10 June 2022
EMA/609606/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kineret

International non-proprietary name: anakinra

Procedure No. EMEA/H/C/000363/II/0087

Note

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

Status of this report and steps taken for the assessment

Current step[1]	Description	Planned date	Actual Date	Need for discussion[2]
☐	Start of procedure	22 Feb 2022	22 Feb 2022	☐
☐	CHMP Rapporteur Assessment Report	28 Mar 2022	28 Mar 2022	☐
☐	CHMP members comments	11 Apr 2022	11 Apr 2022	☐
☐	Updated CHMP Rapporteur Assessment Report	13 Apr 2022	n/a	☐
☐	Request for supplementary information	22 Apr 2022	22 Apr 2022	☐
☐	Submission of MAH responses	11 May 2022	05 May 2022	☐
☐	Re-start of procedure	12 May 2022	12 May 2022	☐
☐	CHMP Rapporteur Assessment Report	25 May 2022	18 May 2022	☐
☐	CHMP members comments	31 May 2022	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	03 June 2022	n/a	☐
☐	Start of written procedure	08 June 2022	08 June 2022	☐
☒	Opinion	10 June 2022	10 June 2022	☐

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Swedish Orphan Biovitrum AB (publ) submitted to the European Medicines Agency on 17 December 2021 an application for a variation.

The following changes were proposed:

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

C.I.13: Submission of the final report from study SAVE-MORE, as requested as part of procedure EMEA/H/C/000363/II/086. This is a prospective, double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of the early start of anakinra treatment guided by suPAR in patients with LRTI by SARS-CoV-2 in improving the clinical state of COVID-19 patients over 28 days as measured by the ordinal scale of the 11-point WHO-CPS.

The requested variation proposed no amendments to the Product Information.

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

The MAH has submitted the final clinical study report (CSR) for the SAVE-MORE study (dated 07.02.22) as requested in the type II variation procedure for extension of indication of Kineret (EMEA/H/C/000363/II/0086).

The database lock for SAVE-MORE occurred on August 18, 2021 (last patient last visit June 28, 2021) and is based on data collected until Day 90 (11-point WHO-CPS data, AE/SAE and study drug administration) for all patients. Safety Day 90 data has been submitted as part of the 3rd request for supplementary information (RSI) and assessed in the CHMP AR for the procedure II/0086. The interim database lock on 29 April 2021 (data submitted in the initial CSR), unblinding, and analysis were performed when the last patient had completed Day 28 but prior to the planned study follow-up of 60 and 90 days.

This final CSR was based on data collected until Day 90 for all patients. The last Day 90 follow-up was completed on June 28, 2021.

Efficacy (primary and secondary endpoints) were previously reported in the iCSR; the only updates to efficacy were time until discharge from the hospital and intensive care unit (ICU) by Day 90. Safety data have been updated to include long-term results from the SAVE-MORE study up to Day 90.

In the final CSR, the number of patients that received dexamethasone during treatment has been revised. Revisions have been made to the clinical overview and summary of clinical efficacy. The percentage of patients receiving dexamethasone has been amended from 86,4% to 85.9%. The dexamethasone percentage in the SmPC (section 5.1) is also proposed by the MAH to be revised in line with the final CSR.

In the final CSR, subgroup analyses including Charlson's comorbidity index (CCI) ≥2 vs <2, soluble urokinase plasminogen activator receptor (suPAR) >9 ng/mL vs ≤9 ng/mL, sex, age ≥65 years vs <65 years, baseline remdesivir use, dexamethasone use, baseline disease severity and the need for oxygen, and BMI category were performed on the primary endpoint. Regardless of subgroup category

anakinra treatment was beneficial.

In the final CSR data on absolute changes of the WHO-CPS scores by day 60 and day 90 from baseline Day 1 were submitted. An ordinal regression analysis showed that anakinra treatment was favourable in reducing the odds for higher scores on the 11-point WHO-CPS at Days 60 and 90 from baseline Day 1 (Day 60 adjusted OR: 0.40, 95% CI: 0.28 to 0.58, p<0.0001; Day 90 adjusted OR: 0.50, 95% CI: 0.34 to 0.74, p=0.001).

Safety data submitted in the final CSR are overall in alignment with safety data up to Day 90 that was earlier submitted and assessed in CHMP AR for the procedure II/0086. The safety profile remains favourable with no new safety signals identified apart from the TEAE hypothermia occurring more frequently in the anakinra+SoC group compared to the placebo+SoC group (7.4% vs. 4.2%) not reported earlier in the treatment of hospitalised adult patients with COVID-19 (OC). The frequency and severity of the subset of ADRs observed (neutropenia, elevated hepatic enzymes, rash, and injection site reactions), following the 10-day dosing regimen of anakinra, were consistent with the known safety profile of anakinra in the licensed indications.

Overall, the single pivotal study SAVE-MORE supports that there is a clinical benefit of anakinra in adult COVID-19 patients with pneumonia who are at risk of developing severe respiratory failure based on suPAR ≥ 6 ng/ml. Also, it was demonstrated that anakinra treatment had a beneficial effect on time to progression to severe respiratory failure, on time until hospital discharge and on mortality, as compared to SoC treatment in the studied population.

The safety profile of Kineret for treatment of adult COVID-19 patients with pneumonia who are at risk of developing severe respiratory failure is in general positive. The overall occurrence of AEs, SAEs including infections, discontinuations and deaths were fewer for Kineret treated patients compared to placebo. No new safety signals were identified in the treatment of hospitalised adult patients with COVID-19. The safety data are overall consistent with the known safety profile of Kineret for the approved indications with no new safety signals.

The benefit-risk balance of Kineret remains positive.

3. Recommendations

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

Variation requested		Type	Annexes affected
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	SmPC

C.I.13: Submission of the final report from study SAVE-MORE, as requested as part of procedure EMEA/H/C/000363/II/086. This is a prospective, double-blind, randomised, placebo-controlled study to evaluate the efficacy and safety of the early start of anakinra treatment guided by suPAR in patients with LRTI by SARS-CoV-2 in improving the clinical state of COVID-19 patients over 28 days as measured by the ordinal scale of the 11-point WHO-CPS. Following review of the final CSR, the section 5.1 of the SmPC is updated to revise the percentage of patients receiving dexamethasone during treatment. The MAH also took the opportunity to make some editorial changes in the product information.

☒ is recommended for approval.

Amendments to the marketing authorisation

The variation leads to amendments to the terms of the Community Marketing Authorisation.

4. EPAR changes

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

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion 'Kineret-H-C-0363-II-87'.

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

5. Introduction

5.1. Medicinal product

Anakinra (Kineret) is currently approved for the treatment of RA in the US (2001), Canada (2002), the EU/EEA (2002), Australia (2003), and Israel (2011). Kineret is also approved for all forms of CAPS in the EU/EEA (2013), Israel (2014), Australia (2014), and Russia (2021) and for the most severe form of CAPS, i.e., NOMID, in the US (2012) and Canada (2017). Additionally, Kineret is approved for Still's disease (including SJIA and AOSD) in the EU/EEA (2018) and for the treatment of SJIA in Australia (2015). Kineret is also approved for FMF in the EU/EEA (2020) and Israel (2020) and for DIRA in the US (2020). Anakinra is a recombinant human IL-1Ra that blocks the biological activity of cytokine IL-1 (IL-1α and IL-1β) by competitively inhibiting its binding to the IL-1RI, thereby controlling active inflammation

5.2. Targeted indication

Section 4.1 Therapeutic Indications: COVID-19

Kineret is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adult patients with pneumonia requiring supplemental oxygen (low- or high-flow oxygen) who are at risk of progressing to severe respiratory failure determined by plasma concentration of soluble urokinase plasminogen activator receptor (suPAR) ≥6 ng/ml (see sections 4.2, 4.4 and 5.1).

