21 May 2026
EMADOC-1700519818-3226352
Human Medicines Division

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

Kineret

Anakinra

Procedure no: EMA/PAM/0000335960

Note

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

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Status of this report and steps taken for the assessment			
Current step[1]	**Description**	**Planned date**	**Actual Date**
☐	CHMP Rapporteur AR	28 April 2026	28 April 2026
☐	CHMP comments	11 May 2026	n/a
☐	Updated CHMP Rapporteur AR	13 May 2026	n/a
☒	CHMP outcome	21 May 2026	21 May 2026

Administrative information

Procedure resources	
Rapporteur	**Thalia Marie Estrup Blicher**

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1. Introduction

On 6 March 2026, the MAH submitted a completed paediatric study for Kineret, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Sobi.ANAKIN-303 is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

Kineret is already authorised for the age subset treated in the study and the administered subcutaneous injection is the approved one. The formulation is the same for all age subsets.

The investigational product anakinra was delivered as a sterile solution for injection, pre-filled in a single-use graduated syringe with the strength 100 mg. The total volume contained in a syringe was 0.67 mL and the concentration of anakinra in the solution was 150 mg/mL. The pre-filled graduated syringe had a pre-attached 29-gauge thin wall half inch needle, a butyl rubber plunger and a latex free rigid integrated needle shield.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Sobi.ANAKIN-303

2.3.2. Clinical study

Sobi.ANAKIN-303, A randomized, double-blind, placebo-controlled, multicenter, phase 3 efficacy and safety study of subcutaneous anakinra in Japanese patients with Still's disease (SJIA and AOSD)

Description

Methods

Study participants

A total of 15 patients (including SJIA and AOSD) were randomized to study treatment. At least a third of the randomized patients were required to be diagnosed with SJIA (disease onset before the age of 16 years), and at least a third of the randomized patients in the study were required to be diagnosed with AOSD (disease onset at the age of 16 years or above).

Inclusion criteria

Inclusion criteria for the core phase

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

1. ICF signed by the patient or a legal guardian representative.

2. Male and female patients, 8 months of age or older with a body weight ≥10 kg.

3. Diagnosis of Still's disease.

4. Criteria for diagnosis of Still's disease:

a. If <16 years of age at disease onset, the diagnosis was according to adapted International League for Associations of Rheumatology (ILAR) criteria i.e., CARRA criteria for SJIA (see Appendix 16.1.1, CSP version 6.0, Appendix 1).

b. If ≥16 years of age at disease onset, the diagnosis was according to Yamaguchi criteria for AOSD (see Appendix 16.1.1, CSP version 6.0, Appendix 1).

5. 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 1 week before enrollment. (Definition of fever: Body temperature ≥38.0°C attributable to the disease)

6. Background Treatment with stable dose of ≤1 mg/kg/d (max 60 mg/d) of oral prednisolone or equivalent for at least 3 days prior to enrollment was permitted.

7. Background Treatment with stable dose of MTX (≤20 mg/m2/week) for at least 4 weeks prior to enrollment was permitted.

8. Female patients of childbearing potential and male patients with female partners of childbearing potential had to use an effective method of contraception during the study (abstinence being a possible option) as well as a negative pregnancy test prior to enrollment for females of childbearing potential and participating in the study.

9. Negative tuberculosis screening confirmed at screening visit by the Mantoux Tuberculin skin test (TST) using purified protein derivative (PPD), or by Interferon-Gamma-Release Assays (IGRAs), e.g., QuantiFERON® TB Gold Plus (QFT-Plus) or T-Spot® (Tuberculosis Test) within 8 weeks prior to enrollment. Negative results had to be complemented by medical history, physical examination and Chest X-Ray. Patients presenting positive TST or IGRA that were not due to a recent PPD vaccination, with or without active or clinical suspicion of latent tuberculosis were not eligible to enter the study. Previously vaccinated for Tuberculosis patients: IGRA positive patients were not eligible to enter the study; TST positive patients with an induration of 15 mm and more were also not eligible to enter the study, TST positive patients (with an induration up to 15 mm) were also not eligible to enter the study, unless an IGRA test was subsequently performed and provided a negative result.

Inclusion criteria for the extension phase

1. Current participation in the study.

2. Informed consent form signed by the patient or a legal guardian representative.

3. Patient experienced clinical benefit while participating in the core phase of the study and was expected to benefit from continued treatment with anakinra, in the opinion of the investigator.

4. Evidence of sustained efficacy with ACR30 response with absence of fever in the 7 days preceding both the Week 44 and Week 54 visits of the core phase.

Exclusion criteria

Exclusion criteria for the core phase

The presence of any of the following excluded a patient from participation to the study:

1. Previous enrollment to this study.

2. Participation in another clinical interventional study within 30 days prior to enrollment.

3. Treatment with an investigational drug within 5 half-lives prior to enrollment.

4. Previous or current treatment with anakinra, or any other IL-1 inhibitor except for canakinumab. Previous treatment with canakinumab was allowed if canakinumab was discontinued for reasons other than lack of efficacy and after a washout period of minimum 130 days (Refer to Exclusion Criteria 5h). Patients who had discontinued canakinumab because of insufficient effect or refractory disease were not allowed to be enrolled in the study.

5. Use of the following therapies prior to enrollment:

a. Narcotic analgesics within 24 hours prior to enrollment.

b. Diaminodiphenyl sulfone within 1 week prior to enrollment or etanercept within 2 weeks prior to enrollment.

c. Intraarticular, intramuscular, or intravenous administration of glucocorticoids within 72 hours (3 days) prior to enrollment, or intravenous immunoglobulin within 4 weeks prior to enrollment.

d. Intravenous immunoglobulin with proven Still's disease modifying effect, leflunomide, infliximab, or adalimumab within 8 weeks prior to enrollment.

e. Thalidomide within 72 hours (3 days) prior to enrollment, cyclosporine within 5 weeks prior to enrollment, tacrolimus hydrate within 2 weeks prior to enrollment, mycophenolate mofetil within 1 week prior to enrollment, 6-mercaptopurine within 48 hours (2 days) prior to enrollment, azathioprine within 72 hours (3 days) prior to enrollment, cyclophosphamide within 96 hours (4 days) prior to enrollment, chlorambucil (not approved in Japan) within 48 hours (2 days) prior to enrollment, Janus kinase (JAK) inhibitors within 5 half-lives prior to enrollment, or any other immunosuppressant within 12 weeks prior to enrollment.

f. Tocilizumab within 4 weeks prior to enrollment or any other immunomodulatory medication within 4 half-lives prior to enrollment.

g. Rituximab within 13 weeks prior to enrollment.

h. Canakinumab within 130 days prior to enrollment.

6. Live vaccines within 4 weeks prior to enrollment.

7. Known presence or suspicion of active, chronic, or recurrent bacterial, fungal or viral infections, including but not limited to tuberculosis, human immunodeficiency virus (HIV) infection, COVID-19 infection, hepatitis B, or C infection at baseline. Patients with acute or chronic hepatitis B virus (HBV) (i.e., with positive hepatitis B surface antigen [HBsAg], except if a documented history of vaccination), or at risk of HBV reactivation (i.e., with negative HBsAg AND positive antibody against hepatitis B core protein [anti-HBc]) were excluded.

8. Clinical evidence of liver disease or liver injury as indicated by presence of abnormal liver tests:

a. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5 x upper limit of normal (ULN), or

b. AST or ALT >3 x ULN accompanied by elevated bilirubin >2 x ULN.

9. Presence of severe chronic kidney disease grades 4 and 5 (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m2).

10. Presence of neutropenia (absolute neutrophil count <1.5 x 109/L).

11. Presence of thrombocytopenia (platelets count <100 x 109/L).

12. Presence or suspicion of MAS at baseline.

13. History or diagnosis of MAS within the last 4 weeks prior to enrollment.

14. History of malignancy within 5 years prior to enrollment. Exceptions were basal cell skin cancer, carcinoma-in-situ of the cervix, or low-risk prostate cancer after curative therapy.

15. Known hypersensitivity to Escherichia Coli (E. Coli)-derived proteins or any components of anakinra, including excipients (citric acid anhydrous, sodium chloride, disodium edetate dihydrate, polysorbate 80 and sodium hydroxide).

16. Pregnant or lactating women.

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

18. Presence of any medical, psychological condition, or laboratory result that in the opinion of the investigator could interfere with the patient's ability to comply with the protocol requirements or make the patient not appropriate for inclusion to the study and treatment with IMP.

Exclusion criteria for the extension phase

1. Inactive disease status achieved at the Week 54 visit in the core phase for a continuous period of at least 6 months.

Treatments

During the RDB period, patients received either anakinra or placebo for 2 weeks. The evaluated dose of anakinra dose was 100 mg/day for patients weighing ≥50 kg and 2 mg/kg/day (max 100 mg/day) for patients with a body weight <50 kg. No dose adjustment during the RDB period was allowed. Patients randomized to the control arm received placebo volumes corresponding to those in the active arm. Anakinra and placebo were administered subcutaneously once a day. During the open-label treatment period in the core phase and the extension phase, all patients received anakinra according to their body weight in accordance with Table 9-1. For a patient who was <16 years old with a body weight inferior to 50 kg, in the case the patient did not respond sufficiently to anakinra treatment at Week 4 visit (i.e., persistence of systemic manifestations [fever, rash, arthritis and/or arthralgia, elevated levels of CRP]), a dose adjustment was allowed at the discretion of the investigator according to actual body weight (rounded to the nearest kg). In that case, the anakinra dose could be increased up to 4 mg/kg/day with a max of 200 mg/day. Otherwise, the investigator could consider whether the patient should continue anakinra or not.

Table 9-1 Investigational medicinal products

Study phase	Investigational product	Daily dose	Dosage form	Route	Dosage regimen
Randomized double-blind period	Anakinra	≥50 kg: 100 mg/day <50 kg: 2 mg/kg/day (max 100 mg/day)	Solution for injection in pre-filled syringe	s.c.	Once daily
	Corresponding volume of placebo	Solution volume equivalent to 100 mg/day (max 100 mg [0.67 mL]) Solution volume equivalent to 2 mg/kg/day (max 100 mg [0.67 mL])	Solution for injection in pre-filled syringe	s.c.	Once daily
Open-label treatment period in the core phase and the extension phase	Anakinra	≥50 kg: 100 mg/day <50 kg: 2 mg/kg/day (max 100 mg/day)	Solution for injection in pre-filled syringe	s.c.	Once daily
	Anakinra dose adjustment	<16 years old and <50 kg: 4 mg/kg/day (max 200 mg/day)	Solution for injection in pre-filled syringe	s.c.	Once daily

Abbreviations: s.c., Subcutaneous

Objective(s)

Primary objective

The primary objective was to demonstrate the efficacy of anakinra compared to placebo in Japanese patients with Still's disease.

Secondary objectives

Secondary objectives in the randomized double-blind period

• To demonstrate the efficacy of anakinra compared to placebo in reducing inflammation in Still's disease.

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

• To evaluate and compare the health status between anakinra treated patients and patients treated with placebo.

Secondary objectives in the open-label treatment period of the core phase

• To evaluate efficacy of anakinra from Week 4 up to Week 54 visit in Still's disease.

• To evaluate the occurrence of inactive disease.

• To evaluate the health status in anakinra treated patients with Still's disease.

• To evaluate sustained efficacy of anakinra in patients responding to study drug at Week 2 visit.

Secondary objectives in the core phase

• To evaluate the occurrence of study drug discontinuation in anakinra treated patients with Still's disease.

• To evaluate glucocorticoids tapering in anakinra treated patients with Still's disease.

• To evaluate the safety of anakinra in patients with Still's disease.

• To evaluate immunogenicity of anakinra in patients with Still's disease.

- To evaluate occurrence of anti-drug antibodies (ADAs), neutralizing antibodies (NAbs) and cross-reactivity.

- To evaluate the impact of ADAs on the safety of anakinra.

- To evaluate the impact of ADAs and NAbs on the efficacy of anakinra.

• To evaluate the PK of anakinra in patients with Still's disease.

Secondary objectives in the extension phase

• To evaluate the long-term efficacy of anakinra in patients with Still's disease.

• To evaluate the safety of anakinra in patients with Still's disease.

• To evaluate immunogenicity of anakinra in patients with Still's disease.

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

- To evaluate the impact of ADAs on the safety of anakinra.

Outcomes/endpoints

Primary endpoint

The primary endpoint was ACR30 response at Week 2 visit with absence of fever attributable to the disease during the 7 days preceding Week 2 visit.

Definition of ACR30 response in SJIA patients:

An improvement of ≥30% from baseline to Week 2 visit, in at least 3 of any 6 variables of the ACR core set listed below, with no more than 1 variable worsening by >30%.

• Physician global assessment of disease activity (visual analogue scale [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 (Child health assessment questionnaire [CHAQ]).

• CRP (mg/L).

Definition of ACR30 response in AOSD patients:

An improvement of ≥30% from baseline to Week 2 visit, in at least 3 of any 6 variables of the ACR core set listed below, with no more than 1 variable worsening by >30%.

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 (Stanford health assessment questionnaire [SHAQ]).

6. CRP (mg/L).

Definition of fever: Body temperature ≥38.0°C attributable to the disease.

Definition of active arthritis: Joint with swelling. In absence of swelling, limitation of range of motion accompanied by either pain on motion or tenderness not due to deformity.

Secondary endpoints

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

• Absence of rash during the 7 days preceding Week 2 visit.

• ACR50, ACR70 and ACR90 response with absence of fever during the 7 days preceding the Week 2 visit.

• Change from baseline in physician global assessment of disease activity (VAS) to Week 2 visit.

• Change from baseline in patient/parent global assessment of overall well-being (VAS) to Week 2 visit.

• Change from baseline in patient/parent global assessment of disease related pain (VAS) to Week 2 visit.

Secondary endpoints during the randomized double-blind period

To demonstrate the efficacy of anakinra compared to placebo in reducing inflammation in Still's disease:

• Change from baseline in CRP, ferritin, hemoglobin, platelets and white blood cells count to Week 2 visit.

To demonstrate early onset of efficacy of anakinra compared to placebo in Still's disease:

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

• Absence of rash during the 24 hours preceding the evaluation visit at Week 1 visit.

• ACR30, ACR50, and ACR70 response with absence of fever during the 24 hours preceding the evaluation visit at Week 1 visit.

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

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

• Change from baseline in patient/parent global assessment of disease related pain (VAS) to Week 1 visit.

• Change in swelling joints count from baseline to Week 1 visit.

• Change in tender joints count from baseline to Week 1 visit.

