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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Kineret

anakinra

Procedure no: EMEA/H/C/000363/P46/031

Note

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

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1. Introduction

On 19 November 2019, the MAH submitted a completed paediatric study for Kineret. The Sobi.ANAKIN-301 study was conducted to obtain an approval in the United States. The completed study report (CSR) is also submitted to the EMA in accordance with Article 46 of Regulation (EC) No1901/2006 (as amended) which states:

"Article 46

1. *Any other marketing authorisation holder-sponsored studies which involve the use in the paediatric population of a medicinal product covered by a marketing authorisation, whether or not they are conducted in compliance with an agreed paediatric investigation plan, shall be submitted to the competent authority within six months of completion of the studies concerned."*

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Sobi.ANAKIN-301 is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

The investigational product anakinra was delivered as a sterile solution for injection, pre-filled in a single-use graduated syringe with the strength of 100 mg. The total volume of injection from one syringe was 0.67 mL and the concentration of anakinra in the solution was 150 mg/mL.

The placebo, as anakinra, was delivered as a sterile solution for injection, in an identical single-use pre-filled graduated syringe. The placebo consisted of the active product vehicle (0.67 mL) but without the active ingredient, anakinra.

2.3. Clinical aspects

2.3.1. Introduction

Study Sobi.ANAKIN-301 was a randomised, double-blind, placebo-controlled, multicenter, phase 3 study. The aim of the study was to demonstrate the efficacy and to evaluate the safety, pharmacokinetics (PK) and immunogenicity of anakinra as compared to placebo in newly diagnosed Still's disease patients (including systemic juvenile idiopathic arthritis [SJIA] and adult-onset Still's disease [AOSD]). Anakinra is approved for the treatment of Still´s disease in the EU/EEA and for the treatment of SJIA in Australia. The Sobi.ANAKIN-301 study was conducted to obtain an approval in the United States. Submission of the final study report was also in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

The study was prematurely terminated on May 23, 2019 due to recruitment difficulties and with this submission, Sobi meets the timeline of reporting clinical data for paediatric patients within 6 months from end of study.

The evaluation of the benefits and the assessment of known and potential risks of anakinra in this study, is based on data from 12 randomised patients, including 8 paediatric patients, treated with anakinra or placebo. A Short Critical Expert Overview is provided and compiled to support the Sobi.ANAKIN-301 Clinical Study Report.

Taken together, the MAH submitted a final report for:

- Sobi.ANAKIN-301

Which is in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

2.3.2. Methods

2.3.2.1. Study objectives

The aim of this phase 3 study was to demonstrate the efficacy and to evaluate the safety, PK, and immunogenicity of anakinra in patients with newly diagnosed Still's disease, including SJIA and AOSD.

Primary objective

The primary objective of this study was:

• To demonstrate efficacy of anakinra versus placebo in Still's disease as assessed by ACR30 response including absence of fever.

Key secondary objective

The key secondary objective of this study was:

• To demonstrate early onset of efficacy of anakinra versus placebo in Still's disease.

Secondary efficacy objectives

The secondary efficacy objectives of this study were:

• To evaluate sustained efficacy of anakinra versus placebo in patients that reached at least ACR30 response at Week 2.

• To evaluate efficacy of anakinra versus placebo during 12 weeks treatment.

• To evaluate time to study drug discontinuation in anakinra versus placebo.

• To evaluate glucocorticoid tapering in anakinra and placebo treated patients.

• To evaluate the efficacy of anakinra in the 2 separate dose groups.

PK objective

The PK objective of this study was:

• To evaluate the PK of anakinra.

Productivity objective

The productivity objective of this study was:

• To evaluate absenteeism from school or work.

Exploratory objectives

The exploratory objectives of this study were:

• To explore PK/PD relationship between IL-1Ra/anakinra serum concentrations and selected efficacy and safety parameters.

• To explore the PK properties of anakinra using population analysis.

• To explore the effect of anakinra on the exploratory inflammatory biomarkers (IL-6, IL-18, calprotectin and neopterin) in the treatment of patients with Still´s disease.

Exploratory objective to be reported separately:

• To collect a blood sample for future analysis for genetic factors potentially contributing to the patient's response to anakinra, safety and tolerability.

Safety objective

The safety objective of this study was:

• To evaluate the safety of anakinra.

Immunogenicity objectives

The immunogenicity objectives of this study were:

• To evaluate occurrence of ADAs, NAbs and cross-reactivity.

• To evaluate ADAs in relation to safety.

• To evaluate ADAs and NAbs in relation to efficacy.

CHMP comments

The MAH proposes a very comprehensive list of efficacy-related, safety-related and pharmacological-(pharmacokinetic)-related objectives. It may be too ambitious for the study.

In the assessment (and due to the few patients actually included in the study, see later), focus will be on the primary objective (to demonstrate efficacy of anakinra versus placebo in Still's disease as assessed by ACR30 response including absence of fever) and the key secondary objective (to demonstrate early onset of efficacy of anakinra versus placebo in Still's disease) as well as the safety objective (to evaluate the safety of anakinra) including but not limited to the immunogenicity of the product.

2.3.2.2. Endpoints

Primary endpoint

The primary efficacy endpoint of this study was:

• ACR30 response at Week 2 with absence of fever attributable to the disease during the 7 days preceding Week 2.

Definition of ACR30 response: An improvement of ≥30 % from baseline in at least 3 of any 6 variables listed below. Also, no more than 1 of the 6 variables may worsen by >30 % from baseline.

1. Physician global assessment of disease activity (VAS).

2. Patient/parent global assessment of overall well-being (VAS).

3. Number of joints with active arthritis.

4. Number of joints with limitation of motion.

5. Assessment of physical function (CHAQ/SHAQ).

6. CRP (mg/L).

Definition of fever: Body temperature ≥38.0 °C (100.4 °F) attributable to the disease.

Secondary endpoints supporting the primary objective

The secondary efficacy endpoints supporting the primary objective of this study were:

• ACR30 response at Week 1 with absence of fever attributable to the disease during 24 hours preceding Week 1.

• ACR50, ACR70 and ACR90 response at Week 1 and Week 2 with absence of fever attributable to the disease during 24 hours before Week 1 and 7 days preceding Week 2.

• Response in the *individual components* of ACR at Week 1 and Week 2. Response is defined as an improvement of ≥30 %, 50 %, 70 % and 90 % from baseline. o Physician global assessment of disease activity (VAS).

o Patient/parent global assessment of overall well-being (VAS).

o Number of joints with active arthritis.

o Number of joints with limitation of motion.

o Assessment of physical function (CHAQ/SHAQ).

o CRP (mg/L).

• Absence of fever during the 7 days preceding Week 2.

Key secondary endpoints

The key secondary efficacy endpoints were:

• Absence of fever during the 24 hours preceding Week 1.

• Change from baseline in physician global assessment of disease activity (VAS) at Week 1.

• Change from baseline in patient/parent global assessment of overall well-being (VAS) at Week 1.

• Change from baseline in CRP at Week 1.

Secondary efficacy endpoints

The secondary efficacy endpoints were:

• Sustained ACR response with absence of fever at Week 4, Week 8 and Week 12 compared to ACR response at Week 2.

• ACR30, ACR50, ACR70 or ACR90 response with absence of fever 24 hours before Week 1 or during the 7 days preceding the visit at Week 2, Week 4, Week 8 and Week 12.

• Absence of rash 24 hours before Week 1 or during the 7 days preceding Week 2, Week 4, Week 8 and Week 12.

• Change from baseline in CRP, Hb, platelet count and ferritin at Week 1, Week 2, Week 4, Week 8 and Week 12.

• Change from baseline in patient/parent global assessment of disease related pain (VAS) at Week 1, Week 2, Week 4, Week 8 and Week 12.

• Inactive disease at Week 12.

• Change from baseline in JADAS27 at Week 2 and Week 12.

• Time to study drug discontinuation for any reason.

• Time to study drug discontinuation due to lack of efficacy or progressive disease.

• Number of patients who have initiated tapering of glucocorticoids at Week 12.

• Number of patients with decreased dose of glucocorticoids by at least 50 % at Week 12 compared to baseline.

• Percentage decrease of glucocorticoid dose at Week 12 compared to baseline.

• Efficacy endpoints as described above (to evaluate the objective of efficacy of anakinra in the 2 separate dose groups).

PK endpoint

The PK endpoint was:

• Anakinra trough serum concentrations and repeated-dose PK parameters at Week 12.

Productivity endpoint

The productivity endpoint was:

• Number of days off school or work due to Still's disease.

Exploratory endpoints

The exploratory endpoints were:

• Population PK/PD parameter estimates and associated covariates describing intra- and inter-individual variability in respective parameter estimate.

• Population PK parameter estimates and associated covariates describing intra-and inter-individual variability in respective parameter estimate.

• Change from baseline in exploratory inflammatory biomarkers at Week 1, Week 2 and Week 12.

Safety endpoint

The safety endpoint was:

• AEs (including MAS), vital signs and laboratory safety assessments.

Immunogenicity endpoints

The immunogenicity endpoints were:

• Occurrence of ADAs, NAbs, and cross-reactivity and titer levels of ADA and NAbs at baseline, Week 1, Week 2, Week 4, Week 8 and Week 12.

• Occurrence and titer levels of ADAs in relation to AEs at Week 1, Week 2, Week 4, Week 8 and Week 12.

• Occurrence and titer levels of ADA, including NAb in relation to ACR response and CRP at Week 1, Week 2, Week 4, Week 8 and Week 12.

CHMP comments

The chosen endpoints are considered relevant for the corresponding objectives of the study. As stated above, the list of objectives for (and thereby the list of endpoints in) the study is indeed very comprehensive and focus will be on the primary endpoint, the key secondary endpoint and the safety endpoints.

2.3.2.3. Variables

Primary efficacy measurement

ACR with absence of fever

The ACR30 criteria were used to determine efficacy defined as improvement from baseline of at least 30 % in at least 3 response variables 1 to 6, with no more than one variable 1 to 6 worsening by more than 30 % and no intermittent fever attributable to the disease during the preceding 7 days.

The variables listed below are included in ACR:

1. Physician global assessment of disease activity (on a 0 to 100 mm VAS).

2. Patient/parent global assessment of overall well-being (on a 0 to 100 mm VAS).

3. Number of joints with active arthritis.

4. Number of joints with limitation of motion.

5. Assessment of physical function (CHAQ/SHAQ).

6. CRP (mg/L).

Secondary efficacy measurements

Physician global assessment of disease activity

- Patient/parent global assessment of overall well-being
- Number of joints with active arthritis
- Assessment of physical function (CHAQ, SHAQ, CRP, Fever)
- Rash
- Global assessment of the patient disease related pain
- Inactive disease
- JADAS27
- Absenteeism from school or work
- Safety – (S)AEs
- PK measurements

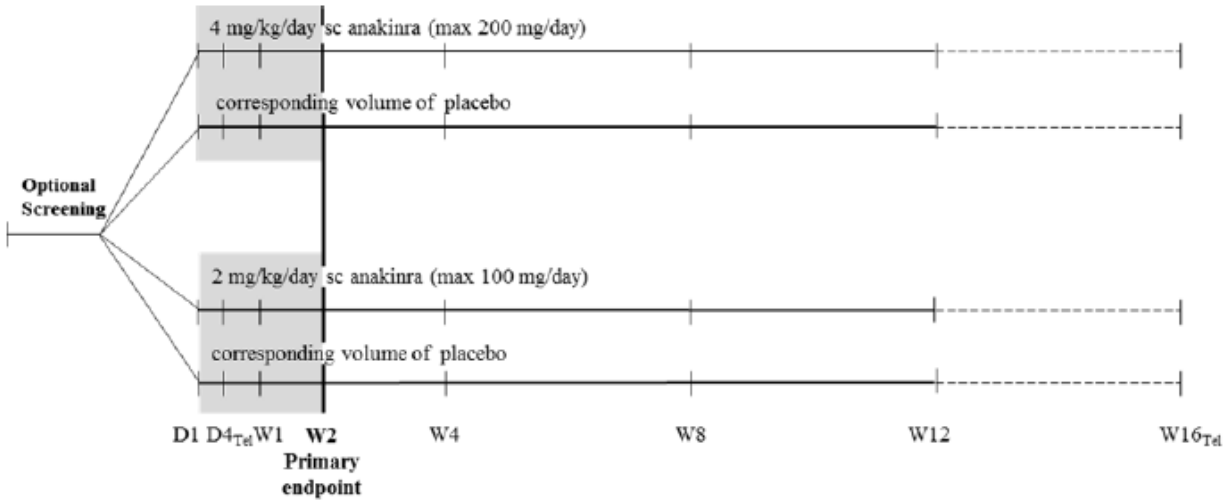
CHMP comments

The MAH has presented the endpoints for the study. In line with the primary objective and the primary endpoint, the Primary efficacy measurement was ACR with absence of fever. ACR is a validated scale that describes the change in disease activity. It is endorsed that the MAH has included specific focus on fever as Still's disease, is characterized by high spiking fevers. Several of the secondary variables are items included in the ACR30 scale. Overall, the chosen variables are in accordance with the EMA Guideline (Guideline on clinical investigation of medicinal products for the treatment of juvenile idiopathic arthritis, EMA/CHMP/239770/2014 Rev.2) and acceptable.

2.3.2.4. Study design and Setting

An overview of the study design is provided in Figure 9.1.

Figure 9.1 Study design for the study protocol Sobi.ANAKIN-301



This was a 12-week randomised, double-blind, placebo-controlled study with 2 dose levels of anakinra and a 4-week safety follow-up after last dose of IMP in patients with Still's disease. The primary endpoint was evaluated at Week 2. Sustained efficacy and time to study drug discontinuation was evaluated during the full treatment period.

A total of 81 patients with Still's disease were to be randomised, 54 to anakinra and 27 to placebo treatment. At least a third of the randomised patients should have had a disease onset before the age of 16, and at least a third of the randomised patients in the study should have had a disease onset at the age of 16 or above. Since the recruitment rate was slow, it was decided to close the study prematurely.

