14 May 2020
EMA/297768/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kineret

International non-proprietary name: anakinra

Procedure No. EMEA/H/C/000363/II/0073

Note

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

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Status of this report and steps taken for the assessment			
Description	**Planned date**	**Actual Date**	**Need for discussion**
Start of procedure:	14 Jan 2020	14 Jan 2020	☐
PRAC Rapporteur Assessment Report	24 Feb 2020	20 Feb 2020	☐
PRAC members comments	28 Feb 2020	n/a	☐
CHMP members comments	02 Mar 2020	n/a	☐
Updated PRAC Rapporteur Assessment Report	03 Mar 2020	n/a	☐
Start of written procedure	10 Mar 2020	10 Mar 2020	☐
PRAC endorsed relevant sections of the assessment report	10 Mar 2020	10 Mar 2020	☐
Request for supplementary information	12 Mar 2020	12 Mar 2020	☐
MAH submission of responses	14 Apr 2020	14 Apr 2020	☐
Re-start of procedure	16 Apr 2020	16 Apr 2020	☐
PRAC Rapporteur Assessment Report	30 Apr 2020	28 Apr 2020	☐
PRAC members comments	04 May 2020	n/a	☐
CHMP members comments	04 May 2020	n/a	☐
Updated PRAC Rapporteur Assessment Report	05 May 2020	n/a	☐
Start of written procedure	12 May 2020	12 May 2020	☐
PRAC endorsed relevant sections of the assessment report	12 May 2020	12 May 2020	☐
Opinion	14 May 2020	14 May 2020	☒

List of abbreviations

Abbreviation	Term
AE	Adverse event
AOSD	Adult-Onset Still's Disease
bDMARD	Biologic Disease-modifying antirheumatic drug
CAPS	Cryopyrin associated periodic syndromes
CRF	Case report form
CSR	Clinical study report
DMARD	Disease-modifying antirheumatic drug
EMA	European Medicines Agency
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
ESI	Events of special interest
EU/EEA	European Union/ European Economic Area
HLH	Haemophagocytic lymphohistiocytosis (Interchangeable with MAS)
IL-1	Interleukin-1
IL-6	Interleukin-6
ILAR	International League of Associations for Rheumatology
IR	Incidence rate
IRCCS	Istituto di Ricerca e Cura a Carattere Scientifico (Institute for treatment and research)
JIA	Juvenile idiopathic arthritis
LLT	Lowest level term
MAS	Macrophage activation syndrome (Interchangeable with HLH)
NA	Not applicable
NSAID	Non-steroidal anti-inflammatory drug
PASS	Post authorisation safety study
PRINTO	Paediatric Rheumatology International Trials Organization
PSUR	Periodic safety update report
PT	Preferred Term
py	Patient-year
RMP	Risk management plan
SAE	Serious adverse event
SAP	Statistical analysis plan
sDMARD	Synthetic Disease-modifying antirheumatic drug
SJIA	Systemic juvenile idiopathic arthritis
Sobi	Swedish Orphan Biovitrum
SOC	System organ class
SmPCs	Summary of Product Characteristics

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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 18 December 2019 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-302) listed as a category 3 study in the RMP. This is a non-interventional, post-authorisation safety study to evaluate long-term safety of anakinra (Kineret) in patients with systemic juvenile idiopathic arthritis. The RMP version 5.1 has also been submitted to reflect completion of the study.

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

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

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.

Anakinra is approved in the treatment of rheumatoid arthritis, cryopyrin-associated periodic syndromes (CAPS) and Still's disease (including systemic juvenile idiopathic arthritis (SIJA) and adult-onset still's disease (AOSD).

Within this variation procedure, the MAH submitted the final study results of a non-interventional, post-authorisation safety study to evaluate long-term safety of anakinra (Kineret) in patients with SJIA. The study was agreed upon with EMA in a previous variation procedure and was listed as a category 3 study in the risk management plan (RMP). The submission of the final study report is also in accordance with Article 46 of Regulation (EC) No 1901/2006 (Paediatric Regulation) which sets out the obligation for MAHs to submit any MAH-sponsored studies involving the use of an authorised medicinal products in the paediatric population to the competent authority.

The non-interventional study used data from the Pharmachild JIA registry. Data were collected from 2004 to 30 September 2018. Patients included in the study were male and female patients diagnosed with SJIA according to the Pharmachild JIA registry study criteria and treated with Kineret.

A total of 306 patients from 15 different countries were included in the study, with the majority of patients from Europe (299 patients; 97.7%). Boys and girls were equally represented, which is in accordance with the disease characteristics. Median and mean age at time of Kineret treatment was 8.0 and 8.2 years, respectively with min and max age being 0.8 and 20.3 years, respectively.

The safety-related variables were as follows: (1) The occurrence of non-serious adverse events (AEs) of at least moderate severity and serious adverse events (SAEs), including macrophage activation syndrome (MAS) as an event of special interest (ESI), (2) the duration of Kineret treatment in a real-world setting, (3) the reasons for Kineret treatment discontinuation.

- The occurrence of non-serious AEs of at least moderate severity and SAEs, including MAS as an ESI.

The most common AE was administration site reaction which is already included in the SmPC with a frequency very common.

A total of 99 patients experienced a total of 201 AEs of at least moderate intensity thus, approximately two-thirds (209 patients, 68%) did not report any AEs of at least moderate in intensity.

A total of 56 SAEs were reported during the study; IR(95% CI):11.0(7.9-15.2). The majority of SAEs were reported within the initial 6 months of treatment. Most SAEs were reported within the MeDRA term system organ class (SOC) 'Injury, poisoning and procedural complications' and were mainly reported to be injection and infusion related reactions. Based on the results of this study and study Sobi.ANAKIN-301 (reviewed under EMA/H/C/000363/P46/031), the MAH has committed to submit a variation to update the section 4.8 description of the 'injection site reactions' of the SmPC. The updated text will describe that in 12 patients with Still's disease treated for 12 weeks in the placebo-controlled study, ISRs occurred in both treatment groups, of which all were mild in severity.

During the study period, 11 patients (3.6%) experienced 12 episodes (11 SAEs and 1 non-serious AE) of MAS on Kineret treatment. The IR of the first occurrence was 2.2 per 100 py. It is well-known that patients with Still's disease have an increased risk of spontaneous development of MAS. It is also well-known that MAS often develops due to certain triggers including infections and certain medication however, a causal relationship between Kineret and MAS has not (yet) been established. The present study is not designed to decide on a potential relationship between Kineret and MAS. There was no pattern in the timing of MAS in relation to duration of Kineret treatment. Based on the results of this study and study Sobi.ANAKIN-301, the MAH has committed to update the product information later this year to reflect the incidence rate of MAS.

- The duration of Kineret treatment in a real-world setting.

Almost half (46%) of the patients were at some point treated with Kineret for at least 12 months and approximately one-fourth (28%) were treated for at least 24 months. The majority (n=259; 85%) of patients were only treated with one course of Kineret and only very few (n=6; <2%) of the patients received ≥3 treatment courses.

- The reasons for Kineret treatment discontinuation.

The majority (3/4) of the patients discontinued Kineret treatment at some time during the study period. At all-time windows, the most common reason for discontinuation was lack of efficacy (23.5-50.0%) with the percentage of patients discontinuing for this reason despite variations, being fairly stable over time. The second most common reason for discontinuation of Kineret treatment was remission (reported in 18.3-55.9% of the discontinuations). The proportion increased over time (up to 18 months) indicating that long-term treatment may result in remission of the disease. AEs of at least moderate severity was the third most common reason for discontinuations within the first 6 months (15.6%). Additionally, mild AEs and intolerance were reported in 3.7% and 7.3% of the discontinuations, respectively. Discontinuations due to AEs (any degree) and Intolerance decreased over time indicating that at least the most severe/bothersome AEs were most common in the beginning of the treatment. Numeric, slightly more patients with concomitant treatment discontinued due to AE and/or intolerance; this could be explained by the fact that concomitant treatment increases the risk of more adverse events, but the differences are small and neither statistically significant nor clinically relevant.

Despite limitations due to the study design, the present study provides valuable information regarding Kineret-treatment of children and adolescents with Still's disease. The reported safety profile is mostly in line with the observations from previous studies (e.g. the pivotal phase III study used for the MAA). The MAH has committed to submit a Type II variation application for relevant updates of the

SmPC based on this study and also for completeness based on study Sobi.ANAKIN-301 (reviewed under EMA/H/C/000363/P46/031).

Overall, no new safety concerns have been identified from the study and the safety profile of Kineret is in line with what is already known. The benefit-risk balance of Kineret (anakinra) remains unchanged.

3. Recommendations

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

Variation accepted		**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-302) listed as a category 3 study in the RMP and in accordance with Article 46 of Regulation (EC) No 1901/2006. This is a non-interventional, post-authorisation safety study to evaluate long-term safety of anakinra (Kineret) in patients with systemic juvenile idiopathic arthritis. The RMP version 5.3 has also been updated to reflect the completion of the study.

☒ is recommended for approval.

Amendments to the marketing authorisation

The variation requires amendments to the Risk Management Plan (version 5.3).

4. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Kineret-H-C-000363-II-73'

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

5. Introduction

Anakinra (ATC code: L04AC03; trade name: Kineret) is a human IL-1 receptor antagonist that blocks the biological activity of cytokine IL-1 (IL-1α and IL-1β) by competitively inhibiting its binding to the IL-1 receptor type 1, thereby controlling active inflammation.

Kineret was first approved in the US in 2001 for treatment of rheumatoid arthritis (RA), and subsequently in the EU/EEA for RA and all forms of Cryopyrin-Associated Periodic Syndromes (CAPS). In 2018, Kineret was approved in the EU/EEA in adult and paediatric 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.

Still's disease is an autoinflammatory disorder with few approved treatment options. The pathogenesis of Still's disease is not completely understood. Clinical and laboratory observations suggest an inappropriate activation of the innate immune system, with hypersecretion of proinflammatory cytokines such as IL-1 and IL-6 as an important mechanism of the disease. The typical clinical features of Still's disease include high spiking intermittent fever, maculopapular rash, lymphadenopathy, hepatosplenomegaly, serositis, and marked increase in acute-phase reactants. Still's disease is also associated with chronic arthritis or arthralgias, as well as complications such as joint damage, growth impairment, osteoporosis, amyloidosis, and the potentially fatal MAS[1,2,3,4,5]. One of the most severe complications in Still's disease is MAS, a type of secondary HLH. In general, the literature suggests that 7-17% of all paediatric patients with Still's disease develop full-blown MAS, but the true frequency of MAS may be higher since subclinical and mild MAS have been reported to occur in another 30-40% of these patients[5,6] .

A non-interventional PASS, using the Pharmachild JIA register via the associated PRINTO network, has been performed in collaboration with PRINTO. The study was agreed upon with EMA in Procedure No. EMEA/H/C/000363/II/0056. The PASS was included in Section III.2-3 of the Kineret EU RMP version 4.5, as a category 3 activity. The EU RMP version 4.5 was approved by EMA following the approval of Still's indication in April 2018. In the EU RMP version 4.9, also approved by EMA, the due date for the submission of the PASS report had been updated to December 31, 2019. The study has been registered in the public EU PAS register and on clinicaltrials.gov, and the collected safety data will be reported in PSUR and RMP updates as applicable.

The primary objective of PASS Sobi.ANAKIN-302 was to evaluate the long-term safety of Kineret in paediatric patients with Still's disease in routine clinical care, including MAS.

CHMP comments

The MAH has correctly presented the background for anakinra (Kineret), the use of the product within the approved indications including Still’s disease.

The MAH has also correctly identified the safety issues leading the study to be imposed.

