older with a body weight of 10 kg or above, for the treatment of CAPS, including Neonatal-Onset Multisystem Inflammatory Disease (NOMID)/ Chronic Infantile Neurological, (CINCA), Muckle-Wells Syndrome (MWS) and Familial Cold Autoinflammatory Syndrome (FCAS).

The primary objective of Sobi.ANAKIN-201 was to evaluate the safety of Kineret treatment in CAPS patients in routine clinical care with focus on serious infections, malignancies, injection site reactions (ISRs), allergic reactions and medication errors, including re-use of the syringe.

The secondary objectives of the study were to evaluate the Kineret dosage over time, the proportions of patients who discontinue Kineret treatment temporarily or permanently and the proportion of patients who are transferred to another IL-1 blocking treatment.

CHMP comments

The MAH has sufficiently described the product, the disease (CAPS) and the background for the present Post-Approval Safety Study (PASS).

6. Non-interventional Post-Authorisation Safety Study (PASS) results

6.1. Methods – analysis of data submitted

6.1.1. Study design

This was a multicenter, non-interventional, non-controlled PASS to collect prospective data in routine clinical care where CAPS patients are treated with the Kineret graduated syringe. The planned duration of the follow-up period for each patient was to be 3 years. Patients were to be treated according to the approved dose recommendation for CAPS in the SmPC (Section 4.2 Posology and method of administration). In case the patient discontinued the Kineret treatment prematurely before 3 years, the data collection was to be discontinued (see below) and the patient was to be withdrawn from the study. Data was captured at least once every year. However, investigators were encouraged to collect data at 6 months intervals if the patient had routine visits more frequently than once a year.

If the patient permanently discontinued the Kineret treatment before the 3-year visit, study data was to be collected up to and including the last day of Kineret treatment. The recording of this data could, however, be performed at the next scheduled doctor's appointment/contact. If the patient had a

planned or spontaneous temporary discontinuation of Kineret treatment, the patient could stay in the study. Other reasons for discontinuation/withdrawal of a patient from the study could be lost to follow-up, withdrawal of consent or incorrect enrollment, i.e. the subject did not meet the required eligibility criteria for the study at the time of inclusion.

Data capture

At the first time point of data capture, the following baseline data was to be collected:

- Visit date.
- Date of informed consent by the patient and/or caregiver.
- Gender.
- Date of birth.
- Race.
- CAPS subtype (FCAS, MWS or NOMID/CINCA, or combination of subtypes.
- Date of onset of CAPS symptoms.
- Date of CAPS diagnosis.
- Date of initiation of Kineret treatment.
- Date of initiation of Kineret treatment with graduated syringe.
- Kineret dose administered (mg/day) and body weight.
- History of other IL-1 blocking treatment.
- History of malignancies.

Date of birth, date of onset of CAPS symptoms and date of CAPS diagnosis were to be used to calculate age, disease duration and time since onset of CAPS symptoms.

The following data was to be collected at each post-Baseline visit:

- Visit date.
- Occurrence of AEs related to serious infections, malignancies, ISRs and allergic reactions.
- Medication errors, including re-use of the syringe.
- Kineret dose administered (mg/day) and body weight.
- Start and stop date of any temporary discontinuation of Kineret treatment.
- Start date for permanent discontinuation of Kineret treatment.
- Reason for temporary or permanent discontinuation of Kineret treatment, including but not limited to, any AE leading to treatment discontinuation.
- Transfer to any another IL-1 blocking treatment at discontinuation of Kineret treatment.

Pre-specified adverse events

For patients who have already used the Kineret graduated syringe before enrollment into the study, pre-specified non-serious AEs were collected from when the patient has signed the (informed consent form) ICF until the last Year 3 data entry. For patients who have not used the Kineret graduated syringe previously, the pre-specified non-serious AEs were collected from the first day that the patient

use the Kineret graduated syringe after ICF until the last Year 3 data entry. For patients who permanently discontinued Kineret treatment before the Year 3 data entry, any pre-specified nonserious AEs occurring within 3 days after the last dose were collected.

The pre-specified AEs (serious infections, new malignancies, ISRs and allergic reactions), both non-serious and serious, related and not related to Kineret, were reported during the study period as part of the primary endpoint of the study, see Section 6.2.3 (Main results).

The following pre-specified AEs, both non-serious and serious, related and not related to Kineret, reported during the study period were to be captured in the study database.

- Serious infections.
- Malignancies.
- ISRs.
- Allergic reactions.

All other (non-pre-specified) non-serious AEs were to be reported through routine pharmacovigilance procedures and not via the (electronic case report form) eCRF.

All SAEs were to be entered into the study database (eCRF) as well as the Sobi safety database and required reconciliation.

Medication errors

Medication errors were to be collected by asking about the presence of infections of the injection site, re-use of syringe, overdosing, under-dosing or other medication errors since the previous recording. Other medications errors were to be collected by asking the patient if they have had any other problems with using the syringe or administering the right dose. All medication errors were to be reported as AEs, independent of outcome.

Kineret dose

To calculate the Kineret dose in mg/kg/day, the Kineret dose (mg/day) was to be recorded at Baseline visit and on visits at year 1, 2 and 3 (and if applicable, at 6 months interval visits and/or at the time of permanent discontinuation of Kineret treatment).

Body weight

The body weight was to be recorded at Baseline visit and on visits at year 1, 2 and 3 (and if applicable, at 6 months interval visits and/or at the time of permanent discontinuation of Kineret treatment). Body weight was used to calculate the administered Kineret dose in mg/kg/day.

Permanent discontinuation of Kineret treatment

Permanent discontinuation of Kineret treatment was to be recorded, including the reasons for the permanent discontinuation and the date of the last dose taken. The primary reason for the treatment discontinuation was classified as one of the following:

- AE (to be specified).
- Other reason (to be specified).

In case the primary reason for the treatment discontinuation is an AE, the AE was to be recorded in the study database, even if it is not one of the pre-specified AEs.

Patients registered as having permanently discontinued Kineret treatment were not to re-enter the study even if the Kineret treatment was re-instituted.

Temporary discontinuation of Kineret treatment

Temporary discontinuation of Kineret treatment was to be recorded, including the reasons for the temporary discontinuation and the start date of the temporary discontinuation. In addition, the date of the re-institution of the Kineret treatment was to be recorded. The primary reason for the temporary treatment discontinuation was classified as one of the following:

- AE (to be specified).
- Other reason (to be specified).

In case the primary reason for the temporary treatment discontinuation was an AE, the AE was to be recorded in the study database, even if it is not one of the pre-specified AEs.

Patients transferred to another IL-1 blocking treatment

If the patient was transferred to another IL-1 blocking treatment after the discontinuation of the Kineret treatment, the IL-1 blocking treatment was to be recorded together with the date of the discontinuation. The IL-1 blocking treatment was then classified as one of the following:

- Canakinumab.
- Other IL-1 blocking treatment (to be specified).

CHMP comments

The study design was a multicenter, non-interventional, non-controlled trial, that collected prospective data in patients with a diagnosis of CAPS, and treated with anakinra syringe according to body weight. Follow up was 3 years. Data were collected every 6^{th} or 12^{th} Months.