CHMP comments

The present study was a randomised, double-blinded placebo-controlled study intending to include 81 patients with Still's disease. This study design is overall endorsed and the randomised double-blinded design reduces the risk of bias. Considered the labelled indication for Kineret (*"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."*) and the treatment options for Still's disease, it is not quite understood that the study is placebo-controlled rather than using another active comparator however, as the total study duration was 12 weeks, this is overall considered acceptable. Of note, both effect and lack of effect of Kineret treatment of patients with Still's disease have been reported to occur after 12 weeks treatment thus, the study only provides information regarding short-term treatment effect. Most adverse events (AEs) are reported in the initial (4-8) weeks (1-2 months) of treatment thus though the study does not contribute with information regarding the long-term safety, it is expected that the majority of the most common AEs will be captured in this study. These issues with regard to the study design will not be pursued.

2.3.2.5. Treatments

Investigational Product(s):

The patients received treatment for 12 weeks, anakinra or placebo depending on the randomisation. Both treatments were provided as sterile solutions. The dose was adjusted to the actual body weight, rounded to the nearest kg, and remained the same during the study.

The placebo was given in a corresponding volume to the anakinra dose meaning:

- 1 injection per day:
  - o Patients randomised to 2 mg/kg/day (max 100 mg/day) or placebo.
  - o Patients randomised to 4 mg/kg/day (max 200 mg/day) or placebo, with a body weight <29 kg.
- 2 injections per day:
  - o Patients randomised to 4 mg/kg/day (max 200 mg/day) or placebo, with a body weight ≥29 kg.

After study drug discontinuation, the patients were to be treated according to standard of care at the discretion of the investigator.

CHMP comments

The treatments are sufficiently described. Patients were randomised to two different doses of anakinra or corresponding placebo. The two doses (2 mg/kg/day (max 100 mg/day) and 4 mg/kg/day (max 200 mg/day)) are in accordance with the posology for the paediatric population with Still's disease which according to the SmPC is as follows: *"Children weighing less than 50 kg are dosed by body weight with a starting dose of 1-2 mg/kg/day, patients weighing 50 kg or more are dosed with 100 mg/day. In children with inadequate response the dose can be escalated up to 4 mg/kg/day."*

2.3.2.6. Subjects

Inclusion criteria

A patient had to fulfil all of the following criteria in order to be included in the study:

1. Signed informed consent.

2. Male and female patients with a body weight ≥10 kg.

3. Diagnosis of Still's disease: a. If <16 years of age at disease onset, according to adapted ILAR criteria i.e., CARRA criteria for SJIA b. If ≥16 years of age at disease onset, according to Yamaguchi criteria.

4. If on glucocorticoid treatment, a stable dose for at least 1 week prior to randomisation. Maximum dose allowed was 1 mg/kg/day, up to a maximum of 60 mg/day.

5. If on methotrexate treatment, a stable dose for at least 8 weeks prior to randomisation. Maximum dose allowed was 20 mg/m^2/week. If prior treatment with methotrexate, discontinuation was required at least 4 weeks prior to randomisation.

6. Active disease confirmed by the following 3 signs and symptoms: a. Active arthritis in ≥1 joint. b. CRP >30 mg/L. c. At least one fever episode attributable to the disease within one week before randomisation. (Definition of fever: body temperature ≥38.0 °C)

7. Female patients of childbearing potential had to use an effective method of contraception during the study (abstinence being a possible option) as well as present a negative pregnancy test prior to randomisation.

8. Negative IFNγ release assay or PPD test within 2 months prior to randomisation. If not available, a test should be performed at day of randomisation.

Exclusion criteria

The presence of any of the following excluded patients from inclusion in the study:

1. Diagnosis of Still's disease more than 6 months prior to randomisation.

2. (a) Previous randomisation into this study, (b) Participation in another concurrent clinical interventional study within 30 days of randomisation, (c) Treatment with an investigational drug within 5 half-lives prior to randomisation.

5. Previous or current treatment with anakinra, canakinumab or any other IL-1 inhibitor.

6. Use of the following therapies prior to randomisation: (a) Narcotic analgesics within 24 hours prior to randomisation, (b) Dapsone or etanercept within 3 weeks prior to randomisation, (c) Intraarticular, intramuscular or intravenous administration of glucocorticoids or intravenous Ig within 4 weeks prior to randomisation, (d) Intravenous Ig with proven Still's disease modifying effect, leflunomide, infliximab, or adalimumab within 8 weeks prior to randomisation, (e) Thalidomide, cyclosporine, mycophenolate mofetil, 6-mercaptopurine, azathioprine, cyclophosphamide, chlorambucil, or any other immunosuppressant within 12 weeks prior to randomisation, (f) Tocilizumab within 12 weeks prior to randomisation or any other immunomodulatory medication within 4 half-lives prior to randomisation, (g) Rituximab within 26 weeks prior to randomisation, (h) Live vaccines within 1 month prior to randomisation.

8. Known presence or suspicion of active, chronic or recurrent bacterial, fungal or viral infections, including tuberculosis, HIV infection or hepatitis B or C infection.

9. (a) Clinical evidence of liver disease or liver injury as indicated by presence of abnormal liver tests (AST or ALT >5 x ULN, or AST or ALT >3 x ULN accompanied by elevated bilirubin >2 x ULN), (b) Presence of severe renal function impairment CKD stages 4 and 5 (estimated creatinine clearance <30 mL/min/1.73m^2), (c) History of malignancy within 5 years. Exceptions are basal cell skin cancer, carcinoma-in-situ of the cervix or low-risk prostate cancer after curative therapy, (d) Presence of any medical or psychological condition or laboratory result that in the opinion of the investigator can interfere with the patient's ability to comply with the study protocol requirements or makes the patient not appropriate for inclusion to the study and treatment with IMP.

11. Presence of neutropenia (ANC <1.5 x 109/L).

12. (a) Presence or suspicion of MAS at baseline, (b) A diagnosis of MAS within 2 months prior to randomisation.

15. Known hypersensitivity to *E coli*-derived proteins, or any components of Kineret (anakinra).

16. Pregnant or lactating women.

17. Foreseeable inability to cooperate with given instructions or study procedures.

CHMP comments

In- and exclusion criteria are adequately and sufficiently described. Patients with a diagnosis of Still's disease >6 months prior to randomisation was excluded. This ensures that only newly diagnosed patients were included. This should be kept in mind when interpreting the results as these may not be generalized to the entire population with Still's disease. Patients with short disease duration may be more likely to improve in the ARC30 (patients with short disease duration are expected to be able to improve better than patients with long-term disease in the parameter of number of joints with limited motion (even through physical therapy)) and patients with one previous episode of MAS may be more at risk of new episodes; with a disease duration of <6 months, the patients may not have had time to develop the first episode.

It is noted that there was no age limit for inclusion in the study, thereby not only paediatric but also adult patients could be included.

2.3.2.7. Data sources and measurements

This study was conducted in compliance with the protocol, study specific procedures, ARO SOPs, Sobi SOPs (e.g. for unblinding of SUSARs, statistical analysis and study reporting), the ICH GCP guideline (Harmonised Guideline: Integrated addendum to ICH E6 (R1) 2016), and applicable regulatory requirements.

Sobi systematically reviewed the study quality management to identify, evaluate and control risks to study critical processes and data which would affect patient safety and reliability of study data.

Sobi had a systematic, prioritized, risk-based approach to monitoring and a combination of on-site and centralized monitoring.

Monitoring visits to the study site were performed periodically during the study, to help ensure compliance with the study protocol, study specific procedures and applicable regulatory requirements. Source documents were reviewed for verification of agreement with data in CRFs. All patient ICFs were reviewed.

Sobi was responsible for independent quality assurance audits of the clinical study processes at the company sites. Audits of selected clinical investigator sites were also conducted to assess and help assure compliance with GLP and applicable regulatory requirements.

CHMP comments

The MAH ensures that the study was conducted according to the ICH Guidelines as well as applicable regulatory requirements. Further, the MAH ensures that no information was unblinded prior to database lock. This is endorsed.

2.3.2.8. Study size

Assuming the ACR30 response rate with absence of fever at Week 2 is 65% in patients receiving anakinra and 25% in placebo patients, 81 evaluable patients (54 anakinra and 27 placebo) would be required to ensure 90 % power in demonstrating that anakinra improves clinical features of Still's disease using a 2-sided test at a 5% significance level. These assumptions were based on the canakinumab (Ruperto et al. 2012) and tocilizumab (De Benedetti et al. 2012) phase 3 clinical studies in patients with SJIA where 65% to 85% of active patients and 10% to 25% of placebo patients responded at 2 weeks, as well as the study by Nordstrom et. al. in AOSD, where 50 % of anakinra treated patients were in remission after 4 weeks of treatment (Nordstrom et al. 2012).

Since recruitment was stopped before the planned number of evaluable patients had been included, it was anticipated that at least 12 patients would be randomised and included in the analyses.

CHMP comments

The MAH has sufficiently described that assumption for the sample size calculation. A total of 81 patients were to be included in the study.

However, since the study was prematurely closed due to difficulties in recruitment of patients, the planned sample size was not reached (13 randomised patients vs. 81 planned patients). Consequently, statistics cannot be adequately applied to the study which remains descriptive.

2.3.2.9. Statistical methods

General statistical approaches

The comparison of interest was between anakinra (2 mg/kg and 4 mg/kg combined) and placebo. Due to the small number of patients, results are not provided by individual dose groups. The randomisation was stratified by age at onset of disease (<16 years, ≥16 years) and glucocorticoid use (yes, no), but

due to the very small number of patients for levels of the stratification factors within each treatment group, descriptive statistics and statistical analyses were generally not performed by stratification factors. For primary and key secondary efficacy endpoints, the dose-level information and stratification allocation are included in a patient listing.

All statistical tests were 2-sided and performed using a 5% significance level, if not stated otherwise. Results are presented as the estimated value for each treatment group, anakinra and placebo, the estimated difference between groups, the associated 95% 2-sided confidence interval and p-value.

Continuous data were summarized using descriptive statistics: n, mean, SD, median, minimum and maximum, unless otherwise indicated.

Categorical data were summarized using counts and percentages.

Statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc, Cary, North Carolina, US).

Analysis related to the primary objective

The primary endpoint, ACR30 response at Week 2 with absence of fever attributable to the disease during the 7 days preceding Week 2, was analyzed using the mITT population. No missing data imputation was used, other than that described. Patients who had discontinued study drug prior to Week 2 were treated as non-responders in the analysis.

The null and alternative hypotheses with respect to the primary efficacy endpoint were defined as:

H0: Panakinra = Pplacebo

HA: Panakinra ≠ Pplacebo

where P was the proportion of patients with ACR30 response as defined for the primary endpoint. Fisher's exact test was used to test the hypothesis at the 2-sided significance level of α=0.05.

Sensitivity analysis of the primary endpoint

As a sensitivity analysis for both the primary analysis of ACR30 (+ absence of fever) at Week 2 and the supportive analysis of ACR30 (+ absence of fever) at Week 1, a comparison of treatment groups including the actual response data for patients who had discontinued study drug was performed using the ACR assessment closest to Week 2 or Week 1. However, patients with study drug discontinuation due to progressive disease were still treated as non-responders as in the main analysis. The same exact methods as for the primary analysis were used.

A tipping point analysis was planned for the primary efficacy endpoint, if the primary efficacy endpoint resulted in a statistically significant outcome. The number of responders that could potentially be observed among patients with a missing ACR30 outcome at Week 2 (e.g. when non-response was assigned in the primary analysis due to discontinuation of study drug) in the anakinra group versus the placebo group were presented in a basic tipping point display. Pairs of number of responders in the anakinra and placebo group that lead to statistical significance were marked and pairs that lead to non-significance were not marked. The tipping point boundary is the staircase region between marked and unmarked rectangles (Yan et al. 2009).

Analysis related to secondary efficacy endpoints, supporting the primary objective

Analysis related to the key secondary efficacy objective, Analysis related to other secondary efficacy endpoints, PK analyses and Analysis of safety data are described in the SAP and the CSR.

Handling of missing data and outliers

For all endpoints related to the primary objective the following imputation were used:

• Patients that discontinued study drug prior to Week 2 were set to non-responders.

• For patients with missing information in any of the ACR30 components, that specific component was set to no change. For patients with missing information on fever, the patients were treated as having a presence of fever.

For the key secondary endpoints, the following imputation was used:

• Patients with missing information on fever during 24 hours preceding Week 1 were treated as having a presence of fever in the analysis.

For the other secondary endpoints, no imputation was performed, i.e., all presentations are based on observed data.

To assess if AEs were treatment emergent, if medications were prior or concomitant, and to determine the duration of Still's diagnosis partly missing onset/stop dates were imputed according to the rules specified in the SAP. Completely missing dates were not imputed.

CHMP comments

The MAH has sufficiently described the statistical methods. These are overall acceptable. Due to the early termination of the study and the few patients included, sample size was not met and that should be kept in mind when interpreting the statistical results.

The MAH informs that handling of missing data was made by imputation and patients who discontinued study drug prior to Week 2 were set to non-responders. As more patients in the placebo group compared to the anakinra group discontinued, this imputation may favour anakinra. In this context, it should be noted that the majority of patients (4 patients) treated with placebo discontinued due to lack of efficacy/disease progression thus, from a medical point of view, the imputation appears reasonable. Nevertheless, it cannot be ruled out that the two patients discontinuing due to AEs (one patient) and 'patient withdrawal' (1 patient) could have responded to the treatment. Therefore, the sensitivity analysis is endorsed.

2.3.2.10. Changes in the conduct of the study and Amendments

The enrolment target of the study was 81 patients. The recruitment of patients started in November 2017. In April 2019, 13 patients had been recruited. Despite continuous significant efforts from Sobi and high engagement and commitment by investigators to identify eligible patients, the number of suitable patients was smaller than anticipated. Sobi concluded that meeting the enrolment target was not feasible within reasonable time and decided to close the recruitment in May 2019.