[1] Cabane J, Michon A, Ziza JM, Bourgeois P, Bletry O, Godeau P, et al. Comparison of long term evolution of adult onset and juvenile onset Still's disease, both followed up for more than 10 years. Ann Rheum Dis. 1990;49(5):283-5.
[2] Packham JC, Hall MA. Long-term follow-up of 246 adults with juvenile idiopathic arthritis: functional outcome. Rheumatology (Oxford). 2002;41(12):1428-35.
[3] Gurion R, Lehman TJ, Moorthy LN. Systemic arthritis in children: a review of clinical presentation and treatment. Int J Inflam. 2012;2012:271569.
[4] Ravelli A, Grom AA, Behrens EM, Cron RQ. Macrophage activation syndrome as part of systemic juvenile idiopathic arthritis: diagnosis, genetics, pathophysiology and treatment. Genes Immun. 2012;13(4):289-98.
[5] Gerfaud-Valentin M, Jamilloux Y, Iwaz J, Seve P. Adult-onset Still's disease. Autoimmun Rev. 2014;13(7):708-22.
[6] Minoia F, Davi S, Horne A, Demirkaya E, Bovis F, Li C, et al. Clinical features, treatment, and outcome of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a multinational, multicenter study of 362 patients. Arthritis Rheumatol. 2014;66(11):3160-9.

6. Clinical Safety aspects

Not applicable as the PASS was a Post-Authorisation Safety Study (PASS) (see section 7.).

7. Non-interventional Post-Authorisation Safety Study (PASS)

7.1. Methods – analysis of data submitted

7.1.1. Study design and setting

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

This study was based on secondary use of data from the Pharmachild JIA registry. Data were extracted and analysed for all male and female patients classified as SJIA, as per the ILAR classification criteria[7] [8], included in the Pharmachild JIA registry, who were ever treated with Kineret subsequently to SJIA diagnosis.

No treatment assignment or randomization was applicable.

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

CHMP comments

The study was designed as a non-interventional pharmacovigilance registry study utilizing already available data from the Pharmachild JIA registry. As such, all methodological weaknesses known to be associated with register studies also apply to this study. The Pharmachild JIA registry is a registry collecting data from patients with JIA including patients with SJIA. It is endorsed that both retrospective and prospective data (defined as from December 2011) in included as this provides more data; total data-collection time has been 14 years (from 2004 till September 2018).

7.1.2. Subjects

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

CHMP comments

Patients included in the present study were male and female patients diagnosed with SJIA according to the Pharmachild JIA registry study criteria and treated with Kineret. There were no restrictions with regard to disease duration or severity other than patients were treated with anakinra, which according to the labelled indication is indicated *"for the treatment of Still's disease […] with active systemic features of moderate to high disease activity, or in patients with continued disease activity after*

[7] Kotter I, Wacker A, Koch S, Henes J, Richter C, Engel A, et al. Anakinra in patients with treatment-resistant adult-onset Still's disease: four case reports with serial cytokine measurements and a review of the literature. Semin Arthritis Rheum. 2007;37(3):189-97.
[8] Raffeiner B, Botsios C, Dinarello C, Ometto F, Punzi L, Ramonda R. Adult-onset Still's disease with myocarditis successfully treated with the interleukin-1 receptor antagonist anakinra. Joint Bone Spine. 2011;78(1):100-1.

treatment with NSAIDs or glucocorticoids." This indicates that the included patients were overall severely affected of the disease. There were also no restrictions with regard to the patients' demographics or baseline characteristics. This is endorsed as this optimizes the possibility of including more patients into the study and also of obtaining 'real world' data.

7.1.3. Variables

The endpoints to support the objective for the study were:

• The occurrence of non-serious AEs of at least moderate severity and SAEs, including MAS as an ESI.

• The duration of Kineret treatment in a real-world setting.

• The reasons for Kineret treatment discontinuation.

The MedDRA dictionary SOC Immune system disorders includes a specific PT called Haemophagocytic lymphohistiocytosis (HLH, equivalent to macrophage activation syndrome (MAS)), which in the literature and in current clinical practice is referred to as Macrophage Activation Syndrome (MAS) when occurring in patients with SJIA, as per the recent ACR/EULAR classification criteria[5,6] . In this report these terms are used as synonymous interchangeably.

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

• Demographics (date of birth, sex, ethnicity, country).

• Date of disease onset, i.e. 'occurrence of the first clinical manifestation consistent with the disease', and date of diagnosis.

• Start and stop date of Kineret treatment.

• Start and stop dates of all other SJIA related medications, i.e. sDMARDs or bDMARDs, and systemic glucocorticoids.

• AE SOC/LLT term as per MedDRA dictionary.

• Start date of non-serious AEs of at least moderate severity.

• Start date of all SAEs.

• Report type for AEs: initial or follow-up.

• Date of death.

• Specification of trigger event for incident MAS cases: disease flare, infection, changes of treatment and other.

• Reasons for discontinuation of Kineret treatment: adverse event (moderate/severe/serious event or mild event), intolerance, dose change, inefficacy, remission, surgery, pregnancy or other reason.

CHMP comments

The safety-related variables are according to the data obtained from the Pharmachild JIA registry and are as follows: (1) The occurrence of non-serious AEs of at least moderate severity and SAEs, including MAS as an ESI, (2) The duration of Kineret treatment in a real-world setting, (3) The reasons for Kineret treatment discontinuation.

Overall, the safety-related outcomes are considered to be in accordance with the objectives of the study. Due to the study design, it is not possible to include information regarding mild AEs however,

information regarding discontinuation due to AEs (including mild AEs) is collected. Overall, as this is a PASS, it is considered acceptable that only data regarding moderate and severe AEs as well as SAEs are included.

Collection of demographics and baseline (including disease baseline) characteristics is endorsed.

7.1.4. Data sources and measurement

PRINTO (www.printo.it) is a non-profit, non-governmental, international research network founded in 1996. PRINTO initially included 14 European countries (now 88 countries, 640 centers worldwide with 1,348 members today), with the goal to foster, facilitate and co-ordinate the development, conduct, analysis, and reporting of international, multi-center, clinical trials and/or outcome standardization studies in children with paediatric rheumatic diseases.

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

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

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

CHMP comments

The MAH has sufficiently described the data sources, PRINTO and the Pharmachild registry. Data was collected retrospective as well as prospectively and handled equally. This is acceptable. It is informed that "A medical monitor evaluated all reported AEs. This person was able to raise queries to the centers and request further clarifications." The MAH has clarified that the data remained blinded for the medical monitor. The focus was to ensure the right diagnoses (ILAR) and adverse events. It was informed that the medical monitor also was the principle investigator of one of the PRINTO sites thus theoretical, it cannot be excluded that the medical monitor recognized his/her 'own' patients. However, a total of 259 patients were included in the study. Overall, this is not expected to affect the study results.

7.1.5. Bias

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

From a time perspective the data collected in the retrospective components envisioned two steps[9] :

Step 1: A census (e.g. collection of patient identification number, age, JIA type and type of treatment) was required from each center before retrospective chart review of safety data initiated to avoid

[9] Jamilloux Y, Gerfaud-Valentin M, Martinon F, Belot A, Henry T, Seve P. Pathogenesis of adult-onset Still's disease: new insights from the juvenile counterpart. Immunol Res. 2015;61(1-2):53-62.

selection biases (e.g. to have the proper denominator against which evaluating the successful data collection).

Step 2: Retrospective chart revision for the collection of moderate/severe non-serious AEs and SAEs until the time of the last available visit. This retrospective chart review was considered successful if at least 70% of the patients listed in the census would have been retrieved.

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

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

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

CHMP comments

The MAH has adequately discussed potential bias in this study. The general risks of bias related to the study deign (e.g. the study being non-controlled and depending on the information obtained in the registry including the risk of missing data) are relevant to consider. Furthermore, it is agreed that the IRs for AEs while exposed to Kineret may be both/either under- or overestimated if the exposure-related of patient-time is misclassified.

7.1.6. Study size

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

CHMP comments

No formal sample size calculation was made for this study. The MAH informs that all (306) patients enrolled in the Pharmachild JIA registry and fulfilling all inclusion criteria were included in the study. This is endorsed. Considered an annual incidence of 1-20 in 900,000 children and a total data-

collection time of approximately 14 years; it seems reasonable that a total of 306 patients were included in the Pharmachild JIA registry as per 30 September 2018.

With a total study population of 306 patients it is expected that very common (≥1/10) and common (≥1/100 to <1/10) AEs will be reported however, uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000) AEs will most likely not be reported. This is considered a weakness to the study.

7.1.7. Data transformation

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

Data are cleaned and remotely monitored by designated PRINTO personnel on an ongoing basis to check the accuracy of data. If necessary, additional and more precise information can be requested by the PRINTO personnel. Technical management of the database is handled by PRINTO. No individual patient listings were obtained for this study, only summary outputs were reported.

The following variables were derived for this study:

• Time since disease onset was calculated as the difference between 'start date' of Kineret treatment and 'Disease onset'.

• Time from disease onset to first center visit was calculated as the difference between first date center visit and 'Disease onset'.

• Time since SJIA diagnosis was calculated as the difference between 'start date' of Kineret treatment and 'JIA diagnosis date'.

• Age at start of treatment with Kineret was calculated as the difference between 'Birth date' and start date of Kineret treatment.

• Age categories at baseline as follows, Infant (<2 years), Child (2 years - <12 years), Adolescent (12 years - <8 years), Adult (≥18 years), and Unknown.

• Ethnicity classification with categories 'Caucasian, 'Other'.

• History of MAS (Yes/No). Derived by identifying any known or recorded episodes of MAS prior to baseline.

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

CHMP comments

The MAH has adequately and sufficiently described data transformation.

7.1.8. Statistical methods

7.1.8.1. Main summary measures

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

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

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

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

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

7.1.8.2. Main statistical methods

There were five main analysis sets:

• The complete set, including all patients with SJIA in the registry who have received Kineret at least once following a diagnosis of SJIA as per investigator judgement and enrolled before the cut-off date for the current study (30 September 2018).

• The long-term treatment set-12, including those patients from the complete set with 12 months or more of continuous Kineret treatment*.

• The long-term treatment set-18, including those patients from the complete set with 18 months or more of continuous Kineret treatment*.

• The long-term treatment set-24, including those patients from the complete set with 24 months or more of continuous Kineret treatment*.

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

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

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

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

Number of years with Kineret treatment, i.e. patient time under risk and the IR per 100 patient-years were calculated.

The following rules were applied:

• AEs occurring outside Kineret treatment exposure, i.e. before, and when Kineret treatment was paused or stopped were not counted.

• The exposure to Kineret treatment was calculated from baseline until the end of the time window, date of discontinuation of the Kineret treatment exposure, last visit or death.

• The periods outside Kineret treatment exposure were excluded from the patient-time.

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

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

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

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

• Number of AEs (non-serious AEs of at least moderate intensity and serious AEs) and IRs (95% CI) by SOC, PT and time window (the complete set).

• Number of SAEs and IRs (95% CI) by SOC, PT and time window (the complete set).

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

• Number of AEs (non-serious AEs of at least moderate intensity and serious AEs) and IRs (95% CI) by SOC, PT and time window (the long-term treatment set-12, the long-term treatment set-18 and the long-term treatment set-24).

• Number of SAEs and IRs (95% CI) by SOC, PT and time window (the long-term treatment set-12, the long-term treatment set-18 and the long-term treatment set-24).

The incidence proportion for each reported AE term was calculated overall and within time windows.

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

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

• Number of patients and incidence proportions of SAEs by SOC, PT and time window (the complete set).

The IR of MAS was analysed with respect to 1st occurrence and recurrence respectively. The rationale for this was to account for a biological distinction in altered risk following a first event.

For the analyses, the 1st occurrence of MAS was defined to occur at or after baseline regardless of whether the patient had a history of MAS or not. The cumulative probability of a first event of MAS over time was estimated for the complete set.

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

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

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

7.1.8.3. Missing values

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

CHMP comments

The MAH has adequately and sufficiently explained the statistical methods applied.

The MAH informs that the analyses were based on available data thus, no imputations of missing data were made. Considered this is a PASS and the overall design of the study, this is acceptable.

7.1.9. Quality control

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

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

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

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

CHMP comments

The MAH has sufficiently explained the quality assurance.