The study was conducted with a primary objective to evaluate the safety, with focus on serious infections, malignancies, ISRs, allergic reactions and medication errors, including re-use of the syringe. The secondary objective was to evaluate the Kineret dosage over time, hereunder to assess the proportions of patients who discontinue Kineret treatment, and the proportion of patients who are transferred to another IL-1 blocking treatment.

The above defined endpoints match this purpose of both the primary and secondary study objectives.

6.1.2. Setting

Patients were enrolled according to the approved treatment recommendation for CAPS in the SmPC (Section 4.1, Therapeutic indications and 4.2 Posology and method of administration). If the patient received Kineret outside of the approved treatment recommendations for CAPS (e.g. patient treated despite contraindication) the patient was not to be enrolled in this study. CAPS patients eligible for inclusion in the study could either already be using the Kineret graduated syringe or just about to start Kineret treatment with the graduated syringe.

The study inclusion criteria that applied at enrollment were:

1) Informed consent by the patient and/or caregiver;

2) Kineret treatment according to the SmPC, as confirmed by the investigator.

No specific exclusion criteria were applied. Hence the study population should be representative of the population of CAPS patients treated in routine clinical care.

Clinical sites and investigators treating CAPS paediatric and adult patients were identified via the Eurofever registry, organized and maintained by PRINTO. By September 2013, 225 CAPS patients had been enrolled in the Eurofever registry. The site feasibility was done by the Pediatric Rheumatology International Trials Organization (PRINTO) by asking a number of investigators in the Eurofever registry for their interest and capability to recruit patients in this non-interventional PASS.

The selection of participating countries, clinical sites and investigators was based on;

- Availability of the Kineret graduated syringe (Kineret 100 mg/0.67 ml solution for injection in pre-filled syringe) during the period of study enrollment;
- Location of larger clinical sites treating CAPS patients with Kineret.

The study could include both pediatric and adult patients.

CHMP comments

The setting is well described and achieves the best opportunities to include as many individuals with a diagnosis of CAPS as possible. Due to the rarity of the disease, it can be difficult to include enough patients, however, as the Eurofever registry has 225 CAPS patients registered, it should be possible to include more individuals with a diagnosis of CAPS. Therefore, the MAH is asked to explain why only 12 out of the 225 individuals with CAPS were included in this study. **(see other concerns sections (OC))**

6.1.3. Variables

Primary endpoints

The primary endpoints of the study were:

- Rate of serious infections;
- Rate of new malignancies;
- Rate of injection side reactions (ISRs);
- Rate of allergic reactions;
- Rate of medication errors including re-use of syringe.

Medication errors were to be further classified as infections of the injection site, re-use of syringe, over- or under-dosing, or other medication errors.

The rates were calculated for events which are treatment-emergent, defined as events which start after the date of the first dose of Kineret using the graduated syringe and after the date of informed consent (i.e., after the later of the two dates). The events which start after the Kineret treatment had been terminated, start during a temporary discontinuation of Kineret treatment or after the completion of the study are not be included for the calculation of the rates.

The rates were calculated as the number of events divided by the total cumulative exposure to Kineret treatment in the study (patient years). The cumulative exposure to the Kineret treatment were calculated for the period corresponding to the evaluation period of the treatment-emergent AEs, i.e. from the date of the first dose of Kineret using the graduated syringe or date of informed consent (later of the two dates) until the date of temporary discontinuation of the Kineret treatment or study completion (first of the two dates). The period during which Kineret treatment had been temporarily discontinued was excluded from the cumulative exposure.

Secondary endpoints

The secondary endpoints of the study were:

- Kineret dose (mg/kg/day) at Baseline visit and at year 1, 2 and 3.
- Proportion of patients who discontinued Kineret treatment permanently including the reasons for the permanent discontinuations.
- Proportion of patients who discontinued Kineret treatment temporarily including the reasons for the temporary discontinuations.
- Proportion of patients who were transferred to another IL-1 blocking treatment.

CHMP comments

Concerning the outcome new malignancies, it is of relevance to make a longer follow up than 3 years. Most malignancies have a long induction period, and therefore, they do not necessarily appear before the end of this study. An analysis with an outcome of malignancy, can with advantage include time with temporarily discontinuation, due to long induction periods of most cancers. However, in this setting, temporarily discontinuation was excluded from the categorization of time in exposure. This is of relevance in all the immediate appearing outcomes (including rate of serious infections, rate of injection side reactions, rate of allergic reactions, and rate of medication errors including re-use of syringe), but not concerning the rate of malignancies. Thus, due to safety concerns about appearance of new cancers, which must be of great importance in the safety follow up perspective, the MAH should explain how this safety concern about risk of malignancies will be followed in future safety studies. **(OC)**

Of note, the above described secondary endpoint "Kineret dose at Baseline and visit 1, 2 and 3", may more adequately be described as a 'variable' rather than an 'endpoint' – this will however, not be pursued.

6.1.4. Data sources

The PRINTO network organized the data collection. The source for all data was the patients' medical records. The investigators verified the transfer of relevant prospective data to the eCRF designed for the study in a web-based data entry tool. English was the official language used for all forms completed by the investigators.

CHMP comments

The MAH has sufficiently described the data sources.

6.1.5. Bias

The uncontrolled study design was deemed acceptable for this non-interventional PASS. Accordingly, the study design carried the general limitations inherent in an uncontrolled design, e.g., statistical inference and generalizability. More particularly, the study design allowed patients previously treated with Kineret to take part in the study. This might potentially give rise to bias, since patients who discontinued Kineret treatment early might be underrepresented.

CHMP comments

The design allowed patients previously treated with Kineret to take part in the study. This is also of importance according to both the primary and secondary endpoint. It is a baseline characteristic, that should be measured, and as a minimum be reported in the results section, to enable to clarify if it has an impact on the results of the analyses. In the above sections, it is not specified how this was handled and therefore, the MAH is asked to clarify how they handled patients that previously used Kineret, and how this possibly affected the results of the analyses. The MAH should also inform

how the timing and duration of the patients were treated with Kineret before entry into this study **(OC).**

6.1.6. Study size

The planned duration of the enrollment period was 1 year and the study was estimated to enroll 15 to 20 CAPS patients. The study could include both paediatric and adult patients.

CHMP comments

The study was estimated to enroll 15 to 20 CAPS patients. The MAH is asked to clarify what this estimated number of CAPS patients, is based on. **(OC)**

6.1.7. Data transformation

The data was collected on-line via the secured PRINTO website on a dedicated server. Technical management of the database was handled by PRINTO. The web system has been accessible only to authorized personnel through unique individual usernames and passwords to allow record traceability. The completed eCRFs are the sole property of the Giannina Gaslini Institute and should not be made available in any form to third parties, except for authorized representatives of appropriate Regulatory Authorities, ECs and if applicable a monitor appointed by SOBI.

Investigators' access to the eCRFs has been restricted to the patients under their care. The data was cleaned and remotely monitored by PRINTO on an ongoing basis to check the accuracy of data. If necessary, PRINTO asked for additional or more precise information from the sites.

The data management process was documented in the data management plan.

CHMP comments

The MAH has sufficiently described the process for data transformation.