The study was completed after 13 randomised patients.

The early stopping of the study decreased the sample size for the final analysis. Consequently, some of the analyses methods outlined in the study protocol were revised and adapted. The changes to the planned analyses were based on blinded data. The study protocol amendments and the SAP were finalized before unblinding.

A *post-hoc* analysis of the total number of TEAEs and event rates (TEAEs by patient years of IMP exposure) was performed for each treatment group.

Reasons for the administrative and substantial protocol amendments are provided in version 4 of the CSP, dated July 3, 2018. The substantial study protocol amendments are listed in Table 9.5 in the CSR.

CHMP comments

The most important change in conduct of the study was the premature closure of the study due to difficulties in recruitment of patients. The study was closed after 18 months where only 13 patients had been randomised. Considered this major change in the conduct of the study, none of the amendments to the study protocol are expected to affect the results in any clinically relevant degree. All changes to the study protocol were made prior to database lock; only the analysis of the total number of TEAEs and event rates (TEAEs by patient years of IMP exposure) for each treatment group was decided *post-hoc*.

2.3.3. Study patients

2.3.3.1. Disposition of patients

A flow-chart of the disposition of patients in the study, including reasons for discontinuing the study, is presented in Table 14.1.1.1.

A total of 17 patients were screened whereof 4 patients were screen failures. 13 patients were randomised to study treatment whereof one patient was incorrectly randomised and did not receive study treatment. This patient was excluded from all analyses sets. 12 patients were treated with study drug: 6 patients with anakinra (2 patients to 2 mg/kg/day [max 100 mg/day] and 4 patients with 4 mg/kg/day [max 200 mg/day]), and 6 patients with placebo. In the CSR, the 2 anakinra dose groups are reported as one, except for the PK results where the 2 anakinra dose groups are presented separately. One placebo patient was found to have lymphoma, not Still's disease, and was excluded from the main analysis set (mITT) for failing to satisfy major disease-specific entry criteria. The mITT set comprised 6 anakinra patients and 5 placebo patients.

Reasons for discontinuing the study included AE, lack of efficacy, progressive disease, and withdrawal by patient for the placebo group. All anakinra patients completed the study, whereas no placebo patients completed the study.

All study sites were located in the US and Canada. No patients were randomised in Canada.

Table 14.1.1.1 Patient disposition (All enrolled patients)

	Number (%) of patients		
	Anakinra (N = 7)	**Placebo (N = 6)**	**Total (N = 17)**
Enrolled[a]			17 (100.0)
Randomized	7 (100.0)	6 (100.0)	13 (76.5)
Received study treatment	6 (85.7)	6 (100.0)	12 (70.6)
Completed 2 weeks of study treatment	6 (85.7)	4 (66.7)	10 (58.8)
Discontinued study treatment early (before Week 2)	0 (0.0)	2 (33.3)	2 (11.8)
Adverse event	0	0	0
Death	0	0	0
Positive tuberculosis-test[b]	0	0	0
Lack of efficacy	0	1 (16.7)	1 (7.7)
Lost to follow-up	0	0	0
Physician decision	0	0	0
Pregnancy	0	0	0
Progressive disease	0	1 (16.7)	1 (7.7)
Study terminated by sponsor	0	0	0
Withdrawal by patient	0	0	0
Protocol violation	0	0	0
Other	0	0	0
Completed 12 weeks of study treatment	6 (85.7)	0 (0.0)	6 (35.3)
Discontinued study treatment early (anytime)	0 (0.0)	6 (100.0)	6 (35.3)
Adverse event	0	1 (16.7)	1 (7.7)
Death	0	0	0
Positive tuberculosis-test[b]	0	0	0
Lack of efficacy	0	2 (33.3)	2 (15.4)

CHMP comments

A total of 13 patients were randomised (7 patients were randomised to anakinra, 6 were randomised to placebo). One patient was incorrectly randomised (to anakinra-treatment but the patient did not fulfill the inclusion criteria of having active disease with CRP>30 mg/L). This patient did not receive study treatment and is correctly excluded from all analyses sets. Thus, 12 patients received study treatment (6 in each treatment group). Likewise, one placebo-treated patient was diagnosed with lymphoma and not Still's disease. This patient was also excluded from the ITT.

All but 2 patients (treated with placebo) completed the 2 weeks treatment. The MAH informs that the mITT set (which is used for evaluation of the primary and key secondary endpoints) consisted of 11 patients (6 treated with anakinra and 5 treated with placebo).

Only 6 patients (all treated with anakinra) completed the 12 weeks' treatment, thus data for the PK endpoint *("Anakinra trough serum concentrations and repeated -dose PK parameters at Week 12"*) are only evaluated based on 6 patients. Similar, several of the secondary endpoints were based on clinical effect measured at 12 weeks and thus, the interpretation of these results must be made with caution and cannot be compared to placebo.

The 6 placebo-treated patients were discontinued due to lack of efficacy/disease progression (4 patients), AE (lymphoma, 1 patient) and Withdrawal by patient (1 patient). As previously discussed, lack of efficacy/disease progression was expected to occur in the placebo-treated group.

Due to the overall low number of patients in both treatment groups, no firm conclusions can be made.

2.3.3.2. Demographic and other baseline characteristics

Demography

The demographics are summarized in Table 10.4.

The treatment groups (anakinra and placebo) were balanced with regards to demographics. The gender distribution among the 11 patients was 6 males and 5 females.

Table 10.4 Demographics (mITT set)

	Anakinra (N = 6)	Placebo (N = 5)	Total (N = 11)
Age (years)			
n	6	5	11
Mean (SD)	12.3 (19.3)	14.4 (13.2)	13.3 (16.0)
Median (min, max)	4.5 (1, 51)	7.0 (3, 32)	6.0 (1, 51)
Sex, n (%)			
Male	4 (66.7)	2 (40.0)	6 (54.5)
Female	2 (33.3)	3 (60.0)	5 (45.5)
Race, n (%)			
White	5 (83.3)	4 (80.0)	9 (81.8)
Black or African American	1 (16.7)	1 (20.0)	2 (18.2)
Ethnicity, n (%)			
Hispanic or Latino	1 (16.7)	0	1 (9.1)
Not Hispanic or Latino	5 (83.3)	5 (100.0)	10 (90.9)
Baseline weight[a] (kg)			
<16 years			
n	5	3	8
Mean (SD)	27.3 (29.1)	18.8 (2.2)	24.1 (22.5)
Median (min, max)	12.5 (11, 79)	20.0 (16, 20)	18.1 (11, 79)
≥16 years			
n	1	2	3
Mean (SD)	86.2	67.3 (1.9)	73.6 (11.0)
Median (min, max)	86.2 (86, 86)	67.3 (66, 69)	68.6 (66, 86)
Baseline height[a] (cm)			
<16 years			
n	5	2	7
Mean (SD)	109.3 (36.2)	113.0 (7.8)	110.4 (29.8)
Median (min, max)	87.6 (84, 168)	113.0 (107, 119)	107.4 (84, 168)
≥16 years			
n	1	2	3
Mean (SD)	168.0	165.1 (10.8)	166.1 (7.8)
Median (min, max)	168.0 (168, 168)	165.1 (158, 173)	168.0 (158, 173)

Source: DM_ITT_T.SAS 2019-10-22T08:06:53 Z9FRBE.
Abbreviations: mITT, Modified intention to treat; N, Number; n, Number; SD, Standard deviation.
[a] By age at diagnosis group.

Baseline disease characteristics

The primary Still's disease characteristics are presented in Table 10.5.

Age at Still's disease diagnosis and symptom onset was similar across groups. The study included a higher number of pediatric patients (n=8) than adult patients (n=3). Both symptom and disease duration were longer in the anakinra group, as compared to placebo.

Table 10.5 Primary Still's disease characteristics (mITT set)

	Anakinra (N = 6)	Placebo (N = 5)	Total (N = 11)
Age at Still's disease diagnosis (years)			
n	6	5	11
Mean (SD)	12.2 (19.4)	14.4 (13.2)	13.2 (16.1)
Median (min, max)	4.0 (1, 51)	7.0 (3, 32)	6.0 (1, 51)
Age at Still's disease symptom onset, n (%)			
<16 years	5 (83.3)	3 (60.0)	8 (72.7)
≥16 years	1 (16.7)	2 (40.0)	3 (27.3)
Symptom duration[a] (days)			
n	6	5	11
Mean (SD)	109.0 (78.0)	32.4 (18.7)	74.2 (69.1)
Median (min, max)	84.5 (31, 222)	32.0 (12, 60)	48.0 (12, 222)
Disease duration (days)			
n	6	5	11
Mean (SD)	23.3 (29.9)	2.2 (1.1)	13.7 (23.8)
Median (min, max)	7.0 (1, 65)	2.0 (1, 4)	2.0 (1, 65)

Source: DC_ITT_T.SAS 2019-10-22T08:06:57 Z9FRBE.
Abbreviations: mITT, Modified intention to treat; N, Number; n, Number; SD, Standard deviation.
[a]Screening date - disease symptom onset date + 1. If only year and month is present for symptom onset, the 15th of the month is used. If only year is present, June 30th is used.

CHMP comments

The study was conducted with the aim of supporting a marketing authorisation application for anakinra in the US. In Europe, *'the clinical study report was solely submitted to meet the obligation of Article 46 to submit any MAH-sponsored studies involving the use of an authorised medicinal product including a paediatric population'*.

As expected with the few patients included in each treatment group, small differences were observed. Mean and median age was higher in the placebo group compared to the anakinra group (median age: 7.0 vs. 4.5 years, respectively). On the contrary, mean and median weight was higher in the anakinra group. In both treatment groups, the majority of patient were diagnosed <16 years however, both disease duration and symptom duration were noticeable longer in the anakinra group. None of the patients (in either treatment group) were treated with glucocorticoids at time of inclusion and concomitant medication for the treatment of Still´s disease was not given to any of the anakinra patients during the study drug treatment period. Overall, there were no marked differences in the medical history between the 2 treatment groups.

2.3.4. Efficacy evaluation

2.3.4.1. Primary efficacy endpoint

2.3.4.1.1. ACR30 response at Week 2 with absence of fever attributable to the disease during the 7 days preceding Week 2

The primary efficacy endpoint was analysed using the mITT set and was based on the following imputations:

• Patients who discontinued study drug prior to Week 2 were set to non-responders.

• For patients with missing information in any of the ACR30 components, that specific component was set to no change. For patients with missing information on fever, the patients were treated as having a presence of fever.

The comparison between the treatment groups in ACR30 response at Week 2 is presented in Table 11.1. The difference in response rate (1.00) was statistically significant in favour of anakinra.

Table 11.1 ACR30 response with absence of fever at Week 2 (mITT set)

			Comparison between groups in response		
Group	N	Number (%) of patients with response[a]	Difference in response rate[b]	95% exact CI for difference	Fisher's exact test p-value
Anakinra	6	6 (100.0)	1.00	0.42, 1.00	0.0022
Placebo	5	0			

Source: ACR30W2_ITT_T.SAS 2019-10-22T08:13:40 Z9FRBE.
Abbreviations: ACR, American college of rheumatology; CI, Confidence interval; mITT, Modified intention to treat; N, Number.
[a] ACR30 response is defined as an improvement of ≥30% from baseline in at least 3 of any 6 variables listed in the protocol, and with absence of fever attributable to the disease during the 7 days preceding Week 2, and no more than 1 of the 6 variables has a worsening of >30%.
[b] A positive difference in response rates favors anakinra.

A sensitivity analysis of the primary endpoint is presented in Table 11.2. This analysis includes actual response data at the Week 2 assessment for patients who discontinued study drug for other reasons than progressive disease before Week 2, instead of treating these as non-responders regardless of their ACR30 response. The result confirmed the results of the primary analysis.

Table 11.2 ACR30 response with absence of fever at Week 2, sensitivity analysis including response data for patients who discontinued study drug for other reasons than progressive disease (mITT set)

			Comparison between groups in response		
Group	N	Number (%) of patients with response[a]	Difference in response rate[b]	95% exact CI for difference	Fisher's exact test p-value
Anakinra	6	6 (100.0)	0.80	0.17, 0.99	0.0152
Placebo	5	1 (20.0)			

Source: ACR30W2_ITTSA_T.SAS 2019-10-22T08:13:46 Z9FRBE.
Abbreviations: ACR, American college of rheumatology; CI, Confidence interval; mITT, Modified intention to treat; N, Number.
[a] ACR30 response is defined as an improvement of ≥30% from baseline in at least 3 of any 6 variables listed in the protocol, and with absence of fever attributable to the disease during the 7 days preceding Week 2, and no more than 1 of the 6 variables has a worsening of >30%.
[b] A positive difference in response rates favors anakinra.

There were 2 placebo patients who discontinued study drug prior to Week 2 and were set to non-responders in the primary efficacy endpoint analysis.

One of the patients discontinued study drug due to lack of efficacy at Week 1 (the investigator reported that laboratory tests indicated worsening anemia, worsening liver function tests, increased LDH and increased ferritin). Glucocorticoid treatment was initiated the following day and was still ongoing at Week 2 when the patient did have an ACR30 response. This is the placebo patient that is a responder in the sensitivity analysis described above.

The other patient discontinued study drug due to progressive disease before Week 1 (the investigator reported ongoing fevers, rash appearing more extensively, rising ferritin [from 1543 to 5593], decreased WBC, Hb, platelets and fibrinogen). Treatment with glucocorticoids and IL-1 inhibitor (commercially available anakinra) was initiated 3 days respectively 2 days prior the Week 1 assessments and these treatments were still ongoing at the Week 2 assessment, and the patient had an ACR30 response at that time point.

CHMP comments

While interpreting the results for the primary endpoint, it should be kept in mind, firstly that the patient-population was a population of newly diagnosed patients with possibility for improvement in the individual components included in the ACR. Secondly, it should also be kept in mind that the ACR response criteria is a dichotomous variable with a positive (=responder) or negative (=non-responder) outcome.