7.2. Results

7.2.1. Participants

As stated in the protocol, 307 patients were preliminary identified for inclusion in the analysis. On 30 September 2018, the cut-off date for inclusion in the study, a total of 306 patients were identified as meeting all inclusion criteria. These were patients with SJIA as per ILAR classification criteria, who had received Kineret at least once subsequently to disease onset (complete set).

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

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

CHMP comments

306 patients from 15 different countries are included in the study. The majority of the patients (299 patients; 97.7%) were from Europe. A total of 13 European countries from all geographical parts of Europe (Northern, Southern, Eastern and Western parts) contributed with data. Thus, the results are considered to be representative for the European population.

7.2.2. Descriptive data

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

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

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

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

Abbreviations: SD, Standard deviation; N, number of patients; min, minimum value; max, maximum value; q1, the first quartile; q3, the third quartile.
[a] Baseline date may be postponed for the long-term treatment set 12, 18 and 24.
[b]Age at baseline for the complete set. Age at baseline or at index date for the long-term treatment set 12,18 and 24.
[c]First visit in the clinic center.

CHMP comments

The demographic and baseline characteristics are sufficiently described. Boys and girls were equally represented, which is in accordance with the disease characteristics. Median and mean age at time of Kineret treatment was 8.0 and 8.2 years, respectively with min and max age being 0.8 and 20.3

years, respectively. Approximately 2/3 (69%) of the patients were <12 years old. Mean time from diagnosis till initiation of Kineret treatment was 2.0 years, thus, mean and median age at diagnosis was approximately 6 years, which is in accordance with the known disease characteristics. As only 5 patients were ≥18 years, this is not considered to impact the results in any clinically relevant degree.

Mean time since SJIA onset and mean time since SJIA diagnose was 2.0 and 1.7 years, respectively indicating a lap of approximately 0.3 years (approximately 3-4 months) between the initial symptoms and diagnosis; this is expectable. A mean time of approximately 1.7 years between SJIA diagnosis and initiation of treatment with Kineret indicate that a substantial proportion of patients may have been treated with other anti-inflammatory treatment prior to Kineret; this is according to the treatment guidelines and the labelled indication for Kineret (which is: *"for the treatment of Still's disease […] with active systemic features of moderate to high disease activity, or in patients with continued disease activity after treatment with NSAIDs or glucocorticoids."*).

7.2.3. Outcome data, Main results

The duration of Kineret treatment is presented in section 7.2.3.1. . Reasons for Kineret discontinuation are summarized in section 7.2.3.2. . Concomitant medications are summarized in section 7.2.3.3. .

7.2.3.1. Duration of Kineret treatment

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

Overall, the 306 patients had a total of 360 courses of Kineret treatment and the mean duration of a treatment course with Kineret was 17.0 (standard deviation 21.1) months and the median duration was 8.9 (first quartile of 3.1, third quartile of 23.5) months (Table 2). The shortest treatment course was 0.2 months, whereas the longest course was 109.9 months.

Six months after first Kineret dose, a total of 184/306 patients (60.1%) were still continuously exposed. Similarly, after 12, 18 and 24 months, there were 134, 97 and 85 patients respectively still continuously on Kineret treatment (Table 2).

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

Table 2 Duration of treatment with Kineret, overall and by treatment time window (The complete set)

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

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

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

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

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

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

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

CHMP comments

It is reassuring that almost half (46%) of the patients were at some point treated for at least 12 months and approximately one-fourth (28%) were treated for at least 24 months. However, the most important is not treatment duration but reasons for discontinuations (see below).

The majority (n=259; 85%) of patients were only treated with one course of Kineret and only very few (n=6; <2%) of the patients received ≥3 treatment courses.

7.2.3.2. Reasons for Kineret treatment discontinuation

Out of the 306 patients, 233 patients (76.1%) discontinued Kineret at least once (Table 3), censored patients excluded). In total, there were 268 discontinuations with 281 reasons recorded. The most frequent reason for Kineret discontinuation were inefficacy with 121 occurrences out of 281 reasons in total (43.1%). Similarly, remission was recorded in 30.6% of all reasons. AEs were represented in 10.0% of all reasons for discontinuations (AEs of at least moderate intensity 8.2% and AEs of mild intensity 1.8%). Intolerance was given as the reason for discontinuation in 5.0% of the cases.

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

Table 3 Reasons for discontinuation of Kineret treatment, overall and by time window (The complete set)

Time window[a]	**Overall**		**1-6 months**		**7-12 months**		**13-18 months**		**19-24 months**		**>24 months**	
N-total number of patients	**306**		**306**		**194**		**144**		**106**		**104**	
Total number of reasons for discontinuations	**281**		**109**		**53**		**34**		**13**		**72**	
Reason[b]	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Adverse event at least of moderate intensity	23	8.2	17	15.6	2	3.8	3	8.8	0	0.0	1	1.4
Intolerance	14	5.0	8	7.3	3	5.7	1	2.9	0	0.0	2	2.8
Dose change	2	0.7	1	0.9	1	1.9	0	0.0	0	0.0	0	0.0
Inefficacy	121	43.1	51	46.8	20	37.7	8	23.5	6	46.2	36	50.0
Remission	86	30.6	20	18.3	21	39.6	19	55.9	4	30.8	22	30.6
Surgery	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Pregnancy	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Other reason	23	8.2	7	6.4	5	9.4	3	8.8	2	15.4	6	8.3
Mild adverse event[c]	5	1.8	4	3.7	1	1.9	0	0.0	0	0.0	0	0.0
Change therapy	11	3.9	2	1.8	2	3.8	2	5.9	1	7.7	4	5.6
No compliance	4	1.4	0	0.0	2	3.8	0	0.0	1	7.7	1	1.4
Other	3	1.1	1	0.9	0	0.0	1	2.9	0	0.0	1	1.4
Unknown	12	4.3	5	4.6	1	1.9	0	0.0	1	7.7	5	6.9
Number of patients discontinued[d]	233	76.1	102	33.3	50	25.8	33	22.9	13	12.3	61	58.7
Number of discontinuations[e]	268	87.6	103	33.7	50	25.8	33	22.9	13	12.3	69	66.3

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

CHMP comments

Overall, the majority (3/4) of the patients discontinued Kineret treatment at some time during the study period. At all time windows, the most common reason for discontinuation was lack of efficacy (23.5-50.0%) with the percentage of patients discontinuing for this reason despite variations, being fairly stable over time. This indicates that patients who initially benefit from the treatment may not continue doing so. After 19 months treatment, approximately half of the patients had discontinued due to lack of efficacy. There were no clear differences in baseline characteristics between the group

of patients discontinuing due to lack of efficacy and the remaining patients thus, no predictive baseline characteristics were identified.

The second most common reason for discontinuation of Kineret treatment was remission (reported in 18.3-55.9% of the discontinuations). The proportion increased over time (up to 18 months) indicating that long-term treatment may result in remission of the disease. This is reassuring.

Adverse events (AEs) of at least moderate severity was the third most common reason for discontinuations within the first 6 months (15.6%). Additionally, mild AEs and Intolerance were reported in 3.7% and 7.3% of the discontinuations, respectively. Discontinuations due to AEs (any degree) and Intolerance decreased over time indicating that at least the most severe/bothersome AEs were most common in the beginning of the treatment. Numeric, slightly more patients with concomitant treatment discontinued due to AE and/or intolerance; this could be explained by the fact that concomitant treatment increases the risk of more adverse events, but the differences are small and neither statistically significant nor clinically relevant.

7.2.3.3. Concomitant medications

The latest treatment regimen of sDMARDs, bDMARDs and glucocorticoids received at any time from disease onset to the first dose of Kineret is presented in Table 4. Out of 306 patients, 94 (30.7%) had not been treated with either sDMARDs, bDMARDs or glucocorticoids before starting with Kineret (Table 4). The remaining 212 patients (69.3%, derived from Table 4 had received at least one of these treatments. Among the 212 patients, 78 (36.8%) were treated with various combinations of sDMARDs, bDMARDs and glucocorticoids before starting with Kineret and also continued with those concomitantly with Kineret treatment and 134 (63.2%, derived from Table 4) had stopped treatment before they started with Kineret.

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

Table 4 Latest treatment regimen of sDMARDs, bDMARDs and glucocorticoids (by decreasing order) receiving at any time from disease onset to the first dose of Kineret (The complete set).

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

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

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

CHMP comments

A total of 94 (30.7%) of the patients were not treated with any of the listed products prior to Kineret. Considered the labelled indication (*"for the treatment of Still's disease […] with active systemic features of moderate to high disease activity, or in patients with continued disease activity after treatment with NSAIDs or glucocorticoids."*), it is expectable that a proportion of patients has not been treated with any other DMARDs prior to initiation of Kineret treatment. Thus, the proportion of patients not being treated with any of the listed products prior to Kineret is of an expected magnitude Of these 94 patients, 49 (52%) patients were enrolled from the Netherlands, 15 (16%) patients were enrolled from Spain, 14 (15%) patients from France and 9 (10%) patients were enrolled from Italy. Half (n=51; 53%) of the 94 patients were enrolled from two centres (one in the Netherlands and one in Spain). This may indicate that the choice of treatment is at least to a certain degree according to local (national and centre-specific) guidelines. Overall, the pattern is in accordance with the development of treatment recommendations of patients with Still's disease; Historically, most patients were initially treated with NSAIDs and glucocorticoids but due to the adverse event profile of long-term treatment with glucocorticoids, biologic agents (especially the interleukin (IL) 1 and IL-6 inhibitors) are being used more often as single therapy at disease onset because they are effective in reducing clinical symptoms in patients with disease and have a different AE profile.

The most common treatment prior to initiation of Kineret was 'Glucocorticoids only', 'bDMARDs only' and a combination of these. This is in accordance with the treatment guidelines. Twenty (20; 65.4%) patients were treated with a triple- or quatro- combination of drugs.

Totally 78 (36.8%) patients continued initial treatment after initiation of Kineret. The most common combination was Kineret + glucocorticoids. It is well-known that treatment with high-dose glucocorticoids should be gradually reduced, and in accordance with this, the MAH informs that a total of 42 (54%) were treated concomitantly with both Kineret and glucocorticoid. However, of these patients, 31 (74%) were treated with glucocorticoids for ≥2 months indication that for these patients the concomitant treatment may have been therapeutic rather than a short overlapping period when tapping down the glucocorticoid treatment.

7.2.4. Adverse events/adverse reactions

7.2.4.1. Adverse events by PT and SOC

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

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

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

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

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

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

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

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

The majority of the "injection site reactions" (ISRs) occurred early after start of Kineret. The 3 infusion related reactions reported were related to a concomitantly administered drug (tocilizumab).

CHMP comments

Among the 306 patients included in the study, a total of 201 AEs were identified. The overall IR was 39.5 (95% CI 30.8-50.6) per 100 py. For all SOCs, the majority of AEs were reported within the first 6 months of treatment (confirmed by 95%CIs values). The most common AEs were within the SOC 'General disorders and administration site conditions' with the most common AE being Administration site reactions. Also, Injection related reactions were commonly reported under the SOC 'Injury, poisoning and procedural complications' but only one patient reported both 'Injection related reaction' and 'administration site reaction'. All other administration site reactions were reported in 1 patient each. Of note, Reactions at administration site is a known very common (≥1/10) AE according to the SmPC.

Other commonly reported AEs were reported within the SOCs 'Gastrointestinal reactions' and 'Skin and subcutaneous tissue disorders'. Among the 'Skin and subcutaneous tissue disorders', a total of 10 cases of Urticaria, Rash and Pruitus were reported; this could represent allergic reactions to Kineret. Of note, in the present study, there are no reports on allergic reactions; which according to the SmPC is an Uncommon adverse reaction (frequency: (≥1/1.000 to <1/100)).