6.1.8. Statistical methods

Main summary measures

The presence of serious infections, new malignancies, ISRs, allergic reactions and medications errors are presented as rates, calculated as the number of events divided by the total cumulative exposure to Kineret treatment in the study (patient years). 95 % confidence intervals are calculated for the rate of each of the five event types. In addition to the rate, the distribution of the severity, relationship to Kineret treatment and seriousness are presented.

Main statistical methods

All enrolled patients were included in the analysis. The analyses were conducted primarily for the total study population. In addition, the subgroup of patients who were already using Kineret at baseline and the subgroup who initiated Kineret treatment at baseline were to be analysed separately. In the primary analyses, the analysis period covered the time from Baseline visit until the last visit. For the rate of malignancies, a secondary analysis was conducted by including the time from the initiation of Kineret treatment until the last study visit.

All endpoints were summarized using 95% confidence intervals and descriptive statistics. No formal statistical comparison was to be done.

Missing values

For incompletely recorded dates, a missing day was replaced by 15 and a missing month by 6. However, in case of missing data on the date of onset of an AE, if it was not obvious whether the AE is treatment-emergent or not, the AE was classified as treatment-emergent.

Sensitivity analyses

No sensitivity analyses have been planned for this study.

Amendments to the statistical analysis plan

A separate statistical analysis plan SAP was written for this study, there were no amendments to the original SAP.

CHMP comments

Overall, the MAH has sufficiently described the statistical methods used in the study.

In the section above, it is stated that a secondary analysis was conducted, which included the time from initiation of Kineret treatment until the last study visit. The MAH is asked to clarify if the analyses include time of Kineret treatment before entry into the study, and how long these periods of exposures were concerning the exposed individuals (see previous **OC**). As the design is setup now, regarding the time of exposure with Kineret, it is impossible to rule out a cancer risk on the long-term basis.

6.1.9. Quality control

The collection of data followed the routine clinical care in treatment of the patients. The source for all collected data was the patients' medical records. It was the responsibility of the investigator to ensure completion and to review and approve all eCRFs. At all times, the investigator had the final responsibility for the accuracy and authenticity of all patient data entered into the eCRFs.

The web system used for data collection provided validation control and it is not expected to have missing data related to mandatory questions. However, all the data entered into the web system was reviewed by the PRINTO Coordinating Centre for completeness and accuracy.

PRINTO personnel checked the completeness and coherence of the data and if any relevant query was raised during the check, PRINTO was to contact the investigator to verify the correctness and consistency of the data and retrieve missing data if available. In case of discrepancies, specific queries were to be issued and solved through the Query Ticket system.

Data could be updated or modified only upon request to the PRINTO helpdesk. Issues that arise and that were not possible to resolve within the entry tool may be managed by a site review. Data were validated on an ongoing basis, and, a specific validation process was applied. All validation of data was described in detail in the DMP.

CHMP comments

The MAH has sufficiently described the processes for data quality control.

6.2. Results

6.2.1. Participants

All CAPS patients treated at the selected sites and meeting the inclusion criteria were eligible for entry. The duration of the enrollment period was 1 year and 11 months and the study enrolled a total of 12

CAPS patients. Table 1 presents the characteristics of the study patient population at the Baseline visit. The median (Q1; Q3) age at baseline was 25.3 (5.4; 50.2).

Of the 12 patients, 9 (75 %) were males and 3 (25%) females. 8 (66.6%) patients had been diagnosed with MWS, 2 (16.7%) with FCAS and 2 (16.7%) with NOMID/CINCA. The median (Q1; Q3) age at CAPS onset vas 2.5 (0.0; 11.4) years while the median (Q1; Q3) age at CAPS diagnosis was 24.4 (5.0; 47.2) years. The median (Q1; Q3) disease duration (years from onset to Baseline visit) was 15.5 (2.5; 45.2) years. There were no patients with history of malignancies.

Table 1 Characteristics of the study patient population at Baseline visit

Patients at Baseline visit, n	12
Gender, n (%)	
Male	9 (75.0)
Female	3 (25.0)
Ethnicity, n (%)	
White	10 (83.3)
Black	2 (16.7)
Age at Baseline visit, years	
median (1^{st}-3^{rd} quartile)	25.3 (5.4-50.2)
min; max	1.4; 54.9
CAPS subtype, n (%)	
FCAS	2 (16.7)
MWS	8 (66.6)
NOMID/CINCA	2 (16.7)
Age at CAPS onset, years	
median (1^{st}-3^{rd} quartile)	2.5 (0.0-11.4)
min; max	0.0; 29.5
Age at CAPS diagnosis, years	
median (1^{st}-3^{rd} quartile)	24.4 (5.0-47.2)
min; max	0.6; 54.6
Disease duration (years from onset to Baseline visit)	
median (1^{st}-3^{rd} quartile)	15.5 (2.5-45.2)
min; max	1.4; 51.3
Patients with history of malignancies, n (%)	0

Abbreviations: n, Number. Percentages are based on the total number of patients at Baseline visit.

CHMP comments

Due to the rarity of this disease, it was expected that it could be difficult to include enough patients in this study. Twelve (12) patients are not many, and due to small number bias, it can be difficult to evaluate the purpose of this study properly. Within the Eurofever Registry, there are 225 CAPS patients available. The MAH is asked, if there are any plans of keeping this safety study running, with a purpose to secure longer follow periods, and to include more patients. **(OC)**

6.2.2. Descriptive data-Kineret treatment at Baseline

Table 2 presents the patients characteristics with regards to Kineret treatment at Baseline visit. Of the 12 patients included in this study, 1 (8.3%) patient initiated Kineret treatment at baseline and 11 (91.7%) patients were already using Kineret graduated prefilled syringe at baseline. 3 (25%) patients

had a history of using other IL-1 blocking treatments. The median (Q1; Q3) Kineret dose at baseline was 1.7 (1.4; 2.1) mg/kg/day; with 7 (58.3%) patients taking less than 2 mg/kg/day and 5 (41.7%) patients between 2 and 3 mg/kg/day.

Table 2 Study population characteristics with regards to Kineret treatment at Baseline visit

Patients at Baseline visit, n	**12**
Patients already using Kineret at Baseline, n (%)	11 (91.7)
Patients initiating Kineret at Baseline, n (%)	1 (8.3)
Patients with history of other IL-1 blocking treatment, n (%)	3 (25.0)
Kineret dose, mg/kg/day	
All patients, n	12
median (1st-3rd quartile)	1.7 (1.4-2.1)
min; max	1.1; 2.5
Patients already using Kineret at baseline, n	11
median (1st-3rd quartile)	1.7 (1.2-2.0)
min; max	1.1; 2.3
Patients initiating Kineret at baseline, n	1
median (1st-3rd quartile)	2.5
min; max	2.5
Kineret dose by category, n (%)	
Below 2 mg/kg/day	7 (58.3)
Between 2 and 3 mg/kg/day	5 (41.7)
Weight, kg	
All patients, n	12
median (1st-3rd quartile)	61.5 (18.9-86.9)
min; max	8.1; 128.0
Patients already using Kineret at baseline, n	11
median (1st-3rd quartile)	63.0 (25.0-87.8)
min; max	10.7; 128.0
Patients initiating Kineret at baseline, n	1
median (1st-3rd quartile)	8.1
min; max	8.1

Abbreviations: n, Number
Percentages are based on the total number of patients at Baseline visit.