Overall, measured on the ACR30 scale, all patients in the anakinra treatment group responded at Week 2 while none of the patients in the placebo group were responders. The result was statistically significant in favour of anakinra (P[95%CI]=0.0022[0.42;1.00]). Previous studies of Kineret used in the treatment of Still's disease have showed a response rate of 67% and 73% (on the ACR30 scale). These results were obtained after 1 month and 3 months, respectively (corresponding placebo-response was 8%). Taken together, the result for the primary endpoint is in line with previous findings. Further, the result was also supported by the sensitivity analysis. The result however, must be carefully evaluated as it is based on few patients, on a dichotomous scale and measured after 2 weeks. Thus, generalisation to the entire population of patients with Still's disease or long-term effect cannot be made.

2.3.4.2. Secondary endpoints supporting the primary objective

2.3.4.2.1. ACR30 response at Week 1 with absence of fever attributable to the disease during 24 hours preceding Week 1

The comparison between the treatment groups in ACR30 response at Week 1 is presented in Table 11.3. There was a numerically higher proportion of responders in the anakinra group, but the difference was not statistically significant.

Table 11.3 ACR30 response with absence of fever at Week 1 (mITT set)

			Comparison between groups in response		
Group	N	Number (%) of patients with response[a]	Difference in response rate[b]	95% exact CI for difference	Fisher's exact test p-value
Anakinra	6	5 (83.3)	0.23	-0.39, 0.74	0.5455
Placebo	5	3 (60.0)			

Source: ACR30W1_ITT_T.SAS 2019-10-22T08:13:50 Z9FRBE.
Abbreviations: ACR, American college of rheumatology; CI, Confidence interval; mITT, Modified intention to treat; N, Number.
[a] ACR30 response is defined as an improvement of ≥30% from baseline in at least 3 of any 6 variables listed in the protocol, and with absence of fever attributable to the disease during the 24 hours preceding Week 1, and no more than 1 of the 6 variables has a worsening of >30%.
[b] A positive difference in response rates favors anakinra.

CHMP comments

At Week 1, 5 of the 6 anakinra treated patients had ACR30 response. This indicates that treatment with anakinra may have a fast onset in improving the symptoms of the disease.

2.3.4.2.2. ACR50, ACR70 and ACR90 response at Week 1 and Week 2 with absence of fever attributable to the disease during 24 hours before Week 1 and 7 days preceding Week 2

At Week 2, there were statistically significant differences in ACR50, ACR70 and ACR90 responses with absence of fever in favour of anakinra. All 6 anakinra patients had an ACR70 response, and 5 of 6 anakinra patients had an ACR90 response at Week 2. No placebo patients had an ACR30 or greater response in the analysis at Week 2.

At Week 1, there was a statistically significant difference in ACR70 response with absence of fever in favour of anakinra. There was a numerically greater response in favour of anakinra in ACR30, ACR50 and ACR90 responses with absence of fever at Week 1. However, these differences were not statistically significant.

CHMP comments

At Week 2, all 6 anakinra patients had an ACR50 and an ACR70 response, and 5 of 6 anakinra patients had an ACR90 response. This supports the effect of anakinra demonstrated by the primary efficacy evaluation. The differences to placebo were statistically significant for both ACR50, ACR70 and ACR90.

2.3.4.2.3. Response in the individual components of ACR at Week 1 and Week 2

The comparison between the treatment groups in response in individual components of ACR (as defined as an improvement of ≥30 %, 50 %, 70 % and 90 % from baseline), including physician global assessment of disease activity (VAS), patient/parent global assessment of overall well-being (VAS), number of joints with active arthritis, number of joints with limitation of motion, assessment of physical function CHAQ/SHAQ, and CRP, at Week 2 is presented in Tables included in Table 11.4.

There were statistically significant differences in ≥30%, 50%, 70% and 90% improvement rates of CRP at Week 1 and Week 2 in favour of anakinra. There were numerically greater response rates for all other individual components in favour of anakinra, however, the differences did not reach statistical significance.

Table 11.4 Individual components of ACR30 response at Week 2 (mITT set)

ACR component	Group	N	Number (%) of patients with response[a]	Comparison between groups in response: Difference in response rate[b]	95% exact CI for difference	Fisher's exact test p-value
Physician global assessment of disease activity (VAS)	Anakinra	6	5 (83.3)	0.23	-0.39, 0.74	0.5455
	Placebo	5	3 (60.0)			
Patient/parent global assessment of overall wellbeing (VAS)	Anakinra	6	6 (100.0)	0.50	-0.17, 0.93	0.1333
	Placebo	4	2 (50.0)			
Number of joints with active arthritis	Anakinra	6	5 (83.3)	0.43	-0.21, 0.86	0.2424
	Placebo	5	2 (40.0)			
Number of joints with limitation of motion	Anakinra	6	5 (83.3)	0.43	-0.21, 0.86	0.2424
	Placebo	5	2 (40.0)			
Assessment of physical function CHAQ/SHAQ	Anakinra	6	4 (66.7)	0.47	-0.17, 0.87	0.2424
	Placebo	5	1 (20.0)			
CRP (mg/L)	Anakinra	6	6 (100.0)	0.80	0.17, 0.99	0.0152
	Placebo	5	1 (20.0)			

Source: ACR30W2C_ITT_T.SAS 2019-10-22T08:13:54 Z9FRBE.
Abbreviations: ACR, American college of rheumatology; CHAQ, Childhood health assessment questionnaire; CI, Confidence interval; CRP, C-reactive protein; mITT, Modified intention to treat; N, Number; SHAQ, Stanford health assessment questionnaire; VAS, Visual analog scale where 0 indicate no disease activity or very well wellbeing and 100 indicate very severe disease activity or very poor wellbeing.
[a] Response is defined as an improvement of ≥30% from baseline in the component.
[b] A positive difference in response rates favors anakinra.

CHMP comments

After 2 weeks' treatment, an improvement in all individual components of the ACR30 scale was observed. At least 5 of the 6 anakinra treated patients reported an improvement in number of joints with active arthritis, number of joints with limitation of motion, assessment of physical function, global assessment of disease activity and global assessment of overall well-being. These components are however, expected to be related with each other. If the number of joints with active arthritis is decreased, there may be fewer joints with limitation of motion and this will lead to a better assessment of physical function, and an improvement in global assessment of disease activity and overall well-being. Thus, the individual components are inter-related. Only the improvement on CRP was statistically significant.

Results for the individual components of the ACR50, ACR70 and the ACR90 were all supporting the effect of anakinra. In the anakinra treatment group, for all individual components in all response-scales (ACR50, ACR70 and ACR90), ≥4 patients responded (with the exception of Number of joints with active arthritis at the ACR90 response where 3 of the 6 anakinra treated patients responded). In the placebo group, only ≤2 patients were responders of the individual components at all response scales (ACR50, ACR70 and ACR90).

2.3.4.2.4. Absence of fever during the 7 days preceding Week 2

The comparison between the treatment groups in absence of fever at Week 2 is presented in Table 11.5. There was a statistically significant difference in the proportion of patients with absence of fever in favour of anakinra. Patients with missing values (1 placebo patient) or discontinuing study drug prior

to Week 2 (2 placebo patients) were regarded as having fever, as described in Section 9.7.1.3 and Section 9.7.2.

Table 11.5 Absence of fever during the 7 days preceding Week 2 (mITT set)

Group	N	Number (%) of patients with absence of fever	Comparison between groups in response		
			Difference in proportions[a]	95% exact CI for difference	Fisher's exact test p-value
Anakinra	6	6 (100.0)	1.00	0.42, 1.00	0.0022
Placebo	5	0			

Source: ACRFVW2_ITT_T.SAS 2019-10-22T08:13:58 Z9FRBE.
Abbreviations: CI, Confidence interval; mITT, Modified intention to treat; N, Number.
[a] A positive difference in response rates favors anakinra.

CHMP comments

With regard to Fever, all patients treated with anakinra (but none of the placebo-treated patients) were absence of fever during the first week of treatment (i.e. during the 7 days preceding Week 2). Fever (continuously or with one or two daily spikes) is a cardinal symptom of Still's disease and therefore it is endorsed that special attention to this symptom is made. Furthermore, it is reassuring that fever disappear as this indicates an effect of the treatment. Overall, this supports the shown effect on the ACR-scales.

It is acknowledged that the 3 patients with missing data were regarded as having fever; this is in accordance with the SAP however, as all 3 patients were treated with placebo, this assumption may have favoured anakinra in the direct comparison. Nevertheless, as the total number of patients is small and as all anakinra-treated patients had absence of fever, the issue will not be pursued.

2.3.4.3. Key secondary efficacy endpoints

To evaluate early onset of efficacy of anakinra versus placebo in Still's disease, various parameters were measured at Week 1.

For the key secondary endpoints, the following imputations were used:

- Patients who had missing information on fever during 24 hours preceding Week 1 were treated as having a presence of fever in the analysis.
- For the continuous key secondary endpoints repeated measures models were used to handle missing data.

2.3.4.3.1. Absence of fever during the 24 hours preceding Week 1

The comparison between the treatment groups in absence of fever at Week 1 is presented in Table 11.6. There was no statistically significant difference between treatment groups.

Table 11.6 Absence of fever during the 24 hours preceding Week 1 (mITT set)

Group	N	Number (%) of patients with absence of fever	Comparison between groups in response: Difference in proportions[a]	95% exact CI for difference	Fisher's exact test p-value
Anakinra	6	6 (100.0)	0.20	-0.39, 0.72	0.4545
Placebo	5	4 (80.0)			

Source: ACRFVW1_ITT_T.SAS 2019-10-22T08:14:01 Z9FRBE.
Abbreviations: CI, Confidence interval; mITT, Modified intention to treat; N, Number.
[a] A positive difference in response rates favors anakinra.

2.3.4.3.2. Change from baseline in physician global assessment of disease activity (VAS) at Week 1

The comparison between the treatment groups in change from baseline in physician global assessment of disease activity (VAS 0 to 100 mm) at Week 1 is presented in Table 14.2.1.15. There was a numerically greater change from baseline in favour of anakinra (mean change: -46.3) versus placebo (mean change: -30.0). However, the difference was not statistically significant.

Table 14.2.1.15 Change from baseline in physician global assessment of disease activity (VAS 0-100 mm) at Week 1 (mITT set)

Group / Time point	Absolute value: n	Mean (SD)	Median	Min	Max	Change from baseline: n	Mean (SD)	Median	Min	Max
Anakinra										
Baseline	6	60.4 (22.7)	61.1	30.0	89.0					
Week 1	6	14.0 (18.2)	6.5	2.2	50.0	6	-46.3 (32.6)	-45.3	-86.8	-2.5
Placebo										
Baseline	5	52.8 (15.2)	57.0	34.0	73.0					
Week 1	5	22.7 (11.2)	22.0	8.0	37.0	5	-30.0 (18.5)	-21.0	-51.0	-12.1
Difference (anakinra-placebo) in change from baseline										
H-L difference							-14.3			
95% CI of difference[a]							-59.9, 24.0			
p-value[b]							0.3290			

Source: GVASW1_ITT_T.SAS 2019-10-22T08:15:21 Z9FRBE.
Abbreviations: CI, Confidence interval; H-L, Hodges-Lehmann; mITT, Modified intention to treat; n, Number; SD, Standard deviation; VAS, Visual analogue scale where 0 indicates no disease activity and 100 indicates very severe disease activity.
[a] The exact 95% confidence intervals based on the Wilcoxon rank statistic for the Hodges-Lehmann estimate of the treatment difference.
[b] Wilcoxon-Mann-Whitney non-parametric test.

2.3.4.3.3. Change from baseline in patient/parent global assessment of overall well-being (VAS) at Week 1

The comparison between the treatment groups in change from baseline in physician global assessment of disease activity (VAS 0 to 100 mm) at Week 1 is presented in Table 14.2.1.16. There was a numerically greater change from baseline in favour of anakinra (mean change: -53.7) versus placebo (mean change: -25.0). However, the difference was not statistically significant.

Table 14.2.1.16 Change from baseline in patient/parent global assessment of overall well-being (VAS 0-100 mm) at Week 1 (mITT set)

	Absolute value					Change from baseline				
Group Time point	n	Mean (SD)	Median	Min	Max	n	Mean (SD)	Median	Min	Max
Anakinra										
Baseline	6	69.8 (19.4)	66.5	52.0	97.0					
Week 1	6	16.2 (26.9)	4.6	3.0	70.7	6	-53.7 (27.7)	-49.0	-92.8	-13.3
Placebo										
Baseline	4	47.3 (29.4)	53.5	8.0	74.0					
Week 1	5	18.5 (17.7)	7.0	3.3	42.0	4	-25.0 (31.7)	-16.5	-67.0	0.0
Difference (anakinra-placebo) in change from baseline										
H-L difference							-33.4			
95% CI of difference[a]							-76.0, 20.0			
p-value[b]							0.1714			

Source: VAS02W1_ITT_T.SAS 2019-10-22T08:15:25 Z9FRBE.
Abbreviations: CI, Confidence interval; H-L, Hodges-Lehmann; mITT, Modified intention to treat; n, Number; SD, Standard deviation; VAS, Visual analogue scale where 0 indicates very well and 100 indicates very poor.
[a] The exact 95% confidence intervals based on the Wilcoxon rank statistic for the Hodges-Lehmann estimate of the treatment difference.
[b] Wilcoxon-Mann-Whitney non-parametric test.

2.3.4.3.4. Change from baseline in CRP at Week 1

The comparison between the treatment groups in change from baseline in CRP at Week 1 is presented in Table 14.2.1.17.

There was a statistically significant difference in favour of anakinra (mean change: -109.6 mg/L) versus placebo (mean change: -22.7 mg/L) in change from baseline CRP.