According to the SmPC, the most serious AE besides of 'Anaphylactic reactions' is 'Serious infections'. A total of 52 cases of Infections were reported during the study. Seriousness of the reported infections is not reported but of note, the Table presents "AEs (non-serious AEs of at least moderate intensity

and serious AEs)". Overall, there is no pattern in the reported infections and no infections are reported in more than 6 cases; this includes Pneumonia (totally 5 cases) and gastroenteritis (totally 6 cases).

Haemophagocytic lymphohistiocytosis (equivalent to MAS) is reported in a total of 12 cases; this is discussed further in section '7.2.4.5. MAS as an event of special interest' below.

Overall, except for 'Haemophagocytic lymphohistiocytosis' (MAS, reported in 12 cases), 'Constipation' (reported in 6 cases) is the only AEs reported in more than 5 cases, not already included in the SmPC.

7.2.4.2. Incidence proportions of AEs (including SAEs)

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

Among the 306 patients included in the study, 99 patients experienced at least one AE, for an incidence proportion of 32.4% across an average treatment duration of 1.66 years.

Overall, the total number of AEs was 201, meaning an average of 0.66 AEs per patient. Among the patients who had at least one AE the average was 2 AEs per patient.

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

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

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

CHMP comments

A total of 99 patients experienced a total of 201 AEs of at least moderate intensity thus, approximately two-thirds (209 patients, 68%) did not report any AEs of at least moderate in intensity. This is reassuring. Of the 99 patients, 42 (42.4%) patients discontinued due to AEs and Intolerance.

Overall, there are only small differences between the number of AEs and the number of patients with AEs (see section 6.2.4.1 'Adverse events by PT and SOC' above). The most pronounced difference is observed in the SOC 'Infections and infestations', where 36 patients reported a total of 52 AEs. No specific pattern is observed. Five (5) patients reported neutropenia/pancytopenia as an SAE. It is

reassuring that the MAH informs that *"None of the 5 patients reporting neutropenia/pancytopenia had infections."* However, only 5 patients were reported to have neutropenia/pancytopenia but despite no clinical symptoms were reported among these patients, it is agreed that this is a SAE due to the increased risk of infections, anaemia and/or bleedings.

Haemophagocytic lymphohistiocytosis (equivalent to MAS) is reported in a total of 12 patients; this is discussed further in section '7.2.4.5. MAS as an event of special interest' below.

7.2.4.3. Serious adverse events by PT and SOC

Table 4 in the clinical trial report reports the number of SAEs with the related IRs and 95% CI by SOC, PT overall and according to 5 consecutive time windows for Kineret treatment: 1-6 months, 7-12 months, 13-18 months, 19-24 months and >24 months after first injection of Kineret. In Table 5 of the clinical trial report the same data are reported by overall PT by decreasing frequency of occurrence.

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

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

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

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

No malignancies or SAEs leading to death occurred during Kineret exposure.

CHMP comments

A total of 56 serious AEs (SAEs) were reported during the study; IR(95% CI):11.0(7.9-15.2). The majority of SAEs were reported in the first time window, i.e. within the initial 6 months of treatment.

Most SAEs were reported within the SOC 'Injury, poisoning and procedural complications' and were mainly reported to be Injection- and infusion related reactions (8 cases in total). Of note, in the Tabulated list of adverse reactions in section 4.8 of the SmPC 'Administration site reactions' is reported as a very common (≥1/10) AE. According to the SmPC, the reactions are most commonly reported within the first 2 weeks' treatment and disappear within 4-6 weeks. This is in line with the results from the present study, where the majority of 'Administration site reactions' were reported within the initial 6 months. The SmPC also states *"In 43 CAPS patients followed for up to 5 years no patient permanently or temporarily discontinued Kineret treatment due to injection site reactions."* The MAH

has committed to submit a Type II variation application to include information regarding Injection site reactions in section 4.8 of the SmPC. The application will be submitted during year 2020.

With the exception of the Injection related reactions (IR[95%CI] = 1.2[0.5-2.6]) and Haemophagocytic lymphohistiocytosis (equivalent to macrophage activation syndrome (MAS)) (IR[95%CI] = 2.2[1.1-4.1]), no PT SAEs were reported with an IR[95%CI] >1.0 which is reassuring. Haemophagocytic lymphohistiocytosis (MAS) is discussed in section '7.2.4.5. MAS as an event of special interest' below.

7.2.4.4. AEs (including SAEs) in patients with continuous Kineret treatment

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

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

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

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

CHMP comments

These results are in line with the results presented in the previous section. The majority of AEs were reported in the first treatment period (i.e. within the first 6 months) and the SOCs with most AEs and SAEs were 'Infections and infestations' and 'Injury, poisoning and procedural complications'.

Please see previous sections for further assessment.

7.2.4.5. MAS as an event of special interest

In total, 11 patients experienced 12 events (11 SAEs and 1 non-serious AE) of MAS on Kineret treatment. The IR of the first occurrence was 2.2 per 100 py Table 5.

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

The IR for first occurrence of MAS while on Kineret was lower in patients without a history of MAS (IR (95% CI) = 2.1 per 100 py (1.1-3.9). The IR for a second occurrence of MAS was higher (IR=16.1 per

100 py) compared to IR of the first occurrence. However, it should be noted that only 1 patient had a second occurrence.

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

After stopping Kineret, MAS was reported in 8 patients (Table 7). The earliest recurrence occurred in the time window 90-180 days. There was no indication of a "rebound effect" after discontinuing Kineret, i.e. no indication of an increase in MAS incidence immediately after stopping Kineret. Different triggers have been identified as possible causes of MAS (Table 8), disease flares (4 events, 33.3%), changes of treatments (3 events, 25.0%), and infections (2 events, 16.7%) being the most frequent.

Table 5 Number of first occurrence and recurrence of MAS events and incidence rates, overall and by history of MAS (The complete set)

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

Abbreviations: MAS, macrophage activation syndrome ('MAS' is equal to MedDRA Preferred Term: Haemophagocytic lymphohistiocytosis, MedDRA version 21.1); N, number of patients starting Kineret treatment; 95% CI, 95% Confidence Interval.
[a]number of MAS events. Only MAS occurring during Kineret exposed periods (incl. 2 days post stop) are counted.
[b]only time during periods with Kineret treatment (incl. 2 days post stop) counted.
[c]incidence rate per 100 patient years; number of events/∑patient time;
[d]the 1st occurrence of MAS is defined to occur at or after baseline regardless of whether the patient had a history of MAS or not; For the 1th occurence: time at risk is calculated from the first dose until the 1st event-MAS, last dose, last follow-up, or data-lock point for the report, whichever occurs first.

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

Table 6 Number of first occurrence of MAS events by history of MAS and time since first injection with Kineret (The MAS-1 set)

	History of MAS at baseline		**No History of MAS recorded at baseline**		**Total**	
N	**1**		**18**		**19**	
Time since first injection with Kineret	**n**	**%**	**n**	**%**	**n**	**%**
MAS during Kineret treatment						
1 -30 days	0	0.0	4	40.0	4	36.4
31-180 days	0	0.0	3	30.0	3	27.3
181-365 days	1	100.0	0	0.0	1	9.0
>365 days	0	0.0	3	30.0	3	27.3
Total	1	100.0	10	55.6	11	57.9
Mean time[a] (sd;min;max)	358		270 (395; 4; 968)		278 (375; 4; 968)	
MAS after Kineret is stopped						
1 -30 days	0	0.0	0	0.0	0	0.0
31-180 days	0	0.0	0	0.0	0	0.0
181-365 days	0	0.0	2	25.0	2	25.0
>365 days	0	0.0	6	75.0	6	75.0
Total	0	0.0	8	44.4	8	42.1
Mean time[a] (sd;min;max)	-		873 (725; 220; 2377)		873 (725; 220; 2377)	
Overall						
1 -30 days	0	0.0	4	22.2	4	21.0
31-180 days	0	0.0	3	16.7	3	15.8
181-365 days	1	100.0	2	11.1	3	15.8
>365 days	0	0.0	9	50.0	9	47.4
Total	1	100.0	18	100.0	19	100.0
Mean time[a] (sd;min;max)	358		538 (628; 4; 2377)		528 (612; 4; 2377)	

Abbreviations: MAS, macrophage activation syndrome ('MAS' is equal to MedDRA Preferred Term: Haemophagocytic lymphohistiocytosis, MedDRA version 21.1); N, number of patients, SD, standard deviation; min, minimum value; max, maximum value; n, number of MAS events.
The MAS-1 set, including patients who have been diagnosed a first time with MAS following start of Kineret treatment. All events following the first dose of Kineret, regardless of whether the patient is on Kineret treatment exposure are counted.
[a] presented in days.

Table 7 Number of first occurrence of MAS events by time since Kineret discontinuation (The MAS-1 set)

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

Abbreviations: MAS, macrophage activation syndrome ('MAS' is equal to MedDRA Preferred Term: Haemophagocytic lymphohistiocytosis, MedDRA version 21.1); N, number of patients with first occurrence of MAS, n, number of MAS events.
The MAS-1 set, including patients who have been diagnosed a first time with MAS following start of Kineret treatment. All events following the first dose of Kineret, regardless of whether the patient is on Kineret treatment exposure are counted.
[a] percentages are calculated in relation to number of first occurrence of MAS events after kineret is stopped.

Table 8 Trigger events for MAS events during simultaneous Kineret treatment (The MAS-1 set)

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

Abbreviations: MAS, macrophage activation syndrome ('MAS' is equal to MedDRA Preferred Term: Haemophagocytic lymphohistiocytosis, MedDRA version 21.1); N, number of patients, n, number of MAS events.
The MAS-1 set, including patients who have been diagnosed a first time with MAS following start of Kineret treatment. All events following the first dose of Kineret, regardless of whether the patient is on Kineret treatment exposure are counted.

CHMP comments

During the study period, 11 patients (3.6%) experienced 12 episodes of MAS (one patient experienced two episodes; this patient had a history of MAS prior to Kineret treatment). It is well-known that patients with Still's disease have an increased risk of spontaneous development of MAS. It is also well-known that MAS often develops due to certain triggers including infections and certain medication however, a causal relationship between Kineret and MAS has not (yet) been established. The present study is not designed to decide on a potential relationship between Kineret and MAS (of note, it has been reported that MAS occurs in up to 25% of the patients with SJIA). In the present study, the IR for first episode of MAS during Kineret treatment was 2.1/100 py (95%CI: 11-3.9). There was no pattern in the timing of MAS in relation to duration of Kineret treatment.

The MAH reports on trigger events. In 3 (25%) cases, change of treatment was considered to be the trigger event. The MAH should describe the changes in medication for these 3 patients in more details. Further, in the present SmPC, the only information concerning MAS in section 4.8 is as follows: "*There are no indications either from this study or from post-marketing adverse reaction reports that the*

overall safety profile in patients with CAPS or Still's disease is different from that in patients with RA, with the exception of the risk for development of MAS in patients with Still's disease. The adverse reactions table below therefore applies to Kineret treatment of RA, CAPS and Still's disease. Additional information on MAS is provided below." However, the MAH has committed to submit a Type II variation application to include updated information regarding MAS in (section 4.4 and) section 4.8 of the SmPC. The application will be submitted during year 2020.

7.3. PRAC's Discussion and Conclusion

7.3.1. Discussion

Kineret (anakinra, ATC code: L04AC03) 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. In 2018, Kineret was approved in the EU/EEA in adult and paediatric patients for the treatment of Still's disease, including SJIA and AOSD, with the following wording of the labelled indication: *"for the treatment of Still's disease […] with active systemic features of moderate to high disease activity, or in patients with continued disease activity after treatment with NSAIDs or glucocorticoids."*

The present PAS study was agreed upon with EMA in Procedure No. EMEA/H/C/000363/II/0056. The PASS was included in Section III.2-3 of the Kineret EU RMP version 4.5, as a category 3 activity. The primary objective of the present study was to evaluate the long-term safety of Kineret in paediatric patients with Still's disease in routine clinical care, including the risk of MAS.

The study was an international, non-interventional, single-armed, pharmacovigilance registry study of long-term safety utilizing available data from the Pharmachild JIA registry. Patients included were male and female patients diagnosed with SJIA according to the Pharmachild JIA registry study criteria and treated with Kineret. There were no restrictions with regard to disease duration or severity other than patients were treated with anakinra. There were also no restrictions with regard to the patients' demographics or baseline characteristics. This is endorsed as this optimized the possibility of including more patients into the study and also to obtain 'real world' data.

The safety-related variables were according to the data obtained from the Pharmachild JIA registry. Overall, the safety-related outcomes are considered to be in accordance with the objectives of the study. Due to the study design, it is not possible to include information regarding mild AEs however, information regarding discontinuation due to AEs (including mild AEs) was collected. As this is a PASS, it is considered acceptable that only data regarding moderate and severe AEs as well as SAEs are included. The MAH has adequately and sufficiently discussed the data sources, risks of bias, data management including handling of missing data and the statistical methods. Due to the study design, no sample size calculation was made, this is accepted. A medical monitor evaluated all reported AEs. The focus was to ensure the right diagnoses (ILAR) and adverse events and if necessary, the medical monitor was able to raise queries to the centers and request further clarifications. All information remained blinded.

A total of 306 patients from 15 different countries were included in the study. The majority of the patients (299 patients; 97.7%) were from Europe. A total of 13 European countries from all geographical parts of Europe (Northern, Southern, Eastern and Western parts) contributed with data. Thus, the results are considered to be representative for the European population.

Boys and girls were equally represented, which is in accordance with the disease characteristics. Median and mean age at time of Kineret treatment was 8.0 and 8.2 years, respectively with min and max age being 0.8 and 20.3 years, respectively. Approximately 2/3 (69%) of the patients were <12 years old. Mean time from diagnosis till initiation of Kineret treatment was 2.0 years. As only 5 patients were ≥18 years, this is not considered to impact the results in any clinically relevant degree.

It is reassuring that almost half (46%) of the patients were at some point treated for at least 12 months and approximately one-fourth (28%) were treated for at least 24 months. The majority (n=259; 85%) of patients were only treated with one course of Kineret and only very few (n=6; <2%) of the patients received ≥3 treatment courses.

Overall, the majority (3/4) of the patients discontinued Kineret treatment at some time during the study period. At all time windows, the most common reason for discontinuation was lack of efficacy (23.5-50.0%) with the percentage of patients discontinuing for this reason despite variations, being fairly stable over time. This indicates that patients who initially benefit from the treatment may not continue doing so. After 19 months treatment, approximately half of the patients had discontinued due to lack of efficacy. When looking at baseline characteristics, there were no predictive factors for the group of patients discontinuing due to lack of efficacy (e.g. disease severity, age, etc.).

The second most common reason for discontinuation of Kineret treatment was remission (reported in 18.3-55.9% of the discontinuations). The proportion increased over time (up to 18 months) indicating that long-term treatment may result in remission of the disease. This is reassuring. When looking at baseline characteristics, there were no predictive factors for the group of patients who obtained remission of the disease (e.g. disease severity, prior treatments, etc.).

A total of 30.7% of the patients were not treated with any of the listed products prior to Kineret. The most common treatment prior to initiation of Kineret was 'Glucocorticoids only', 'bDMARDs only' and a combination of these. This is in accordance with the treatment guidelines. Twenty (20; 65.4%) patients were treated with a triple- or quatro- combination of drugs.

Totally 78 (36.8%) patients continued initial treatment after initiation of Kineret. The most common combination was Kineret + glucocorticoids. It is well-known that treatment with high-dose glucocorticoids should be gradually reduced. However, among the 42 patients, who were concomitantly treated with both Kineret and glucocorticoid, 31 (74%) patients were treated with glucocorticoids for ≥2 months. This may indicate that for these patients the concomitant treatment was therapeutic rather than a short overlapping period when tapping down the glucocorticoid treatment.

Adverse events (AEs) of at least moderate severity was the third most common reason for discontinuations within the first 6 months (15.6%). Additionally, mild AEs and Intolerance were reported in 3.7% and 7.3% of the discontinuations, respectively. Discontinuations due to AEs (any degree) and Intolerance decreased over time indicating that at least the most severe/bothersome AEs were most common in the beginning of the treatment.

Among the 306 patients included in the study, a total of 201 AEs were identified. The overall IR was 39.5 (95% CI 30.8-50.6) per 100 py. For all SOCs, the majority of AEs were reported within the first 6 months of treatment (confirmed by non-overlapping 95%CIs values). The most common AEs were within the SOC 'General disorders and administration site conditions' with the most common AE being Administration site reactions. Also Injection related reactions were commonly reported under the SOC 'Injury, poisoning and procedural complications'. Of note, Reactions at administration site is a known very common (≥1/10) AE according to the SmPC.

Other commonly reported AEs were reported within the SOCs 'Gastrointestinal reactions' and 'Skin and subcutaneous tissue disorders'. Among the 'Skin and subcutaneous tissue disorders', a total of 10

cases of Urticaria, Rash and Pruritus were reported; this could represent allergic reactions to Kineret. Of note, in the present study, there are no reports on allergic reactions; which according to the SmPC is an Uncommon adverse reaction (frequency: (≥1/1.000 to <1/100)).

According to the SmPC, the most serious AE besides of 'Anaphylactic reactions' is 'Serious infections'. A total of 52 cases of Infections were reported during the study. Seriousness of the reported infections is not reported but of note, the Table presents "AEs (non-serious AEs of at least moderate intensity and serious AEs)". Overall, there is no pattern in the reported infections and no infections are reported in more than 6 cases; this includes Pneumonia (totally 5 cases) and gastroenteritis (totally 6 cases).

Overall, except for 'Haemophagocytic lymphohistiocytosis' (MAS, reported in 12 cases), 'Constipation' (reported in 6 cases) is the only AEs reported in more than 5 cases, not already included in the SmPC. However, constipation is a common disorder among children in general, and no update of the SmPC is needed.

A total of 99 patients experienced a total of 201 AEs of at least moderate intensity thus, approximately two-thirds (209 patients, 68%) did not report any AEs of at least moderate in intensity. This is reassuring. Of the 99 patients, 42 (42.4%) patients discontinued due to AEs and Intolerance.

Overall, there are only small differences between the number of AEs and the number of patients with AEs. The most pronounced difference is observed in the SOC 'Infections and infestations', where 36 patients reported a total of 52 AEs. No specific pattern is observed. Five (5) patients reported neutropenia/pancytopenia; which is a (potential) serious AE. It is reassuring that in the present study, none of the patients developed symptoms (e.g. infections).

A total of 56 serious AEs (SAEs) were reported during the study; IR(95% CI):11.0(7.9-15.2). The majority of SAEs were reported in the first time window, i.e. within the initial 6 months of treatment.

Most SAEs were reported within the SOC 'Injury, poisoning and procedural complications' and were mainly reported to be Injection- and infusion related reactions (8 cases in total). Of note, in the Tabulated list of adverse reactions in section 4.8 of the SmPC 'Administration site reactions' is reported as a very common (≥1/10) AE. According to the SmPC, the reactions are most commonly reported within the first 2 weeks' treatment and disappear within 4-6 weeks. This is in line with the results from the present study, where the majority of 'Administration site reactions' were reported within the initial 6 months. The SmPC also states *"In 43 CAPS patients followed for up to 5 years no patient permanently or temporarily discontinued Kineret treatment due to injection site reactions."* Considered that this study reports a total of 10 cases of Infusion-/injection-related reactions, and Injection site pain/reaction graduated as serious AEs, it is endorsed that the MAH plans to submit a Type II variation application later in Year 2020 including an update of the information regarding Injection related reactions in section 4.8 of the SmPC.

With the exception of the Injection related reactions (IR[95%CI] = 1.2[0.5-2.6]) and Haemophagocytic lymphohistiocytosis (equivalent to macrophage activation syndrome (MAS)) (IR[95%CI] = 2.2[1.1-4.1]), no PT SAEs were reported with an IR[95%CI] >1.0 which is reassuring.

During the study period, 11 patients (3.6%) experienced 12 episodes of MAS (one patient experienced two episodes; this patient had a history of MAS prior to Kineret treatment). It is well-known that patients with Still's disease have an increased risk of spontaneous development of MAS. It is also well-known that MAS often develops due to certain triggers including infections and certain medication however, a causal relationship between Kineret and MAS has not (yet) been established. The present study is not designed to decide on a potential relationship between Kineret and MAS (of note, it has been reported that MAS occurs in up to 25% of the patients with SJIA). In the present study, the IR

for first episode of MAS during Kineret treatment was 2.1/100 py (95%CI: 11-3.9). There was no pattern in the timing of MAS in relation to duration of Kineret treatment.

The MAH reports on trigger events. In 3 (25%) cases, change of treatment was considered to be the trigger event. The MAH should describe the changes in medication for these 3 patients in more details. Further, in the present SmPC, the only information concerning MAS in section 4.8 is as follows: *"There are no indications either from this study or from post-marketing adverse reaction reports that the overall safety profile in patients with CAPS or Still's disease is different from that in patients with RA, with the exception of the risk for development of MAS in patients with Still's disease. The adverse reactions table below therefore applies to Kineret treatment of RA, CAPS and Still's disease. Additional information on MAS is provided below."* Therefore, it is endorsed that the MAH plans to submit a Type II variation application later in Year 2020 including an update of the information regarding MAS in the Kineret SmPC.

7.3.2. Conclusion

Despite limitations due to the study design, the present study provides valuable information regarding Kineret-treatment of children and adolescents with Still's disease. The reported safety profile is mostly in line with the observations from previous studies (e.g. the pivotal phase III study used for the MAA). The MAH has committed to submit a Type II variation application for relevant updates of the SmPC; this application will be submitted within year 2020.

The benefit-risk balance of Kineret (anakinra) remains positive.

8. Risk management plan

The MAH submitted an updated RMP version 5.1, signed 16th December 2019 with data lock point of 1st May 2018, with this application. The (main) proposed RMP changes were the following:

- Update of the RMP to reflect completion of the PASS study in patients with Still's disease (Sobi.ANAKIN-302).

The currently approved RMP version is 4.9, approved 14th March 2019 under procedure EMEA/H/C/000363/II/0064/G.

Version 5.0 is under evaluation in procedure EMEA/H/C/000363/II/0070 covering a proposed new indication, Familial Mediterranean fever.

Version 5.1, subject of this procedure, builds further on version 5.0 rather than from approved version 4.9.

PART II: SAFETY SPECIFICATION

Part II Module SVII – Identified and potential risks

The table in section SVII.3.1 on Macrophage activation syndrome (MAS) has been updated to delete reference to the Sobi.ANAKIN-302 study and instead refer to the ongoing PASS study in CAPS patients.

PART III: PHARMACOVIGILANCE PLAN

III.2 Additional pharmacovigilance activities

Reference to study Sobi.ANAKIN-302 has been deleted.

III.3 Summary table of additional pharmacovigilance activities

Reference to study Sobi.ANAKIN-302 has been deleted.

The revised summary table is as follows:

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization - None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances - None				
Category 3 - Required additional pharmacovigilance activities				
Sobi.ANAKIN-201 (PRINTO/Eurofever Registry) (non-interventional) Recruitment completed, follow-up ongoing	Follow the safety of European CAPS patients treated with Kineret.	Emphasis on • serious infections • malignancies • injection site reactions • allergic reactions • medication errors, including reuse of the syringe	Annual update	Reported within PSURs.
			Final report	31 Dec 2020

PRINTO: Paediatric Rheumatology International Trials Organisation

PART V: RISK MINIMISATION MEASURES

V.3 Summary of risk minimisation measures

Reference to study Sobi.ANAKIN-302 as an additional pharmacovigilance activity has been deleted in relation to the important potential risk *Macrophage activation syndrome (not applicable for RA or CAPS)*. No other changes have been made to the table with reference to the approved version in RMP 4.9.