CHMP comments

The majority (11) of all (12) included patient were already in treatment with Kineret at baseline, and only one patient initiated Kineret treatment at the beginning of this study. This further emphasizes the need for clarification of the time of exposure with Kineret at baseline of this study.

6.2.3. Main results

Outcome data

All 12 patients enrolled in this study have been included in the analysis of results.

Primary endpoint

All treatment emergent AEs (as defined in Section 8.3.1) reported during the study period are presented in Table 3.

A total of 7 treatment emergent AEs were reported during a total of 26.1 patient years of treatment, with an overall rate of 26.8 (95% CI 4.2-169.6) per 100 patient years. All treatment emergent AEs were observed in 1 patient and considered unrelated to Kineret by the investigator. 2 AEs were

considered serious treatment emergent AEs due to hospitalization (1 tonsillitis and 1 urinary tract infection.

No AE were considered severe, 6 (85.7%) AEs were considered of moderate severity and 1 (14.3%) was considered of mild severity, see Table 4.

Table 3 All treatment-emergent adverse events reported during the study period

Total treatment-emergent adverse events	Total, e(%)[n] [a]	Related, e (%)[n][a]	Un-related, e (%)[n][a]
Any treatment-emergent AE	7 (100.0)[1]	0[0]	7 (100.0)[1]
Severe	0[0]	0[0]	0[0]
Moderate	6 (85.7)[1]	0[0]	6 (85.7)[1]
Mild	1 (14.3)[1]	0[0]	1 (14.3)[1]
Any serious treatment-emergent AE	2 (28.6)[1]	0[0]	2 (28.6)[1]
Death	0[0]	0[0]	0[0]

Percentages are based on the total treatment-emergent adverse events.
[a]e(%)[n], n: Number of patients with at least an event, e: Number of events.

Table 4 All pre-specific treatment-emergent adverse events by severity reported during the study period

Type of event	Total		
	Events[a]	Patient years[b]	Rate[c] (95% CI)
Infections			
Mild	1	26.1	3.8 (0.6-24.2)
Moderate	6	26.1	23.0 (3.6-145.4)
Severe	0	26.1	0.0
Malignancies (during the study period)			
Mild	0	26.1	0.0
Moderate	0	26.1	0.0
Severe	0	26.1	0.0
All malignancies (including the time from the initiation of Kineret treatment)[d]			
Mild	0	34.9	0.0
Moderate	0	34.9	0.0
Severe	0	34.9	0.0
Injection Site Reactions			
Mild	0	26.1	0.0
Moderate	0	26.1	0.0
Severe	0	26.1	0.0
Allergic reactions			
Mild	0	26.1	0.0
Moderate	0	26.1	0.0
Severe	0	26.1	0.0
Medication errors including re-use of syringe			
Mild	0	26.1	0.0
Moderate	0	26.1	0.0
Severe	0	26.1	0.0

Abbreviation: 95% CI, 95% Confidence Interval.
A patient can contribute with multiple adverse events.
[a]Only adverse events occurring during Kineret exposed periods are counted.
[b]Only time during periods with Kineret treatment are counted. The period during which Kineret treatment has been temporarily discontinued is excluded from the cumulative exposure.
[c]Incidence rate per 100 patient years; number of events/∑patient time.
[d]For this analysis are considered all malignancies and the time from the initiation of Kineret treatment until the last study visit

Table 5 presents a detailed list of all pre-specified treatment emergent AEs reported during the study. All 7 reported AEs were classified as infections: 5 (71.4%) tonsillitis, 1 (14.3%) urinary tract infection and 1 (14.3%) upper respiratory tract infection. All 7 pre-specified treatment-emergent AEs were observed in 1 patient.

Table 5 Details of all pre-specific treatment-emergent adverse events reported during the study period

Pre-specified treatment-emergent adverse events	e(%)[n]
Total infections [a],	7(100.0)[1][c]
Urinary tract infection	1 (14.3)[1]
Upper respiratory tract infection	1 (14.3)[1]
Tonsillitis	5 (71.4)[1]
All malignancies [b]	0[0]
Injection Site Reactions	0[0]
Allergic reactions	0[0]
Medication errors including re-use of syringe	0[0]
Any other event for which Kineret has been discontinued	0[0]

[a]Percentages are based on the total number of infections.
[b]Percentages are based on the total number of malignancies.
[c]e(%)[n], n: Number of patients with at least an event, e: Number of events

Secondary endpoints

Table 6 presents the characteristics of the study patient population during follow-up period (1, 2, 3 and >3 years). The median (Q1; Q3) Kineret dose at Year 1, Year 2, Year 3 and Year >3 was 1.6 (1.5;2.3), 1.6 (1.2;2.0), 2.6 (1.7; 3.6) and 1.4 (1.1; 2.0) mg/kg/day, respectively.

In total, 6 (50%) patients permanently discontinued treatment with Kineret. Of those, 2 patients discontinued at Year 1; 3 patients at Year 2; and 1 patient at Year >3; there were no permanent discontinuations of Kineret at Year 3. The reason for permanent discontinuation included change to another IL-1 blocking treatment (5 patients), inefficacy (1 patient) and non-compliance (1 patient). All 5 patients that transferred to another IL-1 blocking treatment reported to have switched to canakinumab.

Only 1 patient temporarily discontinued treatment with Kineret; the discontinuation occurred during Year 2, due to non-compliance. The patient discontinued treatment with Kineret after the laboratory results indicated that the patient had developed neutropenia. The AE was assessed as non-serious and the Kineret dose was adjusted. However, after registering the AE the laboratory results were reviewed and the investigator confirmed that the patient did not had neutropenia as previously reported, as consequence the treatment with Kineret was reintroduced in the original dose.

Table 6 Characteristics of the study patient population during follow-up (during year[a] 1, 2, 3 and Year> 3[b])

	Total (N=12)	Year 1 (N=12)	Year 2 (N=10)	Year 3 (N=7)	Year >3 (N=6)
Total number of patients, n	12	9	10	2	6
Kineret dose[c], mg/kg/day					
median (1st-3rd quartile)	N/A	1.6 (1.5-2.3)	1.6 (1.2-2.0)	2.6 (1.7-3.6)	1.4 (1.1-2.0)
min; max		1.1; 3.9	1.0; 4.4	1.7; 3.7	1.0; 3.2
Weight[d], kg					
median (1st-3rd quartile)	N/A	63.0 (12.4-81.9) 9.8;	75.2 (50.4-102.5) 11.4;	67.0 (14.1-120.0) 14.1;	90.4 (50.5-105.0) 15.5;
min; max		123.9	121.1	120.0	117.0
Patients with permanent discontinuation of Kineret, n (%)	6 (50.0)	2 (22.2)	3 (30.0)	0	1 (16.7)
Reason for permanent discontinuation of Kineret, n (%)	7 (58.3)	2 (22.2)	3 (30.0)	0	2 (33.3)
Inefficacy	1 (8.3)	0	0	0	1 (16.7)
Other-non-compliance	1 (8.3)	0	1 (10.0)	0	0
Other-change to Canakinumab	5 (41.7)	2 (22.2)	2 (20.0)	0	1 (16.7)
Patients with temporary discontinuation of Kineret, n (%)	1 (8.3)	0	1 (10.0)	0	0
Reason for temporary discontinuation of Kineret, n (%)	1 (8.3)	0	1 (10.0)	0	0
Other-non-compliance	1 (8.3)	0	1 (10.0)	0	0
Patients transferred to another IL-1 blocking treatment, n (%)					
Canakinumab	5 (41.7)	2 (22.2)	2 (20.0)	0	1 (16.7)
Other	0	0	0	0	0

Abbreviations: N, Number of patients ongoing; n, number of patients with visits

Percentages are based on the total number of patients in each year.