• Change from baseline in CRP, ferritin, hemoglobin, platelets and white blood cells count to Week 1 visit.

To evaluate and compare the health status between patients treated with anakinra and placebo was:

• Change from baseline to Week 2 visit, in EQ-5D-Y Proxy (4 to 7 years of age), EQ-5D-Y (8 to 15 years of age) and EQ-5D-3L (≥16 years of age).

Secondary endpoints during the open-label treatment period of the core phase

To evaluate efficacy of anakinra from Week 4 up to Week 54 visit in Still's disease:

• Absence of fever during the 7 days preceding the visit.

• Absence of rash during the 7 days preceding the visit.

• ACR30, ACR50, ACR70 and ACR90 response with absence of fever during the 7 days preceding the visit.

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

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

• Change from baseline in patient/parent global assessment of disease related pain (VAS).

• Change in swelling joints count from baseline.

• Change in tender joints count from baseline.

•Change from baseline in CRP, ferritin, hemoglobin, platelets and white blood cells count.

Occurrence of inactive disease:

•Occurrence of inactive disease (see Section 9.5.1.2.14) at Week 8 visit and at the following respective visits up to Week 54 visit.

To evaluate the health status in anakinra treated patients with Still's disease:

•Change from baseline in EQ-5D-Y Proxy (4 to 7 years of age), EQ-5D-Y (8 to 15 yearsof age) and EQ-5D-3L (≥16 years of age) to Week 4, 8, 12, 16, 20, 26, 34, 44 and 54visits.

To evaluate sustained efficacy of anakinra in patients responding to study drug at Week 2 visit:

•ACR30 response with absence of fever during the 7 days preceding the study visits overtime up to 54 weeks visit.

Secondary endpoints during the core phase

Study drug discontinuation

To evaluate the occurrence of study drug discontinuation in anakinra treated patients with Still's disease:

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

•Time to study drug discontinuation due to any reason.

•Number of patients discontinuing study treatment.

Glucocorticoids tapering

To evaluate glucocorticoids tapering in anakinra treated patients with Still's disease:

•Time to initiation of glucocorticoids tapering.

•Percentage decrease of glucocorticoids dose for patients tapering their glucocorticoidsdose at Week 12, 34 and 54 visits compared to baseline.

•Discontinuation of glucocorticoids up to Week 54 visit.

Safety endpoints

To evaluate the safety of anakinra in patients with Still's disease:

•Occurrence of adverse events (AEs); serious adverse events (SAEs) and non-SAEs,deaths and AEs leading to study drug discontinuation at all study visits up to Week 58visit (for patients not entering the extension phase; Week 54 visit for patients entering theextension phase).

•Vital signs changes from baseline, including blood pressure, heart rate and body weight to all study visits up to Week 58 visit (for patients not entering the extension phase; Week 54 visit for patients entering the extension phase). Changes in height in patients younger than 19 years old at all study visits from baseline to Week 54 visit.

•Laboratory safety assessment changes over time, and occurrence of abnormal laboratoryvalues at all study visits up to Week 54 visit.

Immunogenicity endpoints

To evaluate immunogenicity of anakinra in patients with Still's disease:

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

•Occurrence of ADAs, NAbs and cross-reactivity and titer levels of ADAs at baseline,Week 2, 4, 12, 34, 54 and 58 visits (Week 58 Safety Follow-up visit only for patients notentering the extension phase).

2.To evaluate the impact of ADAs on the safety of anakinra:

•Occurrence and titer levels of ADAs in relation to AEs at Week 2, 4, 12, 34, 54 and 58visits (Week 58 Safety Follow-up visit only for patients not entering the extensionphase).

3.To evaluate the impact of ADAs and NAbs on the efficacy of anakinra:

•Occurrence and titer levels of ADAs, and occurrence of NAbs in relation to ACR30response and CRP levels at Week 2, 4, 12, 34, 54 and 58 visits (Week 58 SafetyFollow-up visit only for patients not entering the extension phase).

Pharmacokinetic endpoint

To evaluate the PK of anakinra in patients with Still's disease:

•Anakinra serum concentrations at baseline, Week 1 and 2 visits.

Secondary endpoints during the extension phase

Efficacy endpoints

To evaluate the long-term efficacy of anakinra in patients with Still's disease •ACR30 response with absence of fever attributable to Still's disease during the 7 days preceding the study visits at Week 67 and 80 visits.•Occurrence of inactive disease at Week 67 and 80 visits.

Safety endpoints

To evaluate the safety of anakinra in patients with Still´s disease:

•Occurrence of AEs (SAEs and non-SAEs), deaths, and AEs leading to study drug discontinuation at all study visits from start of the extension phase up to Week 84 visit.

•Occurrence of abnormal laboratory values at all study visits from start of extension phaseup to Week 84 visit.

•Vital signs changes from start of extension phase, including blood pressure, heart rate,and body weight at all study visits up to Week 84 visit. Changes of height in patientsyounger than 19 years old at all study visits from start of extension phase up to Week 84visit.

Immunogenicity objectives and endpoints

To evaluate immunogenicity of anakinra in patients with Still's disease:

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

•Occurrence of ADAs, NAbs, cross-reactivity, and titer levels of ADAs at Week 67 and 84 visits.

2.To evaluate the impact of ADAs on the safety of anakinra:

•Occurrence and titer levels of ADAs in relation to AEs at Week 67 and 84 visits.

Sample size

Randomisation and blinding (masking)

Randomisation

A total of 15 patients were intended to be randomized into the study, 10 patients were intended to be randomized to anakinra and 5 patients to placebo. The different treatment arms for the double-blind period were:

•Anakinra 100 mg/day for patients with a body weight ≥50 kg and anakinra 2 mg/kg/day(max 100 mg/day) for patients with a lower body weight i.e., <50 kg.

•Placebo (corresponding volume of anakinra 100 mg/day or 2 mg/kg/day (max100 mg/day).

The ratio between anakinra and placebo was intended to be 2:1.

The randomization numbers were generated in blocks. Each block included the 2 treatment arms per the ratio described above. The randomization was to be stratified by age at onset of disease (<16 years, ≥16 years) and glucocorticoids use at inclusion (yes, no), with a requirement to randomize at least a third of the patients with an age at onset of disease <16 years and at least a third of the patients with an age at onset ≥16 years.

Although the study was intended to be randomized at a 2:1 ratio, due to an allocation system setting error, the final ratio was close to 1:1. The error did not cause any bias as the patients were still

randomized according to the stratification criteria, albeit with a different allocation ratio, and the study was kept fully blinded.

Blinding and unblinding

The treatment assignment during the 2-week double-blind period was blinded (placebo and active treatment) for the patients, the investigators, the contract research organization (CRO), Sponsor and any personnel involved with the study conduct or evaluation at the investigational sites. Unblinding of treatment was planned for the interim analysis at Week 26 and was conducted on 2 December 2024. Additionally, there were the following unblinding operations during the study before the unblinding for the Week 26 interim analysis.

During the RDB period, the independent IMP monitor verified the accountability of the investigational product. To avoid unexpected unblinding, only the independent IMP monitor verified accountability of investigational product by direct access to the unused investigational product syringes and cartons that were returned by the patient to the study site. The blinded clinical research associates reviewed the accountability log during their on-site monitoring visits.

In the safety analysis for iDMC, independent statistician of the CRO and iDMC secretariat were allowed access to the unblinded data. The independent statistician of the CRO was independent from the study team consisting of staff in charge of development, monitoring, statistical analysis and data management. The iDMC analysis was conducted and the results were submitted to the iDMC by the independent statistician. The iDMC members were allowed to review the unblinded data for an individual patient in case it was needed. The unblinded data management team was formed to conduct unblinded data management activities, notably reconciliation of unblinded external data.

Only the CRO unblinded Trial Master File (TMF) manager and unblinded study team members were allowed access to unblinded paper-based TMF and electronic TMF, which were managed by the TMF manager and the unblinded study team members.

Unblinding of treatment to the Principal Investigator was planned in case there was a need to break the code for an individual patient based on the investigator decision during the study in an emergency situation, for instance, a patient meeting rescue criteria. The Principal Investigator was not to request an authorization to unblind a patient who met rescue criteria from the Sponsor but required to notify the Sponsor that a patient met the rescue criteria and that the Principal Investigator was unblinded. The Sponsor and the CRO needed to remain blinded up to the database lock for the interim analysis at Week 26 visit. During the RDB period, 1 patient met the rescue criteria and the Principal Investigator was unblinded.

To minimize bias from observed efficacy or laboratory changes, a blinded independent physician performed the physician global assessment of disease activity and joints examination during the RDB period. For consistency between evaluations, it was strongly recommended that the assessments were conducted by the same assessor at a study site.

IMP administered at the study site during the first 2 weeks of the study was to be performed by independent, trained and qualified personnel. These personnel were not allowed to perform any evaluation of the patients.

Data sets analysed

A summary of the 3 analysis sets is provided in Table 10-2. All 15 patients were included in the FAS and the safety analysis set. In the PK analysis set, 1 patient was excluded due to "no serum concentration data." The PK samplings were not performed for the patient because the patient completed the PK sampling visits (Week 1 [26 April 2023] and Week 2 [2 May 2023]) before site implementation (25 May 2023) of protocol amendment 3, where PK analyses were added.

Table 10-2 Summary of Study Populations - Core phase (Randomized population)

	Anakinra (N=8) n (%)	Placebo/Anakinra (N=7) n (%)	Total (N=15) n (%)
Safety Analysis Set			
Included	8 (100.0)	7 (100.0)	15 (100.0)
Not included	0	0	0
Full Analysis Set			
Included	8 (100.0)	7 (100.0)	15 (100.0)
Not included	0	0	0
Pharmacokinetic Analysis Set			
Included	8 (100.0)	6 (85.7)	14 (93.3)
Not included	0	1 (14.3)	1 (6.7)
Reasons for not included			
No serum concentration data*	0	1 (14.3)	1 (6.7)

Source: CSR Sobi.ANAKIN-303, Table 14.1.1-2
*PK sampling not performed due to PK sampling visits completed before site implementation of protocol amendment 3 to add PK analysis
Abbreviation: CSR, Clinical study report.

Results

The Sobi.ANAKIN-303 trial, included 5 pediatric patients (5 of 15 enrolled; 33.3%), defined as those with SJIA and disease onset before 16 years of age. No formal analysis was conducted for the pediatric population.

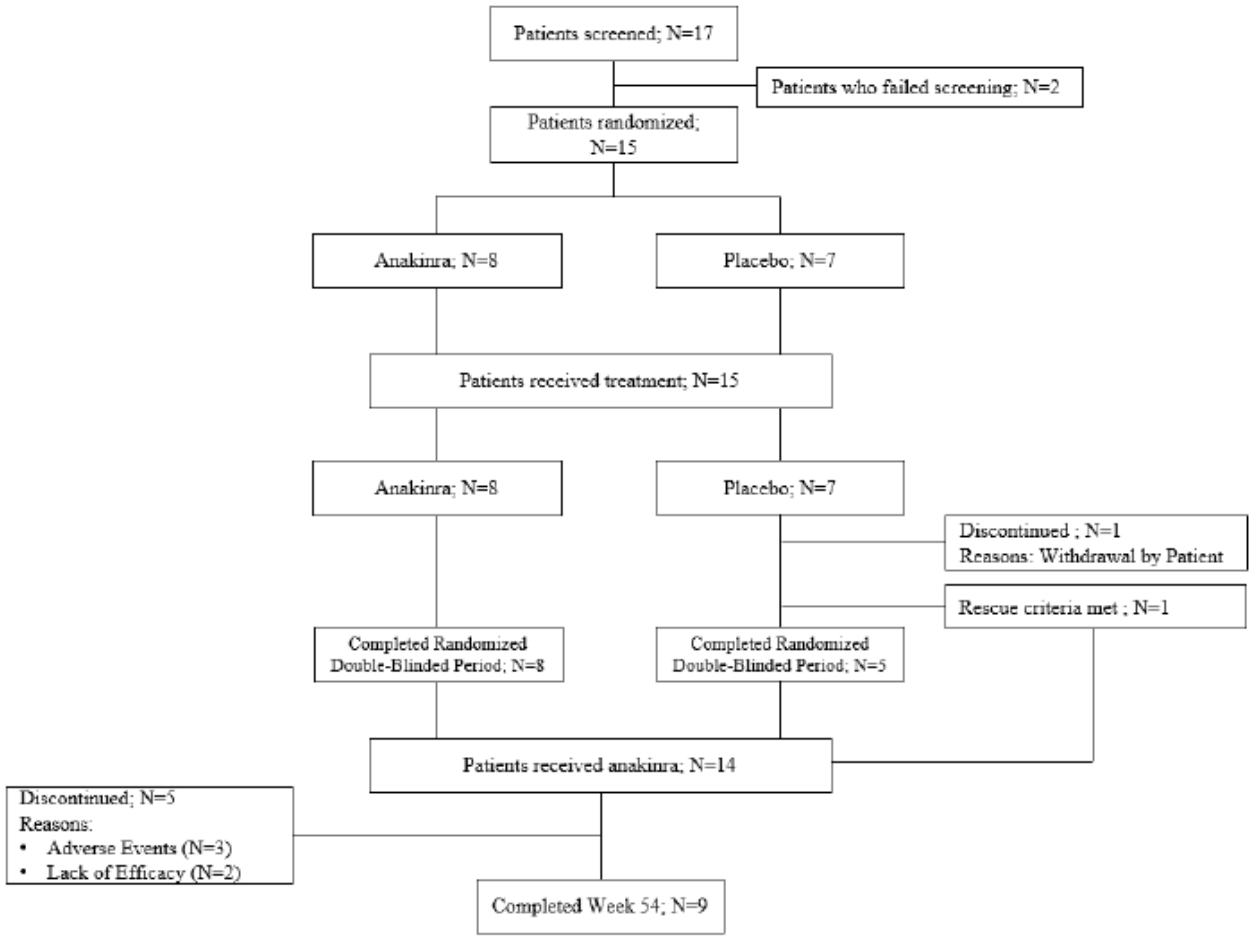
Participant flow

A total of 17 patients were screened and 2 patients were screening failures due to not meeting inclusion criterion 5c and meeting exclusion criterion 5c (1 patient each). All 15 patients who completed screening were randomized to study treatment and received study drug with 8 patients receiving anakinra and 7 patients receiving placebo. During the RDB period, 1 patient in the placebo arm discontinued the study due to withdrawal by the patient. In addition, 1 patient in the placebo arm met the rescue criteria of "Flare which is defined as a worsening of 30% or more in at least 3 of the 6 variables of the ACR core set with recurrence of fever lasting for 3 or more consecutive days" on Day 8, discontinued the RDB period and immediately entered the open-label treatment period. The signs and symptoms which caused the patient meeting rescue criteria were as follows: 64.7% increase in the physician global assessment of disease activity (34 to 56), 69.0% increase in the patient/parent global assessment of overall well-being (42 to 71), 133.3% increase in the number of joints with active arthritis (3 to 7), 49.5% increase in the CRP (43.4 mg/L to 64.9 mg/L), and fever lasting 5 consecutive days (from Day 3 to Day 7). After the treatment switch to anakinra in the open-label treatment period, all these parameters improved by Week 4 (i.e. two weeks after treatment with anakinra was initiated) and the patient achieved ACR30, ACR50, ACR70 and ACR90 response with absence of fever at Week 4.