PART VI – SUMMARY OF THE RISK MANAGEMENT PLAN

The table in Part VI.II.B on MAS has been updated to delete reference to the Sobi.ANAKIN-302 study.

The study has also been deleted from Part VI.II.C.2 Other studies in post-authorisation development plan.

Annexes
Annex 2 - updated to reflect the completed status of study Sobi.ANAKIN-302.

Annex 3 – updated to include the final study report for study Sobi.ANAKIN-302, and protocol removed.

The summary table in annex 8 accurately reflects the changes from RMP version 4.9 to version 5.1.

Following completion of the variation EMEA/H/C/000363/II/0070, the MAH submitted a compiled RMP (RMP version 5.3) taking into account the RMP changes approved in the variation EMEA/H/C/000363/II/0070 (RMP version 5.2) and the changes proposed in the current variation (RMP version 5.1).

8.1. Overall conclusion on the RMP

☒ The changes to the RMP version 5.3 are acceptable.

9. Request for supplementary information

9.1. Major objections

No major objections have been identified.

9.2. Other concerns

9.2.1. Clinical aspects

Question 1 (Methods):

It is informed that *"A medical monitor evaluated all reported AEs. This person was able to raise queries to the centers and request further clarifications."* However, it is unclear, what exactly was evaluated by the medical monitor, whether any changes/corrections made by the medical monitor were recorded and whether the medical monitor was independent from the study. This should be clarified by the MAH.

Question 2 (Duration of Kineret treatment):

The majority of patients were only treated with one course of Kineret however, it is informed that the 306 patients had a total of 360 treatment courses. The MAH should inform how many patients were treated with 1, 2, 3 etc. courses of Kineret during the observation period.

Question 3 (Reasons for Kineret treatment discontinuation):

The MAH is asked to discuss if there are any predictive factors for the group of patients discontinuing due to lack of efficacy (e.g. disease severity, age, etc.).

Question 4 (Reasons for Kineret treatment discontinuation):

The MAH is asked to discuss if there are any predictive factors for the group of patients who obtained remission of the disease (e.g. disease severity, prior treatments, etc.).

Question 5 (Reasons for Kineret treatment discontinuation):

The MAH should inform if discontinuation due to AEs or Intolerance was more pronounced among patients concomitantly being treated with other medication compared to patients in mono-therapy with Kineret.

Question 6 (Concomitant medications):

A total of 30.7% of the patients were not treated with any of the listed products prior to Kineret. The MAH should discuss this proportion and inform if these patients were clustered from single centers/countries or characterized with e.g. mild disease.

Question 7 (Concomitant medications):

The MAH is asked to present data for the number of patients with concomitant treatment with glucocorticoids 1 and 2 months after initiation with Kineret as this may provide an indication of whether the concomitant treatment was (therapeutic) intended or represented a temporary overlap of treatments.

Question 8 (Adverse events by PT and SOC):

The most common AEs were within the SOC 'General disorders and administration site conditions' with the most common AE being Administration site reactions. Also Injection related reactions were commonly reported under the SOC 'Injury, poisoning and procedural complications' It is unclear whether the majority of these AEs are reported by the same patients; please clarify.

Question 9 (Adverse events by PT and SOC):

The MAH should inform if the 5 patients reporting neutropenia and pancytopenia also reported infections- or infestation-related AEs.

Question 10 (Macrophage Activation Syndrome (MAS)):

The MAH reports on trigger events. In 3 (25%) cases, change of treatment was considered to be the trigger event. The MAH should describe the changes in medication for these 3 patients in more details.

9.2.2. Aspects related to Product information

Question 11 (Incidence proportions of (S)AEs):

The MAH is asked to discuss if GI AEs including 'Constipation' should be included in the Tabulated list of adverse reaction in section 4.8 of the SmPC for Kineret.

Question 12 (Serious adverse events by PT and SOC):

The SmPC for Kineret states *"In 43 CAPS patients followed for up to 5 years no patient permanently or temporarily discontinued Kineret treatment due to injection site reactions."* Considered that this study reports a total of 10 cases of Infusion-/injection-related reactions, and Injection site pain/reaction graduated as serious AEs, the MAH is asked to inform if any of these SAEs led to discontinuation of the treatment and to discuss if the new data requires an update of the information provided in section 4.8 of the SmPC.

Question 13 (Macrophage Activation Syndrome (MAS)):

The MAH should consider updating section 4.8 of the SmPC with more information regarding MAS (cross-reference to section 4.4 would be relevant).

Request for a GCP Inspection

N/A

RMP aspects

None.

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

10.1. Clinical aspects

10.1.1. Major objections

No major objections were identified.

10.1.2. Other concerns

Question 1 (Methods):

It is informed that *"A medical monitor evaluated all reported AEs. This person was able to raise queries to the centers and request further clarifications."* However, it is unclear, what exactly was evaluated by the medical monitor, whether any changes/corrections made by the medical monitor were recorded and whether the medical monitor was independent from the study. This should be clarified by the MAH.

MAH's response: The medical monitor of the Pharmachild registry is a pediatric immunologist and pediatric rheumatologist from Utrecht (the Netherlands). The medical monitor is also the principle investigator of one of the PRINTO sites collecting data in Pharmachild, however all data remained blinded and therefore the medical monitor was unable to identify patients from their own site. During the safety review, the medical monitor was able to check that all appropriate patient data had been entered in the electronic database and raise queries in case of missing data.

The medical monitor had access to all entered data but the safety review was focused on safety reports, drug history and ILAR diagnosis. The medical monitor did not "correct" or update any of the data entered by the sites. If further clarifications were needed the medical monitor raised a query to the sites. The medical review performed by the medical monitor was documented in a dedicated field within the eCRF, existing for all safety events.

The Pharmachild medical monitor is MedDRA certified and was able to code the safety events separately to the local site coding and PRINTO coordinating centre. Specific AEs (e.g. infections) were also coded by an adjudication committee. Any discrepancy between the centre coding, PRINTO coding, medical monitor and, if available adjudication committee are solved by consensus (more details in Giancane et al. 2020).

CHMP comments

The MAH has clarified that the data remained blinded for the medical monitor. The focus was to ensure the right diagnoses (ILAR) and adverse events. It was informed that the medical monitor also was the principle investigator of one of the PRINTO sites thus theoretical, it cannot be excluded that the medical monitor recognized his/her 'own' patients. However, a total of 259 patients were included in the study. Overall, this is not expected to affect the study results, and the issue will not be pursued.

Conclusion: Issue resolved.

Question 2 (Duration of Kineret treatment):

The majority of patients were only treated with one course of Kineret however, it is informed that the 306 patients had a total of 360 treatment courses. The MAH should inform how many patients were treated with 1, 2, 3 etc. courses of Kineret during the observation period.

MAH's response: In CSR section 10.4.1 second paragraph and in the CSR Table 19 it is stated that 306 patients had a total of 360 courses of Kineret treatment. The number of patients treated with 1, 2, 3 or 4 courses is presented in Table 1. The majority of the patients (n=259, 84.64 %) had one course of treatment.

Table 1 **Number of patients treated with 1 or more courses of Kineret during the observation period**

Total N of courses for patient	N of patients	% of patients
1	259	84.64
2	41	13.40
3	5	1.63
4	1	0.33
Total	306	100.00

CHMP comments

The MAH has presented the requested data. As observed in Table 1 above, the majority (85%) of the patients received one course of Kineret treatment and only very few (n=6; <2%) of the patients received ≥3 treatment courses.

Conclusion: Issue resolved.

Question 3 (Reasons for Kineret treatment discontinuation):

The MAH is asked to discuss if there are any predictive factors for the group of patients discontinuing due to lack of efficacy (e.g. disease severity, age, etc.).

MAH's response: The study sample size was 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 were included in the study. The purpose of the study was to describe long-term safety of Kineret, utilizing all Kineret treated SJIA patients in an already available registry and therefore no a priori statistical power estimation was performed. Evaluation of predictive factors

for discontinuation of Kineret due to inefficacy were not part of the study objectives, therefore the MAH did not prespecify any predictive analyses in the analysis plan and refrains from performing, interpreting and drawing any conclusions regarding potential predictive factors in this post-hoc setting.

In response to Question 3, the MAH provides Table 2, that shows baseline characteristics grouped by those patients who at least once discontinued due to inefficacy vs all remaining patients (including patients who discontinued due to other reasons and patients who did not discontinue treatment). In this study, data on disease severity was not available.

Table 2 Characteristics of the patients discontinuing due to inefficacy

Total N=306 (100.0 %)	**Patients discontinuing due to inefficacy N=103 (33.7 %)**	**All remaining patients N=203 (66.3 %)**
Female, n (%)	58 (56.3)	96 (47.3)
Male, n (%)	45 (43.7)	107 (52.7)
Age at Kineret start (years), mean (sd, min, max) median (q1,q3)	 7.1 (4.4, 0.8, 20.3) 6.6 (3.2, 10.2)	 8.8 (4.7, 0.8,19.3) 8.8 (4.3, 12.6)
Age groups, n (%)		
Infant (< 2 years)	12 (11.6)	10 (4.9)
Child (2 years - <12 years)	76 (73.8)	134 (66.0)
Adolescent (12 years - <18 years)	13 (12.6)	56 (27.6)
Adult (≥ 18 years)	2 (1.9)	3 (1.5)
Time from SJIA onset to start of Kineret (years), mean (sd, min, max) median (q1,q3)	 2.4 (3.0, 0.0, 13.6) 1.0 (0.3, 3.7)	 1.8 (2.9, 0.0, 16.0) 0.5 (0.1, 1.7)
Time from SJIA diagnosis to start of Kineret (years), mean (sd, min, max) median (q1,q3)	 2.1 (3.0, 0.0, 13.4) 0.7 (0.1, 3.1)	 1.5 (2.8, 0.0, 15.0) 0.2 (0.0, 1.4)

Total N=306 (100.0 %)	Patients discontinuing due to inefficacy N=103 (33.7 %)	All remaining patients N=203 (66.3 %)
Time from SJIA onset to first visit (years), mean (sd, min, max) median (q1, q3)	1.3 (2.3, 0.0, 10.9) 0.2 (0.1, 1.6)	0.7 (1.7, 0.0, 14.9) 0.1 (0.0, 0.4)
Patients with History of MAS, n (%)	3 (2.9)	7 (3.4)
Country of clinic, n (%)		
Croatia	0	1 (0.5)
Denmark	8 (7.8)	11 (5.4)
France	22 (21.4)	27 (13.3)
Germany	1 (1.0)	0
Greece	1 (1.0)	10 (4.9)
Hungary	0	2 (1.0)
Israel	0	3 (1.5)
Italy	18 (17.5)	39 (19.2)
Latvia	1 (1.0)	0
Netherlands	20 (19.4)	57 (28.1)
Norway	6 (5.8)	6 (2.3)
Romania	0	1 (0.5)
Saudi Arabia	1 (1.0)	3 (1.5)
Spain	17 (16.5)	29 (14.3)
Switzerland	8 (7.8)	14 (6.9)
Ethnicity, n (%)		
Caucasian	69 (67.0)	147 (72.4)
Other	34 (33.0)	56 (27.6)
Prior treatment (Latest treatment regimen occurring any time before the first dose of Kineret) n (%)	54 (52.4)	80 (39.4)
Glucocorticoids only	6 (5.8)	26 (12.8)
bDMARDs only	13 (12.6)	11 (5.4)
bDMARDs+glucocorticoids	6 (5.8)	7 (3.4)
MTX+bDMARDs	4 (3.9)	8 (3.9)
MTX only	4 (3.9)	7 (3.4)
MTX+glucocorticoids	2 (1.9)	9 (4.4)
MTX+bDMARDs+glucocorticoids	3 (2.9)	5 (2.5)
sDMARDs+bDMARDs +MTX	3 (2.9)	2 (1.0)
sDMARDs+bDMARDs+MTX+glucocorticoids	3 (2.9)	2 (1.0)
sDMARDs+bDMARDs	3 (2.9)	0
sDMARDs+glucocorticoids	2 (1.9)	1 (0.5)
sDMARDs+MTX	1 (1.0)	1 (0.5)

Total N=306 (100.0 %)	Patients discontinuing due to inefficacy N=103 (33.7 %)	All remaining patients N=203 (66.3 %)
sDMARDs+bDMARDs+glucocorticoids	2 (1.9)	0
sDMARDs+MTX+glucocorticoids	1 (1.0)	1 (0.5)
sDMARDs only	1 (1.0)	0

CHMP comments

As requested, the MAH has presented baseline characteristics for the patients discontinuing due to inefficacy (n=103; 34%) and likewise also for all remaining patients (n=203; 66%). It is agreed with the MAH that there are no clear differences in baseline characteristics between the two groups. There was a numeric tendency towards patients discontinuing due to inefficacy were more often previously

treated with monotherapy. This most likely mirror that in these patients, monotherapy was not sufficient.

Conclusion: Issue resolved.

Question 4 (Reasons for Kineret treatment discontinuation):

The MAH is asked to discuss if there are any predictive factors for the group of patients who obtained remission of the disease (e.g. disease severity, prior treatments, etc.).

MAH's response: The study sample size was 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 were included in the study. The purpose of the study was to describe long-term safety of Kineret, utilizing all Kineret treated SJIA patients in an already available registry and therefore no a priori statistical power estimation was performed. Evaluation of predictive factors

for discontinuation of Kineret due to remission were not part of the study objectives, therefore the MAH did not prespecify any predictive analyses in the analysis plan and refrains from performing, interpreting and drawing any conclusions regarding potential predictive factors in this post-hoc setting.

In response to Question 4, the MAH provides Table 3, that shows baseline characteristics grouped by those patients who at least once discontinued due to remission vs all remaining patients (including patients who discontinued due to other reasons and patients who did not discontinue treatment).

There are differences in standards of care between different countries which might influence the rate of discontinuation when in remission.

Table 3 Characteristics of the patients discontinuing due to remission

Total N=306 (100.0 %)	**Patients discontinuing due to remission N=85 (27.8 %)**	**All remaining patients N=221 (72.2 %)**
Female, n (%)	35 (41.2)	119 (53.9)
Male, n (%)	50 (58.8)	102 (46.1)
Age at Kineret start (years), mean (sd, min, max) median (q1,q3)	 8.1 (4.7, 1.2, 19.3) 8.0 (3.8, 12.0)	 8.3 (4.7, 0.8, 20.3) 7.9 (4.1, 11.8)
Age groups, n (%)		
Infant (< 2 years)	4 (4.7)	18 (8.1)
Child (2 years - <12 years)	59 (69.4)	151 (68.3)
Adolescent (12 years - <18 years)	21 (24.7)	48 (21.7)
Adult (≥ 18 years)	1 (1.2)	4 (1.8)
Time from Kineret start to SJIA onset (years), mean (sd, min, max) median (q1,q3)	 1.5 (3.0, 0.0, 16.0) 0.3 (0.1, 1.5)	 2.2 (2.9, 0.0, 13.6) 0.8 (0.3, 2.8)
Time from Kineret start to SJIA diagnosis (years), mean (sd, min, max) median (q1,q3)	 1.3 (2.9, 0.0, 15.0) 0.1 (0.0, 1.1)	 1.8 (2.9, 0.0, 13.4) 0.3 (0.0, 2.4)
Time from SJIA onset to first visit (years), mean (sd, min, max) median (q1,q3)	 0.6 (1.7, 0.0, 10.8) 0.1 (0.0, 0.3)	 1.0 (2.0, 0.0, 14.9) 0.2 (0.1, 1.1)
Patients with History of MAS, n (%)	1 (1.2)	9 (4.1)
Country of clinic, n (%)		
Croatia	0	1 (0.4)
Denmark	1 (1.2)	18 (8.1)
France	8 (9.4)	41 (18.6)
Germany	0	1 (0.4)
Greece	2 (2.3)	9 (4.1)
Hungary	2 (2.3)	0
Israel	1 (1.2)	2 (0.9)
Italy	12 (14.1)	45 (20.4)
Latvia	0	1 (0.4)
Netherlands	35 (41.2)	42 (19.0)
Norway	2 (2.3)	10 (4.5)
Saudi Arabia	0	4 (1.8)
Romania	1 (1.2)	0
Spain	14 (16.5)	32 (14.5)

Total N=306 (100.0 %)	Patients discontinuing due to remission N=85 (27.8 %)	All remaining patients N=221 (72.2 %)
Switzerland	7 (8.2)	15 (6.8)
Ethnicity, n (%)		
Caucasian	65 (76.5)	151 (68.3)
Other	20 (23.5)	70 (31.7)
Prior treatment (Latest treatment regimen occurring any time before the first dose of Kineret) n (%)	31 (36.5)	103 (46.6)
Glucocorticoids only	12 (14.1)	20 (9.0)
bDMARDs only	3 (3.5)	21 (9.5)
bDMARDs+glucocorticoids	2 (2.4)	11 (5.0)
MTX+bDMARDs	4 (4.7)	8 (3.6)
MTX only	3 (3.5)	8 (3.6)
MTX+glucocorticoids	4 (4.7)	7 (3.2)
MTX+bDMARDs+glucocorticoids	2 (2.4)	6 (2.7)
sDMARDs+bDMARDs +MTX	0	5 (2.3)
sDMARDs+bDMARDs+MTX+glucocorticoids	0	5 (2.3)
sDMARDs+bDMARDs	0	3 (1.4)
sDMARDs+glucocorticoids	0	3 (1.4)
sDMARDs+MTX	1 (1.2)	1 (0.5)
sDMARDs+bDMARDs+glucocorticoids	0	2 (0.9)
sDMARDs+MTX+glucocorticoids	0	2 (0.9)
sDMARDs only	0	1 (0.5)

CHMP comments

As requested, the MAH has presented baseline characteristics for the patients discontinuing due to remission (n=85; 28%) and for all remaining patients (n=221; 72%). The MAH informs *that "There are differences in standards of care between different countries which might influence the rate of discontinuation when in remission"*. This is acknowledged.

Conclusion: Issue resolved.

Question 5 (Reasons for Kineret treatment discontinuation):

The MAH should inform if discontinuation due to AEs or Intolerance was more pronounced among patients concomitantly being treated with other medication compared to patients in monotherapy with Kineret.

MAH's response: There was no marked difference in the frequency of discontinuation due to AEs or intolerance among patients concomitantly being treated with other medication compared to patients in monotherapy with Kineret (Table 4).

Table 4 Reasons for discontinuation due to AEs or intolerance among patients concomitantly being treated with other medication compared to patients in mono-therapy with Kineret

	Patients with concomitant therapy, N=193 (%)	Patients in mono-therapy with Kineret, N=113 (%)
Patients discontinuing due to AE (any degree)	18 (9.3)	8 (7.1)
Patients discontinuing due to Intolerance	9 (4.7)	5 (4.4)
Patients discontinuing due to AE or Intolerance	25 (12.9)	11 (9.7)

CHMP comments

As requested, the MAH has presented data for reasons for discontinuations for the group of patients treated with monotherapy with Kineret and for patients treated with Kineret + another treatment. Numeric, slightly more patients with concomitant treatment discontinued due to AE and/or intolerance; this could be explained by the fact that concomitant treatment increases the risk of more adverse events, but the differences are small and neither statistically significant nor clinically relevant.

Conclusion: Issue resolved.

Question 6 (Concomitant medications):

A total of 30.7% of the patients were not treated with any of the listed products prior to Kineret. The MAH should discuss this proportion and inform if these patients were clustered from single centers/countries or characterized with e.g. mild disease.

MAH's response: Among the 306 patients included in the present study, 94 patients (30.7%) were not previously treated because Kineret was started at disease diagnosis (date of diagnosis was almost identical to Kineret start date). Regarding the geographic distribution of patients: among the 94 patients, 49 (52.1%) were enrolled in the Netherlands (2 centers), 15 (16.0%) from Spain (4 centers), 14 (14.9%) from France (1 center) and 9 (9.6%) from Italy (3 centers) (Table 5). The majority of the patients without prior therapy before starting Kineret were enrolled from only two centers. One center in the Netherlands enrolled 41 out of 94 (43.6%), and one center in Spain enrolled 10 out of 94 (9.4%) patients in this category respectively (Table 6).

In this study, data on disease severity was not available.

Table 5 **Characteristics of the patients without prior therapy before starting Kineret**

Total N=306 (100.0 %)	**Patients without prior therapy before starting Kineret, N=94 (30.7 %)**	**All remaining patients, N=212 (69.3 %)**
Female, n (%)	43 (45.7)	111 (52.4)
Male, n (%)	51 (54.3)	101 (47.6)
Age at baseline (years), mean (sd, min, max) median (q1,q3)	7.7 (4.9, 0.8, 17.7) 6.8 (3.6, 12.2)	8.4 (4.6, 0.8, 20.3) 8.5 (4.3, 11.8)
Age groups, n (%)		
Infant (< 2 years)	12 (12.8)	10 (4.7)
Child (2 years - <12 years)	58 (61.7)	152 (71.7)
Adolescent (12 years - <18 years)	24 (25.5)	45 (21.2)
Adult (>18 years)	0	5 (2.4)
Time from Kineret start to SJIA onset (years), mean (sd, min, max) median (q1,q3)	 0.4 (0.8, 0.0, 5.2) 0.1 (0.1, 0.3)	 2.7 (3.3, 0.0, 16.0) 1.1 (0.4, 4.3)
Time from Kineret start to SJIA diagnosis (years), mean (sd, min, max) median (q1,q3)	 0.1 (0.4, 0.0, 3.0) 0.0 (0.0, 0.0)	 2.4 (3.2, 0.0, 15.0) 0.9 (0.2, 4.0)
Time from SJIA onset to first visit (years), mean (sd, min, max) median (q1,q3)	 0.3 (0.5, 0.0, 3.6) 0.1 (0.0, 0.2)	 1.2 (2.2, 0.0, 14.9) 0.2 (0.1, 1.2)
Country of clinic, n of patients (%)		
Croatia	0	1 (0.5)
Denmark	2 ((2.1), 1 center	17 (3 centers) (8.0)
France	14 (14.9), (1 center)	35 (1 center) (16.5)
Germany	0	1 (0.5)
Greece	0	11 (3 centers) (5.2)
Hungary	0	2 (1 center) (0.9)
Israel	2 (1 center) (2.1)	1 (0.5)
Italy*	9 (3 centers) (9.6)	48 (10 centers) (22.6)
Netherlands*	49 (2 centers) (52.1)	28 (3 centers) (13.2)
Norway	0	12 (2 centers) (5.7)
Romania	0	1 (0.5)
Saudi Arabia	0	4 (1 center) (1.9)
Spain*	15 (4 centers) (16.0)	31 (5 centers) (14.6)
Switzerland	3 (1 center) (3.2)	19 (1 center) (8.9)
Ethnicity, n (%)		
Caucasian	70 (74.5)	146 (68.9)
Other	24 (25.5)	66 (31.1)

* Details of the distribution of patients from centers in Table 6.