[a]Year 1,2,3 and Year > 3 represents the intervals in which the visit date occurs: year 1 is the interval up to and including 12 months after Baseline visit, year 2 is the interval from > 12 months

after the Baseline visit up to including 24 months after Baseline visit, etc.

[b]To account for patients who stayed in the study for more than three years, a Year > 3 is included (all patients, and all visits are thus covered by the table).

[c]If patients have several visits in a year, the mean dose for each patient is calculated.

[d]If patients have several visits in a year, the mean weight for each patient is calculated

CHMP comments

According to Table 5 above, all the 7 pre-specified reported adverse events during the study period, were infections. Due to the known adverse event of Kineret inducing neutropenia, it is considered of interest to know the level of neutrophil granulocytes prior to and during the time with infections. Please provide data if available. **(OC)**

There were no reports of the other pre-defined primary outcomes (i.e. malignancies,, allergic reactions and medication errors, including re-use of the syringe) during the study period. Though reassuring, it is speculated if lack of cases of these other pre-defined primary endpoints may be explained by small number of patients in this study.

According to Table 6, it seems like a majority of the patients included gained weight during the study period. This is a bit reassuring. The MAH is asked to discuss if 'Weight gain' may be an adverse event to Kineret and whether this has been observed in other clinical studies. **(OC)**

6.2.4. Other analyses

Since 11 patients were treated with Kineret graduated prefilled syringe prior to study start, further analysis was done in order to calculate the total Kineret treatment duration (see Table 7).

All 12 patients were included the analysis. The median (min;max) Kineret treatment duration with Kineret was 1154.5 (167;2556) days (approximately 3.1 years).

Table 7 Kineret treatment duration of anakinra

	Anakinra (N = 12)
Duration of exposure (days)	
N	12
Mean (SD)	1266.3 (752.2)
Median (min, max)	1154.5 (167, 2556)
Total exposure (days)	11 034.4

Abbreviations: N, Number; n, Number; SD, Standard deviation. Treatment duration includes also the period prior to baseline when anakinra was used. The period during which anakinra treatment has been temporarily discontinued is excluded from the cumulative exposure time.

CHMP comments

Table 7 gives information about the duration of treatment with Kineret. This includes the 11 patients who were previously treated with Kineret. The design allowed patients previously treated with Kineret to take part in the study, and this is accepted, however, the MAH should present information regarding the timing and duration of previous Kineret-treatment, and clarify, how this previous treatment has an impact on the estimated endpoints of interest. Please see list of questions **(OC)**.

6.2.5. Adverse events/adverse reaction

Since the primary objective of the study was to evaluate the safety of Kineret treatment in CAPS patients, all AE results are described in the Section 6.2.3.

CHMP comments

Please see CHMP comments regarding Main results above.

6.3. Discussion

This PASS study was conducted to address the pre-specified risks from the RMP that included serious infection, malignancies, ISRs and allergic reactions.

The MAH has performed a well conducted multi-centre, non-interventional, non-controlled trial, that samples data prospectively, and that on this background has tried to measure all relevant issues. The primary objective was to evaluate the safety of Kineret treatment in CAPS patients with focus on serious infections, malignancies, ISRs, allergic reactions and medication errors, including re-use of the syringe.

Overall, there are no results that lead to great safety concerns. However, some Other Concerns needs to be addressed by the MAH.

As reported in the results section of the Sobi.ANAKIN-201 study report, there were only included 12 patients. As CAPS is an extremely rare disease it was expected that it could be difficult to include a sufficient number of patients. As the Eurofever registry included 225 CAPS patients, it should be possible to include more individuals with a diagnosis of CAPS. Therefore, the MAH is asked to explain why only 12 out of the 225 individuals with CAPS were included in this study. **(OC)**

Concerning the outcome 'New malignancies', it is of relevance to make a longer follow up period than 3 years. Most malignancies have a long induction period, and are also a rare outcome, and therefore, they do not necessarily appear before the end of the present study. Thus, due to safety concerns about appearance of new cancers, which must be of great importance in the safety follow up perspective, it would be of relevance for the MAH to clarify how this safety concern is planned to be followed in future safety studies. **(OC)**

Further, the study design allowed patients previously treated with Kineret to take part in the study. This is also of importance according to both the primary and secondary endpoints and as such endorsed. It is a baseline characteristic, that should be measured, and as a minimum be reported in the results section, to enable to clarify if it has an impact on the results of the analyses. As neither the study protocol nor the study report provides information of how this was handled, the MAH is asked to clarify how they handled patients that previously used Kineret, and how it possibly affected the results of the analyses. It would especially be of interest to report how the duration and timing of treatment with Kineret before entry into this study, and clarify how this influences the results. **(OC)**

As already mentioned, it would have been optimal if the study included more participants. The study was estimated to enrol 15 to 20 CAPS patients, and included only 12 patients. The MAH is asked to clarify what this estimated number of CAPS patients, is based on, and if there are any plans of keeping this safety study running, with a purpose to secure longer follow periods, and to include more patients. **(OC)**

Furthermore, and due to small number bias, it can be difficult to evaluate the purpose of this study properly. Therefore, the MAH additionally is asked, if there are any plans of keeping this safety study running, with a purpose to secure longer follow periods, and to include more. **(OC)**

One of the primary objectives of the study was to evaluate the safety of Kineret treatment and the risk of serious infections. The study reports 7 pre-specified adverse events classified as infections (i.e. 1 mild, and 2 moderate infections). Due to the known adverse event of Kineret inducing neutropenia described within the SmPC, it is considered of interest to know the level of neutrophil granulocytes prior to and during the time with infections. **(OC)**

During the study, it was noted that the median weight at baseline was 63.0 kg and increased to a median of 90.4 kg at study end. While it is expected that the included children will increase in weight during the 3-years study period, it would not be expected for the adults. According to the SmPC, this is not a known adverse event. The MAH is asked to discuss if 'Weight gain' may be an adverse event to Kineret and whether this has been observed in other clinical studies. **(OC)**

7. Risk management plan

The MAH submitted an updated RMP version 5.4 with this application, with data lock point (DLP) 01 May 2020, signed 17 November 2020. The (main) proposed RMP changes were the following:

- The PASS in CAPS (Sobi.ANAKIN-201) has been completed. The Data lock point of the RMP was updated from May 1, 2018 to May 1, 2020. During this time period the anaSTILLs study (Sobi.ANAKIN-301) was completed and therefore part II and VI of the RMP have been updated with information from this study. In addition, the exposure sections have been updated due to the updated Data lock point as well as the follow-up forms in Annex 4 (minor modifications).