Table 14.2.1.17 Change from baseline in C-reactive protein (mg/L) at Week 1 (mITT set)

Group Time point	Absolute value					Change from baseline				
	n	Mean (SD)	Median	Min	Max	n	Mean (SD)	Median	Min	Max
Anakinra										
Baseline	6	134.3 (73.5)	134.3	55.5	214.6					
Week 1	6	24.7 (53.5)	3.1	1.3	133.9	6	-109.6 (63.4)	-78.4	-195.5	-51.4
Placebo										
Baseline	5	98.9 (29.9)	95.9	61.2	132.2					
Week 1	5	76.1 (52.1)	77.4	6.1	144.3	5	-22.7 (47.1)	-23.3	-73.9	48.4
Difference (anakinra-placebo) in change from baseline										
H-L difference							-68.3			
95% CI of difference[a]							-175.0, -2.2			
p-value[b]							0.0303			

Source: CRPW1_ITT_T.SAS 2019-10-22T08:15:29 Z9FRBE.
Abbreviations: CI, Confidence interval; H-L, Hodges-Lehmann; mITT, Modified intention to treat; n, Number; SD, Standard deviation.
[a] The exact 95% confidence intervals based on the Wilcoxon rank statistic for the Hodges-Lehmann estimate of the treatment difference.
[b] Wilcoxon-Mann-Whitney non-parametric test.

CHMP comments

Key secondary endpoints included change from baseline in (a) physician global assessment of disease activity, (b) patient/parent global assessment of overall well-being, (c) CRP and (d) absence of fever fever during the 24 hours preceding Week 1.

Mean (and median) baseline values for both physician global assessment of disease activity (mean values: 60.4 and 52.8 for anakinra and placebo, respectively) and for patient/parent global assessment of overall well-being (mean values: 69.8 and 47.3 for anakinra and placebo, respectively) were notable lower for the placebo group compared to the anakinra group thus, it may be speculated that there was less room for improvement in the placebo group compared to the anakinra group. For both endpoints, none of the patients in either treatment group worsened during the first week. This could be expected for the anakinra group, but may be a bit surprising for the placebo group not at least as no other immune-modulating or anti-inflammatory treatment was given concomitantly but the observation period of 1 week is short and combined with the low number of patients included, no conclusion can be drawn. Overall, though the changes from baseline were not statistically significant different between the treatment groups (which could be because of the few patients included), the results were numeric better for anakinra for both endpoints. Similar pattern was observed for the absence of fever during the 24 hours preceding Week 1 and also changes in CRP though the difference in change in CRP was statistically significant in favour of anakinra (P=0.0303; 95%CI: -175.0;-2.2).

Taken together, the results support the finding of the primary objective.

4.3.4.4. Other secondary efficacy endpoints

Results for Other secondary efficacy endpoints are presented in the CSR.

CHMP comments

Secondary endpoints included Sustained ACR response with absence of fever at Week 4, Week 8 and Week 12 compared to ACR response at Week 2.

The most important results for the numerous secondary endpoints were that the efficacy of anakinra measured as ACR30, ACR50, ACR70 and ACR90 response was sustained over time up to Week 12. Only one patient in the anakinra group did not obtain ACR-response due to an occasion of fever at Week 4. As all placebo treated patients prematurely stopped treatment, a direct comparison is not relevant; of note, 4 placebo treated patients were withdrawn due to lack of effect/disease progression.

2.3.5. Safety evaluation

An overall summary of TEAEs during the study is presented in Table 12.1.

10 patients reported TEAEs, which were balanced between the anakinra and placebo groups. There were no SAEs in the anakinra group, while there was one SAE (lymphoma) in the placebo group.

No TEAEs led to study withdrawal in the anakinra group. However, one patient in the placebo group, who was diagnosed with lymphoma, was withdrawn from the study.

There were no deaths in the study.

There were no reported MAS cases in patients who received study drug.

Table 12.1 Overall summary of TEAEs during the study (Safety set)

	Number (%) of patients[a]	
	Anakinra (N = 6)	Placebo (N = 6)
Any TEAE	6 (100.0)	4 (66.7)
Any severe TEAE	0	1 (16.7)
Any treatment-emergent non-SAE	6 (100.0)	4 (66.7)
Any treatment-emergent SAE	0	1 (16.7)
Any related TEAE[b]	4 (66.7)	1 (16.7)
Any fatal TEAE	0	0
Any TEAE leading to study drug withdrawn	0	1 (16.7)
Any TEAE leading to study withdrawal	0	1 (16.7)

Source: AESUM_SAF_T.SAS 2019-10-22T08:29:31 Z9FRBE.
Abbreviations: AE, Adverse event; N, Number; SAE, Serious adverse event; TEAE, Treatment emergent adverse event.
[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
[b] Related to study drug, as judged by the investigator.

CHMP comments

The safety evaluation set included all patients who received study treatment thus, 6 patients treated with anakinra and 6 patients treated with placebo. This is endorsed.

All 6 patients treated with anakinra (and 4 patients treated with placebo) experienced at least one treatment emergent AE. The only serious AE reported was also the only AE leading to study drug discontinuation and withdrawal from the study. This was the placebo-treated patient who initially was diagnosed with Still's disease and therefore included in the study. After 21 days, biopsy of lymph nodes showed diffuse large B-cell lymphoma, stage III and the patient was excluded from the study. Importantly, the lymphoma is not considered related to study treatment.

2.3.4.4. Most frequently reported AEs

A summary of all AEs, by SOC and PT, are presented in Table 14.3.1.1 The table summarizes all AEs reported in the study, which consist of TEAEs and other AEs, including 2 AEs that were incorrectly collected outside of the AE reporting period, i.e. before first dose of study treatment or more than 4

weeks after last dose of study treatment, when only SAEs were to be reported according to the study protocol.

A summary of all TEAEs, by SOC and PT, are presented in Table 14.3.1.2. Non-serious infections and infestations were the most frequently reported TEAEs in the anakinra group, of which all were mild in severity. ISRs occurred in both treatment groups, of which all were mild in severity. One patient in the anakinra group presented with alopecia. There was also one report of alopecia in the placebo group, however, it occurred outside of the AE reporting period.

CHMP comments

All patients experienced AE(s). The most frequently reported AE was within the SOC 'Infections and infestations', where 5 patients treated with anakinra and 1 patient treated with placebo reported a total of 5 and 1 AEs, respectively. In the anakinra group, all reported AEs were Upper respiratory tract infections. Rhinorrhoea was reported in 3 anakinra treated patients. Additional, 3 anakinra treated patients reported GI-related AEs including vomiting (2 events), retching, nausea, vomiting, diarrhoea and constipation (1 event each). Within the SOC 'General disorders and administration site conditions', 2 patients treated with anakinra and 1 patient treated with placebo reported injection site reactions, 1 patient in each treatment group reported Injection site erythema, 1 patient (treated with anakinra) reported injection site rash, and 1 patient (treated with placebo) reported injection site pain. Other AEs were reported in ≤1 patient.

Overall, the AEs reported in the present study are in accordance with the AEs listed in the tabulated list of adverse events in section 4.8 of the SmPC for Kineret.

2.3.4.5. Categorization of all AEs

TEAEs classified as related to study medication by the investigator are presented in Table 14.3.1.3. In the anakinra group, AEs classified as related by the investigator were ISRs in 2 patients, injection site erythema and injection site rash in 1 patient, and alopecia in 1 patient. In the placebo group, the AEs classified as related were dizziness and headache in 1 patient.

There were no TEAEs of severe intensity in the anakinra group, while there was one case of lymphoma with severe intensity in the placebo group. All TEAEs in the anakinra group were mild in severity.

The number of TEAEs was also adjusted to the IMP exposure time. The most common TEAEs, number of events and event rate, by SOC and PT, are presented in Table 14.3.1.5.

Total exposure was 1.40 years in the anakinra group and 0.34 years in the placebo group. The total number of individual TEAEs were 29 in anakinra and 8 in placebo. When adjusted to exposure, the overall TEAE event rate was slightly higher in the placebo group compared to the anakinra group (23.76 TEAEs per patient year of exposure in placebo versus 20.69 in anakinra). The event rates for PTs that were reported for both groups, were similar in general.

The SOC with highest exposure-adjusted AE numbers was infections and infestations. Infections and infestations were slightly more frequent in the anakinra group compared with the placebo group (3.57 TEAEs per patient year of exposure in anakinra versus 2.97 placebo).

CHMP comments

Only few of the reported AEs were considered related to study treatment. In the anakinra treatment group, the following TEAEs were considered related to the treatment: Injection site reaction (2 patients), Injection site erythema (1 patient), Injection site rash (1 patient) and Alopecia (1 patient). Injection site reactions are already listed as a very common (≥1/10) AE to Kineret. Alopecia is not listed as an AE to Kineret.

When adjusted for total exposure, Upper respiratory tract infections within the SOC 'Infections and infestations' were also reported more frequently in the anakinra group compared with the placebo

group (3.57 TEAEs per patient year of exposure in anakinra versus 2.97 placebo). Serious infections are already listed as a common (≥1/100 to <1/10) AE to Kineret. Of note, none of the infections reported in the present study were considered serious.

Overall, the reported AEs are in accordance with the AEs listed in the tabulated list of adverse events in section 4.8 of the SmPC for Kineret.

2.3.4.6. Deaths, other SAEs, discontinuations due to AEs, other AEs of special interest and Withdrawal due to AEs

No deaths occurred during the study. Serious TEAEs, by SOC and PT, are presented in Table 12.2. There were no SAEs in the anakinra group. In the placebo group, one patient was confirmed to have the diagnosis of a diffuse large B-cell lymphoma and not Still´s disease, and this was consequently reported as an SAE (Table 12.2).

TEAEs leading to study withdrawal and study drug withdrawal are presented, by SOC and PT, in Table 12.3. In the anakinra group, there were no withdrawals due to AEs. One patient in the placebo group discontinued due to diffuse large B-cell lymphoma. This event was reported as an SAE.

Table 12.2 Serious TEAEs by SOC and PT (Safety set)

	Number (%) of patients[a]	
	Anakinra (N = 6)	Placebo (N = 6)
Any AE	0	1 (16.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (16.7)
Diffuse large B-cell lymphoma stage III	0	1 (16.7)

Source: SAESOCPT_SAF_T.SAS 2019-10-22T08:29:37 Z9FRBE.
Abbreviations: AE, Adverse event; N, Number; PT, Preferred term; SOC, System organ class; TEAE, Treatment emergent adverse event.
[a] Patients with multiple events at the same level of summarization are counted only once at that level. Patients with events at more than one level of summarization are counted once at each of those levels.
Note: MedDRA version 20.1.

Table 12.3 TEAEs by SOC and PT leading to study withdrawal (Safety set)

	Number (%) of patients[a]	
	Anakinra (N = 6)	Placebo (N = 6)
Any AE	0	1 (16.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (16.7)
Diffuse large B-cell lymphoma stage III	0	1 (16.7)

Source: AEWDSOCPT_SAF_T.SAS 2019-10-22T08:29:41 Z9FRBE.
Abbreviations: AE, Adverse event; N, Number; PT, Preferred term; SOC, System organ class; TEAE, Treatment emergent adverse event.
[a] Patients with multiple events at the same level of summarization are counted only once at that level. Patients with events at more than one level of summarization are counted once at each of those levels.
Note: MedDRA version 20.1.

CHMP comments

Only on SAE was reported during the treatment period. This was a 71-year-old female patient initially diagnosed with Still's disease and therefore included in the study but after 21 days treatment with placebo, the patient was admitted to the hospital due to worsening lymphadenopathy over the past 2 to 3 weeks. Histopathological examination of biopsy of lymph nodes showed diffuse large B-cell

lymphoma, stage III. The patient stopped study treatment and was excluded from the study. Importantly, the lymphoma is not considered related to study treatment.

2.3.4.7. Other adverse events of special interest

MAS was defined as an event of special interest in this study. There were no reported cases of MAS in patients who received study drug. One case of MAS occurred during screening in one patient who was not randomised and did not receive study drug.

CHMP comments

None of the included patients were reported with MAS during the study period. While this is reassuring, the few patients included as well as the short treatment- and observation-period should be kept in mind.

2.3.4.8. Clinical laboratory evaluation

At baseline, all patients had signs of systemic inflammation with decreased levels of Hb, increased levels of neutrophils, and all but one had increased levels of thrombocytes. These levels normalized during anakinra treatment and no patients developed neutropenia ($<1.5x10^9$/L) or thrombocytopenia ($<200x10^9$/L).

No elevations of liver enzymes were observed during the study.

In total, 5 out of 6 patients receiving anakinra and 3 out of 5 patients receiving placebo had triglycerides values above the fasting reference limit at some timepoint during the study. These elevations were in most cases transient but more prominent in the anakinra group. There was no dose response relationship. It should be noted that no fasting prior to sampling was required. Total cholesterol levels were within normal limits during the study.

CHMP comments

Still's disease is characterised by elevation of neutrophil leucocytes, CRP (previously discussed) and liver enzymes.

Overall, there were no unexpected findings related to the clinical laboratory values. As expected, all included patients had elevated leucocytes (neutrophils) at time of enrolment. Shortly (at Week 1) after treatment initiation, the leucocytes (neutrophils) decreased; most pronounced in the anakinra group. Mean and median values were normalised after 1 week in the anakinra group and after 4 weeks in the placebo group.

Mean values for serum aspartate aminotransferase increased slightly during the 12 weeks' study period. Mean baseline values for anakinra was 23.8 U/L, and for placebo 43.3 U/L. In the anakinra group, mean value increased slightly during the study period, at Week 2, Week 4 and Week 12, mean values were 32.2 U/L, 35.7 U/L and 31.6 U/L, respectively. In the placebo group, a decrease in mean values were observed; at Week 2 and Week 4 mean values were 30.2 U/L (6 patients), 16.5 U/L (2 patients). A similar pattern was observed for serum alanine aminotransferase though there was a more pronounced difference in baseline values (anakinra mean [min;max] baseline values 12.7 U/L [8;18], median [Q1;Q3]: 12.5 U/L [11.0;14.0]; placebo mean [min;max] baseline values 38.8 U/L [6;88], median [Q1;Q3]: 30.5 U/L [14.5;63.0]. Thus, the changes in alanine aminotransferase may be driven by few outliers. Nevertheless, the conclusion of the MAH, that *"No elevation of liver enzymes were observed during the study"* is not completely agreed. Of note, 'Increased hepatic enzymes' is a known uncommon (≥1/1.000 to <1/100) AE to Kineret.