Table 6 **Details of the distribution of patients from centers of Italy, Netherlands and Spain**

	Patients without prior therapy before starting Kineret, N=94	All remaining patients, N=212
Italy, N (%)	**9 (100.0)**	**48 (100.0)**
Centre 1	3 (33.3)	31(64.6)
Centre 2	2 (22.2)	1 (2.1)
Centre 3	2 (22.2)	4 (8.3)
Centre 4	0	1 (2.1)
Centre 5	0	2 (4.2)
Centre 6	0	1 (2.1)
Centre 7	0	1 (2.1)
Centre 8	0	1 (2.1)
Centre 9	0	2 (4.2)
Centre 10	0	1 (2.1)
Centre 11	2 (22.2)	1 (2.1)
Centre 12	0	2 (4.2)
Netherlands, N (%)	**49 (100.0)**	**28 (100.0)**
Centre 1	41 (83.7)	17 (60.7)
Centre 2	8 (16.3)	9 (32.1)
Centre 3	0	2 (7.1)
Spain, N (%)	**15 (100.0)**	**31 (100.0)**
Centre 1	2 (13.3)	2 (6.4)
Centre 2	10 (66.7)	19 (61.3)
Centre 3	1 (6.7)	3 (9.7)
Centre 4	2 (13.3)	0
Centre 5	0	5 (16.1)
Centre 6	0	2 (6.4)

CHMP comments

The MAH informs that the 94 patients initiating Kineret at time of diagnosis (thus without previous treatment with e.g. glucocorticoids) were enrolled from the Netherlands (49 patients; 52%), Spain (15 patients; 16%), France (14 patients;15%) and Italy (9 patients; 10%). Half (n=51; 53%) of the 94 patients were enrolled from two centres (one in the Netherlands and one in Spain). This may indicate that the choice of treatment is at least to a certain degree according to local (national and centre-specific) guidelines. Overall, the pattern is in accordance with the development of treatment recommendations of patients with Still's disease: Historically, most patients were initially treated with NSAIDs and glucocorticoids but due to the adverse event profile of long-term treatment with glucocorticoids, biologic agents, especially the interleukin (IL) 1 and IL-6 inhibitors, are being used more and more as single therapy at disease onset because they are effective in reducing clinical symptoms in patients with disease refractory to NSAID and glucocorticoid therapy.

Conclusion: Issue resolved.

Question 7 (Concomitant medications):

The MAH is asked to present data for the number of patients with concomitant treatment with glucocorticoids 1 and 2 months after initiation with Kineret as this may provide an indication of whether the concomitant treatment was (therapeutic) intended or represented a temporary overlap of treatments.

MAH's response: Out of 306 patients, 94 (30.7 %) had not been treated with either sDMARDs, bDMARDs or glucocorticoids before starting with Kineret (see CSR Table 21). The remaining 212 patients

(69.3 %, derived from CSR Table 21) had received at least one of these treatments. Among the 212 patients, 78 (36.8 %) were treated with various combinations of sDMARDs, bDMARDs and glucocorticoids before starting with Kineret and also continued with those concomitantly with Kineret treatment. Among the 78 patients, 42 (53.8 %) continued glucocorticoids after initiation of Kineret (Table 21). In more detail, 11 (26.2 %) patients had concomitant treatment with glucocorticoids up to 1 month after start of Kineret, 5 (11.9 %) patients up to 2 months and for 26 (61.9 %) patients for more 2 months (median duration was 264 days, min=64, max=1217, 1q=118, 3q=642, mean=407, sdv=376).

CHMP comments

Approximately one-third of the patients had not been treated with any DMARDs or glucocorticoids prior to initiation of Kineret. Of the 212 (69%) patients who had been treated with glucocorticoids and/or DMARD(s), approximately two-third (n=134; 63%) of the patients discontinued the DMARD/ glucocorticoid treatment when initiating treatment with Kineret. A total of 42 (54%) were treated concomitantly with both Kineret and glucocorticoid, and of these patients, 31 (74%) were treated with glucocorticoids for ≥2 months. This indicates that for these patients the concomitant treatment was therapeutic rather than a short overlapping period when tapping down the glucocorticoid treatment.

Conclusion: Issue resolved.

Question 8 (Adverse events by PT and SOC):

The most common AEs were within the SOC 'General disorders and administration site conditions' with the most common AE being Administration site reactions. Also Injection related reactions were commonly reported under the SOC 'Injury, poisoning and procedural complications' It is unclear whether the majority of these AEs are reported by the same patients; please clarify.

MAH's response: The CSR Table 7 shows the number of patients who had at least one AE per PT/SOC, while the CSR Table 2 and 3 show the number of AEs. For example, for SOC 'General disorders and administration site conditions' there was a total of 23 AEs (CSR Table 2) for 21 patients (CSR Table 7). Similarly, for the PT 'Injection related reaction' belonging to the SOC 'Injury, poisoning and procedural complications', there was a total of 10 AEs (CSR Table 2) for 10 patients (CSR Table 7).

1 patient who reported an 'Injection related reaction' (belonging to the SOC 'Injury, poisoning and procedural complications') also reported an administration site reaction in the SOC 'General disorders and administration site conditions' ('Injection site reaction'). All other administration site reactions were reported in 1 patient each.

CHMP comments

The MAH has clarified that only one patient reported both 'Injection related reaction' and 'administration site reaction'. All other administration site reactions were reported in 1 patient each.

Conclusion: Issue resolved.

Question 9 (Adverse events by PT and SOC):

The MAH should inform if the 5 patients reporting neutropenia and pancytopenia also reported infections- or infestation-related AEs.

MAH's response: None of the 5 patients reporting neutropenia/pancytopenia had infections.

CHMP comments

The MAH has clarified that *"None of the 5 patients reporting neutropenia/pancytopenia had infections."* – This indicate that neutropenia/pancytopenia was not associated with an increased risk of clinical symptoms (e.g. infections) however, only 5 patients were reported to have neutropenia/pancytopenia thus no conclusions or generalisations (to all patients with cytopenia/neutropenia) can be made.

Conclusion: Issue resolved.

Question 10 (Macrophage Activation Syndrome (MAS)):

The MAH reports on trigger events. In 3 (25%) cases, change of treatment was considered to be the trigger event. The MAH should describe the changes in medication for these 3 patients in more details.

MAH's response: The EC approval for the Pharmachild study, as well as the ICF signed by the patients, allows PRINTO to share summary data with pharmaceutical companies. Additional approval is however needed for sharing of raw data. No specific/additional EC approval has been sought for this PAS study as PRINTO has not shared any raw data with the MAH and the study only reports summary outputs. Therefore, the study report and this response cannot include any patient listings and/or patient narratives. Due to this the MAH cannot provide the details requested for the 3 patients mentioned in the question.

CHMP comments

The MAH has informed that *"the study report and this response cannot include any patient listings and/or patient narratives."* This is accepted and the issue will not be pursued.

Conclusion: Issue resolved.

10.1.3. Aspects related to Product information

Question 11 (Incidence proportions of (S)AEs):

The MAH is asked to discuss if GI AEs including 'Constipation' should be included in the Tabulated list of adverse reaction in section 4.8 of the SmPC for Kineret.

MAH's response: There were 18 AEs of at least moderate intensity in the SOC Gastrointestinal disorders reported in 16 patients out of 306 patients in this study (CSR Table 2 and CSR Table 7). The study does not include a control arm and therefore no conclusions on causal relationship could be drawn. However, gastrointestinal symptoms are common in the general pediatric population.

The most frequently reported event in the SOC Gastrointestinal disorders was constipation, with 6 events reported in 6 patients. Constipation is a common symptom in the general population with up to 29.6% children globally developing symptoms (Rajindrajith and Devanarayana 2011). The MAH therefore considers that there is no reason to add GI events including Constipation to 4.8 in the SmPC.

CHMP comments

The MAH has sufficiently justified that GI AEs (including 'Constipation') should not be included in the tabulated list of adverse reactions in section 4.8 of the SmPC. The MAH argues that Constipation is a common condition among children which is acknowledged.

Conclusion: Issue resolved.

Question 12 (Serious adverse events by PT and SOC):

The SmPC for Kineret states *"In 43 CAPS patients followed for up to 5 years no patient permanently or temporarily discontinued Kineret treatment due to injection site reactions."* Considered that this study reports a total of 10 cases of Infusion-/injection-related reactions, and Injection site pain/reaction graduated as serious AEs, the MAH is asked to inform if any of these SAEs led to discontinuation of the treatment and to discuss if the new data requires an update of the information provided in section 4.8 of the SmPC.

MAH's response: Out of the 10 SAEs in CSR Table 5 describing 'Injection related reaction', 'Infusion related reaction', 'Injection site pain' and 'Injection site reaction', 3 were related to a different drug, 1 led to temporary discontinuation and 6 led to permanent discontinuation of Kineret.

In parallel with this procedure for the PAS study, the results of the anaSTILLs study (Sobi.ANAKIN-301) are discussed in another ongoing procedure EMA/H/C/000363/P46/031). The anaSTILLs study was a placebo-controlled study in 12 patients with Still's disease and the CSR was submitted to EMA in November 2019 to meet the obligation of Article 46 since the study included pediatric patients. Based on the results from both this PAS study and the anaSTILLs study, the MAH plans to propose an updated text for the SmPC section 4.8 description of the 'Injection site reactions'. The updated text will be submitted in a future variation later this year and will describe that in 12 patients with Still's disease treated for 12 weeks in the placebo-controlled study, ISRs occurred in both treatment groups, of which all were mild in severity. No patients discontinued treatment due to ISRs. It will also describe that in the PAS study, a non-interventional long-term safety study in 306 pediatric patients with Still´s disease followed for up to more than 9 years, ISRs of moderate or severe intensity had an incidence rate of 1.6 per 100 patient years.

CHMP comments

The MAH informs that no information regarding Injection site reactions will be added to the SmPC during this present procedure. The MAH plans to submit a Type II variation later in 2020. This application will include an update of section 4.8 in the SmPC with information regarding Injection site reactions. This should be accepted as a commitment from the MAH.

Conclusion: Issue mostly resolved.

The MAH should commit to submit a Type II variation application including an update of the SmPC with information regarding Injection site reactions (should be included in section 4.4 of the SmPC).

Question 13 (Macrophage Activation Syndrome (MAS)):

The MAH should consider updating section 4.8 of the SmPC with more information regarding MAS (cross-reference to section 4.4 would be relevant).

MAH's response: relationship with Kineret has been established for MAS. The texts about MAS (and Malignancies) were moved from section 4.8 to section 4.4 in procedure EMEA/H/C/000363/II/0064/G and a Positive Opinion was received in March 2019.

In the SmPC section 4.4 the MAH plans to add results from both this PAS study and from the anaSTILLs study (Sobi.ANAKIN-301) regarding MAS, to be submitted in a future variation later this year. The proposed text will describe that no events of MAS were reported in the company-sponsored clinical studies in Still's disease, and that in the PAS study, a noninterventional long-term safety study in 306 pediatric patients with Still's disease, there was no indication that the frequency of MAS increased during, or directly after, Kineret treatment. The proposed text will also state that the incidence rate of MAS in

the PAS study was 2.4 events per 100 patient years, which is in line with what is expected for pediatric patients with Still's disease.

CHMP comments

The MAH informs that no information regarding MAS will be added to the SmPC during this present procedure. The MAH plans to submit a Type II variation later in 2020. This application will include an update of the SmPC with information regarding MAS. This should be accepted as a commitment from the MAH.

Conclusion: Issue mostly resolved.

The MAH should commit to submit a Type II variation application including an update of the SmPC with information regarding MAS (should be included in section 4.4 and/or section 4.8 of the SmPC).

References

Giancane, G., Swart, J.F., Castagnola, E. et al. Opportunistic infections in immunosuppressed patients with juvenile idiopathic arthritis: analysis by the Pharmachild Safety Adjudication Committee. Arthritis Res Ther 22, 71 (2020).

Rajindrajith S Devanarayana NM. Constipation in Children: Novel Insight Into Epidemiology, Pathophysiology and Management. J Neurogastroenterol Motil 2011;17:35-47.

11. 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

RMP aspects

☒ 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

12. List of remaining outstanding issues

12.1. Major objections

No major objections have been identified.

12.2. Other concerns

Clinical aspects

Outstanding issue 1:
Within year 2020, the MAH should commit to submit a Type II variation application including

a) an update of section 4.8 of the SmPC with information regarding Injection site reactions.

b) an update of section 4.4 and/or section 4.8 of the SmPC with information regarding MAS.

MAH's response:

The MAH committed to submit the relevant variation(s) within 2020.

The MAH also submitted a revised RMP version 5.3 taking into account the changes agreed in this procedure and the changes approved in the variation EMEA/H/C/000363/II/0070.