The currently approved RMP version is 5.3, approved in procedure EMEA/H/C/000363/II/0073 (opinion date 14 May 2020).

PART II: SAFETY SPECIFICATION

Part II Module SIII.2 – Clinical trial exposure

The subsection "Clinical trial safety data in Still's disease" was updated with information from a completed study "anaSTILLs" (Sobi.ANAKIN-301), a randomized, double-blind, placebo-controlled multicenter phase 3 efficacy and safety study in pediatric and adult patients with Still's disease (SJIA and AOSD): Totally 12 patients received study treatment, 6 patients received anakinra and 6 patients received placebo. One of the patients in the placebo group was diagnosed with lymphoma rather than Still's disease. The study duration was 16 weeks which included a 12-week treatment period and a 4-week follow-up period.

Exposure data was updated to reflect estimated exposure in clinical trials until DLP (6 480 PY).

Part II: Module SIV - Populations not studied in clinical trials

The Table "Exposure of special populations included or not in clinical trial development programmes" was adjusted to reflect data from Sobi.ANAKIN-301 and updated post marketing experience.

Part II: Module SV - Post-authorisation experience

Exposure data was updated to reflect estimated exposure in post marketing use until DLP (126 789 PY).

Part II: Module SVII - Identified and potential risks

Throughout this section, reference to Sobi.ANAKIN-301 was added where relevant, and reference to ongoing PASS (Sobi.ANAKIN-201) was removed. These additions do not significantly change the characterisations of the risks.

Part II: Module SVIII - Summary of the safety concerns

Summary of safety concerns remains unchanged upon completion of the PASS Sobi.ANAKIN-201, since the results of the PASS did not provide significant new information to any of the risks due to the low power of the study.

The safety profile of the 12 patients with CAPS included in the study did not differ markedly from the safety profile of the overall Kineret patient population, but extrapolation of results from this study to the entire CAPS subpopulation should be done with caution due to the limitations of the evidence. Thus, it is agreed that the safety concerns remain unchanged.

The unchanged summary of safety concerns is given below.

Important identified risks	Injection site reactions (ISRs)
	Immunogenicity
	Serious infections
	Neutropenia
	Allergic conditions
	Hepatic disorders
Important potential risks	Malignancies
	Macrophage activation syndrome (MAS)
	Medication errors including reuse of syringe
	Pulmonary events (Interstitial lung disease, pulmonary hypertension, alveolar proteinosis)
Missing information	Pregnant women
	Lactating women
	Use in patients with chronic infections
	Use in patients with pre-existing cancers
	Interaction with living vaccines

PART III: PHARMACOVIGILANCE PLAN

III.2 Additional pharmacovigilance activities

Reference to PASS Sobi.ANAKIN-201 was removed from the pharmacovigilance plan. There are no longer any ongoing additional pharmacovigilance activities.

III.3 Summary table of additional pharmacovigilance activities

The table was deleted from the RMP, as no additional pharmacovigilance activities remain.

Questions were raised, based on the assessment of the PASS results, which potentially impact on the pharmacovigilance plan, i.e. a clarification is sought on the future follow up of the IPR "malignancies". A final conclusion on the pharmacovigilance plan is therefore conditional on the outcome of the discussion within this procedure.

PART V: RISK MINIMISATION MEASURES

V.3 Summary of risk minimisation measures

Reference to PASS Sobi.ANAKIN-201 was removed as additional pharmacovigilance activity from the following risks: Injection site reactions, Serious infections, Allergic conditions, Malignancies, Medication errors including reuse of syringe.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

The summary was updated in line with the changes outlined above.

ANNEXES

Annex 2 - updated to reflect the completed status of PASS Sobi.ANAKIN-201.

Annex 3 – the protocol of PASS Sobi.ANAKIN-201 was deleted.

Annex 8 – updated to reflect changes in RMP version 5.4.

7.1. Overall conclusion on the RMP

☒ The changes to the RMP version 5.4 are acceptable.

8. Request for supplementary information

8.1. Major objections

Clinical aspects

None.

RMP aspects

None.

8.2. Other concerns

Clinical aspects

1. Within the Eurofever registry, there are 225 CAPS patients available but the MAH has only included 12 patients in the present study. Please explain why only 12 of the 225 patients were included in the present study.
2. Due to the long induction period and the rare occurrence of malignancies, the evaluated association to Kineret (anakinra) treatment of this endpoint, in the present study, was not expected to find any significant increased risk. The MAH is asked to discuss how to address this issue further.
3. The design allowed patients previously treated with Kineret to take part in the study. This is accepted, however, the MAH should present information regarding the timing and duration of previous Kineret-treatment, and clarify, how this previous treatment has an impact on the estimated endpoints of interest.
4. The study was estimated to enroll 15 to 20 CAPS patients. The MAH is asked to clarify what this estimated number of CAPS patients, is based on.
5. Due to the risk of small number bias the MAH is asked, if there are any plans of keeping this safety study running, with a purpose to secure longer follow periods, and to include more patients.

6. All the observed 7 pre-specified reported adverse events during the study period, was infections. Due to the known adverse event of Kineret inducing neutropenia, it is considered of interest to know the level of neutrophil granulocytes prior to and during the time with infections. Please provide data if available.
7. The majority of patients included in the study gained weight during the study period. According to the SmPC, this is not a known adverse event. The MAH is asked to discuss if 'Weight gain' may be an adverse event to Kineret and whether this has been observed in other clinical studies.

RMP aspects

None.

9. Assessment of the responses to the request for supplementary information

9.1. Other concerns

Clinical aspects

Question 1:

Within the Eurofever registry, there are 225 CAPS patients available but the MAH has only included 12 patients in the present study. Please explain why only 12 of the 225 patients were included in the present study.

MAH's response:

CAPS is a rare disease, which indeed limits the size of the population that could be included in the study. The Eurofever registry enrolled 225 patients (PRINTO Newsletter 2013)[1] with a validated and confirmed diagnosis of CAPS. Information on treatment was available in 94 patients[2].

Among the 94 patients with CAPS, that were analyzed in the Eurofever registry, 86 received at least one anti-IL-1 agent. 61 patients were under anakinra treatment[2], which was also one of the Sobi.ANAKIN-201 study eligibility criteria.

The Eurofever registry is an international initiative which encompasses auto-inflammatory data from 33 countries world-wide, whereas the Sobi.ANAKIN-201 study was limited to the EU. The feasibility study to identify recruiting sites was primarily targeted to UK, France, Germany, the Netherlands, and Italy. This explains a lower number of patients with CAPS.

Furthermore, only patients who provided their consent and who met the eligibility criteria could enter the study, and patients who received Kineret outside of the approved treatment recommendations for CAPS (for example patients treated despite contraindication) were not included in the study. Therefore, there was a low number of patients with CAPS who were potentially eligible for the study compared to the total number of patients with CAPS in the Eurofever registry.

This establishes the scarce recruitment conditions prior to study start, which also were in line with the site feasibility which was done by the Pediatric Rheumatology International Trials Organisation (PRINTO) by asking a number of investigators in the Eurofever registry for their interest and capability to recruit patients in this non-interventional PASS. All CAPS patients treated at the selected sites and meeting the inclusion criteria were eligible for entry in the study.