Section 5.1 Pharmacodynamic Properties: Clinical efficacy and safety in COVID-19

The safety and efficacy of Kineret was evaluated in patients with COVID-19 pneumonia ≥18 years of age with a risk of developing severe respiratory failure in a randomized doubleblind placebo-controlled study. The patient population enrolled into the SAVE-MORE study was hospitalized with confirmed COVID-19 pneumonia (LRTI radiologically confirmed by chest X-ray or CT) and was considered to be at risk of developing SRF, determined by an elevation in suPAR (≥6 ng/ml). Patients had suPAR level ≥6 ng/ml measured by the suPARnostic Quick Triage kit. These patients had not yet progressed to SRF (i.e., exclusion criteria were: pO2/FiO2 ratio less than 150 mmHg or the requirement of mechanical ventilation, NIV, or ECMO). The majority of patients received low- or high-flow supplementary oxygen at screening (81.6%). The study enrolled 606 patients and efficacy analysis was performed in the intention-to-treat (ITT) population comprising of 594 patients of whom 189 patients were randomized to the placebo+SoC arm and 405 patients to the anakinra+SoC arm. The majority of the patients (91.4%) had severe COVID-19 pneumonia and 8.6% of patients had moderate COVID-19 pneumonia at start of treatment. 85.9% of patients received dexamethasone. The mean (SD) duration of Kineret treatment was 8.4 (2.1) days. The primary endpoint of the study was the comparative 11-point WHO Clinical Progression ordinal Scale (CPS) between the two arms of treatment by Day 28. The 11-point WHO CPS provides a measure of illness severity across a range from 0 (not infected); 1-3 (mild disease), 4-5 (hospitalized – moderate disease), 6-9 (hospitalized – severe disease with increasing degrees of NIV, MV and ECMO) to 10 (dead). Of the patients randomised in the SAVE-MORE study 8.6% had a baseline WHO-CPS of 4; 84.7% had a baseline WHO-CPS of 5 and 6.7% had a baseline WHO-CPS of 6. In patients treated with Kineret for up to 10 days a significant improvement of the clinical status according to the WHO-CPS was demonstrated by Day 28 compared to placebo (OR: 0.36 [95% CI 0.26 to 0.50] P<0.001). Improvement of the patients' clinical status was seen by Day 14. The treatment benefit of Kineret was supported by increase in the number of patients fully recovered and reduction in the number of patients who progressed to severe respiratory failure or death compared to placebo. No new safety signals or safety concerns were observed from the use of Kineret for treatment

of COVID-19.

5.3. Objective of the submission

This type II variation is being submitted in order to fulfill the commitment to submit the final CSR for the SAVE-MORE study, a Phase 3, pivotal, confirmatory, prospective, multicenter, double-blind, randomized, placebo-controlled study conducted at 37 study sites (29 in Greece and 8 in Italy) by the Hellenic Sepsis Study Group. This post-authorization measure was agreed with the EMA in procedure No. EMEA/H/C/000363/II/0086 for extension of indication for Kineret.

The primary objective of the study was to evaluate the efficacy of early start of anakinra treatment guided by suPAR in patients with LRTI by SARS-CoV-2 in improving the clinical outcome of COVID-19 over 28 days as measured by the ordinal scale of the 11-point WHO-CPS.

Secondary study objectives were as follows:

- Clinical efficacy of anakinra treatment guided by suPAR in patients with LRTI by SARS-CoV-2 as assessed by:

  o the changes of the ordinal scale of the 11-point WHO-CPS at Days 14 and 28

  from baseline Day 1

  o the changes of the SOFA score at Days 7 and 14 from baseline Day 1

  o the duration of hospital and ICU stay

  o the association of clinical efficacy with the time of start of anakinra from the onset of COVID-19

- Effect of anakinra treatment guided by suPAR on biomarkers of patients with LRTI bySARS-CoV-2

- Safety of anakinra in COVID-19

Efficacy as assessed by the primary and secondary endpoints as well as biomarker data and safety data b Day 28 was reported in the previously submitted iCSR. The final CSR provided in this type II variation submission includes safety data by Day 90, other efficacy endpoints (e.g., 11-point WHO-CPS by Days 60 and 90), and post-hoc subgroup analyses.

CHMP comments

The MAH has submitted the final CSR for the SAVE-MORE study (dated 07.02.22) fulfilling the post-authorisation measure according to procedure No. EMEA/H/C/000363/II/0086 for extension of indication of Kineret.

The database lock for SAVE-MORE occurred on August 18, 2021 (last patient last visit 28th June 2021) and is based on data collected until Day 90 (11-point WHO-CPS data, AE/SAE and study drug administration) for all patients. Safety Day 90 data has been submitted as part of the 3rd RSI and assessed in the CHMP AR. The interim database lock on 29 April 2021(data submitted in the iCSR), unblinding, and analysis were performed when the last patient had completed Day 28 but prior to the planned study follow-up of 60 and 90 days.

This final CSR was based on data collected until Day 90 for all patients. The last Day 90 follow-up was completed on 28 June 2021.

Efficacy (primary and secondary endpoints) were previously reported in the iCSR; the only updates to efficacy were time until discharge from the hospital and ICU by Day 90. Safety data have been updated in the table below to include long-term results from the SAVE-MORE study up to Day 90.

6. Overview of biopharmaceutics

No new information on the biopharmaceutic properties of anakinra is provided in the SAVE-MORE study.

CHMP comments
No new information submitted with the final CSR

7. Overview of clinical pharmacology

No new information on the clinical pharmacology of anakinra is provided in the SAVE-MORE study.

CHMP comments
No new information submitted with the final CSR

8. Clinical Efficacy aspects

Background and overview of clinical efficacy

An overview of the SAVE-MORE study is presented in Table 2.7.3 - 1.

2.7.3 Summary of clinical efficacy

Table 2.7.3 - 1   Pivotal clinical study to support efficacy of anakinra for use in patients with COVID-19 pneumonia

Study identifier/ Country(ies)/ EudraCT number/ Status	Title of the study	Study design	Study treatments	Number of patients	Study population
SAVE-MORE/ Greece and Italy/ 2020-005828-11/ Completed	suPAR-guided Anakinra Treatment for Validation of the Risk and Early Management of Severe Respiratory Failure by COVID-19: The SAVE-MORE Double-blind, Randomized, Phase 3 Confirmatory Trial	Prospective, multicenter, double-blind, placebo-controlled Phase 3 clinical study	Patients were randomly assigned 1:2 to the following treatment groups: Treatment Group 1: placebo+SoC. Placebo injected s.c. q.d. for 10 days Treatment Group 2: anakinra+SoC Anakinra injected s.c. as 100 mg q.d. for 10 days	600 patients planned 606 enrolled Placebo+SoC: 194 Anakinra+SoC: 412 ITT - 594 patients: Placebo+SoC: 189 Anakinra+SoC: 405	Males and females ≥18 years of age hospitalized with confirmed infection by SARS-CoV-2 virus, lower respiratory tract infection (radiologically confirmed), and plasma suPAR ≥6 ng/mL

Abbreviations: COVID-19, Coronavirus disease 2019; q.d., Once daily; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; s.c., Subcutaneous; SoC, Standard-of-care; suPAR, Soluble urokinase plasminogen activator receptor.

Details on the study findings can be found in Section 2.7.3.2.1.

8.1. Disposition and demographics

In the SAVE-MORE study, 1060 patients were screened from December 2020 through March 2021, and 606 patients were enrolled at 37 study sites (29 in Greece and 8 in Italy): 194 patients were randomized to placebo+SoC treatment, and 412 patients were randomized to anakinra+SoC treatment. Of these, 189 patients in the placebo+SoC group and 405 patients in the anakinra+SoC group were included in the FAS/Safety Analysis Set (N=594). 6 patients allocated to the placebo+SoC group and 13 patients in the anakinra+SoC group were reported as lost to follow-up at Day 60. 10

patients allocated to the placebo+SoC group and 17 patients in the anakinra+SoC group were reported as lost to follow-up at Day 90. Disposition of patients is summarized in SAVE-MORE CSR, Figure 10-1. The overall mean age of the 594 patients in the FAS, as previously reported in the iCSR, was 61.9 years, 57.9% of patients were male, and the mean BMI was 29.5 kg/m2. The overall mean (SD) Charlson's Comorbidity Index score for all patients was 2.2 (1.6), and the overall mean (SD) SOFA score was 2.4 (1.1). As per the WHO pneumonia severity classification at the time of screening, the majority of the patients (81.6%) were identified with severe COVID-19 pneumonia, and 18.4% of patients were identified with moderate COVID-19 pneumonia. Furthermore, the SOFA score of organ dysfunction was similar between the 2 groups at baseline (2.4 for anakinra+SoC and 2.5 for placebo+SoC), and the same applied for the WHO-CPS of Day 1 before the start of treatment. The overall median time (Q1 to Q3) from symptom onset to enrollment was 9 days, and the median time from hospital admission to enrollment was 2 days.

CHMP comments

The FAS analysis included 594 patients, of these, 189 patients in the placebo+SoC group and 405 patients in the anakinra+SoC group with disposition and demographics as previously reported in the iCSR.

8.2. Primary efficacy endpoint

The primary endpoint of the SAVE-MORE study was the patient's WHO-CPS score by Day 28 in the FAS population and was previously reported in the iCSR. Anakinra treatment demonstrated significant improvement of the clinical status of patients with COVID-19 as measured by the WHO-CPS score by Day 28 compared to placebo (adjusted OR: 0.36; 95% CI: 0.26 to 0.50; p<0.0001 in favor of anakinra+SoC treatment; SAVE-MORE CSR, Figure 11-1 and Table 11-1). In the multivariate ordinal regression analysis, allocation to the anakinra+SoC treatment was the only variable that was significantly associated with the final outcome.