Taken together, except for a small increase in liver enzymes in the anakinra treatment group, there were no unexpected findings related to the clinical laboratory values.

2.3.4.9. Vital signs

Vital signs

There were no clinically relevant changes in vital signs (blood pressure, heart rate or body weights) over time.

CHMP comments

As stated, there were no clinically relevant changes in blood pressure or, heart rate. Of note, Kineret is not reported to affect neither blood pressure nor heart rate, thus the findings are in accordance with the known safety profile of Kineret.

2.3.4.10. Immunogenicity

The presence of ADAs, NAbs, and cross-reactivity and titer levels are presented in Table 14.3.1.12.

Table 14.3.1.12 Occurrence of immunogenicity endpoints (Safety set)

	Anakinra (N = 6)	Placebo (N = 6)
Anti-drug antibodies		
Baseline	0	0
Week 1	1 (16.7)	0
Week 2	1 (16.7)	1 (16.7)
Week 4	5 (83.3)	0
Week 8	5 (83.3)	0
Week 12	5 (83.3)	0
Neutralizing antibodies		
Baseline	0	0
Week 1	0	0
Week 2	0	0
Week 4	0	0
Week 8	0	0
Week 12	0	0
Crossreactive[a] antibodies		
Baseline	0	0
Week 1	0	0
Week 2	1 (16.7)	0
Week 4	1 (16.7)	0
Week 8	5 (83.3)	0
Week 12	5 (83.3)	0
Neutralizing crossreactive[a] antibodies		
Baseline	0	0
Week 1	0	0
Week 2	0	0
Week 4	0	0
Week 8	0	0
Week 12	0	0

Source: ADA_SAF_T.SAS 2019-10-22T08:30:25 Z9FRBE.
Abbreviations: ADA, Anti-drug antibodies; IL-1RA, Interleukin 1 receptor antagonist; N, Number.
[a]ADA binding to recombinant endogenous like HEK293 cell produced IL-1RA.

Baseline samples were available for 4 of the 6 patients dosed with anakinra, of which all tested negative for ADA. However, all 6 anakinra patients developed ADAs at later time points. One patient tested positive for ADA at one time point only (Week 2), and one patient was ADA positive already at Week 2 and throughout the study (persistent ADAs). The remaining 4 anakinra patients were ADA positive at Week 4 and throughout the study (persistent ADAs).

NAbs were not detected at any time point of ADA detection. In the majority of ADA positive samples (66.7 %), cross-reactivity was found with recombinant endogenous-like IL-1Ra produced in HEK293 cells.

Overall, ADA titers were low (range 4.55 to 31.0) in 3 of anakinra patients throughout the study. However, in the remaining 3 anakinra patients, moderate titers above 100 (range 109 to 385) were seen at some time points during the treatment period.

One placebo patient tested positive for ADA at one time point only (Week 2) in low titer (10.7) and without neutralizing activity, which was not cross-reactive with recombinant endogenous-like IL-1Ra produced in HEK293 cells.

Occurrence and titer levels of ADAs in relation to AEs at Week 1, Week 2, Week 4, Week 8 and Week 12

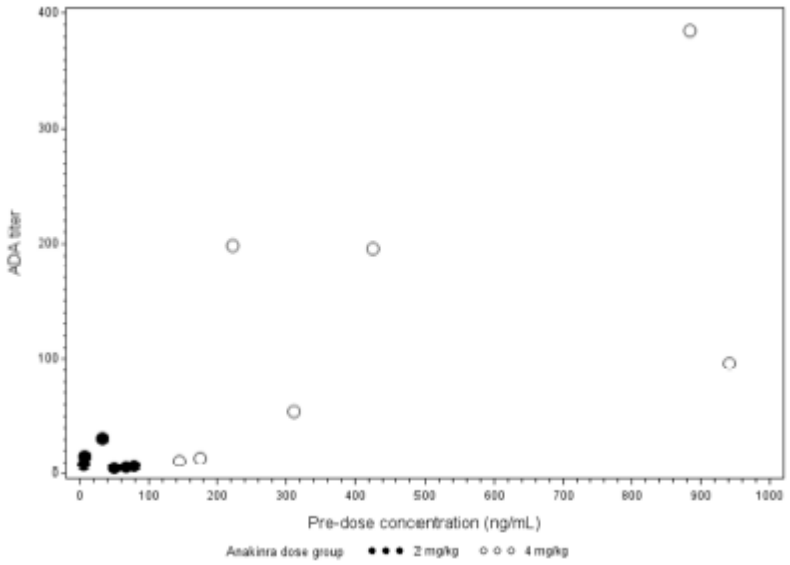
The limited number of patients in the study precluded a full evaluation regarding the impact of ADA/NAb on safety in this patient population. There was no clear pattern of AEs and TEAEs in relation to ADA occurrence and titer.

Occurrence and titer levels of ADA, including NAb in relation to ACR response and CRP at Week 1, Week 2, Week 4, Week 8 and Week 12

The limited number of patients in the study precluded a full evaluation regarding the impact of ADA/NAb on efficacy in this patient population. However, ACR responses and persistent decline of CRP levels were seen despite occurrence of ADA.

Results on pre-dose ADA titer and serum anakinra concentrations are available in 6 anakinra treated patients including a total of 13 observations during Week 1 to Week 12. Based on these data there is no apparent correlation between ADA titer and pre-dose (Figure 1).

Figure 1. Pre-dose serum anakinra concentrations vs. anti-drug antibodies during treatment across timepoints (for patients with both pre-dose PK and ADA titer at a specific timepoint (Week 1 - Week 12))



CHMP comments

During the 12 weeks' treatment period, all of the 6 patients (100%) treated with anakinra developed anti-drug antibodies. One of the patients developed transient antidrug antibodies (during the Week 2 only), the remaining 5 patients developed anti-drug antibodies at Week 2-4 and all of these 5 patients remained positive throughout the study period. None of the patients developed neutralizing antibodies,

which is considered the antibodies most likely to affect the efficacy of anakinra. (Non-neutralizing) antidrug antibody formation is not *per se* expected to affect the efficacy of the treatment.

The relatively high proportion of patients developing antidrug antibodies is in line with a recent study of anakinra treatment of 43 patients (7 adults and 36 children) with cryopyrin-associated periodic syndromes. In this study, the patients were followed over 60 months and during the study period, 83% of the patients developed antidrug antibodies, the majority (79%) within 3 months. Reassuringly, there was no evidence of a decreased efficacy of the treatment among patients developing antidrug antibodies, but there was no information regarding the proportion of patients developing neutralizing antibodies. The authors of the study conclude: *"chronic daily subcutaneous treatment with anakinra is safe and effective regardless of the development and presence of ADA."*[1)] Similarly high incidences of antidrug antibodies development (to anakinra) have been reported in two other studies. One study of anakinra treatment of patients with rheumatoid arthritis (50% of the patients developing antidrug antibodies)[2)] and another study of anakinra treatment of patients with juvenile rheumatoid arthritis (82% of the patients developing antidrug antibodies)[3)].

In the present study, all 6 anakinra treated patients developed cross-reactive antibodies to endogenous like HEK293 cell produced IL-1RA. Indeed, antibody formation (to some degree) is expectable when treatment with biologics is in questions and therefore, it is not unexpected that some patients developed antibodies. It is reassuring that none of the cross-reactive antibodies were neutralizing and that neither efficacy nor safety was affected. Further, data show that there is no apparent correlation between pre-dose and ADA titer.

1) Wikén M, Hallén B, Kullenberg T, et al. Development and effect of antibodies to anakinra during treatment of severe CAPS: sub-analysis of a long-term safety and efficacy study. Clin Rheumatol. 2018 Dec;37(12):3381-3386.
2) Fleischmann RM, Tesser J, Schiff MH, et al. Safety of extended treatment with anakinra in patients with rheumatoid arthritis. Ann Rheum Dis 2006;65:1006–1012.
3) Ilowite N, Porras O, Reiff A, et al. Anakinra in the treatment of polyarticular-course juvenile rheumatoid arthritis: safety and preliminary efficacy results of a randomised multicenter study. Clin Rheumatol (2009) 28:129–137.

2.3.5. PK evaluation

2.3.5.1. Pre-dose concentrations

Anakinra serum pre-dose concentrations during the 12-week treatment period ranged between 7.19 ng/mL and 95.9 ng/mL with 2 mg/kg (max 100 mg/day) anakinra, and between 80.7 ng/mL and 885 ng/mL with 4 mg/kg (max 200 mg/day) anakinra. Pre-dose values more than 2 hours prior to next dose were not included in the summary tables, since these were not considered true pre-dose concentrations.

All but one patient treated with placebo had IL-1Ra concentrations not exceeding 18 ng/mL, based on the first week of treatment when still remaining in the study. In another patient, who discontinued study treatment (placebo) at Day 6 and thereafter initiated commercially available anakinra, serum IL-1Ra concentrations were substantial on Day 9 and Day 16.

2.3.5.2. Serum PK parameters

PK parameters were calculated at Week 12 in 2 paediatric patients (Table 11.7).

In a 1-year-old patient, Cmax (2920 ng/mL) was reached 4.0 hours after administration of 4.1 mg/kg anakinra, and in a 6-year-old patient, Cmax (1060 ng/mL) was reached 2.1 hours after administration of 1.5 mg/kg anakinra. At Week 12, PK parameters CL/F and Vd/F were 139 mL/h/kg and 1187 mL/kg in a 1-year-old patient, and 203 mL/h/kg and 1322 mL/kg in a 6-year-old patient.

Table 11.7 Patient listing of PK parameters at Week 12 (PK set)

Dose group	Subject ID	Age (years)	Dose (mg)	Weight (kg)	GC use	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-24h} (h*ng/mL)	V_d/F (mL/kg)	CL/F (mL/h*kg)	CL/F (mL/h)	$t_{½}$ (h)
2 mg/kg	158-01	6	40	26.7	No	1060	2.117	7375.769	1322.098	203.115	5423.163	4.512
4 mg/kg	109-01	1	50	12.2	No	2920	4.000	29590.746	1186.945	138.501	1689.717	5.940

Source: PP_PK_L.SAS 2019-10-22T08:20:34 Z9FRBE.
Abbreviations: GC, Glucocorticoids; ID, Identification number; PK, Pharmacokinetic.
Parameter abbreviations: AUC_{0-24h}, Area under the serum concentration-time curve during a dosage interval; CL/F, Apparent total clearance of drug from serum after subcutaneous administration; C_{max}, Observed maximum serum concentration of anakinra; t_{max}, Time to reach C_{max} following dose injection; $t_{½}$, Apparent terminal half-life; V_d/F, Apparent volume of distribution following subcutaneous administration.

CHMP comments

The MAH informs that anakinra serum pre-dose concentrations during the 12-week treatment period ranged between 7.19 ng/mL and 95.9 ng/mL with 2 mg/kg (max 100 mg/day) anakinra, and between 80.7 ng/mL and 885 ng/mL with 4 mg/kg (max 200 mg/day) anakinra. Mean values at Week 12 were as shown in Table 14.2.2.1 below:

Table 14.2.2.1 Pre-dose serum concentrations (ng/mL) by visit (PK set)

	Anakinra 2 mg/kg (N = 2)	Anakinra 4 mg/kg (N = 4)	Total anakinra (N = 6)
Week 12			
n	2	2	4
Geom (CV%)	55.999 (81.010)	499.570 (84.114)	167.259 (165.476)
Mean (SD)	64.300 (44.689)	583.500 (426.385)	323.900 (388.746)
Median (Q1, Q3)	64.300 (32.700, 95.900)	583.500 (282.000, 885.000)	188.950 (64.300, 583.500)
Min, max	32.70, 95.90	282.00, 885.00	32.70, 885.00

Source: PC_PK_T.SAS 2019-10-22T08:20:40 Z9FRBE.
Abbreviations: CV%, Coefficient of variation; Geom, Geometric mean; N, Number; n, Number; PK, Pharmacokinetic; Q1, first quartile. Q3, third quartile; SD, standard deviation.
For values below limit of quantification, 0 is used.

While a linear or close to linear dose-exposure relation could be expected with the doses used (2 mg/kg and 4 mg/kg, respectively) the results should be interpreted with caution. Firstly, as previously mentioned, few patients were included in the study and secondly, serum concentrations were sampled at different time points making any comparison even further problematic. Overall, the results are in line with previous studies and importantly, the PK for anakinra is evaluated in previous PK-studies and adequately described in the Kineret SmPC. Therefore, the results from the present study is not considered to add any conclusive data.

2.3.6. CHMP's Discussion and Conclusion on clinical aspects

On 19 November 2019, the MAH submitted a completed paediatric Study Sobi.ANAKIN-301 for Kineret, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Study Sobi.ANAKIN-301 was a randomised, double-blind, placebo-controlled, multicentre, phase 3 study. The aim of the study was to demonstrate the efficacy and to evaluate the safety, pharmacokinetics (PK) and immunogenicity of anakinra as compared to placebo in newly diagnosed Still's disease patients (including systemic juvenile idiopathic arthritis [SJIA] and adult-onset Still's disease [AOSD]). Numerous efficacy-, safety- and pharmacokinetic-related objectives and endpoints were identified, however, as the study was prematurely closed due to difficulties in recruitment, focus in the present assessment report is only made on the primary efficacy endpoint ("*to demonstrate*

efficacy of anakinra versus placebo in Still's disease as assessed by ACR30 response including absence of fever") and the safety (including but not limited to immunogenicity) of anakinra.

Sample size calculation estimated 83 patients to be included in the study, but due to the difficulties in recruitment of patients, only 13 patients were randomised (7 patients were randomised to anakinra, 6 were randomised to placebo). The mITT set (which is used for evaluation of the primary and key secondary endpoints) consisted of 11 patients (6 treated with anakinra and 5 treated with placebo) and only 6 patients (all treated with anakinra) completed the 12 weeks' treatment. Thus, data for the PK endpoint *("Anakinra trough serum concentrations and repeated -dose PK parameters at Week 12"*) are only evaluated based on 6 patients. Similar, several of the secondary endpoints were based on clinical effect measured at 12 weeks and thus, the interpretation of these results must be made with caution and cannot be compared to placebo. The 6 placebo-treated patients were discontinued due to lack of efficacy/disease progression (4 patients), AE (lymphoma, 1 patient) and Withdrawal by patient (1 patient). As expected with the few patients included in each treatment group, small differences in baseline and demographic data were observed.

The study was conducted with the aim of supporting a marketing authorisation application for anakinra in the US. In Europe, *'the clinical study report was solely submitted to meet the obligation of Article 46 to submit any MAH-sponsored studies involving the use of an authorised medicinal product including a paediatric population'*.

For the primary endpoint *"Anakinra trough serum concentrations and repeated -dose PK parameters at Week 12"* measured on the ACR30 scale, all patients in the anakinra treatment group responded at Week 2 while none of the patients in the placebo group were responders. The result was statistically significant in favour of anakinra (P[95%CI]=0.0022[0.42;1.00]). Previous studies of Kineret used in the treatment of Still's disease have showed a response rate of 67% and 73% (on the ACR30 scale). These results were obtained after 1 month and 3 months, respectively (corresponding placebo-response was 8%). Taken together, the result for the primary endpoint is in line with previous findings. Further, the result was also supported by the sensitivity analysis, the key secondary endpoints and the secondary efficacy endpoints. The result however, must be carefully evaluated as it is based on few patients, on a dichotomous scale and measured after 2 weeks. Thus, generalisation to the entire population of patients with Still's disease or long-term effect cannot be made.

At Week 1, 5 of the 6 anakinra treated patients had ACR30 response. This indicates that treatment with anakinra may have a fast onset in improving the symptoms of the disease. Also results for ACR50, ACR70 and the ACR90 as well as the individual components of the ACR50, ACR70 and the ACR90 were supporting the effect of anakinra. When interpreting the results for the individual components, it should be considered that these components may be expected to be inter-related. If the number of joints with active arthritis is decreased, there may be fewer joints with limitation of motion and this will lead to a better assessment of physical function, and an improvement in global assessment of disease activity and overall well-being. It is endorsed that the MAH has included specific focus on fever as Still's disease, is characterized by high spiking fevers. All patients treated with anakinra (but none of the placebo-treated patients) were absence of fever during the first week of treatment (i.e. during the 7 days preceding Week 2. It is acknowledged that the 3 patients with missing data were regarded as having fever; this is in accordance with the SAP however, as all 3 patients were treated with placebo, this assumption may have favoured anakinra in the direct comparison. Nevertheless, as the total number of patients is small and as all anakinra-treated patients had absence of fever, the issue will not be pursued.

The safety evaluation set included all patients who received study treatment thus, 6 patients treated with anakinra and 6 patients treated with placebo. This is endorsed.

All 6 patients treated with anakinra (and 4 patients treated with placebo) experienced at least one treatment emergent AE. The only serious AE reported was also the only AE leading to study drug discontinuation and withdrawal from the study. This was the placebo-treated patient who initially was diagnosed with Still's disease and therefore included in the study. After 21 days, biopsy of lymph nodes showed diffuse large B-cell lymphoma, stage III and the patient was excluded from the study. Importantly, the lymphoma is not considered related to study treatment. None of the included patients were reported with MAS during the study period. While this is reassuring, the few patients included as well as the short treatment- and observation-period should be kept in mind.

The most frequently reported AE was within the SOC 'Infections and infestations', where 5 patients treated with anakinra and 1 patient treated with placebo reported a total of 5 and 1 AEs, respectively. In the anakinra group, all reported AEs were Upper respiratory tract infections. Additional, 3 anakinra treated patients reported GI-related AEs including vomiting (2 events), retching, nausea, diarrhoea and constipation (1 event of each PT). Within the SOC 'General disorders and administration site conditions', 3 patients treated with anakinra reported a total of 5 injection site reactions including injection site erythema and injection site rash. Other AEs were reported in ≤1 patient. Overall, the AEs reported in the present study are in accordance with the AEs listed in the tabulated list of adverse reactions in section 4.8 of the SmPC for Kineret. Only few of the reported AEs were considered related to study treatment. In the anakinra treatment group, the following TEAEs were considered related to the treatment: Injection site reaction (4 patients), and Alopecia (1 patient). Injection site reactions are already listed as a very common (≥1/10) AE to Kineret. Alopecia is not listed as an AE to Kineret. When adjusted for total exposure, upper respiratory tract infections within the SOC 'Infections and infestations' were also reported more frequently in the anakinra group compared with the placebo group Serious infections are already listed as a common (≥1/100 to <1/10) AE to Kineret. Of note, none of the infections reported in the present study were considered serious.

Still's disease is characterized by elevation of neutrophil leucocytes, CRP (previously discussed) and liver enzymes. Overall, there were no unexpected findings related to the clinical laboratory values. As expected, all included patients had elevated leucocytes (neutrophils) at time of enrolment. Shortly (at Week 1) after treatment initiation, the leucocytes (neutrophils) decreased; most pronounced in the anakinra group. Mean and median values were normalised after 1 week in the anakinra group and after 4 weeks in the placebo group. Mean values for serum aspartate aminotransferase increased slightly during the 12 weeks' study period. A similar pattern was observed for serum alanine aminotransferase. Therefore, the conclusion of the MAH, that *"No elevation of liver enzymes were observed during the study"* is not completely agreed. Of note, 'Increased hepatic enzymes' is a known uncommon (≥1/1.000 to <1/100) AE to Kineret.

During the 12 weeks' treatment period, all of the 6 patients (100%) treated with anakinra developed anti-drug antibodies. One of the patients developed transient antidrug antibodies (during the Week 2 only), the remaining 5 patients developed anti-drug antibodies at Week 2-4 and all patients remained positive throughout the study period. None of the patients developed neutralizing antibodies, which is considered the antibodies most likely to affect the efficacy of anakinra. (Non-neutralizing) antidrug antibody formation is not *per se* expected to affect the efficacy of the treatment. The relatively high proportion of patients developing antidrug antibodies is in line with a recent study of anakinra treatment of 43 patients (7 adults and 36 children) with cryopyrin-associated periodic syndromes. In this study, the patients were followed over 60 months and during the study period, 83% of the patients developed antidrug antibodies, the majority (79%) within 3 months. Reassuringly, there was no evidence of a decreased efficacy of the treatment among patients developing antidrug antibodies, but there was no information regarding the proportion of patients developing neutralizing antibodies. The authors of the study conclude: *"chronic daily subcutaneous treatment with anakinra is safe and effective regardless of the development and presence of ADA."* Similar high incidences of antidrug

antibodies development (to anakinra) have been reported in two other studies (reporting antidrug antibodies in 50-82% of the anakinra treated patients). In the present study, all 6 anakinra treated patients developed cross-reactive antibodies to endogenous like HEK293 cell produced IL-1RA. Indeed, antibody formation (to some degree) is expectable when treatment with biologics is in questions and therefore, it is not unexpected that some patients developed antibodies. It is reassuring that none of the cross-reactive antibodies were neutralizing and that neither efficacy nor safety was affected. Further, data show that there is no apparent correlation between pre-dose and ADA titer.

It is acknowledged that the PK-results are based on few patients. Compared to the 2 mg/kg dose, Tmax was doubled, Cmax was increased with 150% for the 4 mg/kg dose and $AUC_{0\text{-}24hours}$ was increased with 400%. There was only a small change in volume of distribution (1322 mL/kg vs. 1187 mL/kg) and the terminal half-life (T½: 4.5 hours vs. 5.9 hours) was comparable between the two patients. While a linear or close to linear dose-exposure relation could be expected with the doses used (2 mg/kg and 4 mg/kg, respectively) the results should be interpreted with caution. Firstly, as previously mentioned, few patients were included in the study and secondly, serum concentrations were sampled at different time points making any comparison even further problematic. Overall, the results are in line with previous studies and importantly, the PK for anakinra is evaluated in previous PK-studies and adequately described in the Kineret SmPC. Therefore, the results from the present study is not considered to add any conclusive information and data.

Conclusively, very few patients were included in the present study and only 6 patients were treated with anakinra. The results seem to support the beneficial effect of anakinra (compared to placebo) with a fast (within 1-2 weeks) improvement in all components of the ACT30 scale. Overall, the safety profile (also based on very few patients and a short follow-up) was in accordance with previous studies and besides of 1 patient with alopecia, no new AEs were reported. All 6 anakinra treated patients developed antidrug antibodies bun none were reported with neutralizing antidrug antibodies. However, cross-reactive antibodies to endogenous like HEK293 cell produced IL-1RA was reported for all patients. PK data is only presented for very few (2-6) patients. Lastly and importantly, while the results are overall reassuring, they cannot be generalised to the entire population of patients with Still's disease and conclusion of the long-term effect and safety cannot be made.

3. CHMP's overall conclusion and recommendation (January 2020)

☒ Not fulfilled:

Based on the data submitted, the MAH should provide additional clarification of the Other concerns listed in Section 4.

4. Additional clarification requested (January 2020)

Based on the data submitted, the MAH should address the following questions as part of this procedure:

The timetable is a 30-day response timetable without clock stop.

4.1. Major objections

No major objections were identified.

4.2. Other concerns

4.2.1. Clinical aspects

Question 1 (Data sources and measurements):

The MAH informs that monitor visits and review of source documents (including patients ICFs) were performed. If this was conducted as part of internal audits this is endorsed however, the MAH should confirm that this did not in any way increased the risk of unblinding data prior to data base lock.

Question 2 (Inclusion criteria and Patient demographic):'

The present CSR is submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. Nevertheless, it is noted that 5 adult patients (>18 years) have been included (Age: 24, 25, 32, 51 and 71 years, respectively). Of these, 2 patients (age 24 and 51 years, respectively) were randomised to anakinra 2 mg/kg. The MAH should clarify why there was no upper age-limit for inclusion and discuss if these 2 adult patients may have influenced the efficacy and/or safety results in any clinically relevant degree.

Question 3 (Efficacy):

At Week 1, 3 (of the 5 (=60.0%)) of the placebo-treated patients had response defined according to ACR30. Similar, with regard to the individual components of physician global assessment of disease activity and patient/parent global assessment of overall well-being, none of the placebo-treated patients worsened during the first week. Considered that no other immune-modulating or anti-inflammatory treatment was given concomitantly, this is unexpected (even the low number of placebo-treated patients taken into account). The MAH should discuss these findings including a discussion of potential reason(s) for this high proportion of patients with treatment response observed in the placebo group.

Question 4 (Immunogenicity):

In the present study, all 6 anakinra treated patients developed cross-reactive antibodies to endogenous like HEK293 cell produced IL-1RA. The possible consequences of this cross-reactive antibody production should be discussed by the MAH.

Question 5 (Immunogenicity):

In order to clarify a possible relation between serum anakinra concentrations and formation of antidrug antibodies, the MAH should (if available) present data for serum anakinra concentrations during the treatment period correlated with the development of antidrug antibodies.

Question 6 (PK evaluation):

Due to the few (6) anakinra treated patients included in the present study, it is understood that the pharmacokinetic results are based on few patients however, within the used doses, a linear or close to linear dose-exposure relation was expected. However, it appears that the mean, median as well as minimum and maximum serum-concentrations for the anakinra 4 mg/kg treatment group is almost a factor 10 of the concentrations observed in the anakinra 2 mg/kg dose. This should be further discussed by the MAH.

Question 7 (PK evaluation):

Pharmacokinetic parameters were presented for 2 paediatric patients (1 and 6 years, respectively). The MAH should clarify why only data from 2 paediatric patients were included as a total of 5 paediatric patients were randomised to treated with anakinra.

Question 8 (PK evaluation):

Compared to the 2 mg/kg dose, Tmax was doubled, Cmax was increased with 150% for the 4 mg/kg dose and $AUC_{0\text{-}24hours}$ was increased with 400%. There was only a small change in volume of distribution (1322 mL/kg vs. 1187 mL/kg) and the terminal half-life (T½: 4.5 hours vs. 5.9 hours) was comparable between the two patients. The MAH should discuss if the presented data from the two paediatric patients can be extrapolated to the general paediatric population.

5. MAH responses to Request for supplementary information (March 2020)

5.1. Major objections

No major objections were identified.

5.2. Other concerns

5.2.1. Clinical aspects

Question 1 (Data sources and measurements):

The MAH informs that monitor visits and review of source documents (including patients ICFs) were performed. If this was conducted as part of internal audits this is endorsed however, the MAH should confirm that this did not in any way increased the risk of unblinding data prior to data base lock.

MAH Response: Monitor visits and review of source documents (including patients ICFs) were performed by qualified personnel at the Academic Research Organization, DCRI according to the ICH GCP guideline.

In addition, audits were of selected clinical investigator sites were conducted to assess and help assure compliance with GCP and applicable regulatory requirements. These audits were initiated by Sobi and conducted according to standard procedures. Section 2.i describes review of blinding and maintenance of the blinding. No information discovered that could be potentially unblinding was disclosed to Sobi prior to data base lock.

CHMP comments

The MAH has described the procedure for the monitor visits and informed that these were conducted according to the ICH GCP guideline. It is ensured that no information was unblinded prior to database lock. This is endorsed.

Conclusion: Issue resolved.

Question 2 (Inclusion criteria and Patient demographic):

The present CSR is submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. Nevertheless, it is noted that 5 adult patients (>18 years) have been included (Age: 24, 25, 32, 51 and 71 years, respectively). Of these, 2 patients (age 24 and 51 years, respectively) were randomised to anakinra 2 mg/kg. The MAH should clarify why there was no upper age-limit for inclusion and discuss if these 2 adult patients may have influenced the efficacy and/or safety results in any clinically relevant degree.

MAH Response: The study was conducted with the aim of obtaining approval for treatment of Still's disease in the United States. Current understanding, based on ample available evidence, is that SJIA

and AOSD represent the same disease continuum, thus study enrollment was not limited to paediatric or adult populations (Cabane et al. 1990, Tanaka et al. 1991, Uppal et al. 1995, Luthi et al. 2002, Pay et al. 2006, Jamilloux et al. 2015b, Nirmala et al. 2015, Vastert et al. 2019). As no upper age limit has been reported for patients presenting with Still's disease, there was no rationale for an upper age limit. However, randomisation was stratified by age <16 years old or onset of disease ≥16 years.

Anakinra already has a marketing authorization for treatment of both adult and paediatric Still's disease patients since April 2018 in the EU. SobiANAKIN-301 was not part of a paediatric investigation plan and the clinical study report was solely submitted to meet the obligation of Article 46 to submit any MAH-sponsored studies involving the use of an authorised medicinal product including a paediatric population.

Since the study was stopped before the planned number of evaluable patients been included, it was not appropriate to conduct formal subgroup analyses due to the small sample size. Data on paediatric patients can therefore not be presented separately.

On review of the data there were no clinically significant differences seen between individual adult and paediatric patients in terms of clinical symptoms, disease duration nor ACR30 response Therefore, Sobi does not consider that the inclusion of 2 adult patients in the anakinra group influenced the safety nor efficacy conclusions of the study.

CHMP comments

The MAH has informed that the study was conducted with the aim of supporting a marketing authorisation application for anakinra in the US. In Europe, *'the clinical study report was solely submitted to meet the obligation of Article 46 to submit any MAH-sponsored studies involving the use of an authorised medicinal product including a paediatric population'*. This is acknowledged.

Conclusion: Issue resolved.

Question 3 (Efficacy):

At Week 1, 3 (of the 5 (=60.0%)) placebo-treated patients had response defined according to ACR30. Similar, with regard to the individual components of physician global assessment of disease activity and patient/parent global assessment of overall well-being, none of the placebo-treated patients worsened during the first week. Considered that no other immune-modulating or anti-inflammatory treatment was given concomitantly, this is unexpected (even the low number of placebo-treated patients taken into account). The MAH should discuss these findings including a discussion of potential reason(s) for this high proportion of patients with treatment response observed in the placebo group.

MAH Response: 5 (83.3%) of anakinra patients and 3 (60%) of placebo patients had a ACR30 response with absence of fever at Week 1.

Sobi has been unable to find published literature where ACR30 response is measured at 7 days. Sobi considers that a time period of one week is not enough to report a deterioration, including individual components such as physician global assessment of disease activity and patient/parent global assessment of overall history of Still's disease.

Clinical rheumatologists report that early in the illness the symptoms of Still's disease flux and this stabilizes over time, therefore this could possibly account for the apparent 3 responders in the placebo group at week 1. Whilst the recruitment to the study was blinded and randomised, the participants who received anakinra had been unwell for longer than those that received placebo. Patients randomised to anakinra had had symptoms for a median of 84.5 days (range 31-222) vs 32.0 days

(range 12-60 days). Additionally, anakinra patients had a longer disease duration with median of 7 days (range 1-65) vs placebo 2 days (range1-4).

However, on review of components suggestive of systemic inflammation, response is already seen at week 1. There was already a significant difference in CRP response, an objective measure of inflammation in systemic disease, between the two groups. All patients had a reduction in CRP in the anakinra group vs only one in the placebo group (p=0.0152), with a change from mean baseline of -109.6 mgl/L (SD: 63.4) in anakinra vs -22.7 mg/L (SD: 47.1) in placebo group (p=0.03). The same pattern was seen with other inflammatory markers. This reduction in systemic inflammation would be predicted to subsequently lead to an improvement in clinical symptoms including joint symptoms as seen at primary end point at week 2.

Additionally, the differences between response in anakinra and control groups in assessment of physical function CHAQ/SHAQ approached significance with no placebo patients reporting a response (anakinra 4 (66.7%) vs 0 (0%): p=0.061). This component is potentially more predictive of a sense of increased general well-being in a disease that manifests as systemic inflammation than some of the other components.

CHMP comments

The MAH has sufficiently discussed the relatively high placebo-response after 1 week. It is mentioned that 1 week of treatment is too early too early to report any deterioration however, the finding was 'absence of fever after 1 week'. Considered the inclusion criteria (At least one fever episode attributable to the disease within one week before randomisation (definition of fever: body temperature ≥38.0 °C)) 'absence of fever' is not considered a deterioration but rather a possible 'placebo-effect'. Either way, only few patients were included in the present study and the issue will not be pursued.

Conclusion: Issue resolved.

Question 4 (Immunogenicity):

In the present study, all 6 anakinra treated patients developed cross-reactive antibodies to endogenous like HEK293 cell produced IL-1RA. The possible consequences of this cross-reactive antibody production should be discussed by the MAH.

MAH Response: As with all biopharmaceuticals there is always a risk of immunogenicity with induction of ADA and NAbs. The incidence of ADA was high however, the titers were low and no NAbs were detected in the Sobi.ANAKIN-301 study. Thus, the cross-reactive low-titer ADAs that were found in serum from dosed patients were not neutralizing, and the ADA did not affect efficacy nor safety. The presence or absence of ADAs appear to have no clinical impact in any of the studies performed, and there are no indications from the literature that ADAs against anakinra cross-react with endogenous IL-1Ra in patients. Further, there are no indications from reports received by Sobi that Still's disease would worsen after withdrawal of anakinra. In addition, there are literature articles (e.g. ter Haar et al. 2019) describing cessation of anakinra in asymptomatic patients without recurrence of Still's disease symptoms. In patients with flares after withdrawal of anakinra, symptoms are generally controlled by reinstitution of anakinra.

CHMP comments

Indeed, antibody formation (to some degree) is expectable when treatment with biologics is in questions and therefore, it is not unexpected that some patients developed antibodies. It is reassuring that none of the cross-reactive antibodies were neutralizing and that neither efficacy nor safety was affected.

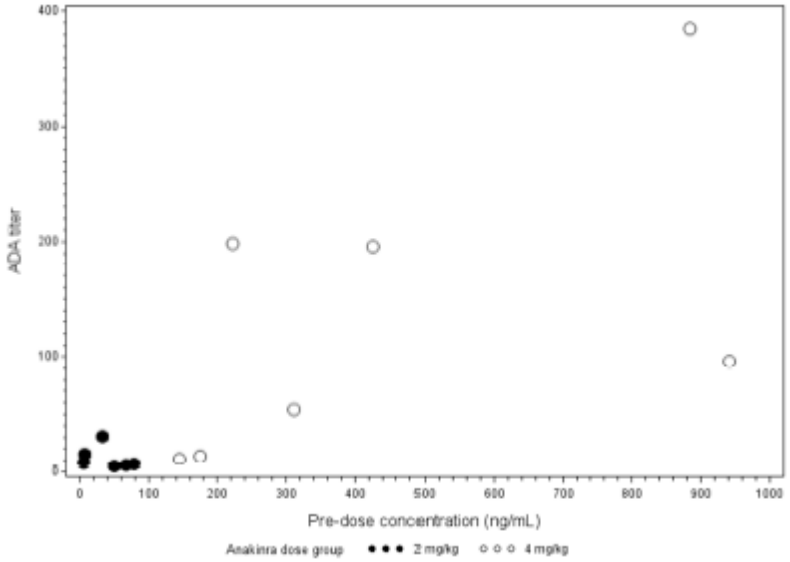
Conclusion: Issue resolved.

Question 5 (Immunogenicity):

In order to clarify a possible relation between serum anakinra concentrations and formation of antidrug antibodies, the MAH should (if available) present data for serum anakinra concentrations during the treatment period correlated with the development of antidrug antibodies.

MAH Response: Results on pre-dose ADA titer and serum anakinra concentrations are available in 6 anakinra treated patients including a total of 13 observations during Week 1 to Week 12. Based on these data there is no apparent correlation between ADA titer and pre-dose (Figure 1).

Figure 1. Pre-dose serum anakinra concentrations vs. anti-drug antibodies during treatment across timepoints (for patients with both pre-dose PK and ADA titer at a specific timepoint (Week 1 - Week 12))



CHMP comments

The MAH has presented the requested data. It is agreed that there is no apparent correlation between pre-dose and ADA titer.

Conclusion: Issue resolved.

Question 6 (PK evaluation):

Due to the few (6) anakinra treated patients included in the present study, it is understood that the pharmacokinetic results are based on few patients however, within the used doses, a linear or close to linear dose-exposure relation was expected. However, it appears that the mean, median as well as minimum and maximum serum-concentrations for the anakinra 4 mg/kg treatment group is almost a factor 10 of the concentrations observed in the anakinra 2 mg/kg dose. This should be further discussed by the MAH.

MAH Response: The number of patients included in the present study was substantially lower than planned. A total of 81 patients with Still's disease were planned to be enrolled (54 to anakinra and 27 to placebo treatment). Due to the premature termination of the study due to difficulties to enroll

patients a total of 13 patients were randomised, of which 12 patients (6 males, 6 females) received study treatment; 6 patients received anakinra and 6 patients received placebo.

Consequently, pre-dose anakinra concentrations were measured in only 2 patients on 2 mg/kg anakinra and 4 patients on 4 mg/kg anakinra, with at the most 3 individual results at a certain time-point. Also, the actual time-point for the pre-dose samples varied, and samples collected as early as 2 hours before the dose were included, which may have increased the inter-patient variability in the results Based on this limited number of patients the MAH does not find it relevant to draw any conclusion on the dose-proportionality of the anakinra serum levels. Also, anakinra pre-dose levels are in the same concentration range as observed in earlier study in SJIA patients (study 990758).

CHMP comments

The MAH argues that due to the low number of patients, no firm conclusions ca be drawn. This is of course agreed. Further, serum concentrations were sampled at different time points making any comparison even further problematic. The PK for anakinra is evaluated in previous PK-studies and therefore, the results from the present study is not considered conclusive.

Conclusion: Issue resolved.

Question 7 (PK evaluation):

Pharmacokinetic parameters were presented for 2 paediatric patients (1 and 6 years, respectively). The MAH should clarify why only data from 2 paediatric patients were included as a total of 5 paediatric patients were randomised to treated with anakinra.

MAH Response: Since the study was terminated before all patients had been enrolled consequently repeated PK samples after multiple-dose PK were only collected in 2 patients treated with anakinra with a disease onset <6 years of age.

As described in the Clinical Study Report (Section 9.3) samples for PK were collected according to 2 different sampling schedules in accordance with the Clinical Study Protocol.

Collection of pre-dose blood samples was collected in all patients at all visits e.g. Week 1, 2, 4, 8 and 12. In addition, at Week 12 blood samples were collected before, 2, 4, 6 and 8 hours after administration of IMP (anakinra or placebo) in a sub-set of patients. The aim with these samples was to calculate serum PK parameters after multiple-dose administration of anakinra. This sampling schedule was planned to be applied in patients at a pre-selected number of the sites.

The planned target per dose level was 5 patients with disease onset <6 years, 5 patients with disease onset ≥6 to <16 years and 5 patients with a disease onset ≥16 years.

CHMP comments

The MAH has r the sampling schedule (time points for sampling collection). Further, as mentioned by the MAH (in response to an other question), fewer than expected patients were included in the study. Thus, in any way few (patients with) PK samples is to be expected.

Conclusion: Issue resolved.

Question 8 (PK evaluation):

Compared to the 2 mg/kg dose, Tmax was doubled, Cmax was increased with 150% for the 4 mg/kg dose and $AUC_{0\text{-}24hours}$ was increased with 400%. There was only a small change in volume of distribution (1322 mL/kg vs. 1187 mL/kg) and the terminal half-life (T½: 4.5 hours vs. 5.9 hours) was

comparable between the two patients. The MAH should discuss if the presented data from the two paediatric patients can be extrapolated to the general paediatric population.

MAH Response: The actual doses administered in these two patients were 1.5 and 4.2 mg/kg, i.e. the administered doses differed by a factor 2.8. The time-course of the serum concentration time profiles was similar in these 2 patients with tmax at 2.1 and 4.0 hours post-dose and T½ of 4.5 and 5.9 hours. Cmax was a factor 2.8-fold higher, whereas AUC0-24hours differed by a factor 4. The slightly larger dose adjusted AUC0-24hours was due to differences in CL, 203 mL/min/kg in the 6 year-old child and 138 mL/min/kg in the 1-year old child. As pointed out volume of distribution was comparable in these patients.

Overall, the PK results in these 2 patients are in line with current data. The anakinra serum exposure is similar to these in the Sobi sponsored study in SJIA patients (study 990758), where the exposure was documented for up to 28 weeks treatment with mean (SD) dose-normalised plasma concentrations 240 (222) ng/mL/kg. Due to the sparse sampling in study 990758, CL was not calculated. However, CL values in the 2 patients in our study was in line with what is reported in the publication by Urien et al, even if not following strictly the PK model with higher BW adjusted CL for lower BW.

In conclusion, even if PK parameters were calculated in 2 pediatric patients in the current study the PK results reported in these 2 patients aged 6 and 1 year, were comparable with current data.

CHMP comments

The MAH has clarified that (as mentioned in the previous (assessment of) responses) PK samples were collected at different time points. Further, only few patients were included. Therefore, the data is not considered conclusively. The PK for anakinra is evaluated in previous PK-studies and is sufficiently described in the SmPC.

Conclusion: Issue resolved.

6. CHMP's updated overall conclusion and final recommendation (April 2020)

☒ Fulfilled:

No regulatory action required. See section 2.3.6.