The duration of the enrollment period was planned to be 1 year and the study was estimated to enroll 15-20 CAPS patients, both of which were agreed to by the EMA during procedure EMEA/H/C/363/X/42 (CAPS indication) and the EMA approved RMP v 3.2. As a consequence, the slow enrolment rate after the study initiation reflected this limited patient population circumstance.

Between Nov 2014 and the end of 2015, a total of 7 study sites had been initiated in France, the UK, and the Netherlands. However, by Oct 2016 only 3 sites had enrolled a total of 12 patients (1 site in the Netherlands and 2 sites in the UK). Despite regular inquiries at sites that had not enrolled patients, no additional patients appeared to be available for inclusion. Faced with these realities, the MAH requested to close the study for enrolment, and this was agreed to by the EMA on 24 October 2016. Taken all together, these reasons explain the limited number of patients in the study, i.e. 12 patients.

CHMP comment

The MAH has clarified that though the Eurofever Registry had a total of 225 CAPS patients, only 12 of these 225 patients were included in the present PASS.

Of the 225 patients, treatment information was available for only 94 patient and of these, 61 patients received treatment with anakinra. Thus, within the Eurofever Registry, a total of 61 patients were potential candidates to be included in the PASS. However, only European patients were to be included and recruitment sites were limited to DE, FR, IT, NL and UK which further limited the total number of potential patients to be included.

The MAH states that the reasons mentioned above together with the inclusion criteria in general were the main reason for the few (and lower than expected) number of patients actual included in the PASS. Of note, the expected number of patients to be included was 15-20 thus, only three (3) patients were lacking to obtain the expected number of patients to be included. Further of note, the planned number of 15-20 patients were agreed by the EMA and likewise, EMA was also consulted when it was decided to close the study when a total of 12 patients were included. Before the decision of closing the study, efforts were made to reach a higher number of patients to be included and for the same reason, the study had been prolonged. However, these actions did not result in inclusion of more patients.

Conclusion: The MAH has sufficiently explained the reasons for the low number (n=12) of patients included in the PASS. Issue solved.

Question 2:

Due to the long induction period and the rare occurrence of malignancies, the evaluated association to Kineret (anakinra) treatment of this endpoint, in the present study, was not expected to find any significant increased risk. The MAH is asked to discuss how to address this issue further.

MAH's response:

In the primary analyses, the analysis period covered the time from the Baseline visit until the last visit. For the rate of malignancies, a secondary analysis was conducted by including the time from initiation of the Kineret treatment until the last study visit. Although any malignancies that occurred during the

study were to be reported, this brief study was not designed to investigate induction of malignancies in patients undergoing anakinra treatment. Such events must be considered rare, as the overall frequency of malignancies in clinical studies in patients with rheumatoid arthritis, including long-term follow-up data, has not been observed to be higher in anakinra-treated patients.

The Sobi.ANAKIN-201 PASS study was designed to address the effectiveness of the risk minimization measures for medication errors, including re-use of the syringe. The study also addresses the pre-specified risks from the RMP which can be captured at the patients' routine visits to the clinic (i.e. serious infections, malignancies, ISRs and allergic reactions). In a previous CAPS study 03-AR-0298, there were no adverse reactions denoting malignancies.

Nevertheless, since most of the patients in study Sobi.ANAKIN-201 had begun anakinra treatment prior to enrolment, the total exposure time and hence the potential for malignancy induction, if any, was in principle longer than the exposure they received during the study. In addition, malignancies in patients with CAPS and other auto-inflammatory disorders receiving anakinra treatment are captured and reported as a consequence of post-marketing pharmacovigilance activities.

Malignancies are described as an important potential risk in the RMP and are monitored as a Target medical event.

CHMP comment

The MAH informs that though 'malignancies' were included as an event of interest, it was not expected to find any events; this is due to the short observation time and the low number of patients included in the study. This is acknowledged. Malignancies are included as an important potential risk in the RMP and as such, there is still focus on a potential increased risk of developing malignancies related to the anakinra treatment. This is considered sufficient.

Conclusion: Issue solved.

Question 3:

The design allowed patients previously treated with Kineret to take part in the study. This is accepted, however, the MAH should present information regarding the timing and duration of previous Kineret-treatment, and clarify, how this previous treatment has an impact on the estimated endpoints of interest.

MAH's response:

Since CAPS is a rare disease with a limited number of patients available for clinical trials, previous use of Kineret was not an exclusion criterion for study participation. In the study, only 1 of the 12 patients started anakinra treatment at baseline; the other 11 patients had started treatment with Kineret prior to enrolment (see Figure 1).

Figure 1 Sobi.ANAKIN-201: Anakinra exposure prior to study enrolment

It is known that the development of ISRs in patients who had not previously experienced ISRs is uncommon after the first month of therapy (currently approved Kineret SmPC). In general, allergic reactions usually occur early in treatment. Thus, for these two primary endpoints, such reactions would not be expected for most of the patients included in this study. The absence of any reported ISRs and allergic reactions in the study is likely a reflection of the fact that only 1 patient started with Kineret treatment at baseline.

For the other primary endpoints of the study, rates of serious infections, new malignancies, and medication errors including syringe re-use, the impacts of previous Kineret exposure and subcutaneous administration experience are likely to differ. The impact of these factors on development of serious infections was likely minimal since infections can arise at any time during treatment. However, all of the infection-related events reported in the study (7 events, 2 serious, none severe, and none considered related to treatment) occurred in the one patient (Patient #4) who was Kineret-naïve at baseline. For malignancies, the impact is discussed in our response to question #2 above. For medication errors, these events were likely to be lower in patients with previous experience with the Kineret syringe than in patients naïve to this treatment.

For the secondary endpoints related to treatment discontinuation, many factors are involved in the decision to withdraw treatment temporarily or permanently, or to transfer to another IL-1 antagonist, and it is unclear how exposure to Kineret prior to the study would have affected these events.

CHMP comment

The MAH has presented the requested data (Figure 1 in the response above). Only 1 patient of the total 12 included patients were treatment naïve when included in the study. The MAH correctly concludes that this may have affected the reporting of ISR as these tend to occur early in the treatment. On the other hand, serious infections, malignancies and medication errors (all these being other primary endpoints) may occur at any time during the treatment and therefore, the fact that the majority of patients had been treated with anakinra prior to inclusion into the study is not considered to have influenced the results. On the contrary, malignancies may tend to occur as a late adverse reaction and the risk may accumulate with the treatment exposure. Thus, this primary endpoint may have the highest likelihood to have a higher risk of being reported due to the treatment prior to enrolment.

Conclusion: Issue solved.

Question 4:

The study was estimated to enrol 15 to 20 CAPS patients. The MAH is asked to clarify what this estimated number of CAPS patients, is based on.

MAH's response:

See response to Q1.

The study population was agreed with EMA in procedure EMEA/H/C/363/X/42 (CAPS indication) and the EMA approved RMP v 3.2 in the same procedure. EMA was consulted and accepted to stop recruitment at 12 patients.