A total of 14 patients started the open-label treatment period, including 1 patient who met the rescue criteria and directly entered it. During the open-label treatment period, 5 patients discontinued the study, and 9 patients completed the open-label treatment period. The reasons for discontinuation were AEs (3 patients) and lack of efficacy (2 patients). Of the 9 patients who completed the open-label

treatment period, 1 patient entered the extension phase. Eight patients entered the Safety Follow-up and completed the study without entering the extension phase.

Figure 10-1 Disposition of patients in the study



Source: CSR Sobi.ANAKIN-303, Table 14.1.1-1 and Table 14.2.3-5
Abbreviation: CSR, Clinical study report.

Table 10-1 Patient Disposition - Core phase (All Enrolled Patients)

	Anakinra n (%)	Placebo/Anakinra n (%)	Total n (%)
Informed consent	-	-	17
Passed Screening [a]	-	-	15 (88.2)
Screen failure [a]	-	-	2 (11.8)
Reasons [b]			
SCREEN FAILURE	-	-	2 (100.0)
Randomized	8	7	15
Randomized, but not treated [c]	0	0	0
Received IMP [c]	8 (100.0)	7 (100.0)	15 (100.0)
Core phase completers [c]	5 (62.5)	4 (57.1)	9 (60.0)
Withdrawals in RDB Period [c]	0	1 (14.3)	1 (6.7)
Reasons [d]			
Withdrawal by Patient	0	1 (100.0)	1 (100.0)
Withdrawals in Open-Label Treatment Period [c]	3 (37.5)	2 (28.6)	5 (33.3)
Reasons [e]			
Adverse Events	2 (66.7)	1 (50.0)	3 (60.0)
Lack of Efficacy	1 (33.3)	1 (50.0)	2 (40.0)

Source: CSR Sobi.ANAKIN-303, Table 14.1.1-1
Abbreviations: CSR, Clinical study report; IMP, Investigational medical product; RDB, Randomized double-blind.
[a] Denominator: Consented patients.
[b] Denominator: Screen failure.
[c] Denominator: Randomized patients.
[d] Denominator: Withdrawals in RDB Period.
[e] Denominator: Withdrawals in open-label treatment period.

Recruitment

Baseline data

In terms of demographics, of the 15 patients included, 2 were male and 13 were female. A total of 5 patients (33.3%) were aged under 16 years old (SJIA) and 10 patients (66.7%) were aged 16 years old or older (AOSD) at disease onset. The anakinra arm included more SJIA patients (4 patients) than the placebo arm (1 patient). The median weight was 48.50 kg (range: 10.3 to 94.4 kg) in the anakinra arm and 53.30 kg (range: 12.5 to 89.2 kg) in the placebo arm. There were 8 patients (53.3%) treated with glucocorticoids at inclusion, which comprised 4 patients (50.0%) in the anakinra arm and 4 patients (57.1%) in the placebo arm.

As for this p46 the subgroup data for the paediatric subset is presented:

14.1.7-1 Subgroup Analysis for Demographic and Other Baseline Characteristics for SJIA (< 16 years) - Core Phase (Safety Analysis Set)

	Anakinra (N=4) n (%)	Placebo/ Anakinra (N=1) n (%)	Total (N=5) n (%)
Age at onset of disease (years)			
<16	4 (100.0)	1 (100.0)	5 (100.0)
=>16	0	0	0
Symptom duration (days)			
n	3	1	4
Missing (%)	1 (25.0)	0	1 (20.0)
Mean (SD)	92.3 (88.8)	28.0 (-)	76.3 (79.3)
Median	67.0	28.0	47.5
[Min , Max]	[19 , 191]	[28 , 28]	[19 , 191]
Disease duration (days)			
n	4	1	5
Mean (SD)	41.5 (68.6)	7.0 (-)	34.6 (61.4)
Median	10.5	7.0	7.0
[Min , Max]	[1 , 144]	[7 , 7]	[1 , 144]
Age at randomization (years)			
n	4	1	5
Mean (SD)	5.8 (4.8)	3.0 (-)	5.2 (4.3)
Median	4.5	3.0	3.0
[Min , Max]	[2 , 12]	[3 , 3]	[2 , 12]
=> 8 months to <= 2 years	2 (50.0)	0	2 (40.0)
> 2 years to < 4 years	0	1 (100.0)	1 (20.0)
=> 4 years to < 8 years	1 (25.0)	0	1 (20.0)
=> 8 years to < 16 years	1 (25.0)	0	1 (20.0)
=> 16 years	0	0	0
Gender			
Male	1 (25.0)	0	1 (20.0)
Female	3 (75.0)	1 (100.0)	4 (80.0)

14.1.7-1 Subgroup Analysis for Demographic and Other Baseline Characteristics for SJIA (< 16 years) - Core Phase (Safety Analysis Set)

	Anakinra (N=4) n (%)	Placebo/ Anakinra (N=1) n (%)	Total (N=5) n (%)
Height (cm) [1]			
n	4	1	5
Mean (SD)	113.5 (36.8)	94.0 (-)	109.6 (33.0)
Median	105.0	94.0	94.0
[Min , Max]	[83 , 161]	[94 , 94]	[83 , 161]
Weight (kg)			
n	4	1	5
Mean (SD)	21.45 (16.46)	12.50 (-)	19.66 (14.81)
Median	15.15	12.50	12.50
[Min , Max]	[10.3 , 45.2]	[12.5 , 12.5]	[10.3 , 45.2]
<50	4 (100.0)	1 (100.0)	5 (100.0)
=>50	0	0	0
Not Done	0	0	0
BMI (kg/m^2)			
n	4	1	5
Mean (SD)	14.85 (1.94)	14.15 (-)	14.71 (1.71)
Median	14.51	14.15	14.15
[Min , Max]	[12.9 , 17.4]	[14.1 , 14.1]	[12.9 , 17.4]
Race			
American Indian or Alaska Native	0	0	0
Asian	4 (100.0)	1 (100.0)	5 (100.0)
Black	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
White	0	0	0
Other	0	0	0
Glucocorticoids use at inclusion			
Yes	1 (25.0)	0	1 (20.0)
No	3 (75.0)	1 (100.0)	4 (80.0)

	Anakinra (N=4) n (%)	Placebo/ Anakinra (N=1) n (%)	Total (N=5) n (%)
Glucocorticoids use at inclusion (mg/day)			
n	1	0	1
Mean (SD)	10.000 (-)	- (-)	10.000 (-)
Median	10.000	-	10.000
[Min , Max]	[10.00 , 10.00]	[- , -]	[10.00 , 10.00]

Abbreviation: SD, Standard deviation.
[1] Height is measured for patients who is younger than 19 years old.

14.1.7-2 Subgroup Analysis for Demographic and Other Baseline Characteristics for SJIA (< 16 years) - Core Phase (Full Analysis Set)

	Anakinra (N=4) n (%)	Placebo/ Anakinra (N=1) n (%)	Total (N=5) n (%)
Age at onset of disease (years)			
<16	4 (100.0)	1 (100.0)	5 (100.0)
=>16	0	0	0
Symptom duration (days)			
n	3	1	4
Missing (%)	1 (25.0)	0	1 (20.0)
Mean (SD)	92.3 (88.8)	28.0 (-)	76.3 (79.3)
Median	67.0	28.0	47.5
[Min , Max]	[19 , 191]	[28 , 28]	[19 , 191]
Disease duration (days)			
n	4	1	5
Mean (SD)	41.5 (68.6)	7.0 (-)	34.6 (61.4)
Median	10.5	7.0	7.0
[Min , Max]	[1 , 144]	[7 , 7]	[1 , 144]
Age at randomization (years)			
n	4	1	5
Mean (SD)	5.8 (4.8)	3.0 (-)	5.2 (4.3)
Median	4.5	3.0	3.0
[Min , Max]	[2 , 12]	[3 , 3]	[2 , 12]
=> 8 months to <= 2 years	2 (50.0)	0	2 (40.0)
> 2 years to < 4 years	0	1 (100.0)	1 (20.0)
=> 4 years to < 8 years	1 (25.0)	0	1 (20.0)
=> 8 years to < 16 years	1 (25.0)	0	1 (20.0)
=> 16 years	0	0	0
Gender			
Male	1 (25.0)	0	1 (20.0)
Female	3 (75.0)	1 (100.0)	4 (80.0)

	Anakinra (N=4) n (%)	Placebo/ Anakinra (N=1) n (%)	Total (N=5) n (%)
Height (cm) [1]			
n	4	1	5
Mean (SD)	113.5 (36.8)	94.0 (-)	109.6 (33.0)
Median	105.0	94.0	94.0
[Min , Max]	[83 , 161]	[94 , 94]	[83 , 161]
Weight (kg)			
n	4	1	5
Mean (SD)	21.45 (16.46)	12.50 (-)	19.66 (14.81)
Median	15.15	12.50	12.50
[Min , Max]	[10.3 , 45.2]	[12.5 , 12.5]	[10.3 , 45.2]
<50	4 (100.0)	1 (100.0)	5 (100.0)
=>50	0	0	0
Not Done	0	0	0
BMI (kg/m^2)			
n	4	1	5
Mean (SD)	14.85 (1.94)	14.15 (-)	14.71 (1.71)
Median	14.51	14.15	14.15
[Min , Max]	[12.9 , 17.4]	[14.1 , 14.1]	[12.9 , 17.4]
Race			
American Indian or Alaska Native	0	0	0
Asian	4 (100.0)	1 (100.0)	5 (100.0)
Black	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
White	0	0	0
Other	0	0	0
Glucocorticoids use at inclusion			
Yes	1 (25.0)	0	1 (20.0)
No	3 (75.0)	1 (100.0)	4 (80.0)

	Anakinra (N=4) n (%)	Placebo/ Anakinra (N=1) n (%)	Total (N=5) n (%)
Glucocorticoids use at inclusion (mg/day)			
n	1	0	1
Mean (SD)	10.000 (-)	- (-)	10.000 (-)
Median	10.000	-	10.000
[Min , Max]	[10.00 , 10.00]	[- , -]	[10.00 , 10.00]

Abbreviation: SD, Standard deviation.
[1] Height is measured for patients who is younger than 19 years old.

Number analysed

Table 10-2 Summary of Study Populations - Core phase (Randomized population)

	Anakinra (N=8) n (%)	Placebo/Anakinra (N=7) n (%)	Total (N=15) n (%)
Safety Analysis Set			
Included	8 (100.0)	7 (100.0)	15 (100.0)
Not included	0	0	0
Full Analysis Set			
Included	8 (100.0)	7 (100.0)	15 (100.0)
Not included	0	0	0
Pharmacokinetic Analysis Set			
Included	8 (100.0)	6 (85.7)	14 (93.3)
Not included	0	1 (14.3)	1 (6.7)
Reasons for not included			
No serum concentration data*	0	1 (14.3)	1 (6.7)

Source: CSR Sobi.ANAKIN-303, Table 14.1.1-2
*PK sampling not performed due to PK sampling visits completed before site implementation of protocol amendment 3 to add PK analysis
Abbreviation: CSR, Clinical study report.

Other treatments

All enrolled patients used both prior and concomitant medication. The most commonly reported prior medication was oral prednisolone (8 patients, 53.3%), followed by oral paracetamol (7 patients, 46.7%). The most commonly reported concomitant medication was oral prednisolone (9 patients, 60.0%), followed by topical betamethasone butyrate propionate (8 patients, 53.3%). The use of concomitant medications was generally balanced between arms.

Efficacy results

Primary efficacy endpoint

ACR30 response with absence of fever at Week 2

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 (hereafter, ACR30 response with absence of fever at Week 2), and was analyzed using the FAS. The comparison between the treatment arms in ACR30 response with absence of fever at Week 2 is presented in Table 11-1. A total of 7 patients (87.5%) in the anakinra arm and 1 patient (14.3%) in the placebo arm achieved ACR30 response with absence of fever at Week 2. The treatment difference was 73.2% (90% CI: 29.3, 94.8) and the corresponding p-value was 0.009, confirming the statistically significant difference when comparing the anakinra arm to the placebo arm.

In sensitivity analysis 1, the handling of "patients who discontinued study drug prior to Week 2 were set to ACR30 non-responders" was altered to "for patients who discontinued study drug prior to Week 2 due to the reason other than progressive disease, ACR30 at Week 2 was imputed using the last observed ACR30 assessment before study drug discontinuation occurring prior to Week 2 visit."

In sensitivity analysis 2, regardless of the intercurrent event, there was no imputation for missing data.

In both sensitivity analyses, the number of patients who achieved ACR30 response with absence of fever at Week 2 in anakinra arm and placebo arm was identical with the primary analysis.

Since there were no patients with missing ACR30 component at baseline, sensitivity analysis 3 was not performed.

A tipping point analysis was performed as an additional sensitivity analysis to evaluate how imputation of patients with a missing ACR30 outcome at Week 2 influences the result. In this analysis, the patient who discontinued the study during the RDB period and was imputed as non-responder, was now instead imputed to a responder. The difference in the primary endpoint, ACR30 response with absence of fever at Week 2, between anakinra arm and placebo arm remained statistically significant.

Table 11-1 Summary of ACR30 responses with absence of fever at Week 2 (Full Analysis Set)

	Anakinra (N=8)	Placebo (N=7)
Number of patients with ACR30 response	7 (87.5)	1 (14.3)
Treatment difference (90% CI) [a]	73.2 [29.3, 94.8]	-
P-value [b]	0.009	-

Source: CSR Sobi.ANAKIN-303, Table 14.2.1-1
Abbreviations: ACR, American College of Rheumatology; CI, Confidence interval; CSR, Clinical study report. 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%.
[a] A positive difference in response rates favors anakinra. The Clopper & Pearson method is used to calculate confidence interval.
[b] Fisher's exact test at the one-sided significance level of α=0.05.

Secondary endpoints supporting the primary objective

Absence of fever, absence of rash, and ACR50, ACR70 and ACR90 response with absence of fever at Week 2

The comparisons between treatment arms for absence of fever, absence of rash, and ACR50, ACR70 and ACR90 response with absence of fever at Week 2 are presented in Table 11-2. Absence of Fever At baseline, the absence of fever was observed in 1 patient (12.5%) in the anakinra arm and 2 patients (28.6%) in the placebo arm. By Week 2, the number of patients with absence of fever in the anakinra arm increased to 7 patients (87.5%), and decreased to 1 patient (14.3%) in the placebo arm. The treatment difference at Week 2 was 73.2% (90% CI: 29.3, 94.8) when comparing the anakinra arm to the placebo arm. Absence of Rash At baseline, the absence of rash was observed in 3 patients (37.5%) in the anakinra arm and 3 patients (42.9%) in the placebo arm. By Week 2, the number of patients with absence of rash in the anakinra arm increased to 7 patients (87.5%), and decreased to 1 patient (14.3%) in the placebo arm. The treatment difference at Week 2 was 73.2% (90% CI: 29.3, 94.8) when comparing the anakinra arm to the placebo arm. ACR50 Response with Absence of Fever At Week 2, 7 patients (87.5%) in the anakinra arm achieved ACR50 response with absence of fever, compared to 1 patient (14.3%) in the placebo arm. The treatment difference at Week 2 was 73.2% (90% CI: 29.3, 94.8) when comparing the anakinra arm to the placebo arm. ACR70 Response with Absence of Fever At Week 2, 7 patients (87.5%) in the anakinra arm achieved ACR70 response with absence of fever, compared to 1 patient (14.3%) in the placebo arm. The treatment difference at Week 2 was 73.2% (90% CI: 29.3, 94.8) when comparing the anakinra arm to the placebo arm. ACR90 Response with Absence of Fever At Week 2, 5 patients (62.5%) in the anakinra arm achieved ACR90 response with absence of fever, compared to 1 patient (14.3%) in the placebo arm. The treatment difference at Week 2 was 48.2% (90% CI: 3.8, 80.4) when comparing the anakinra arm to the placebo arm.

Table 11-2 Summary of the responder endpoints at Baseline and Week 2 (Full Analysis Set)

	Anakinra (N=8)	Placebo (N=7)
Absence of fever		
Baseline [a]	1 (12.5)	2 (28.6)
Week 2		

	Anakinra (N=8)	Placebo (N=7)
Number of responders	7 (87.5)	1 (14.3)
Treatment difference (90% CI) [b]	73.2 [29.3, 94.8]	-
P-value [c]	0.009	-
Absence of rash		
Baseline [a]	3 (37.5)	3 (42.9)
Week 2		
Number of responders	7 (87.5)	1 (14.3)
Treatment difference (90% CI) [b]	73.2 [29.3, 94.8]	-
P-value [c]	0.009	-
ACR50 response with absence of fever		
Week 2		
Number of responders	7 (87.5)	1 (14.3)
Treatment difference (90% CI) [b]	73.2 [29.3, 94.8]	-
P-value [c]	0.009	-
ACR70 response with absence of fever		
Week 2		
Number of responders	7 (87.5)	1 (14.3)
Treatment difference (90% CI) [b]	73.2 [29.3, 94.8]	-
P-value [c]	0.009	-
ACR90 response with absence of fever		
Week 2		
Number of responders	5 (62.5)	1 (14.3)
Treatment difference (90% CI) [b]	48.2 [3.8, 80.4]	-
P-value [c]	0.084	-

Source: CSR Sobi.ANAKIN-303, Table 14.2.1-6
Abbreviations: ACR, American College of Rheumatology; CI, Confidence interval; CSR, Clinical study report.
ACR50: An improvement of ≥ 50% from baseline to Week 2, in at least 3 of any 6 variables of the ACR core set, with no more than 1 variable worsening by > 30%, with absence of fever attributable to the disease within the last 7 days. The same definition applies to ACR70 and 90 with their respective percentages of improvement (i.e. 70% or 90%), and worsening (i.e. 30%).
The conclusions are taken from the p-value and the inconsistency with the CI is due to different methodologies used.
[a] Fever and rash are collected at screening as Still's disease diagnosis.
[b] A positive difference in response rates favors anakinra. The Clopper & Pearson method is used to calculate confidence interval.
[c] Fisher's exact test at the one-sided significance level of α=0.05.

Change from baseline in VAS-endpoints at Week 2

Physician global assessment of disease activity (VAS)

The median physician global assessment of disease activity (VAS) score at baseline was 64.0 in the anakinra arm and 62.0 in the placebo arm. By Week 2, the median VAS score in the anakinra arm decreased to 7.0, while in the placebo arm it decreased to 16.0. The median change from baseline at

Week 2 was -35.5 in the anakinra arm, compared to -15.0 in the placebo arm. The treatment difference at Week 2 was -17.5 (90% CI: - 46.0, 13.0) when comparing the anakinra arm to the placebo arm.

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

The median patient/parent global assessment of overall well-being (VAS) score at baseline was 50.5 in the anakinra arm and 50.0 in the placebo arm. By Week 2, the median VAS score in the anakinra arm decreased to 0.0, while in the placebo arm it decreased to 35.0. The median change from baseline at Week 2 was -34.5 in the anakinra arm, compared to -27.0 in the placebo arm. The treatment difference at Week 2 was -21.5 (90% CI: -53.0, 11.0) when comparing the anakinra arm to the placebo arm.

Patient/parent global assessment of disease related pain (VAS)

The median patient/parent global assessment of disease related pain (VAS) score at baseline was 66.0 in the anakinra arm and 65.0 in the placebo arm. By Week 2, the median VAS score in the anakinra arm decreased to 2.0, while in the placebo arm it decreased to 31.0. The median change from baseline at Week 2 was -45.5 in the anakinra arm, compared to -19.0 in the placebo arm. The treatment difference at Week 2 was -19.5 (90% CI: -60.0, 10.0) when comparing the anakinra arm to the placebo arm.

Secondary endpoints during the randomized double-blind period

Efficacy of anakinra compared to placebo in reducing inflammation in Still's disease

Change from baseline in CRP, ferritin, hemoglobin, platelets and white blood cells count to Week 2

CRP

The median CRP levels at baseline were 57.20 mg/L in the anakinra arm and 83.10 mg/L in the placebo arm. By Week 2, the median CRP level in the anakinra arm decreased to 1.80 mg/L, while in the placebo arm it decreased to 45.10 mg/L. The median change from baseline at Week 2 was -41.90 mg/L in the anakinra arm, compared to -38.00 mg/L in the placebo arm. The treatment difference at Week 2 was -17.95 mg/L (90% CI: -70.40, 31.50) when comparing the anakinra arm to the placebo arm.

Ferritin

The median ferritin levels at baseline were 1576.45 µg/L in the anakinra arm and 2424.90 µg/L in the placebo arm. By Week 2, the median ferritin level in the anakinra arm decreased to 84.70 µg/L, while in the placebo arm it decreased to 878.50 µg/L. The median change from baseline at Week 2 was -1157.85 µg/L in the anakinra arm, compared to -888.50 µg/L in the placebo arm. The treatment difference at Week 2 was -106.50 µg/L (90% CI: -2760.20, 1415.30) when comparing the anakinra arm to the placebo arm.

Hemoglobin

The median hemoglobin levels at baseline were 99.0 g/L in the anakinra arm and 105.0 g/L in the placebo arm. By Week 2, the median hemoglobin level in the anakinra arm increased to 122.5 g/L, while in the placebo arm it slightly increased to 116.0 g/L. The median change from baseline at Week 2 was 14.5 g/L in the anakinra arm, compared to -2.0 g/L in the placebo arm. The treatment difference at Week 2 was 15.0 g/L (90% CI: 6.0, 22.0) when comparing the anakinra arm to the placebo arm.

Platelets

The median platelet count (×109/L) at baseline was 434.0 in the anakinra arm and 355.0 in the placebo arm. By Week 2, the median platelet count in the anakinra arm decreased to 317.0, while in the placebo arm it was 378.0. The median change from baseline at Week 2 was -100.0 in the anakinra arm, compared to -41.0 in the placebo arm. The treatment difference at Week 2 was -63.5 (90% CI: -182.0, 23.0) when comparing the anakinra arm to the placebo arm.

White Blood Cells Count

The median white blood cell count (×109/L) at baseline was 12.6 in the anakinra arm and 14.1 in the placebo arm. By Week 2, the median white blood cell count in the anakinra arm decreased to 7.5, while in the placebo arm it was 11.5. The median change from baseline at Week 2 was -5.5 in the anakinra arm, compared to -0.3 in the placebo arm. The treatment difference at Week 2 was -5.7 (90% CI: -17.9, 0.7) when comparing the anakinra arm to the placebo arm.

Safety results

Exposure

The median treatment duration of anakinra was 14.0 days in the RDB period and 363.5 days in the open-label treatment period. The median daily dose of anakinra was 95.0 mg in the RDB period and 98.8 mg in the open-label treatment period.

Subgroup analyses for SJIA (less than 16 years at disease onset) of the extent of exposure and total duration of anakinra treatment in days in the safety analysis set are provided in Table 14.1.8-1 and subgroup analyses of extent of exposure and total daily dose of anakinra in mg in the safety analysis set are provided in Table 14.1.8-3.

14.1.8-1 Subgroup Analysis for Extent of exposure: total duration of anakinra treatment in days for SJIA (< 16 years) - Core Phase (Safety Analysis Set)

Period	Statistics	Anakinra (N=4)	Placebo/ Anakinra (N=1)	Total (N=5)
Randomized DB Period				
	n	4	-	4
	Mean (SD)	14.0 (0.0)	-	14.0 (0.0)
	Median	14.0	-	14.0
	[Min , Max]	[14 , 14]	-	[14 , 14]
Open-Label Treatment Period				
	n	4	1	5
	Mean (SD)	241.0 (167.7)	365.0 (-)	265.8 (155.5)
	Median	297.0	365.0	362.0
	[Min , Max]	[7 , 363]	[365 , 365]	[7 , 365]
Overall				
	n	4	1	5
	Mean (SD)	255.0 (167.7)	365.0 (-)	277.0 (153.3)
	Median	311.0	365.0	365.0
	[Min , Max]	[21 , 377]	[365 , 365]	[21 , 377]

Abbreviations: DB, Double-Blind; SD, Standard deviation.
Total duration of anakinra treatment in days during the core phase is calculated for each patients as follows: Total duration of anakinra treatment in days during the core phase = (Date of last treatment in the period - Date of first treatment in the period) + 1

14.1.8-3 Subgroup Analysis for Extent of exposure: total daily dose of anakinra in mg for SJIA (< 16 years) - Core Phase (Safety Analysis Set)

Period	Statistics	Anakinra (N=4)	Placebo/ Anakinra (N=1)	Total (N=5)
Randomized DB Period				
	n	4	-	4
	Mean (SD)	42.5 (33.0)	-	42.5 (33.0)
	Median	30.0	-	30.0
	[Min , Max]	[20 , 90]	-	[20 , 90]
Open-Label Treatment Period				
	n	4	1	5
	Mean (SD)	67.5 (73.6)	29.9 (-)	60.0 (65.9)
	Median	37.2	29.9	29.9
	[Min , Max]	[19 , 177]	[30 , 30]	[19 , 177]
Overall				
	n	4	1	5
	Mean (SD)	64.8 (72.3)	29.9 (-)	57.8 (64.5)
	Median	34.3	29.9	29.9
	[Min , Max]	[19 , 172]	[30 , 30]	[19 , 172]

Abbreviations: DB, Double-Blind; SD, Standard deviation.
Total daily dose of anakinra in mg is calculated for each patients as follows:
Total daily dose of anakinra in mg = Total dosage of anakinra (mg) in the period / Total duration of anakinra treatment in days during the core phase

Adverse events

Randomized double-blind period

An overall summary of TEAEs during the RDB period is presented in Table 12-1. In the anakinra arm, 6 patients (75.0%) experienced at least 1 TEAE, with 11 events. In the placebo arm, 3 patients (42.9%) experienced TEAEs, with 3 events. In the anakinra arm, 4 patients (50.0%) experienced TEAEs assessed as related to study drug by the investigator, with 7 events. No treatment-related TEAEs were reported in the placebo arm. No severe TEAEs were reported in either the anakinra or the placebo arm. Similarly, no patient had fatal TEAEs, serious TEAEs, TEAEs leading to study drug withdrawal, SUSARs, or AESIs of DRESS or pulmonary events. There was no macrophage activation syndrome reported during the RDB period. No patient had TEAE caused by a device deficiency.

Table 12-1 Overview of Treatment-emergent Adverse Events - RDB Period (Safety Analysis Set)

	Anakinra (N=8) n (%) [E]	Placebo (N=7) n (%) [E]	Total (N=15) n (%) [E]
Any TEAE	6 (75.0) [11]	3 (42.9) [3]	9 (60.0) [14]
Any severe TEAE	0 [0]	0 [0]	0 [0]
Any serious TEAE (including death)	0 [0]	0 [0]	0 [0]
Any non-serious TEAE	6 (75.0) [11]	3 (42.9) [3]	9 (60.0) [14]
Any related TEAEs [a]	4 (50.0) [7]	0 [0]	4 (26.7) [7]
Any related severe TEAEs [a]	0 [0]	0 [0]	0 [0]
Any related serious TEAEs [a]	0 [0]	0 [0]	0 [0]
Any fatal TEAEs	0 [0]	0 [0]	0 [0]
Any TEAEs leading to study drug withdrawal	0 [0]	0 [0]	0 [0]
Any SUSAR	0 [0]	0 [0]	0 [0]
Any DRESS or pulmonary event (interstitial lung disease, pulmonary hypertension, and alveolar proteinosis)	0 [0]	0 [0]	0 [0]

Source: CSR Sobi.ANAKIN-303, Table 14.3.1-1
Abbreviations: AE, Adverse event; CSR, Clinical study report; DRESS, Drug reaction with eosinophilia and systemic symptoms; IMP, Investigational medical product; MedDRA, Medical Dictionary for Regulatory Activities; RDB, Randomized double-blind; SUSAR, Suspected unexpected serious adverse reaction; TEAE, Treatment-emergent adverse event.
TEAE is defined as an AE with a start date/time after the first administration of IMP and within 28 days after stopping therapy.
Each category shows the number of patients with at least one event.
Patients with multiple events in the same category are counted only once in that category.
N is the number of patients in each arm; n is the number of patients in corresponding category; E is the total number of events.
MedDRA ver. 27.1

[a] Related to study drug, as judged by the investigator.

Open-label treatment period

An overall summary of TEAEs during the open-label treatment period is presented in Table 12-2.

In total, 13 patients (92.9%) experienced at least 1 TEAE, with 75 events. A total of 10 patients (71.4%) experienced TEAEs assessed as related to study drug by the investigator, with 21 related events. Severe TEAEs were reported in 4 patients (28.6%), with 5 events. Serious TEAEs were reported in 5 patients (35.7%), with 6 events. No patient had fatal TEAEs, treatment-related serious TEAEs, SUSARs, or DRESS or pulmonary events reported. Three patients (21.4%) experienced a TEAE leading to study drug withdrawal. One TEAE of macrophage activation syndrome (PT: haemophagocytic lymphohistiocytosis) was reported during the open-label treatment period. The event was reported as severe, serious, and assessed as not related to the study drug by the investigator. Due to the event, the patient discontinued the study drug, and the event was resolving. No patient had TEAE caused by a device deficiency.

	Anakinra (N=8)	Placebo/Anakinra (N=6) [c]	Total (N=14)
	n (%) [E]	n (%) [E]	n (%) [E]
Any TEAE	7 (87.5) [46]	6 (100.0) [29]	13 (92.9) [75]
Any severe TEAE	3 (37.5) [4]	1 (16.7) [1]	4 (28.6) [5]
Any serious TEAE (including death) [a]	4 (50.0) [5]	1 (16.7) [1]	5 (35.7) [6]
Any non-serious TEAE	7 (87.5) [41]	6 (100.0) [28]	13 (92.9) [69]
Any related TEAEs [b]	5 (62.5) [10]	5 (83.3) [11]	10 (71.4) [21]
Any related severe TEAEs [b]	0 [0]	0 [0]	0 [0]
Any related serious TEAEs [b]	0 [0]	0 [0]	0 [0]
Any fatal TEAEs	0 [0]	0 [0]	0 [0]
Any TEAEs leading to study drug withdrawal	2 (25.0) [2]	1 (16.7) [1]	3 (21.4) [3]
Any SUSAR	0 [0]	0 [0]	0 [0]
Any DRESS or pulmonary event (interstitial lung disease, pulmonary hypertension, and alveolar proteinosis)	0 [0]	0 [0]	0 [0]

Source: CSR Sobi.ANAKIN-303, Table 14.3.1-2
Abbreviations: AE, Adverse event; CSR, Clinical study report; DRESS, Drug reaction with eosinophilia and systemic symptoms; IMP, Investigational medical product; MedDRA, Medical Dictionary for Regulatory Activities; RDB, Randomized double-blind; SUSAR, Suspected unexpected serious adverse reaction; TEAE, Treatment-emergent adverse event.
TEAE is defined as an AE with a start date/time after the first administration of IMP and within 28 days after stopping therapy.
Each category shows the number of patients with at least one event.
Patients with multiple events in the same category are counted only once in that category.
N is the number of patients in each arm; n is the number of patients in corresponding category; E is the total number of events.
MedDRA ver. 27.1
[a] Any serious TEAE including death was collected, but there was no death reported.
[b] Related to study drug, as judged by the investigator.
[c] Patients who were assigned to placebo treatment during the RDB period initiated anakinra treatment in the open-label treatment period after Week 2 visit.

Most frequently reported adverse events

Randomized double-blind period

All TEAEs by SOC and PT during the RDB period are presented in Table 12-4. TEAEs reported in more than 1 patient in the anakinra arm were injection site reaction (4 patients, 50.0%) and insomnia (2 patients, 25.0%).

Table 12-4 Treatment-emergent Adverse Events by SOC and PT - RDB Period (Safety Analysis Set)

System Organ Class Preferred Term MedDRA	Anakinra (N=8) n (%) [E]	Placebo (N=7) n (%) [E]	Total (N=15) n (%) [E]
Number of patients reporting any TEAE	6 (75.0) [11]	3 (42.9) [3]	9 (60.0) [14]
General disorders and administration site conditions	5 (62.5) [8]	0 [0]	5 (33.3) [8]
Application site erythema	1 (12.5) [1]	0 [0]	1 (6.7) [1]
Injection site reaction	4 (50.0) [7]	0 [0]	4 (26.7) [7]
Infections and infestations	1 (12.5) [1]	1 (14.3) [1]	2 (13.3) [2]
COVID-19	0 [0]	1 (14.3) [1]	1 (6.7) [1]
Cytomegalovirus viraemia	1 (12.5) [1]	0 [0]	1 (6.7) [1]
Psychiatric disorders	2 (25.0) [2]	0 [0]	2 (13.3) [2]
Insomnia	2 (25.0) [2]	0 [0]	2 (13.3) [2]
Skin and subcutaneous tissue disorders	0 [0]	2 (28.6) [2]	2 (13.3) [2]
Asteatosis	0 [0]	2 (28.6) [2]	2 (13.3) [2]

Source: CSR Sobi.ANAKIN-303, Table 14.3.1-3
Abbreviations: AE, Adverse event; CSR, Clinical study report; IMP, Investigational medical product; MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred term; RDB, Randomized double-blind; SOC, System organ class; TEAE, Treatment-emergent adverse event.
TEAE is defined as an AE with a start date/time after the first administration of IMP and within 28 days after stopping therapy.
Patients with multiple events at the same level of summarization are counted only once at that level.
N is the number of patients in each arm; n is the number of patients in corresponding category; E is the total number of events.
MedDRA ver. 27.1

Open-label treatment period

All TEAEs by SOC and PT during the open-label treatment period are presented in Table 12-5. TEAEs reported in more than 1 patient in total were injection site reaction (9 patients, 64.3%), COVID-19 and nasopharyngitis (3 patients, 21.4% each), and influenza, paronychia, dyslipidaemia, steroid diabetes, Still's disease and miliaria (2 patients, 14.3% each).

Table 12-5 Treatment-emergent Adverse Events by SOC and PT - Open-Label Treatment Period (Safety Analysis Set)

System Organ Class Preferred Term MedDRA	Anakinra (N=8) n (%) [E]	Placebo/Anakinra (N=6) [a] n (%) [E]	Total (N=14) n (%) [E]
Number of patients reporting any TEAE	7 (87.5) [46]	6 (100.0) [29]	13 (92.9) [75]
Blood and lymphatic system disorders	1 (12.5) [1]	0 [0]	1 (7.1) [1]
Lymphadenopathy	1 (12.5) [1]	0 [0]	1 (7.1) [1]
Gastrointestinal disorders	2 (25.0) [2]	0 [0]	2 (14.3) [2]
Toothache	1 (12.5) [1]	0 [0]	1 (7.1) [1]
Vomiting	1 (12.5) [1]	0 [0]	1 (7.1) [1]
General disorders and administration site conditions	4 (50.0) [9]	5 (83.3) [11]	9 (64.3) [20]
Chest pain	0 [0]	1 (16.7) [2]	1 (7.1) [2]
Injection site reaction	4 (50.0) [9]	5 (83.3) [9]	9 (64.3) [18]
Hepatobiliary disorders	0 [0]	2 (33.3) [2]	2 (14.3) [2]
Hepatic steatosis	0 [0]	1 (16.7) [1]	1 (7.1) [1]
Hyperbilirubinaemia	0 [0]	1 (16.7) [1]	1 (7.1) [1]
Immune system disorders	0 [0]	1 (16.7) [1]	1 (7.1) [1]
Haemophagocytic lymphohistiocytosis	0 [0]	1 (16.7) [1]	1 (7.1) [1]
Infections and infestations	6 (75.0) [22]	2 (33.3) [4]	8 (57.1) [26]
COVID-19	3 (37.5) [3]	0 [0]	3 (21.4) [3]
Cytomegalovirus infection	0 [0]	1 (16.7) [1]	1 (7.1) [1]
Folliculitis	0 [0]	1 (16.7) [1]	1 (7.1) [1]
Gastroenteritis	1 (12.5) [1]	0 [0]	1 (7.1) [1]
Hand-foot-and-mouth disease	1 (12.5) [2]	0 [0]	1 (7.1) [2]
Herpes zoster	1 (12.5) [1]	0 [0]	1 (7.1) [1]
Hordeolum	1 (12.5) [1]	0 [0]	1 (7.1) [1]
Influenza	2 (25.0) [3]	0 [0]	2 (14.3) [3]
Nasopharyngitis	2 (25.0) [4]	1 (16.7) [1]	3 (21.4) [5]
Paronychia	1 (12.5) [1]	1 (16.7) [1]	2 (14.3) [2]
Pneumonia mycoplasmal	1 (12.5) [1]	0 [0]	1 (7.1) [1]
Upper respiratory tract infection	1 (12.5) [5]	0 [0]	1 (7.1) [5]
Investigations	1 (12.5) [1]	1 (16.7) [1]	2 (14.3) [2]
Alanine aminotransferase increased	1 (12.5) [1]	0 [0]	1 (7.1) [1]
Hepatic enzyme increased	0 [0]	1 (16.7) [1]	1 (7.1) [1]
Metabolism and nutrition disorders	1 (12.5) [2]	2 (33.3) [2]	3 (21.4) [4]
Dyslipidaemia	1 (12.5) [1]	1 (16.7) [1]	2 (14.3) [2]
Steroid diabetes	1 (12.5) [1]	1 (16.7) [1]	2 (14.3) [2]
Musculoskeletal and connective tissue disorders	2 (25.0) [4]	1 (16.7) [2]	3 (21.4) [6]

System Organ Class Preferred Term MedDRA	Anakinra (N=8) n (%) [E]	Placebo/Anakinra (N=6) [a] n (%) [E]	Total (N=14) n (%) [E]
Arthralgia	0 [0]	1 (16.7) [1]	1 (7.1) [1]
Psoriatic arthropathy	1 (12.5) [1]	0 [0]	1 (7.1) [1]
Still's disease	2 (25.0) [3]	0 [0]	2 (14.3) [3]
Tenosynovitis	0 [0]	1 (16.7) [1]	1 (7.1) [1]
Psychiatric disorders	1 (12.5) [1]	1 (16.7) [1]	2 (14.3) [2]
Depression	1 (12.5) [1]	0 [0]	1 (7.1) [1]
Insomnia	0 [0]	1 (16.7) [1]	1 (7.1) [1]
Skin and subcutaneous tissue disorders	2 (25.0) [4]	3 (50.0) [5]	5 (35.7) [9]
Asteatosis	0 [0]	1 (16.7) [1]	1 (7.1) [1]
Drug eruption	1 (12.5) [1]	0 [0]	1 (7.1) [1]
Eczema	0 [0]	1 (16.7) [1]	1 (7.1) [1]
Miliaria	1 (12.5) [1]	1 (16.7) [1]	2 (14.3) [2]
Pruritus	0 [0]	1 (16.7) [1]	1 (7.1) [1]
Psoriasis	1 (12.5) [1]	0 [0]	1 (7.1) [1]
Skin atrophy	0 [0]	1 (16.7) [1]	1 (7.1) [1]
Urticaria	1 (12.5) [1]	0 [0]	1 (7.1) [1]

Source: CSR Sobi.ANAKIN-303, Table 14.3.1-12
Abbreviations: AE, Adverse event; CSR, Clinical study report; IMP, Investigational medical product; MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred term; RDB, Randomized double-blind; SOC, System organ class; TEAE, Treatment-emergent adverse event.
TEAE is defined as an AE with a start date/time after the first administration of IMP and within 28 days after stopping therapy.
Patients with multiple events at the same level of summarization are counted only once at that level.
N is the number of patients in each arm; n is the number of patients in corresponding category; E is the total number of events.
MedDRA ver. 27.1
[a] Patients who were assigned to placebo treatment during the RDB period initiated anakinra treatment in the open-label treatment period after Week 2 visit.

Categorization of all adverse events

Randomized double-blind period

All TEAEs assessed as related to study drug by the investigator by SOC and PT during the RDB period are presented in Table 12-7.

In the anakinra arm, 4 patients (50.0%) experienced TEAE assessed as related to study drug by the investigator. All treatment-related TEAEs were injection site reaction. In the placebo arm, no treatment-related TEAE was reported. No severe TEAE was reported in either treatment arm.

Table 12-7 Related Treatment-emergent Adverse Events by SOC and PT - RDB Period (Safety Analysis Set)

System Organ Class Preferred Term MedDRA	Anakinra (N=8) n (%) [E]	Placebo (N=7) n (%) [E]	Total (N=15) n (%) [E]
Number of patients reporting any related TEAE	4 (50.0) [7]	0 [0]	4 (26.7) [7]
General disorders and administration site conditions	4 (50.0) [7]	0 [0]	4 (26.7) [7]
Injection site reaction	4 (50.0) [7]	0 [0]	4 (26.7) [7]

Source: CSR Sobi.ANAKIN-303, Table 14.3.1-7
Abbreviations: AE, Adverse event; CSR, Clinical study report; IMP, Investigational medical product; MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred term; RDB, Randomized double-blind; SOC, System organ class; TEAE, Treatment-emergent adverse event.
TEAE is defined as an AE with a start date/time after the first administration of IMP and within 28 days after stopping therapy.
Patients with multiple events at the same level of summarization are counted only once at that level.
N is the number of patients in each arm; n is the number of patients in corresponding category; E is the total number of events.
MedDRA ver. 27.1
Related to study drug, as judged by the investigator.

Open-label treatment period

All TEAEs assessed as related to study drug by the investigator by SOC and PT during the open-label treatment period are presented in Table 12-8.

A total of 10 patients (71.4%) experienced TEAE assessed as related to study drug by the investigator during the open-label treatment period. The most common related TEAE was injection site reaction (9 patients, 64.3%), followed by folliculitis, herpes zoster and dyslipidaemia (1 patient each, 7.1%).

There were 5 severe TEAEs including Still's disease (2 events in 1 patient), and haemophagocytic lymphohistiocytosis, COVID-19 and pneumonia mycoplasmal (1 event in 1 patient each). None of these TEAEs were assessed as related to study drug by the investigator. Haemophagocytic lymphohistiocytosis was resolving and other events were resolved.

Table 12-8 Related Treatment-emergent Adverse Events by SOC and PT - Open-Label Treatment Period (Safety Analysis Set)

System Organ Class	Anakinra (N=8)	Placebo/Anakinra (N=6) [a]	Total (N=14)
Preferred Term MedDRA	n (%) [E]	n (%) [E]	n (%) [E]
Number of patients reporting any related TEAE	5 (62.5) [10]	5 (83.3) [11]	10 (71.4) [21]
General disorders and administration site conditions	4 (50.0) [9]	5 (83.3) [9]	9 (64.3) [18]
Injection site reaction	4 (50.0) [9]	5 (83.3) [9]	9 (64.3) [18]
Infections and infestations	1 (12.5) [1]	1 (16.7) [1]	2 (14.3) [2]
Folliculitis	0 [0]	1 (16.7) [1]	1 (7.1) [1]
Herpes zoster	1 (12.5) [1]	0 [0]	1 (7.1) [1]
Metabolism and nutrition disorders	0 [0]	1 (16.7) [1]	1 (7.1) [1]
Dyslipidaemia	0 [0]	1 (16.7) [1]	1 (7.1) [1]

Source: CSR Sobi.ANAKIN-303, Table 14.3.1-16
Abbreviations: AE, Adverse event; CSR, Clinical study report; IMP, Investigational medical product; MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred term; RDB, Randomized double-blind, SOC, System organ class; TEAE, Treatment-emergent adverse event.
TEAE is defined as an AE with a start date/time after the first administration of IMP and within 28 days after stopping therapy.
Patients with multiple events at the same level of summarization are counted only once at that level.
N is the number of patients in each arm; n is the number of patients in corresponding category; E is the total number of events.

MedDRA ver. 27.1
[a] Patients who were assigned to placebo treatment during the RDB period initiated anakinra treatment in the open-label treatment period after Week 2 visit.
Related to study drug, as judged by the investigator.

Serious adverse events

There were no death in the study.

Other serious adverse events

Randomized double-blind period

No patient had any serious TEAE or SUSAR during the RDB period.

Open-label treatment period Serious TEAEs by SOC and PT during the open-label treatment period are presented in Table 12-10.

There were 6 serious TEAEs including Still's disease (3 events in 2 patients) and haemophagocytic lymphohistiocytosis, COVID-19 and pneumonia mycoplasmal (1 event in 1 patient each) during the open-label treatment period.

Two serious events of Still's disease were reported in the same subject, a Japanese patient in the anakinra arm who had a serious TEAE of SJIA relapse (PT: Still's disease) on Day 23. The TEAE was severe and assessed as not related to study drug by the investigator. At the TEAE onset, the dose of the study drug was 90 mg. The dose of the study drug was increased from 90 mg to 190 mg. The TEAE was resolved. This patient also had another serious TEAE of SJIA relapse (PT: Still's disease) on Day 239. The TEAE was severe and assessed as not related to study drug by the investigator. At the

TEAE onset, the dose of the study drug was 190 mg. The patient discontinued the study drug on Day 246.

One event of Still's disease was reported as serious, moderate, and not assessed as related to study drug by the investigator. Due to the event of Still's disease, the patient discontinued the study drug, and the event was resolving.

Haemophagocytic lymphohistiocytosis was reported as serious, severe, and assessed as not related to study drug by the investigator. Due to the event of haemophagocytic lymphohistiocytosis, the patient discontinued the study drug, and the event was resolving.

COVID-19 was reported as serious, severe and assessed as not related to study drug by the investigator. Due to the event of COVID-19, anakinra treatment was interrupted, and the event was resolved.

A Japanese patient in the anakinra arm had a serious TEAE of mycoplasma pneumonia (PT: pneumonia mycoplasmal) on Day 198. The TEAE was severe and assessed as not related to study drug by the investigator. At the TEAE onset, the dose of the study drug was 20 mg. The study drug was interrupted (Day 200) and resumed (Day 205). The TEAE was resolved.

There was no SUSAR during the open-label treatment period.

Table 12-10 Serious Treatment-emergent Adverse Events by SOC and PT - Open-Label Treatment Period (Safety Analysis Set)

System Organ Class	Anakinra (N=8)	Placebo/Anakinra (N=6) [a]	Total (N=14)
Preferred Term MedDRA	n (%) [E]	n (%) [E]	n (%) [E]
Number of patients reporting any serious TEAE	4 (50.0) [5]	1 (16.7) [1]	5 (35.7) [6]
Immune system disorders	0 [0]	1 (16.7) [1]	1 (7.1) [1]
Haemophagocytic lymphohistiocytosis	0 [0]	1 (16.7) [1]	1 (7.1) [1]
Infections and infestations	2 (25.0) [2]	0 [0]	2 (14.3) [2]
COVID-19	1 (12.5) [1]	0 [0]	1 (7.1) [1]
Pneumonia mycoplasmal	1 (12.5) [1]	0 [0]	1 (7.1) [1]
Musculoskeletal and connective tissue disorders	2 (25.0) [3]	0 [0]	2 (14.3) [3]
Still's disease	2 (25.0) [3]	0 [0]	2 (14.3) [3]

Source: CSR Sobi.ANAKIN-303, Table 14.3.1-14
Abbreviations: AE, Adverse event; CSR, Clinical study report; IMP, Investigational medical product; MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred term; RDB, Randomized double-blind; SOC, System organ class; TEAE, Treatment-emergent adverse event.
TEAE is defined as an AE with a start date/time after the first administration of IMP and within 28 days after stopping therapy.
Patients with multiple events at the same level of summarization are counted only once at that level.
N is the number of patients in each arm; n is the number of patients in corresponding category; E is the total number of events.
MedDRA ver. 27.1
[a] Patients who were assigned to placebo treatment during the RDB period initiated anakinra treatment in the open-label treatment period after Week 2 visit.

Discontinuations due to adverse events

Randomized double-blind period

There was no TEAE leading to study drug withdrawal during the RDB period.

Open-label treatment period

There were 3 TEAEs, reported as Still's disease (2 events in 2 patients) and haemophagocytic lymphohistiocytosis (1 event in 1 patient), leading to study drug withdrawal. All of these events were also reported as serious TEAEs.

Other adverse events of special interest

There was no DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) and no pulmonary Event reported during the study.

Laboratory values

As TEAEs classified in SOC investigation, 1 event of alanine aminotransferase increased and 1 event of hepatic enzyme increased were reported in 1 patient each during the open-label period in the core phase. Both events were considered mild, not serious and assessed as not related to study drug by the investigator. Alanine aminotransferase increased was resolved during the anakinra treatment. The outcome of hepatic enzyme increased was not reported as of the data cut-off date of the core phase because the patient entered the extension phase. Additionally, 1 event of liver function test abnormal was reported during Safety Follow-up. This event was considered mild, not serious and assessed as not related to study drug by the investigator. The liver function test abnormal was not resolved as of the data cut-off date.

Two events of dyslipidaemia were reported in 2 patients. A patient in the anakinra arm had high values for total cholesterol (5.95 mmol/L to 9.34 mmol/L), low density lipoprotein (LDL) cholesterol (3.70 mmol/L to 5.97 mmol/L) and triglycerides (1.85 mmol/L to 3.76 mmol/L) in the core phase and a TEAE of dyslipidaemia was reported. The event was reported as mild, not serious, assessed as not related to study drug by the investigator and the dose of anakinra was not changed. The event was not resolved as of the data cut-off date. A patient in the placebo arm had high values for total cholesterol (5.92 mmol/L to 8.38 mmol/L), LDL cholesterol (3.70 mmol/L to 4.78 mmol/L) and triglycerides (1.80 mmol/L to 3.53 mmol/L) after switching to anakinra treatment and a TEAE of dyslipidaemia was reported. The event was reported as mild, not serious, assessed as related to study drug by the investigator and the dose of anakinra was not changed. The outcome of the event was not reported as of the data cut-off date of the core phase because the patient entered the extension phase.

There were no clinically relevant changes in vital signs (blood pressure and heart rate), body weight and height over time and there were no other relevant observations related to safety in physical examination findings.

Immunogenicity

Occurrence of ADA, NAbs and cross-reactivity at baseline, Week 2, Week 4, Week 12, Week 34, and Week 54

Baseline samples were available for all patients in both arms, of which 5 of 15 patients (33.3%) tested positive and 10 of 15 patients (66.7%) tested negative for ADA in total. At Week 12, 12 patients (80.0%) were ADAs positive, comprising 8 patients (53.3%) with treatment-induced ADA, 3 patients (20.0%) with treatment-boosted ADA, and 1 patient (6.7%) with treatment-unaffected ADA. At Week 54, 9 patients (60.0%) were ADAs positive, comprising 5 patients (33.3%) with treatment-induced ADA, 3 patients (20.0%) with treatment-boosted ADA, and 1 patient (6.7%) with treatment-unaffected ADA. Overall, ADA titers ranged from 4.00 to 1680.00. In ADA positive samples, cross-reactivity was found with IL-1Ra produced by human embryonic kidney cells in 1 patient (6.7%) at baseline, 1

patient (6.7%) at Week 2, 6 patients (40.0%) at Week 4, 11 patients (73.3%) at Week 12 and Week 34, 9 patients (60.0%) at Week 54, and 4 patients (26.7%) at study drug discontinuation. NAbs were detected in 4 patients (26.7%) at Week 12 and 0 patients (0%) at Week 54.

In the overall core phase, 14 of 15 patients (93.3%) had at least 1 treatment-induced or treatment-boosted ADA positive sample, comprising 9 patients (60.0%) with treatment-induced ADA and 5 patients (33.3%) with treatment-boosted ADA. NAbs were detected in 6 patients (40.0%) in overall core phase.

There was no clear pattern of TEAEs, ACR30 or CRP in relation to ADA or NAb occurrence and titer.

As this is a paediatric procedure the TEAEs are presented for the paediatric population:

14.3.1-44 Subgroup Analysis for Overview of Treatment-emergent Adverse Events for SJIA (< 16 years) - Randomized DB Period (Safety Analysis Set)

	Anakinra (N=4) n (%) [E]	Placebo (N=1) n (%) [E]	Total (N=5) n (%) [E]
Any TEAE	3 (75.0) [5]	0 [0]	3 (60.0) [5]
Any severe TEAE	0 [0]	0 [0]	0 [0]
Any serious TEAE (including death)	0 [0]	0 [0]	0 [0]
Any non-serious TEAE	3 (75.0) [5]	0 [0]	3 (60.0) [5]
Any related TEAEs *1	2 (50.0) [4]	0 [0]	2 (40.0) [4]
Any related severe TEAEs	0 [0]	0 [0]	0 [0]
Any related serious TEAEs	0 [0]	0 [0]	0 [0]
Any fatal TEAEs	0 [0]	0 [0]	0 [0]
Any TEAEs leading to study drug withdrawal	0 [0]	0 [0]	0 [0]
Any SUSAR	0 [0]	0 [0]	0 [0]
Any DRESS or pulmonary event (interstitial lung disease, pulmonary hypertension, and alveolar proteinosis)	0 [0]	0 [0]	0 [0]

Abbreviations: DB, Double-Blind; DRESS, Drug reaction with eosinophilia and systemic symptoms; E, Event SUSAR, Suspected unexpected serious adverse reaction.
All AEs at all study visits up to Week 58 visit (for patients not entering the extension phase; Week 54 visit for patients entering the extension phase) are presented
TEAE (Treatment-emergent adverse events) is defined as an AE with a start date/time after the first administration of IMP and within 28 days after stopping therapy.
Each category shows the number of patients with at least one event.
Patients with multiple events in the same category are counted only once in that category.
N is the number of patients in each group; n is the number of patients in corresponding category; E is the total number of events.
MedDRA ver. 27.1
*1: Related to study drug, as judged by the investigator

14.3.1-52 Subgroup Analysis for Overview of Treatment-emergent Adverse Events for SJIA (< 16 years) - Open-Label Treatment Period (Safety Analysis Set)

	Anakinra (N=4) n (%) [E]	Placebo/ Anakinra (N=1) *2 n (%) [E]	Total (N=5) n (%) [E]
Any TEAE	3 (75.0) [28]	1 (100.0) [4]	4 (80.0) [32]
Any severe TEAE	2 (50.0) [3]	0 [0]	2 (40.0) [3]
Any serious TEAE (including death)	2 (50.0) [3]	0 [0]	2 (40.0) [3]
Any non-serious TEAE	3 (75.0) [25]	1 (100.0) [4]	4 (80.0) [29]
Any related TEAEs *1	3 (75.0) [7]	1 (100.0) [3]	4 (80.0) [10]
Any related severe TEAEs	0 [0]	0 [0]	0 [0]
Any related serious TEAEs	0 [0]	0 [0]	0 [0]
Any fatal TEAEs	0 [0]	0 [0]	0 [0]
Any TEAEs leading to study drug withdrawal	1 (25.0) [1]	0 [0]	1 (20.0) [1]
Any SUSAR	0 [0]	0 [0]	0 [0]
Any DRESS or pulmonary event (interstitial lung disease, pulmonary hypertension, and alveolar proteinosis)	0 [0]	0 [0]	0 [0]

Abbreviations: DRESS, Drug reaction with eosinophilia and systemic symptoms; E, Event; SUSAR, Suspected unexpected serious adverse reaction.
All AEs at all study visits up to Week 58 visit (for patients not entering the extension phase; Week 54 visit for patients entering the extension phase) are presented
TEAE (Treatment-emergent adverse events) is defined as an AE with a start date/time after the first administration of IMP and within 28 days after stopping therapy.
Each category shows the number of patients with at least one event.
Patients with multiple events in the same category are counted only once in that category.
N is the number of patients in each group; n is the number of patients in corresponding category; E is the total number of events.
MedDRA ver. 27.1
*1: Related to study drug, as judged by the investigator
*2: Patients who are assigned to placebo treatment during the randomized double-blind period will initiate anakinra treatment in open-label treatment period after week 2 visit

14.3.1-60 Subgroup Analysis for Treatment-emergent Adverse Events by SOC and PT for SJIA (< 16 years) - Randomized DB Period (Safety Analysis Set)

System Organ Class Preferred Term MedDRA	Anakinra (N=4) n (%) [E]	Placebo (N=1) n (%) [E]	Total (N=5) n (%) [E]
Number of patients reporting any TEAE	3 (75.0) [5]	0 [0]	3 (60.0) [5]
General disorders and administration site conditions	3 (75.0) [5]	0 [0]	3 (60.0) [5]
Application site erythema	1 (25.0) [1]	0 [0]	1 (20.0) [1]
Injection site reaction	2 (50.0) [4]	0 [0]	2 (40.0) [4]

Abbreviations: DB, Double-Blind; E, Event; PT, Preferred term; SOC, System organ class.
TEAE (Treatment-emergent adverse events) is defined as an AE with a start date/time after the first administration of IMP and within 28 days after stopping therapy.
Patients with multiple events at the same level of summarization are counted only once at that level.
N is the number of patients in each group; n is the number of patients in corresponding category; E is the total number of events.
MedDRA ver. 27.1

14.3.1-68 Subgroup Analysis for Treatment-emergent Adverse Events by SOC and PT for SJIA (< 16 years) - Open-Label Treatment Period (Safety Analysis Set)

System Organ Class Preferred Term MedDRA	Anakinra (N=4) n (%) [E]	Placebo/Anakinra (N=1) *1 n (%) [E]	Total (N=5) n (%) [E]
Number of patients reporting any TEAE	3 (75.0) [28]	1 (100.0) [4]	4 (80.0) [32]
Blood and lymphatic system disorders	1 (25.0) [1]	0 [0]	1 (20.0) [1]
Lymphadenopathy	1 (25.0) [1]	0 [0]	1 (20.0) [1]
Gastrointestinal disorders	1 (25.0) [1]	0 [0]	1 (20.0) [1]
Vomiting	1 (25.0) [1]	0 [0]	1 (20.0) [1]
General disorders and administration site conditions	3 (75.0) [7]	1 (100.0) [2]	4 (80.0) [9]
Injection site reaction	3 (75.0) [7]	1 (100.0) [2]	4 (80.0) [9]
Infections and infestations	2 (50.0) [15]	1 (100.0) [2]	3 (60.0) [17]
Folliculitis	0 [0]	1 (100.0) [1]	1 (20.0) [1]
Hand-foot-and-mouth disease	1 (25.0) [2]	0 [0]	1 (20.0) [2]
Hordeolum	1 (25.0) [1]	0 [0]	1 (20.0) [1]
Influenza	2 (50.0) [3]	0 [0]	2 (40.0) [3]
Nasopharyngitis	1 (25.0) [3]	1 (100.0) [1]	2 (40.0) [4]
Pneumonia mycoplasmal	1 (25.0) [1]	0 [0]	1 (20.0) [1]
Upper respiratory tract infection	1 (25.0) [5]	0 [0]	1 (20.0) [5]
Musculoskeletal and connective tissue disorders	1 (25.0) [2]	0 [0]	1 (20.0) [2]
Still's disease	1 (25.0) [2]	0 [0]	1 (20.0) [2]
Skin and subcutaneous tissue disorders	1 (25.0) [2]	0 [0]	1 (20.0) [2]
Miliaria	1 (25.0) [1]	0 [0]	1 (20.0) [1]
Urticaria	1 (25.0) [1]	0 [0]	1 (20.0) [1]

Abbreviations: E, Event; PT, Preferred term; SOC, System organ class.
TEAE (Treatment-emergent adverse events) is defined as an AE with a start date/time after the first administration of IMP and within 28 days after stopping therapy.
Patients with multiple events at the same level of summarization are counted only once at that level.
N is the number of patients in each group; n is the number of patients in corresponding category; E is the total number of events.
MedDRA ver. 27.1
*1: Patients who are assigned to placebo treatment during the randomized double-blind period will initiate anakinra treatment in open-label treatment period after week 2 visit.

2.3.3. Discussion on clinical aspects

The MAH presented the results from a randomized, double-blind, placebo-controlled, multicenter, phase 3 efficacy and safety study of subcutaneous anakinra in 15 Japanese patients with Still's disease. The Sobi.ANAKIN-303 trial, included 5 paediatric patients (5 of 15 enrolled; 33.3%), defined as those with SJIA and disease onset before 16 years of age. No formal analysis was conducted for the paediatric population.

The primary endpoint was met (anakinra superior to placebo). A total of 7 patients (87.5%) in the anakinra arm and 1 patient (14.3%) in the placebo arm achieved ACR30 response with absence of fever at Week 2. The treatment difference was 73.2% (90% CI: 29.3, 94.8) and the results of sensitivity analyses confirmed the difference. Anakinra was also superior to placebo in terms of absence of fever, absence of rash, ACR50 and ACR70 responses with absence of fever but not ACR90 at Week 2.

However, with 15 patients these results do not justify any conclusion on efficacy other than be supportive of other data.

Larger median improvements in disease activity, overall well-being, disease related pain, and inflammation markers including CRP, ferritin, platelets, and white blood cells count were observed in the anakinra arm than the placebo arm. The difference to placebo could be observed at Week 1 and persisted through Week 54 for 9 patients (5 patients initially randomized to the anakinra arm and 4 patients initially randomized to the placebo arm who switched to anakinra treatment). However, 6 patients discontinued the study (1 patient due to withdrawal by patient, 3 patients due to an AE, 2 patients due to lack of efficacy).

As far as possible to judge from the small numbers the response seen was consistent between SIJA and AODS.

Safety:

Most patients treated with anakinra experienced at least 1 TEAE, comprising 6 of 8 patients (75.0%) in the RDB period and 13 of 14 patients (92.9%) in the open-label treatment period.

Most TEAE preferred terms were assessed as not related to study drug by the investigator, whereas all injection site reactions were assessed as related to study drug by the investigators.

TEAEs reported in the core as well as the RDB phase were reported similar to the occurrence in all previous studies with injection site reactions being the most common.

There was no fatal TEAE during the study.

There were 7 serious TEAEs in 6 patients during the core phase, 6 serious TEAEs in 5 patients during the open-label treatment period and 1 serious TEAE in 1 patient during safety follow-up. There were 5 severe TEAEs in 4 patients during the core phase, all of which occurred in the open-label treatment period and were also reported as serious. There were 3 TEAEs (2 events of relapse of Still's disease and 1 event of haemophagocytic lymphohistiocytosis) leading to study drug withdrawal during the core phase.

One paediatric patient had a serious TEAEs of severe relapses of Still's disease (2 events in 1 patient). Due to the first event, the dose of anakinra was increased and the event resolved. Due to the second event, the patient discontinued the study drug, and the event was resolved.

Another paediatric patient had a severe mycoplasma pneumonia and due to the event, anakinra treatment was interrupted, and the event was resolved.

None of the serious TEAEs were assessed as related to study drug by the investigators.

There were no Adverse events of special interest, defined as DRESS or pulmonary events during the study.

There were no clinically relevant changes over time in clinical laboratory parameters (except for CRP and ferritin which showed improvement rapidly after treatment with anakinra), in vital signs (blood pressure and heart rate), body weight and height.

Regarding immunogenicity, 14 of 15 patients had at least 1 treatment-induced or treatment-boosted ADA positive sample, and 6 patients had positive NAb results. However, evaluation of the ADA results did not indicate any effects on efficacy or safety results.

Overall safety results were in line with the known safety and tolerability profile of anakinra, and no new safety concern was reported. The most common AE was injection site reaction. As far as possible to judge from the small numbers there was no obvious difference between paediatric and adult patients regarding safety.

2.3.4. Clinical pharmacology

2.3.4.1. Bioanalytical methods

PK assessment and ADA analysis were conducted. NAb analysis was performed.

PK assay

The analytical performance of all acceptable anakinra runs is summarised below:

Item	Results	Hyperlink
Methodology	ECLIA (MSD) - Validation report YDE/113.	Appendix B
Biological Matrix	Human Serum	Appendix E and Section 3.3
Anticoagulant	N/A	N/A
Analyte of Interest	Anakinra	Appendix D and Section 3.1
Partial validation: Intra-run precision	LLOQ (3.00 ng/mL): 2.2% LQC (5.00 ng/mL): 2.3% MQC (22.0 ng/mL): 2.6% HQC (75.0 ng/mL): 2.5% ULOQ (100 ng/mL): 7.4%	Section 4.2 and Table 8
Partial validation: Intra-run bias	LLOQ (3.00 ng/mL): -10.7% LQC (5.00 ng/mL): -10.8% MQC (22.0 ng/mL): -10.9% HQC (75.0 ng/mL): -7.6% ULOQ (100 ng/mL): -9.0%	Section 4.2 and Table 8
Partial validation: Selectiviity (Japanese serum)	10/10 acceptable (unspiked) 9/10 acceptable (LLOQ) 10/10 acceptable (HQC)	Section 4.2, Table 9 and Table 10
Calibration Curve Range	3.00 to 100 ng/mL (anchor points at 0.500, 1.00 and 2.00 ng/mL)	Table 12 and Table 13 Section 4.3
Inter-Run Bias	LQC (5.00 ng/mL): -9.0% MQC (22.0 ng/mL): -9.1% HQC (75.0 ng/mL): -7.6%	Table 14 and Section 4.4
Inter-Run Precision	LQC (5.00 ng/mL): 5.3% MQC (22.0 ng/mL): 4.0% HQC (75.0 ng/mL): 6.2%	Table 14 and Section 4.4
Study Samples	236 samples received (118 primary and 118 back-up samples) and 118 analysed. 51 repeat analyses required	Table 15, and Section 3.8 Table 17
Incurred Sample Reproducibility	21 samples selected for reanalysis (17.8% of total samples analysed). 71.4% reanalysed samples were within ±30% of original concentration.	Table 16 and Section 4.6
Analytical runs	10 analytical runs performed. 10/10 runs passed and 7/7 runs containing study samples met acceptance	Appendix C

ADA assay

Partial validation of the analytical method for the determination of anti-anakinra in human serum was carried out to re-assess all cut-points following the use of new critical reagents and Japanese serum.

The validated method was then successfully used to analyse human serum samples from the core phase of clinical study SOBI.ANAKIN-303.

The analytical performance of all acceptable runs is summarised below:

Methodology	ECLIA	
Instrumentation	MSD QuickPlex SQ120	
Item	**Result**	**Hyperlink**
Analytical Method	YDE/065	Section 3.6 and Appendix B
Biological matrix	Japanese human serum	Section 3.5 and Appendix E
Analytical Standards	Anti-anakinra Anakinra (Kineret) HEK IL-1ra	Section 3.1, 3.2 and 3.3
Critical Reagents	Biotinylated Anakinra Sulfo-tagged Anakinra MSD gold Streptavidin coated plate	Section 3.4
Partial validation: Screening cut-point	Normalisation factor (NF) = 5.66 Plate specific CP = Mean NC + 5.66	Section 4.2
Partial validation: Confirmatory cut-point	Confirmatory cut point = 0.816	Section 4.2
Partial validation: HEK IL-1ra confirmatory cut-point	HEK IL-1ra confirmatory cut point = 0.791	Section 4.5
Partial validation: Titration cut-point	Titration normalisation factor = 9.22 Titration plate specific CP = Mean NC + 9.22	Section 4.2
Study samples	190 samples (95 primary samples and 95 back-up samples) received	Section 3.9 and Appendix F
Anti-anakinra: Intra-assay Precision range (Sample Analysis)	NC: 1.6% - 9.6% LPC (4 ng/mL): 1.2% - 7.2% HPC (500 ng/mL): 0.8% - 16.3%	Section 4.7 and Table 15
Anti-anakinra: Inter-assay Precision (Sample Analysis)	NC: 8.5% LPC (4 ng/mL): 6.3% HPC (500 ng/mL): 36.4%	Section 4.7 and Table 15
Anti- anakinra: Inter-assay Precision of Ratio (Confirmatory Assay)	LPC (4 ng/mL): 2.9% HPC (500 ng/mL): 30.2%	Section 4.7 and Table 16
Anti- anakinra: Inter-assay Precision of Ratio (HEK IL-1ra Confirmatory Assay)	LPC (4 ng/mL): 3.5% LPC (10 ng/mL): 6.8% HPC (500 ng/mL): 31.3%	Section 4.7 and Table 17

An addendum to the final report documents the results obtained for the analysis of samples collected during the extension phase of the clinical trial ANAKIN-303. One subject (two samples) pursued in the extension phase of the trial.

NAb assay

An Interim Study Report v1.0 was issued 2025-01-31. A version 2.0 report was issued November 2025 including samples from the extension phase. This analysis is not final yet.

The purpose of this study was to analyse human serum samples for neutralising antibodies (NAbs) towards Anakinra - a human recombinant IL-1 receptor antagonist (IL-1Ra) - and towards IL-1Ra produced in HEK cells (HEK-IL-1Ra) from the clinical study ID ANAKIN-303 (1), using a validated cell based immunoassay in 96-well plate format (5, 6). The assay was re-validated prior to this study (3). 97 samples were recieved and 67 samples analysed.

Positive and negative control sample performance is summarized in Table 6 and Table 7. The overall CV in the screening assays (plate 1, 2, 4 and 6) was NC 18%, BC 12%, LQC 17% and HQC 19% for the normalised RLU values. In the cross-reactivity assay (plate 1, 3 and 5) the overall CV was NC 4%, BC 9%, LQC 8% and HQC 12% for the normalised RLU values. All parameters were within the validated limits of the method.

Conclusion

Anakinra NAbs in samples from the clinical study ANAKIN-303 were successfully analyzed. The results are considered valid and accurate based on the performance of the assay. 9 of 67 samples were reported as positive in the screening assay. 0 of 9 samples were reported as positive in the cross-reactivity assay.

2.3.4.2. Discussion of Bioanalytical methods

No Summary of Biopharmaceutics was submitted with this application.

Full documentation of bioanalytical conduct was presented in 5 respective bioanalytical reports submitted with the rest of the study information (Annexes 16.1.13).

PK: Final report issued November 2024.

ADA: A final report issued July 2025. A final addendum to final report was issued October 2025.

NAbs: A report version 1.0 issued September 2025. A report version 2.0 was issued November 2025.

Documentation of method performance was sufficient with incurred sample reproducibility, run summaries, cut point evaluation and performance of QC’s and controls. The bioanalytical program is considered in good control and well-documented.

2.3.4.3. Pharmacokinetics

PK analysis (Clinical overview)

The PK objective of study Sobi.ANAKIN-303 in the core phase was:

To evaluate the PK of anakinra in patients with Still's disease.

PK samples were collected to evaluate the pharmacokinetics of anakinra in patients with Still's disease. Serum concentrations of anakinra were determined at baseline, Week 1, and Week 2 visits in patients with evaluable PK data. Samples were collected prior to Investigational Medicinal Product administration and at 15 minutes (±5 minutes) and 4 hours (±15 minutes) post dose.

In the anakinra arm (8 patients), on Day 1, the geometric mean anakinra serum concentrations (coefficient of variation [CV]%) were 235.46 (57.95) µg/L at 15 minutes post dose and 586.40 (33.67) µg/L at 4 hours post dose. At Week 1, the geometric mean serum concentrations (CV%) were 151.51 (263.12) µg/L at pre-dose, 418.52 (42.51) µg/L at 15 minutes post dose, and 795.57 (14.00) µg/L at 4 hours post dose. At Week 2, corresponding values were 166.66 (133.16) µg/L at pre-dose, 384.24 (40.70) µg/L at 15 minutes post dose, and 823.80 (33.34) µg/L at 4 hours post dose.

In patients below 16 years of age in the anakinra arm, PK results were similar to those observed in the overall population at all visits. PK parameters at Week 1 and Week 2 were also comparable between pediatric and adult patients.

In the placebo arm (1< 16 and 6 ≥ 16 years of age), following the switch to anakinra treatment at Week 2, geometric mean anakinra serum concentrations (CV%) were 301.05 (68.45) µg/L at 15 minutes post dose and 943.41 (49.35) µg/L at 4 hours post dose, demonstrating serum concentrations comparable to those observed following the first dose of anakinra in patients randomized to the anakinra arm.

Legacy pharmacokinetic information (Study report)

The pharmacokinetics (PK) of anakinra are well characterized in healthy volunteers and RA patients. The bioavailability is high (~95%), time to maximum plasma concentration (tmax) is about 6 hours and anakinra serum concentrations decline with a half-life of 4 to 6 hours following subcutaneous administration to RA patients. The exposure increases in approximate proportion to dose and accumulation is modest following once daily administration and approximately 80% of anakinra is eliminated by the kidney. In juvenile idiopathic arthritis (JIA) patients, trough anakinra concentrations were lower in the age group 3 to 6 years compared to older children and in 22 SJIA patients, clearance was higher in children with a lower body weight (Urien 2013).

The PK, antigenicity, safety and tolerability of anakinra have been evaluated in an open-label phase 1 study (0541) in 30 Japanese healthy adult volunteers following a single 3 hours intravenous (i.v.) infusion of either saline (n=6) or anakinra (n=24) with 4 subjects at each dose level 1, 2, 3, 5, 7 and 10 mg/kg. Anakinra plasma and urine concentrations were determined in samples up to 24 hours post-dose. Plasma PK data and urine PK data were analyzed descriptively.

The anakinra plasma concentration declined in parallel for all dose groups with a mean terminal half-life of 3.39 hours. The maximum plasma concentration (Cmax) and area under the plasma concentration-time curve from zero to infinity values increased in proportion to dose, indicating linear PK. The mean plasma clearance values were dose independent. The proportion of anakinra recovered in 24-hour urine collections was small and increased with increasing anakinra dose ranging from less than 0.01% after the 1 mg/kg dose to 7.78% after the 10 mg/kg dose.

PK profiles after intravenous infusion of anakinra have also been assessed in non-Japanese (i.e., Caucasian/Hispanics) subjects (0530). Based on studies 0541 and 0530, plasma clearance was comparable in Japanese and non-Japanese subjects. Consequently, it is suggested that there is no clinically relevant difference in systemic PK between Japanese and non-Japanese, indicating that anakinra is unlikely to be affected by ethnic factors with respect to systemic PK.

Recent legacy PK data as found in clinical study report of Sobi.ANAKIN-301:

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			40	26.7	No	1060	2.117	7375.769	1322.098	203.115	5423.163	4.512
4 mg/kg			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.

Demographics (Appendix 16.2.4)

16.2.4.1 Listing of Demographics and Baseline Characteristics - Core Phase (Randomized population)

Treatment Group	Patient number	Date of Informed Consent	Date of Randomization	Gender	Race	Age at randomization	Age at onset of disease
Anakinra		2023-09-12	2023-09-15		ASIAN		>=16
Anakinra		2024-01-24	2024-01-25		ASIAN		<16
Anakinra		2023-07-24	2023-07-25		ASIAN		>=16
Anakinra		2024-01-12	2024-01-15		ASIAN		>=16
Anakinra		2023-11-17	2023-11-20		ASIAN		<16
Anakinra		2024-01-04	2024-01-05		ASIAN		>=16
Anakinra		2023-12-26	2023-12-28		ASIAN		<16
Anakinra		2024-04-22	2024-04-25		ASIAN		<16
Placebo/ Anakinra		2023-04-12	2023-04-18		ASIAN		>=16
Placebo/ Anakinra		2023-08-31	2023-09-07		ASIAN		>=16
Placebo/ Anakinra		2024-01-04	2024-01-10		ASIAN		>=16
Placebo/ Anakinra		2024-01-22	2024-01-24		ASIAN		>=16
Placebo/ Anakinra		2023-12-13	2023-12-14		ASIAN		<16
Placebo/ Anakinra		2024-05-02	2024-05-08		ASIAN		>=16
Placebo		2024-02-29	2024-03-06		ASIAN		>=16

16.2.4.1 Listing of Demographics and Baseline Characteristics - Core Phase (Randomized population)

Treatment Group	Patient number	Symptom duration (days) [1]	Disease duration (days) [2]	Height (cm) [3]	Baseline Body Weight (kg) [4]	BMI (kg/m^2)	Glucocorticoids use at inclusion	Glucocorticoids use at inclusion (mg/day)	FAS
Anakinra		197	153	-	94.4	-	Yes	9	Y
Anakinra		19	5	83	10.4	15.096530701	No	-	Y
Anakinra		28	4	-	66.6	-	No	-	Y
Anakinra		-	4	-	51.8	-	Yes	25	Y
Anakinra		-	16	86	10.3	13.926446728	No	-	Y
Anakinra		75	28	-	63.8	-	Yes	50	Y
Anakinra		67	1	124	19.9	12.942247659	No	-	Y
Anakinra		191	144	161	45.2	17.437598858	Yes	10	Y
Placebo/ Anakinra		23	13	-	59.6	-	Yes	60	Y
Placebo/ Anakinra		24	-5	-	51.4	-	No	-	Y
Placebo/ Anakinra		46	11	-	53.3	-	Yes	30	Y
Placebo/ Anakinra		-	5	-	40.9	-	No	-	Y
Placebo/ Anakinra		28	7	94	12.5	14.146672703	No	-	Y
Placebo/ Anakinra		-	2	-	54.9	-	Yes	20	Y
Placebo		-	330	-	89.2	-	Yes	2.5	Y

Abbreviations: FAS, Full Analysis Set
[1] Symptom duration = Date of enrollment – Date of onset of Still's disease symptoms +1
[2] Disease duration = Date of enrollment – Date of Still's disease diagnosis +1
[3] Height is measured for patient who is younger than 19 years old.
[4] Baseline is defined as the last non-missing value taken before the first dose of study drug.

Listing of drug concentrations – Core Phase

Treatment Group	Patient number	Parameter (Unit)	Visit	Time Point	Collected Date	Concentration
Anakinra		Anakinra serum concentrations (ug/L)	Baseline	Pre-dose	2023-09-15	<3.00
				15 minutes	2023-09-15	340
				4 hours	2023-09-15	692
			Week 1	Pre-dose	2023-09-22	591
				15 minutes	2023-09-22	536
				4 hours	2023-09-22	911
			Week 2	Pre-dose	2023-09-29	184
				15 minutes	2023-09-29	398
				4 hours	2023-09-29	693
		Anakinra serum concentrations (ug/L)	Baseline	Pre-dose	2024-01-25	<3.00
				15 minutes	2024-01-25	183
				4 hours	2024-01-25	550
			Week 1	Pre-dose	2024-02-01	84.4
				15 minutes	2024-02-01	648
				4 hours	2024-02-01	855
			Week 2	Pre-dose	2024-02-08	142
				15 minutes	2024-02-08	642
				4 hours	2024-02-08	667
		Anakinra serum concentrations (ug/L)	Baseline	Pre-dose	2023-07-25	<3.00
				15 minutes	2023-07-25	622
				4 hours	2023-07-25	1120
			Week 1	Pre-dose	2023-08-01	163
				15 minutes	2023-08-01	386
				4 hours	2023-08-01	947

Treatment Group	Patient number	Parameter (Unit)	Visit	Time Point	Collected Date	Concentration
Anakinra		Anakinra serum concentrations (ug/L)	Week 2	Pre-dose	2023-08-08	288
				15 minutes	2023-08-08	222
				4 hours	2023-08-08	953
		Anakinra serum concentrations (ug/L)	Baseline	Pre-dose	2024-01-15	<3.00
				15 minutes	2024-01-15	155
				4 hours	2024-01-15	511
			Week 1	Pre-dose	2024-01-22	244
				15 minutes	2024-01-22	276
				4 hours	2024-01-22	708
			Week 2	Pre-dose	2024-01-29	311
				15 minutes	2024-01-29	440
				4 hours	2024-01-29	869
		Anakinra serum concentrations (ug/L)	Baseline	Pre-dose	2023-11-20	<3.00
				15 minutes	2023-11-20	338
				4 hours	2023-11-20	643
			Week 1	Pre-dose	2023-11-27	9.14
				15 minutes	2023-11-27	268
				4 hours	2023-11-27	631
			Week 2	Pre-dose	2023-12-04	33.4
				15 minutes	2023-12-04	301
				4 hours	2023-12-04	525
		Anakinra serum concentrations (ug/L)	Baseline	Pre-dose	2024-01-05	5.5
				15 minutes	2024-01-05	114
				4 hours	2024-01-05	430

Treatment Group	Patient number	Parameter (Unit)	Visit	Time Point	Collected Date	Concentration
Anakinra		Anakinra serum concentrations (ug/L)	Week 1	Pre-dose	2024-01-11	684
				15 minutes	2024-01-11	589
				4 hours	2024-01-11	742
			Week 2	Pre-dose	2024-01-18	799
				15 minutes	2024-01-18	620
				4 hours	2024-01-18	700
		Anakinra serum concentrations (ug/L)	Baseline	Pre-dose	2023-12-28	<3.00
				15 minutes	2023-12-28	214
				4 hours	2023-12-28	603
			Week 1	Pre-dose	2024-01-05	56.4
				15 minutes	2024-01-05	255
				4 hours	2024-01-05	867
			Week 2	Pre-dose	2024-01-11	51.8
				15 minutes	2024-01-11	247
				4 hours	2024-01-11	992
		Anakinra serum concentrations (ug/L)	Baseline	Pre-dose	2024-04-25	4.25
				15 minutes	2024-04-25	191
				4 hours	2024-04-25	385
			Week 1	Pre-dose	2024-05-02	397
				15 minutes	2024-05-02	632
				4 hours	2024-05-02	757
			Week 2	Pre-dose	2024-05-09	184
				15 minutes	2024-05-09	413
				4 hours	2024-05-09	1520

Treatment Group	Patient number	Parameter (Unit)	Visit	Time Point	Collected Date	Concentration
Placebo		Anakinra serum concentrations (ug/L)	Baseline	Pre-dose	2023-09-07	<3.00
				15 minutes	2023-09-07	<3.00
				4 hours	2023-09-07	3.17
			Week 1	Pre-dose	2023-09-12	<3.00
				15 minutes	2023-09-12	3.36
				4 hours	2023-09-12	<3.00
			Week 2	Pre-dose	2023-09-20	<3.00
				15 minutes	2023-09-20	839
				4 hours	2023-09-20	1700
		Anakinra serum concentrations (ug/L)	Baseline	Pre-dose	2024-01-10	3.37
				15 minutes	2024-01-10	14.3
				4 hours	2024-01-10	5.67
			Week 1	Pre-dose	2024-01-17	<3.00
				15 minutes	2024-01-17	<3.00
				4 hours	2024-01-17	<3.00
			Week 2	Pre-dose	2024-01-24	3.44
				15 minutes	2024-01-24	256
				4 hours	2024-01-24	662
		Anakinra serum concentrations (ug/L)	Baseline	Pre-dose	2024-01-24	<3.00
				15 minutes	2024-01-24	<3.00
				4 hours	2024-01-24	<3.00
			Week 1	Pre-dose	2024-01-31	<3.00
				15 minutes	2024-01-31	<3.00
				4 hours	2024-01-31	<3.00

Treatment Group	Patient number	Parameter (Unit)	Visit	Time Point	Collected Date	Concentration
Placebo		Anakinra serum concentrations (ug/L)	Week 2	Pre-dose	2024-02-07	<3.00
				15 minutes	2024-02-07	195
				4 hours	2024-02-07	743
		Anakinra serum concentrations (ug/L)	Baseline	Pre-dose	2023-12-14	<3.00
				15 minutes	2023-12-14	<3.00
				4 hours	2023-12-14	<3.00
			Week 2	Pre-dose	2023-12-21	<3.00
				15 minutes	2023-12-21	328
				4 hours	2023-12-21	625
		Anakinra serum concentrations (ug/L)	Baseline	Pre-dose	2024-03-06	3.7
				15 minutes	2024-03-06	3.26
				4 hours	2024-03-06	4.43
			Study Drug Discontinuation	Study Drug Discontinuation	2024-03-13	<3.00
		Anakinra serum concentrations (ug/L)	Baseline	Pre-dose	2024-05-08	5.63
				15 minutes	2024-05-08	3.43
				4 hours	2024-05-08	<3.00
			Week 1	Pre-dose	2024-05-15	3.36
				15 minutes	2024-05-15	<3.00
				4 hours	2024-05-15	<3.00
			Week 2	Pre-dose	2024-05-22	3.46
				15 minutes	2024-05-22	180
				4 hours	2024-05-22	1430

2.3.4.4. Discussion of pharmacokinetics

The main aim of this study was to demonstrate efficacy and safety of anakinra in 15 pediatric and adult Japanese patients with Still's disease – not to demonstrate similar pharmacokinetics in this population compared to previously treated populations. PK samples were collected at baseline, Week 1 and in Week 2 of the Core Phase of the clinical study. Placebo patients were dosed in week 2 and data show similar serum concentrations as in patients in the anakinra group at baseline as expected. No tabular summary of obtained exposure data compared to legacy data was presented. No evaluation of ADA potentially impacting exposure was presented. This is acceptable, since PK data was only obtained within the first two weeks after initiation of treatment.

The analysis indicates that PK exposure to anakinra is within the range of previously observed (53 - 8511 ng/mL in SJIA patients as stated in EMA/CHMP/169769/2018, page 18) and that the general and previous description of anakinra PK also applies. In section 5.2 of the SmPC, it is already stated that "*The median steady-state dose-normalized anakinra concentration in SJIA patients over 28 weeks was comparable to that observed in RA patients*". No further amendments are required.

3. CHMP overall conclusion and recommendation

Clinical pharmacology

Serum samples were collected in the core phase of the clinical study and analysed according to protocol documenting exposure to anakinra in patients in both the anakinra and placebo arm. No amendments to the SmPC is required.

☒ **Fulfilled:**

No regulatory action required.

☐ **Not fulfilled:**

4. Request for supplementary information

Not applicable.