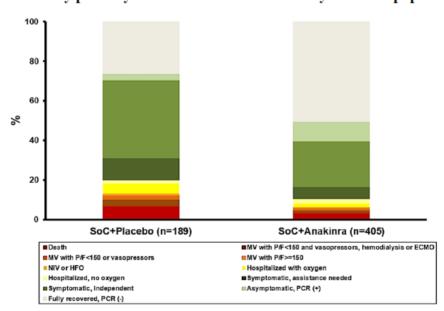**Figure 11-1   Study primary outcome – WHO-CPS at Day 28 – FAS population**

Source: Figure 14.2.1.
Abbreviations: CPS, Clinical progression scale; ECMO, Extracorporeal membrane oxygenation; FAS, Full analysis set; HFO, High flow oxygen; MV, Mechanical ventilation; n, Number of patients; NIV, Noninvasive ventilation; PCR, Polymerase chain reaction; P/F, Respiratory ratio; SoC, Standard-of-care; WHO, World Health Organization.

Table 11-1   Univariate and multivariate ordinal regression analysis of the WHO-CPS at Day 28

	Univariate analysis			Multivariate analysis		
	OR	95% CIs	p-value	OR$_{adj}$	95% CIs	p-value
Group of treatment (anakinra vs placebo)	0.36	0.26-0.49	<0.0001	0.36	0.26-0.50	<0.0001
Intake of dexamethasone (Yes/No)	1.90	1.28-2.83	0.002	1.49	0.59-3.80	0.39
Severe COVID-19 by WHO (Yes/No)	1.95	1.31-2.90	0.001	1.29	0.51-3.27	0.58
BMI >30 kg/m^2 (Yes/No)	1.27	0.87-1.61	0.27	1.10	0.81-1.50	0.53
Country (Italy vs Greece)	1.18	0.74-1.88	0.48	1.25	0.77-2.03	0.35

Source: Modified from Figure 14.2.1.
Abbreviations: BMI, Body mass index; CI, Confidence interval; COVID-19, Coronavirus disease 2019; COVID-ETF, COVID-19 EMA pandemic Task Force; EMA, European Medicines Agency; OR, Odds ratio; OR$_{adj}$, Adjusted OR; vs, Versus; WHO-CPS, World Health Organization-Clinical Progression Scale.
Note: Covariates entered in the multivariate model were those used for stratified randomization according to the advice received by the COVID-ETF.

CHMP comments

The prespecified primary study endpoint, the comparative 11-point WHO-CPS between the two arms of treatment (expressed as the OR for allocation to lower severity after anakinra treatment compared to placebo) by Day 28 was previously reported in the iCSR. This was assessed by ordinal regression analysis unadjusted and adjusted for other factors as given I table 11-1 (administration of dexamethasone, severe COVID-19, BMI>30kg/m^2 and country). The adjusted (multivariate) analysis anakinra+SoC was favourable (OR 0.36; 95 % CI 0.26 to 0.50; P<0.001), hence the primary endpoint was met and statistically significant. No new data was submitted with the final CSR.

Supportive analyses of the primary endpoint

The 3 prespecified analyses supported the primary endpoint measured with the WHO-CPS and confirmed the clinical benefit of anakinra+SoC treatment as follows:

- Significant improvement of the clinical status was already seen by Day 14 in patients receiving anakinra+SoC compared to placebo+SoC (adjusted OR of WHO-CPS by Day 14: 0.58; 95% CI: 0.42 to 0.79; p<0.001; SAVE-MORE CSR, Table 11-3).

Table 11-3 **First supportive analysis of the primary endpoint WHO-CPS at Day 14 - FAS population**

	Univariate analysis			Multivariate analysis		
	OR	95% CIs	p-value	OR_{adj}	95% CIs	p-value
Group of treatment (anakinra vs placebo)	0.57	0.42-0.77	<0.0001	0.58	0.42-0.79	<0.001
Intake of dexamethasone (Yes/No)	2.23	1.53-3.26	<0.0001	1.69	0.70-4.11	0.242
Severe COVID-19 by WHO (Yes/No)	2.23	1.53-3.26	<0.0001	1.36	0.56-3.27	0.493
BMI >30 kg/m^2 (Yes/No)	1.15	0.86-1.56	0.343	1.05	0.78-1.42	0.717
Country (Italy vs Greece)	1.14	0.72-1.79	0.572	1.26	0.79-2.00	0.320

Source: Table 14.2.1.3.
Abbreviations: BMI, Body mass index; CI, Confidence interval; COVID-19, Coronavirus disease 2019; CPS, Clinical Progression Scale; FAS, Full analysis set; OR, Odds ratio; OR_{adj}, Adjusted OR; vs, Versus; WHO, World Health Organization.

- The treatment benefit of anakinra was demonstrated by the increase in the number of patients fully recovered (i.e., discharged and no viral infection) (adjusted OR: 0.36; 95% CI: 0.25 to 0.53; p<0.0001; SAVE-MORE CSR, Table 11-5) and the reduction in the number of patients who progressed to SRF or death (adjusted OR: 0.46; 95% CI: 0.26 to 0.83; p=0.010; SAVE-MORE CSR, Table 11-6).

Table 11-5 **Analysis towards fully resolved or persistent disease (first spectrum) - FAS population**

	Analysis towards fully resolved or persistent disease					
	WHO-CPS 0 (n=254)	WHO-CPS ≥1 (n=340)	Univariate analysis		Multivariate analysis	
Variable			OR (95% CIs)	p-value	OR_{adj} (95% CIs)	p-value
Anakinra treatment	204 (80.3)	201 (59.1)	0.35 (0.23-0.52)	<0.0001	0.36 (0.25-0.53)	<0.0001
Intake of dexamethasone	198 (78.0)	288 (84.7)	1.56 (1.03-2.38)	0.036	*	
Severe COVID-19 by WHO	196 (77.2)	289 (85.0)	1.68 (1.10-2.55)	0.015	1.58 (1.02-2.42)	0.037
BMI >30 kg/m^2	87 (34.3)	129 (37.9)	1.17 (0.84-1.65)	0.36	*	
Patients in Italy	30 (11.8)	36 (10.6)	0.91 (0.55-1.52)	0.72	*	

Source: Table 14.2.1.4.
Abbreviations: BMI, Body mass index; CI, Confidence interval; COVID-19, Coronavirus disease 2019; CPS, Clinical progression scale; FAS, Full analysis set; n, Number of patients; OR, Odds ratio; OR_{adj}, Adjusted OR; WHO, World Health Organization.
Note: WHO-CPS 0 is fully resolved; WHO-CPS ≥1 is presistance.
*Variables not included in the equation after 2 steps of forward analysis.

Table 11-6   Analysis towards allocation into WHO-CPS ≥6 (Yes) or WHO-CPS ≤5 (second spectrum) - FAS population

	Analysis towards allocation into WHO-CPS ≥6 (Yes) or WHO-CPS ≤5					
	WHO-CPS ≤5 (n=543)	WHO-CPS ≥6 (n=51)	Univariate analysis		Multivariate analysis	
Variable			OR (95% CIs)	p-value	OR$_{adj}$ (95% CIs)	p-value
Anakinra treatment	379 (69.8)	26 (51.0)	0.45 (0.25-0.80)	0.007	0.46 (0.26-0.83)	0.010
Intake of dexamethasone	435 (80.1)	51 (100)	*	<0.0001	*	
Severe COVID-19 by WHO	434 (79.9)	51 (100)	*	<0.0001	**	
BMI >30 kg/m^2	199 (36.6)	17 (33.3)	0.81 (0.44-1.50)	0.81	**	
Patients in Italy	59 (10.9)	7 (13.7)	1.57 (0.70-3.49)	0.27	**	

Source: Table 14.2.1.4.
Abbreviations: BMI, Body mass index; CI, Confidence interval; COVID-19, Coronavirus disease 2019; CPS, Clinical Progression Scale; FAS, Full analysis set; n, Number of patients; OR, Odds ratio; OR$_{adj}$, Adjusted OR; WHO, World Health Organization.
Note: *Cannot be computed because one value is zero.
**Variables not included in equation after 2 steps of forward analysis.

- Anakinra treatment prevented the progression to SRF or death by Day 14 (adjusted HR: 0.67; 95% CI: 0.47 to 0.93; p=0.017; SAVE-MORE CSR, Table 11-7) and Day 28 (adjusted HR: 0.66, 95% CI: 0.47 to 0.91; p=0.012; SAVE-MORE CSR, Table 11-8).

Table 11-8   Analysis of time to progression into SRF until Day 28 - FAS population

	Respiratory failure		Univariate analysis		Multivariate analysis	
	No (n=446)	Yes (n=148)	HR (95% CIs)	p-value	HR (95% CIs)	p-value
Variable						
Anakinra treatment	319 (71.5)	86 (58.1)	0.61 (0.44-0.85)	0.003	0.66 (0.47-0.91)	0.012
Intake of dexamethasone	341 (76.5)	145 (98.0)	12.32 (3.93-36.65)	<0.0001	*	
Severe COVID-19 by WHO	339 (76.0)	146 (98.6)	18.91 (4.68-76.33)	<0.0001	17.81 (4.41-71.95)	<0.0001
BMI >30 kg/m^2	157 (35.2)	59 (39.9)	1.17 (0.84-1.63)	0.348	*	
Patients in Italy	39 (8.7)	27 (18.2)	2.17 (1.43-3.30)	<0.0001	2.05 (1.35-3.12)	0.001

Source: Table 14.2.1.7.
Abbreviations: BMI, Body mass index; CI, Confidence interval; COVID-19, Coronavirus disease 2019; FAS, Full Analysis Set; HR, Hazard ratio; n, Number of patients; SRF, Severe respiratory failure; WHO, World Health Organization.
Note: *Variables not included in equation after 3 steps of forward analysis.

CHMP comments

Three supportive analyses of the primary endpoint measured by the 11-point WHO-CPS score was carried out, as reported in the iCSR. Overall the outcomes were beneficial for anakinra+SoC treatment

No new data submitted in the final CSR.

Post-hoc survival analysis

Anakinra+SoC treatment reduced Day 28 mortality compared to placebo+SoC (3.2 % versus 6.9 %; adjusted HR: 0.39, 95% CI: 0.18 to 0.86; p=0.020; SAVE-MORE CSR, Table 11-9).

Table 11-9   Post-hoc survival analysis

	Survivors (N=568)	Non-survivors (N=26)	Univariate analysis HR (95% CIs)	p-value	Multivariate analysis HR (95% CIs)	p-value
Anakinra treatment, n (%)	392 (69.0)	13 (50.0)	0.45 (0.21-0.98)	0.045	0.39 (0.18-0.86)	0.020
Severe COVID-19 by WHO, n (%)	459 (80.8)	26 (100)	27.59 (0.39-1963)	0.127	*	
Intake of dexamethasone, n (%)	460 (81.0)	26 (100)	27.41 (0.37-2018)	0.131	*	
Age, mean (SD)	61.5 (11.9)	71.1 (9.4)	1.08 (1.04-1.11)	<0.0001	1.08 (1.04-1.12)	<0.0001
SOFA score, mean (SD)	2.37 (1.09)	3.15 (1.35)	1.58 (1.25-1.99)	<0.0001	1.48 (1.13-1.94)	0.005
suPAR, median (IQR)	7.6 (2.1)	8.4 (3.3)	1.16 (0.99-1.37)	0.065	*	
Charlson's comorbidity index, mean (SD)	2.19 (1.57)	3.19 (1.20)	1.40 (1.14-1.73)	0.002	*	
pO_2/FiO_2, mean (SD)	247.5 (93.9)	190.6 (71.7)	0.99 (0.98-0.99)	0.002	*	

Source: Table 14.2.1.8.
Abbreviations: CI, Confidence interval; COVID-19, Coronavirus disease 2019; FiO_2, Fraction of inspired oxygen; HR, Hazard ratio; IQR, Interquartile range; N, Total number of patients; n, Number of patients; pO_2, Partial oxygen pressure; SD, Standard deviation; SOFA, Sequential organ failure assessment; suPAR, Soluble urokinase plasminogen activator receptor; WHO, World Health Organization.
Note: *Variables were excluded from the final equation after 4 steps of forward analysis
Survival analysis is censored at Day 28.

CHMP comments

A post-hoc analysis showed that the univariate Cox regression analysis of time to death by Day 28 showed that anakinra treatment reduced the mortality compared to placebo (HR: 0.45, 95% CI 0.21-0.98, P=0.045). Also, 6.9% of patients in the placebo+SoC group and 3.2% of patients in the anakinra+SoC group died by Day 28 (data not shown).

In the final CSR post-hoc subgroup analyses included CCI ≥2 vs <2, suPAR >9 ng/mL vs ≤9 ng/mL, sex, age ≥65 years vs <65 years, baseline remdesivir use, dexamethasone use, baseline disease severity and the need for oxygen, and BMI category were performed on the primary endpoint. These analyses demonstrated that patients benefited from anakinra treatment regardless of subgroup category.

Sensitivity analyses of the primary endpoint

All 5 sensitivity analyses confirmed further the analysis of the primary endpoint (SAVE-MORE CSR, Table 11-10 to Table 11-14).

Table 11-10   Sensitivity analysis 1: PP population

| | Sensitivity analysis 1: PP (SoC+placebo=162; SoC+anakinra=392) | | | | | |
| | Univariate analysis | | | Multivariate analysis | | |
	OR	95% CIs	p-value	OR$_{adj}$	95% CIs	p-value
Group of treatment (anakinra vs placebo)	0.34	0.24-0.48	<0.0001	0.35	0.25-0.48	<0.0001
Intake of dexamethasone (Yes/No)	1.72	1.15-2.59	0.009	1.42	0.47-4.20	0.53
Severe COVID-19 by WHO (Yes/No)	1.76	1.17-2.67	0.007	1.22	0.41-3.68	0.71
BMI >30 kg/m^2 (Yes/No)	1.16	0.84-1.59	0.36	1.11	0.80-1.53	0.43
Country (Italy vs Greece)	1.05	0.65-1.71	0.82	1.15	0.70-1.88	0.58

Source: Table 14.2.1.6.
Abbreviations: BMI, Body mass index; CI, Confidence interval; COVID-19, Coronavirus disease 2019 ; OR, Odds ratio; OR$_{adj}$, Adjusted OR; PP, Per protocol; SoC, Standard-of-care; vs, Versus; WHO, World Health Organization.

Table 11-11   Sensitivity analysis 2: population receiving ≥7 doses of the study drug

| | Sensitivity analysis 2: population receiving ≥7 doses of the study drug (SoC+placebo=177; SoC+anakinra=382) | | | | | |
| | Univariate analysis | | | Multivariate analysis | | |
	OR	95% CIs	p-value	OR$_{adj}$	95% CIs	p-value
Group of treatment (anakinra vs placebo)	0.37	0.28-0.52	<0.0001	0.38	0.27-0.53	<0.0001
Intake of dexamethasone (Yes/No)	1.90	1.27-2.86	0.002	1.14	0.42-3.11	0.79
Severe COVID-19 by WHO (Yes/No)	2.03	1.36-3.05	0.001	1.70	0.63-4.58	0.29
BMI >30 kg/m^2 (Yes/No)	1.19	0.88-1.64	0.26	1.11	0.80-1.53	0.51
Country (Italy vs Greece)	1.21	0.74-1.99	0.44	1.26	0.75-2.10	0.38

Source: Table 14.2.1.6.
Abbreviations: BMI, Body mass index; CI, Confidence interval; COVID-19, Coronavirus disease 2019; OR, Odds ratio; OR$_{adj}$, Adjusted OR; SoC, Standard-of-care; vs, Versus; WHO, World Health Organization.

Table 11-12   Sensitivity analysis 3: complete case analysis

| | Sensitivity analysis 3: complete case analysis (SoC+placebo=188; SoC+anakinra=405) | | | | | |
| | Univariate analysis | | | Multivariate analysis | | |
	OR	95% CIs	p-value	OR$_{adj}$	95% CIs	p-value
Group of treatment (anakinra vs placebo)	0.35	0.26-0.49	<0.0001	0.36	0.26-0.49	<0.0001
Intake of dexamethasone (Yes/No)	1.91	1.28-2.84	0.001	1.51	0.59-2.83	0.39
Severe COVID-19 by WHO (Yes/No)	1.96	1.32-2.92	0.001	1.29	0.51-3.27	0.59
BMI >30 kg/m^2 (Yes/No)	1.19	0.89-1.63	0.24	1.12	0.82-1.52	0.49
Country (Italy vs Greece)	1.21	0.75-1.95	0.43	1.27	0.78-2.08	0.32

Source: Table 14.2.1.6.
Abbreviations: BMI, Body mass index; CI, Confidence interval; COVID-19, Coronavirus disease 2019; OR, Odds ratio; OR$_{adj}$, Adjusted OR; SoC, Standard-of-care; vs, Versus; WHO, World Health Organization.

Table 11-13   Sensitivity analysis 4: responder analysis treating missing values as failures

	Sensitivity analysis 4: responder analysis treating missing values as failures (SoC + placebo=189; SoC + anakinra=405)					
	Univariate analysis			Multivariate analysis		
	OR	95% CIs	p-value	OR$_{adj}$	95% CIs	p-value
Group of treatment (anakinra vs placebo)	0.35	0.25-0.48	<0.0001	0.36	0.26-0.49	<0.0001
Intake of dexamethasone (Yes/No)	1.92	1.29-2.85	0.001	1.49	0.59-3.79	0.39
Severe COVID-19 by WHO (Yes/No)	1.97	1.32-2.93	0.001	1.30	0.52-3.28	0.57
BMI >30 kg/m² (Yes/No)	1.21	0.89-1.65	0.21	1.14	0.83-1.55	0.42
Country (Italy vs Greece)	1.15	0.72-1.84	0.55	1.21	0.74-1.96	0.44

Source: Table 14.2.1.6.
Abbreviations: BMI, Body mass index; CI, Confidence interval; COVID-19, Coronavirus disease 2019; CPS, Clinical progression scale; OR, Odds ratio; OR$_{adj}$, Adjusted OR; SoC, Standard-of-care; vs, Versus; WHO, World Health Organization.
Failure is defined as patients with a WHO-CPS of 10.

Table 11-14   Sensitivity analysis 5: comparison of the unadjusted and the adjusted model

	Unadjusted		Adjusted		
	OR	95% CI	OR	95% CIs	p-value
Group of treatment (anakinra vs placebo)	0.36	0.26-0.49	0.36	0.25-0.50	0.54

Source: Table 14.2.1.6.
Abbreviations: CI, Confidence interval; OR, Odds ratio; vs, Versus.

CHMP comments

Five sensitivity analyses of the primary endpoint were carried out. The first four sensitivity analyses were univariate and multivariate ordinal regression analyses of the primary study outcome (WHO-CPS) at Day 28 in e.g. the PP population.

The first four sensitivity analysis on the primary endpoint were beneficial to anakinra and supported the primary endpoint. The fifth sensitivity analysis shows the impact on the estimated treatment effect when adjusting for stratifying factors.

No new data submitted in the final CSR.

8.3. Secondary efficacy endpoints

Analyses of the secondary efficacy endpoints up to Day 28 (as previously reported in the iCSR) generally showed a significant benefit from anakinra+SoC treatment compared to placebo+SoC treatment (SAVE-MORE CSR, Table 11-15):

Table 11-15   Secondary efficacy endpoints - FAS population

	SoC + placebo	SoC + anakinra	Unadjusted OR[a] (95% CIs)	p-value	Adjusted OR[a] (95% CIs)	p-value
Absolute decrease of WHO-CPS at Day 28 from baseline Day 1, median (IQR)	3 (2.5) N=189	4 (2.0) N=405	0.40 (0.29-0.55)	<0.0001	0.40 (0.29-0.55)	<0.0001
Relative% decrease of WHO-CPS at Day 28 from baseline Day 1, median (IQR)	60 (60) N=189	100 (40) N=405	0.37 (0.26-0.50)	<0.0001	0.37 (0.27-0.51)	<0.0001
Absolute decrease of WHO-CPS at Day 14 from baseline Day 1, median (IQR)	2 (3.0) N=189	3 (2.0) N=405	0.63 (0.46-0.85)	0.003	0.63 (0.46-0.86)	0.003
Relative% decrease of WHO-CPS at Day 14 from baseline Day 1, median (IQR)	50 (60) N=189	60 (55) N=405	0.59 (0.43-0.80)	0.001	0.59 (0.43-0.81)	0.001
Absolute decrease of SOFA score at Day 14 from baseline Day 1, median (IQR)	0 (3) N=66	1 (3) N=120	0.65 (0.38-1.09)	0.107	0.67 (0.39-1.15)	0.150
Relative% decrease of SOFA score at Day 14 from baseline Day 1, median (IQR)	0 (104.2) N=66	25 (94.8) N=120	0.59 (0.35-0.99)	0.049	0.59 (0.35-1.02)	0.061
Absolute decrease of SOFA score at Day 7 from baseline Day 1, median (IQR)	0 (1) N= 184	1 (2) N=392	0.63 (0.46-0.86)	0.004	0.64 (0.47-0.88)	0.007
Relative% decrease of SOFA score at Day 7 from baseline Day 1, median (IQR)	0 (50) N=184	33.3 (50) N=392	0.62 (0.46-0.85)	0.003	0.64 (0.47-0.89)	0.003

Source: Modified from Table 14.2.2.1, Table 14.2.2.2, Table 14.2.2.3, Table 14.2.2.4, Table 14.2.2.5, Table 14.2.2.6, Table 14.2.2.7, Table 14.2.2.8, and Table 14.2.2.9
Abbreviations: CI, Confidence interval; IQR, Interquartile range; FAS, Full analysis set; N, Number of patients analyzed in each group; OR, Odds ratio; SoC, Standard-of-care; SOFA, Sequential organ failure assessment; WHO-CPS, World Health Organization-Clinical Progression Scale.
[a] Ordinal regression analysis.

- The absolute decrease of the 11-point WHO-CPS score from baseline by Day 28 was significantly greater in the anakinra+SoC group compared to placebo+SoC group (adjusted OR: 0.40; 95% CI: 0.29 to 0.55; p<0.0001).

- The absolute decrease of the 11-point WHO-CPS score from baseline by Day 14 was significantly greater in the anakinra+SoC group compared to placebo+SoC group (adjusted OR: 0.63; 95% CI: 0.46 to 0.86; p=0.003).

- The change from baseline in the absolute SOFA score by Day 14 was not statistically significant for the comparison between the anakinra+SoC and placebo+SoC groups (adjusted OR: 0.67; 95% CI: 0.39 to 1.15; p=0.150).

- The decrease of the absolute SOFA score from baseline by Day 7 was significantly greater in the anakinra+SoC group compared to placebo+SoC group (adjusted OR: 0.64; 95% CI: 0.47 to 0.88; p=0.007).

- By Day 90, anakinra reduced the time to hospital discharge (i.e., 1 day shorter in patients treated with anakinra+SoC compared to placebo+SoC) (adjusted HR: 1.26; 95% CI: 0.05 to 1.52; p=0.013; SAVE MORE CSR, Table 11-25). Anakinra also reduced the time to discharge from the ICU by Day 90 (i.e., 7.5 days shorter in patients treated with anakinra+SoC compared to placebo+SoC) (unadjusted HR: 2.31; 95% CI: 1.08 to 4.93; p=0.031; SAVE-MORE CSR, Figure 11-16). Outcomes related to the effect of anakinra treatment on biomarkers were previously reported in the iCSR; see SAVE-MORE CSR, Section 11.1.2.7 for details.

CHMP comments

Analyses of the secondary efficacy endpoints up to Day 28 were previously reported in the iCSR. The results are in favour of anakinra+SoC treatment. In the final CSR, a table with also adjusted OR's have been included (Table 11-15).

The decrease of the WHO-CPS score from baseline to Days 14 and 28 were significantly greater in the anakinra+SoC arm compared to the placebo+SoC arm, and the absolute and relative changes of the WHO-CPS at day 14 from baseline Day1, results are also in favour of anakinra. The absolute and relative changes of the SOFA score at day 7 from baseline Day1 were greater in the anakinra arm as compared to the SoC arm, but not significant by day 14.

Analysis of time to hospital discharge by Day 90 was included in the final CSR showing that Anakinra reduced the time to discharge from the ICU by Day 90 (7.5 days shorter in patients treated with anakinra+SoC compared to placebo+SoC) (unadjusted HR: 2.31; 95% CI: 1.08 to 4.93; p=0.031)

Outcomes related to the effect of anakinra treatment on biomarkers were previously reported in the iCSR.

8.4. *Other efficacy endpoints up to Day 90*

The ordinal regression analysis showed that anakinra treatment reduced the odds for higher scores on the 11-point WHO-CPS at Days 60 and 90 from baseline Day 1 compared to placebo (Day 60 adjusted OR: 0.40, 95% CI: 0.28 to 0.58, p<0.0001; Day 90 adjusted OR: 0.50, 95% CI: 0.34 to 0.74, p=0.001) (SAVE-MORE CSR, Table 11-42 and Table 11-44, respectively). Subgroup analyses including CCI ≥2 vs <2, suPAR >9 ng/mL vs ≤9 ng/mL, sex, age ≥65 years vs <65 years, baseline remdesivir use, dexamethasone use, baseline disease severity and the need for oxygen, and BMI category were performed on the primary endpoint. These analyses demonstrated that patients benefited from anakinra treatment regardless of subgroup category.

Table 11-42   Absolute changes of the WHO-CPS at Day 60 from baseline Day 1

	Univariate analysis			Multivariate analysis		
	OR	95% CIs	p-value	OR$_{adj}$	95% CIs	p-value
Group of treatment (anakinra vs placebo)	0.41	0.29-0.59	<0.0001	0.40	0.28-0.58	<0.0001
Intake of dexamethasone (Yes/No)	2.73	1.61-4.60	0.0001	3.78	1.14-12.58	0.030
Severe COVID-19 by WHO (Yes/No)	2.47	1.49-4.10	0.0004	0.75	0.23-2.41	0.630
BMI >30 kg/m^2 (Yes/No)	1.37	0.97-1.93	0.072	1.20	0.84-1.72	0.302
Country (Italy vs Greece)	2.73	1.42-5.23	0.003	3.18	1.63-6.22	0.001

Source: Table 14.2.3.4
Abbreviations: BMI, Body mass index; CI, Confidence interval; COVID-19, Coronavirus disease 2019; CPS, Clinical Progression Scale; OR, Odds ratio; OR$_{adj}$, Adjusted OR; WHO, World Health Organization.

Table 11-44   Absolute changes of the WHO-CPS Day 90 from baseline Day 1

	Univariate analysis			Multivariate analysis		
	OR	95% CIs	p-value	OR$_{adj}$	95% CIs	p-value
Group of treatment (anakinra vs placebo)	0.50	0.33-0.73	0.0003	0.50	0.34-0.74	0.001
Intake of dexamethasone (Yes/No)	2.90	1.55-5.41	0.001	2.97	0.72-12.20	0.131
Severe COVID-19 by WHO (Yes/No)	2.70	1.48-4.94	0.001	0.99	0.25-3.92	0.996
BMI >30 kg/m^2 (Yes/No)	1.33	0.91-1.96	0.131	1.20	0.82-1.77	0.343
Country (Italy vs Greece)	1.97	0.99-3.93	0.053	2.22	1.10-4.50	0.025

Source: Table 14.2.3.6
Abbreviations: BMI, Body mass index; CI, Confidence interval; COVID-19, Coronavirus disease 2019; CPS, Clinical Progression Scale; OR, Odds ratio; OR$_{adj}$, Adjusted OR; WHO, World Health Organization.

CHMP comments

In the final CSR data on absolute changes of the WHO-CPS scores by day 60 and day 90 from baseline Day 1 were submitted. An ordinal regression analysis showed that anakinra treatment was favourable in reducing the odds for higher scores on the 11-point WHO-CPS at Days 60 and 90 from baseline Day 1 (Day 60 adjusted OR: 0.40, 95% CI: 0.28 to 0.58, p<0.0001; Day 90 adjusted OR: 0.50, 95% CI: 0.34 to 0.74, p=0.001).

8.5. Discussion

CHMP discussion

The MAH has submitted the final CSR for the SAVE-MORE study (dated 07.02.22) fulfilling the post-authorisation measure according to procedure No. EMEA/H/C/000363/II/0086 for extension of indication of Kineret. The database lock for SAVE-MORE occurred on August 18, 2021 (last patient last visit 28th June 2021) and is based on data collected until Day 90 (11-point WHO-CPS data, AE/SAE and study drug administration) for all patients. Efficacy (primary and secondary endpoints) were previously reported in the iCSR; the only updates to efficacy in the table below were time until discharge from the hospital and ICU by Day 90.

In the SAVE-MORE study the efficacy of Kineret had a beneficial effect in patients with COVID-19 pneumonia. The SAVE-MORE study met its primary endpoint and showed a reduction in the WHO-CPS score in patients treated with anakinra+SoC as compared to patients receiving SoC at Day 28. An effect was already present at Day 14.

A favourable effect of Kineret was also found in the secondary endpoints, however, as no hierarchy was predefined the results are not tested for multiplicity and effect estimated should be interpreted with caution. More patients fully recovered by Day 28 in the anakinra arm 50.5% vs 26.5 % in the placebo arm and the proportion of patients with severe outcome (WHO-CP score ≥ 6) was higher in the placebo arm than in the anakinra arm.

	Unadjusted		Adjusted		
	OR	95 % CI	OR	95 % CIs	P-value
Group of treatment (anakinra vs placebo)	0.36	0.26-0.49	0.36	0.25-0.50	1.06

Source: Table 14.2.1.6
Abbreviations: CI, Confidence interval; OR, Odds ratio.

Analyses of the secondary efficacy endpoints up to Day 28 were previously reported in the iCSR. The results are in favour of anakinra+SoC treatment. In the final CSR, a table with also adjusted OR's have

been included (Table 11-15).

The decrease of the WHO-CPS score from baseline to Days 14 and 28 were significantly greater in the anakinra+SoC arm compared to the placebo+SoC arm, and the absolute and relative changes of the WHO-CPS at day 14 from baseline Day1, results are also in favour of anakinra. The absolute and relative changes of the SOFA score at day 7 from baseline Day1 were greater in the anakinra arm as compared to the SoC arm, but not significant by day 14.

In the final CSR Subgroup analyses including CCI ≥2 vs <2, suPAR >9 ng/mL vs ≤9 ng/mL, sex, age ≥65 years vs <65 years, baseline remdesivir use, dexamethasone use, baseline disease severity and the need for oxygen, and BMI category were updated performed on the primary endpoint. Regardless of subgroup category anakinra treatment was beneficial.

In the final CSR data on absolute changes of the WHO-CPS scores by day 60 and day 90 from baseline Day 1 were submitted. An ordinal regression analysis showed that anakinra treatment was favourable in reducing the odds for higher scores on the 11-point WHO-CPS at Days 60 and 90 from baseline Day 1 (Day 60 adjusted OR: 0.40, 95% CI: 0.28 to 0.58, p<0.0001; Day 90 adjusted OR: 0.50, 95% CI: 0.34 to 0.74, p=0.001).

Overall the SAVE-MORE pivotal study still supports the clinical benefit of anakinra in adult COVID-19 patients with pneumonia who are at risk of developing severe respiratory failure based on suPAR ≥ 6 ng/ml. This includes a beneficial effect on time to progression to severe respiratory failure, on time until hospital discharge and on mortality, as compared to SoC treatment in the studied population.

9. Clinical Safety aspects

Safety data up to Day 90 are summarized below and provided in the final CSR (SAVE-MORE CSR, Section 12). **There were no new safety signals identified in the long-term safety data.**

9.1. Analysis of adverse events

Overall, the incidence of TEAEs through Day 90 was similar in patients in the anakinra+SoC group (343 patients, 84.7%) compared to the patients in the placebo+SoC group (161 patients, 85.2%) (SAVE-MORE CSR, Table 12-1).

Table 12-1   Overview of treatment-emergent adverse events (safety set)

	Number (%) of patients	
	SoC + placebo (n=189)	SoC + anakinra (n=405)
Patients with any TEAE	161 (85.2)	343 (84.7)
Patients with any treatment-related TEAEs	64 (33.9)	121 (29.9)
Patients with any serious TEAE	41 (21.7)	66 (16.3)
Patients with any TEAE leading to study drug discontinuation	2 (1.1)	3 (0.7)
Patients with any serious TEAE leading to death	17 (9.0)	18 (4.4)

Source: Table 14.1.2, Table 14.3.1, Table 14.3.2.1, Table 14.3.2.2
Abbreviations: n, Number of patients, SoC, Standard-of-care; TEAE, Treatment-emergent adverse event.

The TEAEs occurring more frequently in the anakinra+SoC group compared to the placebo+SoC group were transaminases increased, hypothermia, hypernatraemia, and gamma-glutamyltransferase increased (SAVE-MORE CSR, Table 12-2). TEAEs reported in the majority of patients were suggestive

of advanced COVID-19 and its complications along with the worsening of patient's concurrent clinical conditions. The majority of TEAEs were considered mild (Grade 1) or moderate (Grade 2) in severity (SAVE-MORE CSR, Section 12.1.3). Overall, the Grade 3 severity TEAEs were very few and balanced between the 2 treatment groups.

Table 12-2   Most common treatment-emergent adverse events occurring in >5% of patients in any treatment group (safety set)

	Number (%) of Patients	
	SoC + placebo (n=189)	SoC + anakinra (n=405)
At least one TEAE	161 (85.2)	343 (84.7)
Hyperglyceridemia	63 (33.4)	133 (22.4)
Hyperglycaemia	60 (31.7)	129 (31.9)
Transaminases increased	52 (27.5)	125 (30.8)
Anemia	37 (19.5)	58 (14.3)
Gamma-glutamyltransferase increased	22 (11.7)	56 (13.8)
International normalized ratio increased	32 (16.9)	47 (11.6)
Leukocytosis	20 (10.6)	39 (9.6)
Hypernatraemia	15 (7.9)	39 (9.6)
Sinus bradycardia	19 (10.1)	38 (9.4)
Constipation	14 (7.4)	37 (9.1)
Hyperkalaemia	14 (7.4)	37 (9.1)
Blood pressure increased	20 (10.6)	36 (8.9)
Hypocalcaemia	22 (11.6)	34 (8.4)
Fibrin D dimer increased	25 (13.2)	33 (8.1)
Anxiety	12 (6.3)	33 (8.1)
Hypoglycaemia	16 (8.5)	33 (8.1)
Lymphopenia	24 (11.7)	30 (7.4)
Hypothermia	8 (4.2)	30 (7.4)
Hyponatraemia	24 (12.7)	27 (6.7)
Acute kidney injury	10 (5.2)	26 (6.3)
Thrombocytosis	13 (6.9)	25 (6.2)
Pneumonia	18 (9.5)	22 (5.4)
Amylase increased	13 (6.9)	18 (4.4)
Bilirubin increased	11 (5.9)	17 (4.2)
Activated partial thromboplastin time increased	17 (9.0)	13 (3.2)
Hypokalaemia	10 (5.3)	11 (2.7)
Amylase increased	11 (5.8)	9 (2.2)

Source: Table 14.3.1
Abbreviations: n, Number of patients; SoC, Standard-of-care; TEAE, Treatment-emergent adverse event.
Note: MedDRA version 24.1.

The incidence of serious TEAEs through Day 90 was lower in patients in the anakinra+SoC group (16.3%) compared to the placebo+SoC group (21.7%) (SAVE-MORE CSR, Table 12-6). The most commonly reported serious TEAEs in both treatment groups were pneumonia, nosocomial infections,

bacteremia, and septic shock.

Table 12-6   Most common serious treatment-emergent adverse events (Safety set)

	Number (%) of patients	
	SoC + placebo (n=189)	SoC + anakinra (n=405)
At least one serious TEAE, n (%)	**41 (21.7)**	**66 (16.3)**
Type of serious TEAE, n (%)		
Infections and infestations	**31 (16.4)**	**37 (9.1)**
Bacteremia	6 (3.2)	11 (2.8)
Nosocomial infection	7 (3.7)	10 (2.2)
Pneumonia	16 (8.5)	14 (3.5)
Septic shock	7 (3.7)	6 (1.5)
Vascular disorders	**4 (2.1)**	**9 (2.2)**
Pulmonary embolism	4 (2.1)	6 (1.5)

Source: Table 14.3.2.2
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; n, Number of patients; SoC, Standard-of-care; TEAE, Treatment-emergent adverse event.
Note: MedDRA version 24.1.

A total of 35 (5.9%) patients in the study had an SAE with an outcome of death up to 90 days; 17 (9.0%) patients received placebo+SoC and 18 (4.4%) patients received anakinra+SoC (SAVE-MORE CSR, Table 12-5). Deaths were mostly attributed to the SOC Infections and infestations, either Pneumonia (COVID-19 or bacterial superinfection), Bacteremia, or Septic shock. The spectrum of fatal events was similar between anakinra and placebo treated patients.

Table 12-5   Serious treatment-emergent adverse events with an outcome of death by preferred term (Safety Set)

	Number (%) of patients	
	SoC + placebo (n=189)	SoC + anakinra (n=405)
Patients with TEAE with an outcome of death	**17 (9.0)**	**18 (4.4)**
Septic shock	7 (3.7)	6 (1.5)
Pneumonia	9 (4.7)	5 (1.2)
Bacteremia	2 (1.1)	4 (1.0)
Nosocomial infection	3 (1.6)	4 (1.0)
Pneumomediastinum	1 (0.5)	2 (0.5)
Pneumothorax	2 (1.1)	1 (0.2)
Acute kidney injury	0 (0)	2 (0.5)
Abdominal infection	0 (0)	1 (0.2)
Arterial thrombosis	0 (0)	1 (0.2)
Pyelonephritis acute	0 (0)	1 (0.2)
Thrombocytopaenia	1 (0.5)	0 (0)
Subcutaneous emphysema	1 (0.5)	0 (0)
Transaminases increased	1 (0.5)	0 (0)
Blood creatine phosphokinase increased	1 (0.5)	0 (0)
Cardiac arrest	1 (0.5)	0 (0)
Hypernatraemia	1 (0.5)	0 (0)
Lung empyema	1 (0.5)	0 (0)
Pulmonary embolism	1 (0.5)	0 (0)
Hemorrhagic diathesis	1 (0.5)	0 (0)
Candidemia	1 (0.5)	0 (0)

Source: Listing 16.2.7.2
Abbreviatons: n, Number of patients; SAE, Serious adverse event; SoC, Standard-of-care;
TEAE, Treatment-emergent adverse event.
Note: Death is part of the primary endpoint and as such, exempt from safety reporting as an SAE by itself.

Overall, 5 patients discontinued the treatment due to TEAEs (leukopenia and derangement of LFTs), 2 (1%) patients from the placebo+SoC group and 3 (0.7%) patients from the anakinra+SoC treatment group (SAVE-MORE CSR, Table 12-8). TEAEs reported in the majority of patients were suggestive of advanced COVID-19 and its complications along with the worsening of patient's concurrent clinical conditions. No new safety signals were observed in anakinra-treated patients. The TEAEs observed in patients with COVID-19 are consistent with the known safety profile of anakinra in other indications, especially considering the short treatment course of 10 days.

Table 12-8   Discontinuations due to leukopenia or increase of aminotransferases

	Decision taken by	Number (%) of patients	
		SoC + placebo (n=189)	SoC + anakinra (n= 405)
Premature stop of study drug due to leukopenia	Attending physicians	1 (0.5)	1 (0.2)
Premature stop of study drug due to increase of aminotransferases	Attending physicians	1 (0.5)	2 (0.5)

Source: Table 14.1.2
Abbreviation: n, Number of patients; SoC, Standard-of-care.

CHMP comments

Safety data up to day 90 was reported and assessed in responses to 3rd RSI. The FAS/Safety Analysis Set included 594 patients, of these, 189 patients in the placebo+SoC group and 405 patients in the anakinra+SoC group were included in

The incidence of TEAEs through Day 90 reported in the final CSR was similar in patients in the anakinra+SoC group (343 patients, 84.7%) compared to the patients in the placebo+SoC group (161 patients, 85.2%) (Table 12-1). This is a little higher than reported in responses to the 3rd RSI where 156 (82.5 %) patients treated with placebo + SoC and 335 (82.7 %) patients treated with anakinra + SoC experienced at least 1 TEAE.

In the final CSR the TEAEs occurring more frequently in the anakinra+SoC group compared to the placebo+SoC group were transaminases increased, hypothermia, hypernatraemia, and gamma-glutamyl transferase increased (SAVE-MORE CSR, Table 12-2).

The incidence of serious TEAEs through Day 90 was lower in patients in the anakinra+SoC group (16.3%) compared to the placebo+SoC group (21.7%) (Table 12-6). The most commonly reported serious TEAEs in both treatment groups were pneumonia, nosocomial infections, bacteremia, and septic shock. This is in alignment with earlier reported where 42 patients (22.2 %) treated with placebo + SoC and 66 patients (16.3 %) treated with anakinra + SoC experienced at least 1 serious TEAE. There is one patient less in the placebo+SoC group in the data submitted in the final CSR.

In the final CSR a total of 35 patients (5.9 %) in the study had an SAE with an outcome of death up to 90 days; 17 patients (9.0 %) received placebo + SoC and 18 patients (4.4 %) received anakinra + SoC as reported earlier. In total, 5 patients discontinued the treatment due to TEAEs (leukopenia and derangement of LFTs), 2 (1%) patients from the placebo+SoC group and 3 (0.7%) patients from the anakinra+SoC treatment group as reported earlier.

9.2. Adverse drug reactions

No new safety signals or safety concerns were observed for anakinra for the treatment of COVID-19. Following the 10-day dosing regimen of anakinra, the frequency and severity of the subset of ADRs observed, which included neutropenia, elevated hepatic enzymes, rash, and injection site reactions, were consistent with the known safety profile of anakinra in the licensed indications.

CHMP comments
No new data were provided

9.3. Clinical laboratory evaluations

In the SAVE-MORE study, laboratory measurements were collected during in-patient hospitalization and were not collected during the long-term safety portion of the study. Therefore, all data were previously reported in the iCSR. There were no clinically meaningful changes in clinical laboratory results related to anakinra treatment. Any concerns were attributed to the underlying COVID-19 or other comorbidities.

CHMP comments
No new data were provided

9.4. Discussion

CHMP comments
The MAH has submitted the final CSR for the SAVE-MORE study (dated 07.02.22) fulfilling the post-authorisation measure according to procedure No. EMEA/H/C/000363/II/0086 for extension of indication of Kineret. Safety data have been updated to include long-term results from the SAVE-MORE study up to Day 90. The database lock for SAVE-MORE occurred on August 18, 2021 (last patient last visit 28th June 2021) and is based on data collected until Day 90 (11-point WHO-CPS data, AE/SAE and study drug administration) for all patients. Day 90 data has been reported and assessed in the CHMP AR for procedure II/0086.   Safety data submitted in the final CSR are overall in alignment with safety data up to Day 90 that was earlier submitted and assessed in CHMP AR for procedure II/0086.   The safety profile remains favourable with no new safety signals identified apart from the TEAE hypothermia occurring more frequently in the anakinra+SoC group compared to the placebo+SoC group (7.4% vs. 4.2%) not reported earlier in the treatment of hospitalised adult patients with COVID-19 (OC). The frequency and severity of the subset of ADRs observed (neutropenia, elevated hepatic enzymes, rash, and injection site reactions), following the 10-day dosing regimen of anakinra, were consistent with the known safety profile of anakinra in the licensed indications. Overall the safety profile of Kineret for treatment of adult COVID-19 patients with pneumonia who are at risk of developing severe respiratory failure is positive with no major concerns. The overall occurrence of AEs, SAEs including infections discontinuations and deaths were fewer for Kineret treated patients compared to placebo in the pivotal SAVE-MORE study. The safety data are overall consistent with the known safety profile of Kineret for the approved indications, including infections, however, TEAEs occurring at a higher proportion for Kineret included the increase of liver aminotransferases, hypoglycaemia, hypothermia, electrolyte abnormalities (hypernatraemia, hyperkalaemia), constipation, nausea/vomiting, anxiety, rash, neutropenia, leukopenia and thrombocytopenia. Of these, the increase of liver function tests (hepatic enzyme increased), rash at the injection site (injection site reaction), neutropenia, and thrombocytopenia are already listed ADRs for Kineret, hypernatremia, constipation, hyperkalemia, and anxiety are not. Numbers were however small and it is acknowledged that some of the numerical imbalances in the given TEAEs can indeed reflect different manifestations of underlying disease.

10. PRAC advice

NA

11. Request for supplementary information

11.1. Major objections

Clinical aspects

None.

11.2. Other concerns

Clinical aspects

1. In the final CSR the number of patients that received dexamethasone during treatment has been revised. Revisions have been made to the clinical overview and summary of clinical efficacy. The percentage of patients receiving dexamethasone has been amended from 86,4% to 85.9%. The dexamethasone percentage in the SmPC (section 5.1) is also proposed to be revised in line with the final clinical study report. It is somewhat unclear whether the 0.5% difference is driven by 2 patients (0.5%) allocated to treatment with anakinra were by mistake entered in the database on the time of stratification as in need for dexamethasone intake. These patients in reality did not start dexamethasone. These patients were analysed as not under dexamethasone treatment. The applicant is invited to clarify this.

2. In the fifth sensitivity analysis, numbers given in table 11-14 are in alignment with the numbers given in table 14 in the CHMP AR, however the p-value is different. The MAH is invited to clarify this.

	Unadjusted		Adjusted		
	OR	95 % CI	OR	95 % CIs	P-value
Group of treatment (anakinra vs placebo)	0.36	0.26-0.49	0.36	0.25-0.50	1.06

Source: Table 14.2.1.6
Abbreviations: CI, Confidence interval; OR, Odds ratio.

3. In the final CSR the TEAEs occurring more frequently in the anakinra+SoC group compared to the placebo+SoC group were transaminases increased, hypothermia, hypernatraemia, and gamma-glutamyl transferase increased (SAVE-MORE CSR, Table 12-2). In responses to the 3rd RSI hypothermia (7.4% in the anakinra + SoC group vs. 4.2% in the placebo + Soc group) was not mentioned as a TEAE. The applicant is invited to discuss how hypothermia is defined and why hypothermia was not included in responses earlier.

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

12.1. Major objections

None

12.2. Other concerns

Clinical aspects

Question 1

In the final CSR the number of patients that received dexamethasone during treatment has been revised. Revisions have been made to the clinical overview and summary of clinical efficacy. The percentage of patients receiving dexamethasone has been amended from 86,4% to 85.9%. The dexamethasone percentage in the SmPC (section 5.1) is also proposed to be revised in line with the final clinical study report. It is somewhat unclear whether the 0.5% difference is driven by 2 patients (0.5%) allocated to treatment with anakinra were by mistake entered in the database on the time of stratification as in need for dexamethasone intake. These patients in reality did not start dexamethasone. These patients were analysed as not under dexamethasone treatment. The applicant is invited to clarify this.

Summary of the MAH's response

The MAH acknowledges this observation and that is the reason why MAH has submitted an amended SmPC with the right values, i.e., 85.9%. There was a miscalculation in the original report for the group "Dexamethasone over follow-up due to progression" and the corrected total is 24 patients and not 26 (8+16=24, not 26). Table 1 below is an extract from the interim table 14.1.1 "Baseline characteristics of enrolled patients" showing the mistake.

In the final report, table 14.1.1, the correction for the above patient numbers and the baseline subgroups of dexamethasone corresponding to receiving within Day 1 was applied, see Table 2 below. Accordingly, the groups "Dexamethasone at enrollment" and "Dexamethasone over follow-up due to progression" were merged and the total was corrected to be 510 (486+24; not: 486+26 as previously reported), which is 85.9%. The rationale to merge these 2 groups was because all these 510 patients were receiving dexamethasone on Day 1, no patients started dexamethasone after Day 1, thus the terminology originally chosen was not appropriate.

The MAH would like to provide more information regarding the difference between the dexamethasone subgroup including all 510 patients and the 486 patients included in the dexamethasone strata. All analysis of the dexamethasone subgroup included all 510 patients. However, only 486 had received it before the point of randomisation, therefore only those 486 are included in the dexamethasone strata, as it was a stratification factor. Those patients who started dexamethasone on the same day as treatment (but soon after treatment), i.e., the N=24, are not in the dexamethasone strata. All the analyses were adjusted for dexamethasone using the strata numbers.

The 2-patient difference in this revision is not related to those who were allocated to treatment with anakinra and entered in the database at the time of stratification as in need for dexamethasone by mistake. These 2 patients were always correctly reported and analysed as non-dexamethasone.

Table 1　　　　　**Baseline characteristics of enrolled patients – Extract from interim CSR showing the mistake of 26 while it should have been 24 (16 + 8).**

	SoC + Placebo (N=189)	SoC + Anakinra (N=405)	All patients (N=594)
Co-administered medications, n (%)			
Remdesivir	133 (70.4)	294 (72.6)	427 (71.9)
Dexamethasone at enrollment	160 (84.7)	326 (80.5)	486 (81.8)
Dexamethasone over follow-up due to progression from moderate to severe disease	8 (4.2)	16 (4.4)	26 (4.4)

Source: Table 14.1.1 in the interim CSR

Table 2　　　　　**Baseline characteristics of enrolled patients – Extract from final CSR**

	SoC + Placebo (N=189)	SoC + Anakinra (N=405)	All patients (N=594)
Co-administered medications, n (%)			
Remdesivir	141 (74.6)	298 (73.6)	439 (73.9)
Dexamethasone	168 (88.9)	342 (84.4)	510 (85.9)

showing corrected numbers and merged Dexamethasone groups

Source: Table 14.1.1 in the final CSR Version 2, 07 February 2022

Assessment of the MAH's response

The MAH has provided an explanation for the The percentage of patients receiving dexamethasone has been amended from 86,4% to 85.9%. It was a miscalculation for 2 patients in the original report. The 2-patient difference in this revision is not related to those who were allocated to treatment with anakinra and entered in the database at the time of stratification as in need for dexamethasone by mistake. These 2 patients were always correctly reported and analysed as non-dexamethasone. The table with baseline characteristics has been revised accordingly.

In addition, the MAH has revised section 5.1 in the SmPC to include the correct number 85.9%. The MAH has moved the sentence to a more appropriate place in the section on *Clinical efficacy and safety in COVID-19.* This is acceptable.

Conclusion Issue resolved

Question 2

In the fifth sensitivity analysis, numbers given in table 11-14 are in alignment with the numbers given in table 14 in the CHMP AR, however the p-value is different. The MAH is invited to clarify this.

	Unadjusted		Adjusted		
	OR	95 % CI	OR	95 % CIs	P-value
Group of treatment (anakinra vs placebo)	0.36	0.26-0.49	0.36	0.25-0.50	1.06

Source: Table 14.2.1.6
Abbreviations: CI, Confidence interval; OR, Odds ratio.

Summary of the MAH's response

The MAH would like to thank you for this observation. The MAH confirms that the correct p-value is 0.54 as is listed in Table 11-14 of the final CSR.

Assessment of the MAH's response

The MAH has confirmed that the correct p-value is 0.54.

Conclusion Issue resolved

Question 3

In the final CSR the TEAEs occurring more frequently in the anakinra+SoC group compared to the placebo+SoC group were transaminases increased, hypothermia, hypernatraemia, and gamma-glutamyl transferase increased (SAVE-MORE CSR, Table 12-2). In responses to the 3rd RSI hypothermia (7.4% in the anakinra + SoC group vs. 4.2% in the placebo + Soc group) was not mentioned as a TEAE. The applicant is invited to discuss how hypothermia is defined and why hypothermia was not included in responses earlier.

Summary of the MAH's response

The MAH acknowledges this observation and is confirming that these events were included in the listings in the interim CSR but were omitted by mistake in the interim version of the TEAEs table and in the responses to the 3rd RSI. This was corrected and they were added in the final TEAEs table (7.4% in the anakinra + SoC group vs. 4.2% in the placebo + SoC group).

Hypothermia was determined by the reporting investigators. The definition of hypothermia was not the reason for the omission in the interim version of the TEAEs table.

All hypothermia events were assessed as non-serious and not related by the investigators.

Assessment of the MAH's response

Hypothermia was determined by the reporting investigators. The MAH has amended the final TEAEs table with hypothermia. All events were non-serious and assessed by the investigator as not related

Conclusion Issue resolved

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

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

13. Attachments

1. Product Information (changes highlighted) as adopted by the CHMP on 10 June 2022