CHMP comment

In the response to Question 1, the MAH has sufficiently described the basis for the estimate of including 15-20 patients in the study. Likewise, the MAH has sufficiently described the efforts to include this number (15-20) of patients in the study and the reasons for the lower than anticipated number (n=12) of patients who were actually included in the PASS.

Conclusion: Issue solved.

Question 5:

Due to the risk of small number bias the MAH is asked, if there are any plans of keeping this safety study running, with a purpose to secure longer follow periods, and to include more patients.

MAH's response:

This non-interventional PASS was designed to evaluate the safety of Kineret treatment in CAPS patients in routine clinical care. The duration of the follow up for each patient enrolled in the study was planned to be 3 years. Six patients were followed for 3 years, seven patients were followed for 2 or more years and 10 patients were followed for 1 year or more. The start of data collection was in April 2015, and the recruitment period was planned to end in Oct 2015 but was extended by 3 years until Nov 2018. The end of data collection was planned to be October 2018 but was continued until September 2019. Based on the efforts Sobi has taken as regards the multiple study period extensions, as well as the positive study outcome and the EMA approved study plans, Sobi does not consider a new study warranted.

CHMP comment

The MAH informs that there are no plans of keeping the PASS running. Considered the challenges with recruiting patients, the small number (n=12) it was succeeded to include, the results of the study and last but not least, the usual safety measures which are still ongoing (related to the RMP and the PSURs), it is considered acceptable not to continue with the study. Of note, also the EMA agreed to close the study, well-knowing the data (i.e. the total number of patients actual included and the follow-up time).

Conclusion: Issue solved.

Question 6:

All the observed 7 pre-specified reported adverse events during the study period, was infections. Due to the known adverse event of Kineret inducing neutropenia, it is considered of interest to know the level of neutrophil granulocytes prior to and during the time with infections. Please provide data if available.

MAH's response:

All of the 7 infections reported in the study occurred in a single patient (Patient #4), a child who was 1.4 years old at baseline. The patient experienced 2 serious infections requiring hospitalisation. One was a urinary tract infection and the neutrophil count was reported to be 1.71 x 109/L at a follow-up visit several weeks after this infection had resolved. This was initially interpreted to be non-serious neutropenia and the Kineret dose was reduced from 20 to 16 mg/day, though the original dose of 20 mg/day was reinstated 1 month later. However, on subsequent review, the investigator confirmed that the patient had not had neutropenia (as was previously reported), since a neutrophil count of 1.71 x 109/L is not considered to be neutropenia. Consequently, the event was deleted from the study AE database. In the second infection (tonsillitis), that required hospitalisation for tonsillectomy (SAE), the neutrophil count was also reported to be normal (4.41 x 109/L, Ref. range 1.5–8.5 x 109/L). Hence, none of the infections that occurred in the study were reported to be associated with confirmed neutropenia and there were no abnormal neutrophil counts reported during the study.

CHMP comment

The MAH informs that all 7 AEs of infections were reported in a single patient. Only few results of neutrophil counts were available but these appeared to be within the range of 'Normal'. While this may be considered reassuring, it is not sufficient to draw any conclusions. Importantly, both 'Serious infections' and 'Neutropenia' are mentioned as common (frequency: ≥1/100 to <1/10) adverse reactions in the tabulated list of adverse reactions in section 4.8 of the SmPC and both 'Serious infections' and 'Neutropenia' are also addressed in the SmPC section 4.4 'Special warning and precautions for use'. Thus, the topics are sufficiently addressed in the product information (SmPC).

Conclusion: Issue solved.

Question 7:

The majority of patients included in the study gained weight during the study period. According to the SmPC, this is not a known adverse event. The MAH is asked to discuss if 'Weight gain' may be an adverse event to Kineret and whether this has been observed in other clinical studies.

MAH's response:

Body weight was used to calculate the administered Kineret dose in mg/kg/day and was not intended to be a safety evaluation.

CAPS, particularly the more severe form NOMID, causes growth retardation in children, and heights below the third percentile can be seen in about 75% of patients[3]. Body weights below the 3rd percentile were also described in children with CAPS[4]. In the study by Sibley et al. 2012, 62% of patients with growth below the 3rd percentile at baseline, and who were treated with anakinra showed the largest percentile increases, indicating catch-up growth at 36 months and 60 months (P=0.018 and P=0.021, respectively, versus baseline)[4]. This was also observed for weight gain in 58% of patients (P=0.001 at 36 months and 60 months, versus baseline).

Neven et al. retrospectively analysed the medical records of 10 NOMID/CINCA syndrome patients who had been treated with anakinra for 26-42 months[5]. All patients gained height and exhibited increased BMI. Given that CAPS is associated with growth retardation (including low body weight), the increase in the BMI in patients treated with anakinra should be viewed as a beneficial effect of the medication rather than an AE.

In the Sobi.ANAKIN-201 study, the gain of weight in the paediatric patients is consistent with normal growth curves. Whereas there is a slight tendency to the weight increase in the adult patients (>18 years old). However, the limited number of patients participating to this study cannot conclude to the accountability of anakinra in the weight gain. The table below summarizes the reported weights at baseline and at the time of Kineret discontinuation.

Table 1 **Sobi.ANAKIN-201: Weight of the study population at basline and at the time of Kineret discontinuation**

			Kineret discontinuation	
Patient number	Age (years)	Weight (kg) at baseline	Weight (kg)	Days after baseline
1	1.7	10.7	11.2	154
2	7.3	25.0	24.6	28
3	3.5	12.8	14.1	511
4	1.4	8.1	15.5	1106
5	17.3	63.0	65.0	573
6	19.0	60.0	63.0	573
7	46.0	87.8	92.7	1218
8	51.3	128.0	117.0	1183
9	49.1	85.1	88.1	1120
10	54.9	48.2	50.5	1113
11	31.7	86.0	105.0	1134
12	54.1	116.6	120.0	914

In May 2016, Sobi received a notification from EMA (PRAC) regarding a potential safety issue, weight increase in connection with use of IL-1 blocking drugs, such as anakinra. A signal of weight increase was therefore opened. A review of post-marketing and study data, and a literature review could not confirm the signal. In agreement with the EMA, the signal of weight increase was refuted and closed in September 2016. The signal did not result in changes, either in the Core Data Sheet or in local labels.

CHMP comment

As mentioned in the Question 7 the majority of the included patients gained weight during treatment with anakinra. For the children, this weight gain is considered to be due to normal growth and is as such not a concern. Among the 7 adult patients (aged >18 years), a total of 6 patients gained weight during the treatment with anakinra despite this population should be considered to maintain but not increase weight. One (1) patient lost 11 kg. during treatment with anakinra, 1 patient increased weight with 19 kg whereas the remaining 4 patients increased weight with 2-5 kg. The patients were treated for 2.5–3.2 years.

As mentioned by the MAH, in 2016 'Weight gain' was noted as a potential safety issue related to the treatment with IL-1 blocking agents including anakinra. The signal detection was however, closed without confirmation of a causal relationship between increased weight and the IL-1 blocking agents. There was no request of updating the product information (SmPC) and thus, currently there is no information regarding weight gain in the Kineret SmPC. Based on the few data included in the

present PASS and the outcome of the signal detection in 2016, no further action is currently considered necessary.

Conclusion: Issue solved.

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Conclusion

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance