16 December 2021
EMA/772497/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kineret

International non-proprietary name: anakinra

Procedure No. EMEA/H/C/000363/II/0086

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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List of abbreviations

ACC	American College of Cardiology
ADRs	Adverse drug reactions
AE	Adverse event
AKI	Acute kidney injury
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AOSD	Adult-onset Still's disease
aPPV	Airway pressure release ventilation
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical (classification system)
BMI	Body mass index
CAPS	Cryopyrin-associated periodic syndrome
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
COVID-ETF	COVID-19 EMA pandemic Task Force
CRP	C-reactive protein
CSR	Clinical study report
DAMP	Danger-associated molecular pattern
DLP	Data lock point
DME	Designated medical event
DIRA	Deficiency of IL-1 receptor antagonist
ECDC	European Centre for Disease Prevention and Control
ECMO	Extracorporeal membrane oxygenation
EEA	European Economic Area
EMA	European Medicines Agency
ETF	EMA pandemic Task Force
EU	European Union
FAS	Full Analysis Set
FMF	Familial Mediterranean fever

HAP	Hospital-acquired pneumonia
HR	Hazard ratio
HFO	High-flow oxygen
ICU	Intensive care unit
IL-1	Interleukin-1
IL-1α	Interleukin-1 alpha
IL-1β	Interleukin-1 beta
IL-1RI	Interleukin-1 receptor type I
IL-1Ra	Interleukin-1 receptor antagonist
IL-6	Interleukin-6
i.v.	Intravenous
IVDR	In Vitro Diagnostic Medical Devices Regulation
IVIG	Intravenous immunoglobulin
LOCF	Last Observation Carried Forward
LDH	Lactate dehydrogenase
LRTI	Lower respiratory tract infection
MedDRA	Medical Dictionary for Regulatory Activities
MOFS	Multiple organ failure syndrome
MV	Mechanical ventilation
NIV	Non-invasive ventilation
NOMID	Neonatal-onset multisystem inflammatory disease
NPV	Negative pressure ventilator
OR	Odds ratio
PBMCs	Peripheral blood mononuclear cells
PK	Pharmacokinetic
PP	Per-Protocol
PRES	Posterior reversible encephalopathy syndrome
PT	Preferred term
q.d.	Once daily
Q1	1st quarter
Q3	3rd quarter
RA	Rheumatoid arthritis
RCT	Randomized controlled trial

RECOVERY	Randomized Evaluation of COVID-19 Therapy
REMAP-CAP	Randomised, Embedded, Multi-factorial, Adaptive Platform trial for Community-Acquired Pneumonia
ROC	Receiver operating characteristic
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
s.c.	Subcutaneous
SD	Standard deviation
SJIA	Systemic juvenile idiopathic arthritis
Sobi	Swedish Orphan Biovitrum AB
SoC	Standard of care
SOFA	Sequential organ failure assessment
SRF	Severe respiratory failure
suPAR	Soluble urokinase plasminogen activator receptor
TEAE	Treatment-emergent adverse event
UK	United Kingdom
uPAR	Urokinase plasminogen activator receptor
US	United States
VAP	Ventilator-associated pneumonia
WBC	White blood cells
WHO	World Health Organization
WHO-CPS	World Health Organization-Clinical Progression Scale

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Swedish Orphan Biovitrum AB (publ) submitted to the European Medicines Agency on 8 July 2021 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

C.I.6 - Extension of indication to include treatment of coronavirus disease 2019 (COVID-19) in adult patients with pneumonia who are at risk of developing severe respiratory failure for Kineret; as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 5.6 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Thalia Marie Blicher Co-Rapporteur: Fátima Ventura

Timetable	Actual dates
Submission date:	8 July 2021
Start of procedure:	17 July 2021
CHMP Rapporteur Assessment Report:	10 September 2021
PRAC Rapporteur Assessment Report:	17 September 2021
CHMP Co-Rapporteur Critique:	22 September 2021
PRAC Outcome:	30 September 2021
CHMP members comments:	04 October 2021
Updated CHMP Rapporteurs Joint Assessment Report:	07 October 2021
ETF meeting:	07 October 2021
CHMP Request for supplementary information (RSI):	14 October 2021
MAH's responses submitted to the CHMP on:	16 November 2021
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:	22 November 2021
PRAC members comments:	24 November 2021
Updated PRAC Rapporteur's Assessment Report on the MAH's responses circulated on:	25 November 2021
CHMP Rapporteur's Preliminary Assessment Report on the MAH's responses circulated on:	01 December 2021
PRAC Outcome:	02 December 2021
CHMP members comments:	06 December 2021
Updated CHMP Rapporteur's Assessment Report on the MAH's responses circulated on:	09 December 2021
ETF meeting:	09 December 2021
CHMP Opinion:	16 December 2021

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Coronaviruses (CoV) are positive-stranded ribonucleic acid viruses, named for the crown-like appearance of their spike glycoproteins on the virus envelope. They are a large family of viruses that cause illness ranging from the common cold to more severe diseases such as Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome (SARS-CoV).

In December 2019, pneumonia of unknown cause was identified in clusters of patients in the city of Wuhan, China. A novel enveloped RNA betacoronavirus – severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) – was identified in these patients, and the disease caused by SARS-CoV-2 infection was later designated as coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO) (WHO, 2020) (Zhu, 2020).

Most patients with mild cases of disease recover with symptomatic treatment and supportive care. However, approximately 15% of COVID-19 pneumonia patients with more severe illness frequently require hospitalization (WHO 2020). Approximately 5% of infected patients experience complications related to a severe form of interstitial pneumonia, which may progress to acute respiratory distress syndrome (ARDS) and/or multi-organ failure and death (WHO 2020).

Millions of SARS-CoV-2 infections have been confirmed worldwide, and the rapidly spreading, worldwide outbreak has prompted the WHO to declare COVID-19 a pandemic and public health emergency of international concern.

The indication initially sought as part of this application was:

COVID-19
Kineret is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adult patients with pneumonia who are at risk of developing severe respiratory failure (see section 5.1).

Epidemiology and risk factors

As of June 22, 2021, more than 178 million cases of COVID-19 have been reported globally, including more than 3.8 million deaths. In the EU/EEA, over the month of April 2021, reported hospital and intensive care unit-admission rates for COVID-19 were approximately 175 000 and 25 000, respectively. The majority of patients with COVID-19 have little or no symptoms. Risk factors for more severe COVID-19 infections are among others advanced age and certain underlying medical co-morbidities (e.g. cardiovascular diseases, chronic respiratory diseases, obesity and immune compromised status).

Aetiology and pathogenesis

Coronaviruses (CoV) are enveloped RNA viruses and are important human and animal pathogens. Two coronaviruses have previously been identified as zoonotic infections which have adapted to humans and caused severe respiratory illnesses with high fatality: Severe Acute Respiratory Syndrome coronavirus 1 (SARS-CoV-1) and Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV). SARS-CoV-2 spike glycoprotein (S protein) is a class I transmembrane envelope protein that forms a homo-trimer and mediates binding, fusion, and viral entry into host cells. The S protein is essential for virus infectivity and is the main target of the humoral immune response, as demonstrated by serology analysis of recovered COVID-19 patients (Long, 2020). The S protein mediates binding to the host receptor angiotensin converting enzyme 2 (ACE2), resulting in membrane fusion and entry of the virus into susceptible cells (Hoffmann, 2020).

Transmission of SARS-CoV-2 occurs primarily through person-to-person contact and respiratory droplet transmission (Lai, 2020) (Lewis, 2020). A high background rate of lateral transmission has been observed in households with a documented SARS-CoV-2 infected individual quarantining alongside other household members (Madewell, 2020). Compared to other betacoronavirus infections, the incubation period of SARS-CoV-2 infection (i.e., time before symptoms occur) has features that complicate the control of virus transmission: the period is highly variable (range 2 to 14 days) and it is often characterized by high viral loads and viral shedding (Ellington, 2020).

Clinical presentation and diagnosis

COVID-19 can be classified into 3 clinical stages. In stage 1, an estimated 80 % to 84 % of infected patients are slightly symptomatic. In stage 2a, patients have a non-hypoxemic pneumonia but can advance to a hypoxemic pneumonia in stage 2b or acute respiratory distress syndrome (ARDS) in stage 3 (8, 9). After ~9 to 10 days, 17 % to 20 % of patients can evolve toward more severe stages 2b or 3, with increasing requirement for oxygen necessitating admission into an ICU with non-invasive or invasive MV (8, 9). At the more severe stages of COVID-19, mortality is reaching 60 % (10, 11), and SRF from ARDS is the leading cause of death (12). By preventing the progression from LRTI and pneumonia to ARDS and SRF, the prognosis for patients with COVID-19 would be improved, lives would be saved, and the burden on global healthcare systems during the pandemic would be reduced.

Several commercial detection assays for SARS-CoV-2 RNA or antigen and serological assays for SARS-CoV-2 specific antibodies are available on the market.

Management

Prevention of infection by SARS-CoV-2 and clinical management of the disease are the 2 main strategies to fight the COVID-19 pandemic. Prevention with vaccines is expected to decrease the infection rate; however, emergent SARS-CoV-2 variants may constitute a threat, and the duration of protection following immunization is still unclear. Because of these uncertainties, an effective clinical management of the disease to reduce COVID-19 morbidity and mortality is of great importance. Since the beginning of the COVID-19 pandemic, immunomodulators were suggested as one of the main strategies to attenuate the exaggerated immune response of the host. Currently, a few medicinal products have been approved for the treatment of COVID-19 addressing different targets and various steps in the severity of the disease. Those are presented briefly below.

Velkury (remdesivir, RDV), a broad spectrum anti-viral, was granted conditional approval by the EMA on 25 June 2020 and is indicated for use in adults and adolescents (from 12 years of age and weighing at least 40 kilograms) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at the start of treatment).

Regkirona (regdanvimab) is an antiviral, a recombinant human IgG1 monoclonal antibody that binds to the receptor binding domain (RBD) of the spike(s) protein of SARS-CoV-2 consequently blocking cellular entry and SARS-CoV-2 infection. It has been granted a marketing authorisation on 12/11/2021 for the treatment of adults with coronavirus disease 2019 (COVID-19) who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.

Ronapreve (casirivimab / imdevimab) is a human IgG1 mAbs that bind simultaneously to the S protein receptor binding domain (RBD) and block its interaction with the host receptor, angiotensin-converting enzyme 2 (ACE2). It has been granted a marketing authorisation on 12/11/2021 for the treatment of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19 and the prevention of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg.

RoActemra (is an immunomodulating medicine (a medicine that changes the immune system activity). The active substance in RoActemra, tocilizumab, is a monoclonal antibody, a type of protein designed to attach to a specific target (called an antigen) in the body. It has been authorised for the treatment of adults with COVID-19 who are receiving systemic treatment with corticosteroids and require supplemental oxygen or mechanical ventilation.

EMA's human medicines committee (CHMP) has issued advice (Article 5(3) procedure) on the use of Lagevrio (also known as molnupiravir or MK 4482) for the treatment of COVID-19 on 19/11/2021. The medicine, which is currently not authorised in the EU, can be used to treat adults with COVID-19 who do not require supplemental oxygen and who are at increased risk of developing severe COVID-19. Lagevrio should be administered as soon as possible after diagnosis of COVID-19 and within 5 days of the start of symptoms. The medicine, which is available as capsules, should be taken twice a day for 5 days.

Systemic corticosteroids were not routinely recommended until emerging data from clinical trials, including the RECOVERY trial dexamethasone cohort (Horby et al. 2021), indicated a mortality benefit among patients requiring supplemental oxygen or mechanical ventilation. The EMA issued recommendations on the use of dexamethasone in COVID-19 patients on oxygen or mechanical ventilation (art 5(3) procedure 18 September 2020).

Several other therapeutics are currently under evaluation in Europe.

2.1.2. About the product

Kineret (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. Kineret has a short plasma half-life (4 to 6 hours) and is administered as a daily s.c. injection. The product is supplied as a 100 mg/0.67 mL solution in a single-use, prefilled syringe for s.c. injection.

In the EU, Kineret is currently approved for the treatment of rheumatoid arthritis (RA), all forms of cryopyrin-associated periodic syndromes (CAPS), for Still's disease (including systemic juvenile idiopathic arthritis (SJIA) and adult-onset Still's disease (AOSD)). Kineret is also approved for familial Mediterranean fever (FMF).

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The MAH did not seek formal CHMP scientific advice (SA) for this procedure. However, EMA COVID-ETF SA was initially sought by the principal investigator on the protocol design of the pivotal phase 3 SAVE-MORE study supporting this extension of indication following which the protocol was amended. In addition, EMA COVID-ETF written advice was provided on the draft SAP for the SAVE-MORE study, and the SAP was thereafter amended according to the obtained feedback.

2.1.4. General comments on compliance with GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Anakinra (trade name Kineret) is a human interleukin-1 receptor antagonist (r-metHuIL-1Ra) produced

in an E. coli expression system by recombinant DNA technology. Anakinra is a 153 amino acid polypeptide with a molecular mass of 17.3 kilodaltons, and almost identical to the naturally occurring, non-glycosylated form of human IL-1Ra. Therefore, the MAH submitted a justification for not submitting ERA studies for anakinra, based on the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use EMEA/CHMP/SWP/4447/00 Rev1.

2.2.2. Discussion and conclusion on the non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP. The justification provided by the MAH for not submitting an ERA is considered to be acceptable based on the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use EMEA/CHMP/SWP/4447/00 Rev1.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

- Tabular overview of clinical studies

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/ enrollment closed	suPAR-guided Anakinra Treatment for Validation of the Risk and Early Management of Severe Respiratory Failure by COVID-19	Pivotal, prospective, interventional, multicenter, double-blind, randomized, placebo-controlled	Arm 1: placebo+SoC. Placebo injected s.c. q.d for 10 days Arm 2: anakinra+SoC Anakinra injected s.c as 100 mg q.d for 10 days	600 patients planned in 1:2 randomization; 606 enrolled Arm 1: 194 Arm 2: 412	Males and females ≥18 years of age hospitalized[a] with confirmed infection by SARS-CoV-2 virus, LRTI (radiologically confirmed), and plasma suPAR levels ≥6 ng/mL
SAVE/ Greece/ 2020-001466-11/ ongoing The 1st 130 patients enrolled and compared to a propensity-matched control group was recently published[b]	suPAR-guided Anakinra Treatment for Validation of the Risk and Early Management of Severe Respiratory Failure by COVID-19	Open-label, single-arm, prospective, interventional	Anakinra+SoC Anakinra injected s.c as 100 mg q.d for 10 days	Target: 1000 patients 1st period (April to September 2020): 130, anakinra+SoC; 130, matched SoC (outside SAVE study) Second period (October-December 2020): 525, anakinra+SoC; 117, matched SoC (outside SAVE study)	Males and females ≥18 years of age hospitalized[a] with confirmed infection by SARS-CoV-2 virus, LRTI (radiologically confirmed), and plasma suPAR levels ≥6 ng/mL

Abbreviations: COVID-19, Coronavirus disease 2019; ECMO, Extracorporeal membrane oxygenation; ICU, Intensive care unit; LRTI, Lower respiratory tract infection; MV, Mechanical ventilation; NIV, Noninvasive ventilation; 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.
[a]Patients were excluded if they are in an ICU under MV, NIV, or ECMO.
[b]Kyriazopoulou et al. 2021 (24)

2.3.2. Pharmacokinetics

No PK data were generated in the SAVE and SAVE-MORE studies (i.e., no quantification of anakinra). Further, anakinra was administered at the same dose (i.e. 100 mg) as for the other approved indications (e.g., rheumatoid arthritis, RA) in the EU; therefore, there were no proposed changes to the product information in the clinical pharmacology section.

The PK profile of anakinra has been previously assessed in other patient populations (i.e. RA and Still's disease) characterised by hyper-inflammation associated with elevated cytokines levels close to levels observed in severe COVID-19.

With regards to interactions, treatment with anakinra might upregulate CYP450 enzymes that are suppressed by increased levels of cytokines. This is expected to be a problem for concomitant treatment with medicinal products that have a narrow therapeutic interval, however this is not considered to be the case for remdesivir which is co-administered with anakinra in some patients. Remdesivir is an inhibitor of CYP3A4, OATP1B1 and OATP1B3 *in vitro* and an inducer of CYP1A2 and potentially CYP3A *in vitro*. However, as anakinra is excreted renally, remdesivir is not considered to affect the exposure to anakinra during co-administration.

The dosing in patients with renal impairment is extrapolated from previous studies with anakinra and in other patient populations.

2.3.3. Pharmacodynamics

Mechanism of action

Anakinra neutralises the biologic activity of interleukin 1α (IL 1α) and interleukin 1β (IL 1β) by competitively inhibiting their binding to interleukin 1 type I receptor (IL RI). Interleukin 1 (IL 1) is a pivotal pro-inflammatory cytokine mediating many cellular responses including those important in synovial inflammation.

Primary pharmacology

Severe COVID-19 is associated with high levels of circulating pro-inflammatory cytokines.

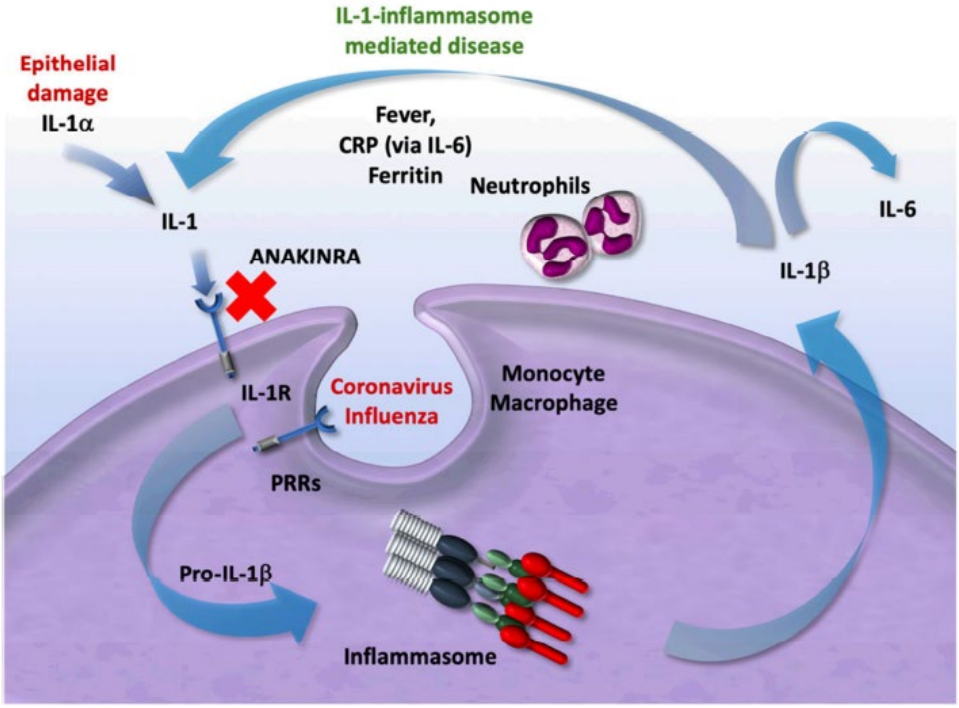
IL-1α is constitutively synthesized as a precursor protein and is stored in epithelial cells, whereas monocytes and macrophages rely on de novo synthesis. The precursor form of IL-1α acts as a Danger-associated molecular pattern (DAMP) molecule when released from cells undergoing pyroptosis. Pyroptosis is an inflammatory form of programmed cell death that is commonly observed with cytopathic viruses. DAMPs and IL-1α stimulate production of IL-1β from monocytes and macrophages.

Both IL-1α and IL-1β possess strong pro-inflammatory effects, and elevated levels of IL-1β have been reported during SARS-CoV-2 infection[1]. SARS-CoV-2 rapidly replicates in the epithelial cells of the lungs; cells are destroyed and release DAMPs, among which IL-1α plays a major role. It has been suggested that the progression from LRTI to SRF in COVID-19 depends on the early release of IL-1α from virally infected lung epithelial cells, which in turn stimulates further cytokine production including IL-1β from alveolar macrophages[2][3][4].

The pathophysiology of SARS-CoV-2 infection and the rationale for use of anakinra is shown below:

[1] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
[2] van de Veerdonk FL, Netea MG. Blocking IL-1 to prevent respiratory failure in COVID-19. Crit Care. 2020;24(1):445.
[3] Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol. 2020;20(6):363-374.
[4] Giamarellos-Bourboulis EJ, Netea MG, Rovina N, Akinosoglou K, Antoniadou A, Antonakos N, et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. Cell Host Microbe. 2020;27(6):992-1000.

Figure 1 Events during SARS-CoV-2 infection and the rationale for use of anakinra



Abbreviations: CRP, C-reactive protein; IL-1, Interleukin-1; IL-1α, Interleukin-1 alpha; IL-1β, Interleukin-1 beta; IL-1R, Interleukin-1 receptor; IL-6, Interleukin-6; PRRs, Pattern recognition receptors; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2.
The SARS-Cov-2 will cause epithelial damage leading to the release of IL-1α that will (1) recruit neutrophils and monocytes to the site of infection and (2) induce IL-1β in monocyte/macrophages. Moreover, the SARS-Cov-2 will induce pro-IL-1β in monocyte/macrophages, which in turn will induce more IL-1 that will recruit and activate more innate immune cells. This autoinflammatory loop where IL-1 (IL-1α and IL-1β) can induce production and release of more IL-1 has to be tightly regulated because an ongoing loop will activate and recruit more innate immune cells independent of the initial trigger. Anakinra blocks the IL-1R and thus will prevent autoinflammation by blocking effects of IL-1α released from dead epithelial cells, as well as IL-1β produced by immune cells. IL-1-induced IL-6 will also be blocked. The autoinflammatory loop can exacerbate from increase innate immune response into uncontrolled MAS a spectrum that associates with increasing ferritin levels.

The rationale for treating patients at risk of progressing to severe COVID-19 with anakinra, is the pathophysiology of SARS-CoV-2 infection where epithelial damage leads to an autoinflammatory loop involving IL-1α and IL-1β release and recruitment of innate immune cells. Anakinra is a recombinant human IL-1 receptor antagonist that competes with IL-1α and IL-1β on the binding sites, blocking the biological activity of IL-1α and IL-1β, and thereby preventing tissue damage. It has been suggested that the progression from lower respiratory tract infection (LRTI) to severe respiratory failure (SRF) in COVID-19 depends on the early release of IL-1α from virally infected lung epithelial cells, which in turn stimulates further cytokine production including IL-1β from alveolar macrophages. Anakinra blocks the biological activity of both IL-1α and IL-1β and has a therapeutic effect in many inflammatory diseases including RA, CAPS, Still's disease, and FMF, as well as in hyperinflammatory disorders. Considering the above information about COVID-19 immunopathology and anakinra mechanism of action, the MAH considered that a positive effect of anakinra in COVID-19 could be expected. The MAH also presented data from a preclinical study using mice challenged with human plasma either from healthy volunteers or from COVID-19 patients that supports the above described rationale.

The risk of progression to SRF in COVID-19 patients was determined by blood levels of a soluble urokinase plasminogen activator receptor (suPAR) of at least 6 ng per ml.

Soluble urokinase plasminogen activator receptor (suPAR):

suPAR is the soluble counterpart of the uPAR receptor, which is anchored in the cell membrane of neutrophils and endothelial cells and is cleaved after the activation of the kalikrein system. Early suPAR increase is an indicator of the release of DAMPs like calprotectin (Renieris et al. 2021, Rodrigues et al. 2021). Calprotectin stimulates the aberrant production of IL-1β by the circulating monocytes of patients with COVID-19 pneumonia (Rodrigues et al. 2021). In an animal model of COVID-19, it was shown that knock-out of another DAMP, namely IL-1α, was protective for the host (Renieris et al. 2021). These observations framed the hypothesis that early increase of suPAR may guide targeted therapeutics against IL-1α and IL-1β in COVID-19 patients. Therefore, in order to identify patients that would benefit from treatment with anakinra, the suPAR biomarker with cut-off ≥ 6 ng/ml was used as an inclusion criterion in the clinical studies (SAVE and SAVE-MORE) submitted to support this extension of indication in COVID-19. No other biomarker was initially considered in the enrichment of the population.

According to the MAH, suPAR can be quickly measured with the CE-marked suPARnostic assays (ViroGates) using lateral-flow quick tests. The assay (suPARnostic Quick Triage kit) used for both SAVE-MORE and SAVE studies met all the essential requirements of Council Directive 98/79/EC as stated in the declaration of conformity submitted as part of this application. All assays for this test have been validated to ensure consistent measurements across the various platforms. Upon request from the CHMP, the MAH confirmed that the manufacturer of suPARnostic run validation programs for all 3 different assays according to Clinical and Laboratory Standards Institute standards to ensure that they all fulfil requirements of repeatability and consistency as also required under the currently applicable Council Directive 98/79/EC for in vitro diagnostic medical devices.

According to the MAH, suPAR was selected as an inclusion criterion based on studies showing that suPAR levels at hospital admission were associated with a risk of progressing into hyperinflammation and SRF in the context of COVID-19 pneumonia. These studies are briefly referenced below. In most of the studies presented, the ROC AUC was numerically higher for suPAR than for other biomarkers. It should be noticed that the cut-off values for suPAR and the patient populations differed between studies. Furthermore, the outcome in the prediction studies was not solely respiratory failure.

- suPAR was initially proposed as a predictor of progression to SRF in COVID-19 by *Rovina et al 2020*. Specifically, the authors reported that plasma suPAR levels ≥6 ng/mL at the time of hospital admission predicted progression to SRF (pO_2/FiO_2 <150 mm Hg requiring MV or continuous positive airway pressure) within 14 days in a cohort of 57 patients hospitalized with COVID-19 pneumonia, with airway pressure release ventilation (aPPV) of 86% and an negative pressure ventilator (NPV) of 92%.
- In a prospective cohort of 187 patients admitted to hospital with COVID-19, suPAR and IL-6 were found to be the blood biomarkers with the best performance to predict a 28-day composite outcome of non-invasive ventilation, intensive care admission, or death *(Arnold et al 2021)*. Simple clinical features alone such as age performed nearly as well as suPAR and IL-6. A cut-off of suPAR of 5.2 ng/ml was used. AUC ROC was 0.81, and the sensitivity and specificity were 0.82 and 0.65, respectively. The AUC for age was 0.70, and the sensitivity and specificity were 0.95 and 0.41, respectively.
- In a prospective cohort of 403 patients hospitalized for COVID-19, the admission levels of plasma suPAR were found to have prognostic utility in predicting severe complications. The incidence of the primary endpoint, a composite outcome for the development of severe complications (including acute respiratory distress syndrome, ICU admission, or death from any cause), was 11.5% (95% CI:6.7to 16.3) in patients with suPAR levels >3.91ng/mL

compared to 2.9% (95% CI:0.4to 5.5) in those with suPAR ≤3.91ng/mL. A competing risk analysis showed that for every increase of 1ng/mL in suPAR level at baseline, there is a corresponding increase of 58% in the hazard of experiencing COVID-19 complications (HR:1.6, 95% CI:1.2 to 2.1, P=0.003). suPAR was significantly associated with incidence of severe COVID-19 complications *(Oulhaj et al 2021)*.

- *Napolitano et al 2021* published a single-center, prospective cohort study of 104 patients hospitalized for COVID-19 and proposed suPAR as a serum biomarker of clinical severity and outcome with a better performance compared to both IL-6 and CRP with the aim to optimize hospital resources. In patients with mild disease, suPAR levels were increased as compared to healthy controls, but they were dramatically higher in severely ill patients. suPAR levels were analyzed in a cohort of severe cases of COVID-19 on the first day of admission in ICU; the cohort showed a significant increase of suPAR levels (3870±1854 pg/mL) as compared to healthy controls (1680 ± 567 pg/mL) and patients with a mild form of COVID-19 (2836 ± 1102 pg/mL). The data suggested that suPAR strongly correlated with the severity of the disease. The non-survivor group had higher levels of serum suPAR (4523 ± 1976 pg/mL). The ROC analysis indicated that the AUCs are much greater for serum suPAR (0.704; P<0.006) than for IL-6 (0.662; P<0.03).
- In a large observational cohort study of 959 patients hospitalized for COVID-19, the prognostic value of suPAR in identifying patients with COVID-19 at risk of progressing to SRF was observed *(ISIC cohort; Meloche et al 2021)*. In a multivariate analysis of severe inflammatory biomarkers, suPAR, IL-6, LDH, and procalcitonin were independently associated with the combined outcome of death/need for MV/dialysis; the AUC in predicting the outcome was the highest for suPAR (0.798, 95% CI: 0.749 to 0.830), followed by procalcitonin (0.750, 95%CI:0.712to 0.784), LDH (0.714, 95% CI: 0.675to 0.749), and IL-6 (0.674, 95%CI:0.624to 0.719).

suPAR has also been investigated in other research projects, where it has been associated with morbidity and mortality in a number of acute and chronic diseases, and as such was considered, by the MAH, to be a prognostic marker of an inflammatory response and not a diagnostic marker for either COVID-19 or other diseases.

The justification to use a suPAR cut-off of 6 ng/ml or more was based on available published evidence as well as on the conducted phase 2 SAVE study.

As the suPAR test might not yet be broadly available in the EU, the MAH proposed to use an alternative score (i.e. the SCOPE score) using other biomarkers of inflammation that are well established. This is presented below.

SCOPE score

suPAR is a biomarker of early deterioration of patients which integrates information on 3 different functions (i.e. inflammatory cascade activation, coagulation, and endothelial-neutrophil interaction). These three functions are up-regulated in COVID-19, which explains why using biomarkers that only carry information for one of the functions cannot provide the integrated information as suPAR does. Moreover, the MAH considered that as the three functions are not equally affected in all COVID-19 patients at the same time point; a set of biomarkers (SCOPE score) integrating the elements of all these three functions, could be used instead in the absence of suPAR. Therefore, in order to investigate more easily accessible biomarkers that would allow to identify COVID-19 patients that might benefit from treatment with anakinra, the use of the SCOPE score was proposed by the MAH. This score includes a combination of biomarkers of inflammation, coagulopathy and endothelial activation (CRP, ferritin, D-dimers, and IL-6) that have been measured in many of the patients involved in the SAVE-

MORE study and that, according to the MAH, could be used to obtain similar prognostic information as suPAR.

Data on the SAVE-MORE population screened for inclusion (both patients with suPAR < 6 and suPAR ≥ 6 ng / mL) was used to validate the proposed SCOPE score. Based on quartiles of CRP, ferritin, D-dimers, and IL-6; each patient was assigned a score for each biomarker of 0, 1, 2 or 3 and a combined score between 0 and 12. The risk of progressing to SRF based on the new score was assessed by the MAH, and it was concluded that a score of 6 or more was associated with the same hazard of progression to SRF as suPAR ≥ 6 ng/ml. This was further elucidated by similar ROC curves.

Both SCOPE and suPAR demonstrated a good performance in differentiating patients that have a higher probability of SRF or death. Nevertheless, the correlation between the suPAR and the SCOPE scores was further explored in the SAVE-MORE study upon request from the CHMP and a Spearman correlation of 0.39 was found. Further, in the current population that was studied, the two biomarkers/scores (suPAR and SCOPE) had only an overlap of 63% (404/639) of the included patients. In the SAVE study, in which an external validation was performed, the results were similar. Therefore, the SCOPE score does not identify the same patients at risk for progression to SRF as the suPAR does. The CHMP ultimately considered that this new screening tool (SCOPE score) was not a valid tool and thus cannot be used in the absence of suPAR to identify COVID-19 patients with pneumonia at risk of progressing to SRF. Upon request from the CHMP, the reference to SCOPE score initially included in SmPC section 5.1 was removed by the MAH.

Overall, the proposed use of suPAR with cut-off ≥ 6 ng/ml to identify patients at risk of progressing to SRF was adequately justified by the MAH. Taking into account that a clinically relevant and statistically significant efficacy was demonstrated in those specific patients, the CHMP considered that the indication should be restricted to patients with suPAR ≥ 6 ng/ml in the absence of robust justification and clinical evidence supporting a broader indication (i.e. regardless of suPAR determination). Relevant information on the suPAR biomarker, including the specific test used as part of the studies, were introduced in SmPC sections 4.1, 4.2, 4.4 and 5.1. See discussion on clinical efficacy.

Considering the decisive role of suPAR for the identification of patients that are suitable for treatment with anakinra in COVID-19, the MAH should ensure that an appropriate and validated test that reliably allows the distinction between patients with suPAR < 6 ng/ml and patients with suPAR ≥ 6 ng/ml is available for all European patients. Such test should be adequately CE-marked as a companion diagnostic under the In Vitro Diagnostic Medical Device Regulation framework.

Proposed dose

The recommended dose of Kineret is 100 mg administered once a day by subcutaneous injection for 10 days.

2.3.4. PK/PD modelling

Not applicable.

2.3.5. Discussion on clinical pharmacology

No PK data were generated in the supportive phase 2 SAVE and single pivotal phase 3 SAVE-MORE studies, and no interaction studies were performed. The lack of PK data and interaction studies is overall considered acceptable by the CHMP, as it was already assessed as part of other approved indications and is not considered to be different in the newly proposed indication.

The recommended dose of Kineret is 100 mg administered once a day by subcutaneous injection for 10 days in adult patients with COVID-19 pneumonia. Upon request from the CHMP, the MAH clarified that the phase 2 SAVE study was considered as a dose finding study and together with data available for other anakinra indications was sufficient to inform the choice of the proposed dose. The data gathered from the SAVE study are accepted to support the 10 days treatment schedule which differs from the other anakinra indications (e.g. RA).

With regards to interactions, treatment with anakinra might upregulate CYP450 enzymes that are suppressed by increased levels of cytokines (e.g. in patients with COVID-19). This is expected to be a problem for concomitant treatment with medicinal products that have a narrow therapeutic interval, however this is not considered to be the case for remdesivir which is co-administered with anakinra in some patients. Remdesivir is an inhibitor of CYP3A4, OATP1B1 and OATP1B3 *in vitro* and an inducer of CYP1A2 and potentially CYP3A *in vitro*. However, as anakinra is excreted renally, remdesivir is not considered to affect the exposure to anakinra during co-administration.

Kineret is eliminated by glomerular filtration and subsequent tubular metabolism. As stated in the current SmPC for anakinra, dosing should be every other day in patients with severe renal impairment (CLcr < 30 ml/min) or end stage renal disease. Upon request from the CHMP, the MAH clarified the information regarding renal impairment was extrapolated from previous studies with anakinra and in other patient populations, which is considered reasonable. In line with other approved indications, a dosing adaptation should apply only to patients with severe renal impairment or end stage renal disease at the time of anakinra treatment start due to COVID-19.

In order to identify patients that would most benefit from treatment with anakinra in COVID-19 pneumonia, suPAR, a biomarker of inflammation, was used in the inclusion criteria to select patients with risk of an unfavourable outcome of the COVID-19 infection. A suPAR level equal to or above 6 ng/ml was required for COVID-19 patients to be included in both SAVE and SAVE-MORE studies. suPAR has been proposed as a prognostic marker of disease severity, not only in COVID-19 patients but also in acute medical patients. suPAR levels in healthy individuals are 2-3 ng/ml and may increase to 9-10 ng/ml in critically ill patients. The hypothesis formulated by the MAH was that early treatment with anakinra guided by the suPAR biomarker may prevent progression to SRF in patients with COVID-19 pneumonia. In addition, it was suggested that plasma concentrations of suPAR ≥6 ng/mL was an early predictor of SRF in those patients. Upon request from the CHMP, the MAH provided further evidence supporting the elevation of suPAR as a reliable prognostic marker for the development of complications in patients with COVID-19 pneumonia who are not yet critically ill. Further, it was considered that in routine clinical practice and in clinical studies, blood biomarkers at the point of hospital admission have limited ability, in isolation, to predict poor outcomes from COVID-19, whilst some of the biomarkers of immune or inflammatory response activation, such as suPAR, were shown to have the best prognostic performance when used alongside clinical information *(Arnold et al 2021)*. According to the MAH, suPAR levels are an indicator of a broad immune and inflammatory activation pathways and is believed to be detected earlier in the disease course and therefore identify a window of opportunity for intervention with anakinra in patients with COVID-19 pneumonia. The MAH also clarified that at the time the SAVE-MORE study was designed, the suPAR cut-off of ≥6 ng/ml was chosen based on the phase 2 SAVE study results and available published evidence. Subsequent evidence cumulated from prospective studies confirmed, according to the MAH, that suPAR is a reliable biomarker for early prognosis of risk for progressing to SRF in COVID-19. This is supported by CHMP.

In addition, the MAH's proposal to initially replace the use of suPAR ≥6 ng/mL with the SCOPE score in the absence of suPAR test was not endorsed by CHMP as suPAR and SCOPE did not identify the same population of patients at risk of progressing to SRF in COVID-19 pneumonia and efficacy was only demonstrated in patients with suPAR ≥6 ng/ml. Therefore, only suPAR with cut-off of ≥6 ng/ml is

considered to be able to identify patients that may benefit from treatment with anakinra in COVID-19. See discussion on clinical efficacy for further information on restriction of indication to COVID-19 patients with suPAR level ≥6 ng/ml.

Considering the decisive role of suPAR for the identification of patients that are suitable for treatment with anakinra in COVID-19 pneumonia, the MAH should ensure that an appropriate and validated test that reliably allows the distinction between patients with suPAR < 6 ng/ml and patients with suPAR ≥ 6 ng/ml is available for all European patients. Such test should be adequately CE-marked as a companion diagnostic under the In Vitro Diagnostic Medical Device Regulation framework.

2.3.6. Conclusions on clinical pharmacology

Overall, similar PK profile and similar drug-drug interaction is expected for anakinra in patients with COVID-19 pneumonia as in other patient populations previously investigated. The absence of PK data and interaction studies in patients with COVID-19 is considered acceptable by the CHMP.

Evidence from SAVE-MORE and SAVE studies as well as from other published studies were provided to support the validity of the biomarker suPAR ≥ 6 ng/ml in predicting an adverse outcome (i.e. SRF) in patients with COVID-19 pneumonia.

In conclusion, based on the data submitted, the CHMP endorsed the proposed dosing regimen for treatment of COVID-19: a 100 mg dose administered once a day by subcutaneous injection for 10 days.

2.4. Clinical efficacy

The MAH submitted one pivotal study in support of the proposed indication and posology in COVID-19: the SAVE-MORE study, which is a pivotal, confirmatory, prospective, multicenter, double-blind, randomized, placebo-controlled study in hospitalized patients with confirmed infection with SARS-CoV-2, LRTI and plasma suPAR levels ≥6 ng/ml. In support of the SAVE-MORE study, the MAH also submitted results from the ongoing open label single arm, prospective phase 2 SAVE study. In addition, the MAH provided references to other clinical studies in which anakinra has been used for the treatment of COVID-19, as requested by the CHMP.

The database lock for the SAVE-MORE study occurred on August 18, 2021 and the final CSR is planned for completion in December 2021. The MAH committed to submit the final CSR as part of a type II variation by end of December 2021. In addition, the CHMP recommended the MAH to provide the final CSR of the phase 2 SAVE study, once available.

The therapeutic indication initially proposed by the MAH was as follows:

Kineret is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adult patients with pneumonia who are at risk of developing severe respiratory failure (see section 5.1).

The final therapeutic indication granted by the CHMP was restricted as follows:

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).

The indication is further discussed in the below discussion on clinical efficacy section.

The recommended dose of Kineret in adult patients with COVID-19 is 100 mg administered once a day by subcutaneous injection for 10 days.

2.4.1. Dose response study

No dose response studies were performed in subjects with COVID-19, which is considered acceptable by the CHMP.

The dose proposed by the MAH (i.e. 100 mg q.d. administered s.c. for 10 days) was chosen based on the results of the proof-of-concept phase 2 SAVE study. This daily dose is similar to the dose described in the SmPC of anakinra for other currently approved indications (e.g. RA).

2.4.2. Main study

SAVE-MORE: suPAR-guided Anakinra Treatment for Validation of the Risk and Early Management of Severe Respiratory Failure by COVID-19

Methods

This was a pivotal, confirmatory, phase 3 RCT to evaluate the efficacy and safety of anakinra guided by suPAR in patients with LRTI by SARS-CoV-2 in improving the clinical state of COVID-19 over 28 days as measured by the ordinal scale of the 11-point WHO-CPS.

Study participants

The sponsor for this study was the Hellenic Institute for the Study of Sepsis (HISS). The study was conducted at 37 study sites (29 in Greece and 8 in Italy).

Overall, the study included subjects who were hospitalised with confirmed SARS-CoV-2, had lower respiratory tract infection (LRTI) based on chest X-ray or in chest computed tomography and a suPAR level $\geq$ 6 ng/ml.

Inclusion criteria

Patients who met all the following inclusion criteria were included in the study:

- Age equal to or above 18 years.
- Male or female gender.
- In case of women, unwillingness to remain pregnant during the study period.
- Written informed consent provided by the patient. For patients without decision-making capacity, informed consent was obtained from a legally designated representative following the national legislation in the Member State where the study was planned.
- Confirmed infection by SARS-CoV-2 virus.
- Findings in chest X-ray or in chest computed tomography compatible with LRTI.
- Need for hospitalization for COVID-19. The need for hospitalization was defined by the attending physician, taking into consideration clinical presentation, requirement for supportive

care, potential risk factors for severe disease, and conditions at home, including the presence of vulnerable persons in the household.

- Plasma suPAR ≥6 ng/mL.

Exclusion criteria

Patients were excluded from participating in the study, if any of the following criteria were met:

- Age below 18 years.
- Denial for written informed consent.
- Any stage IV malignancy.
- Any do not resuscitate decision.
- Any pO_2/FiO_2 ratio less than 150 mmHg, irrespective if the patient was under MV/NIV/ECMO or not.
- Patient was under MV or NIV or ECMO.
- Any primary immunodeficiency.
- <1500 neutrophils/mm3.
- Plasma suPAR <6 ng/mL.
- Known hypersensitivity to anakinra.
- Oral or i.v. intake of corticosteroids at a daily dose ≥0.4 mg/kg prednisone for a period greater than the last 15 days.
- Any anti-cytokine biological treatment in the last 1 month.
- Severe hepatic failure, defined as Child-Pugh stage 3.
- End-stage renal failure necessitating hemofiltration or peritoneal hemodialysis.
- Pregnancy or lactation. Women of child-bearing potential were screened by a urine pregnancy test before inclusion in the study.
- Participation in any other interventional study.

Treatments

Patients were randomly assigned to one of the two treatment groups below:

- Treatment Arm 1: patients received placebo+SoC. Placebo (0.67 mL of 0.9 % NaCl) was injected s.c. once daily for 10 days.
- Treatment Arm 2: patients received anakinra+SoC. Anakinra was injected s.c. as 100 mg once daily for 10 days.

The medicinal product was administered on the same time ±2 hours every day. In case the patient was discharged (sent home) alive before the completion of 10 days of treatment, treatment was stopped prematurely. It was explicitly stated that the minimum number of days of treatment was 7.

Standard-of-care (SoC)

The SoC options were decided by taking the following into consideration: the current algorithm for the management of COVID-19 by the WHO; the current algorithm for the management of COVID-19 by the NIH; and the WHO suggestion for remdesivir.

The SoC for patients enrolled in the SAVE-MORE study included the following:

For patients not in need of oxygen support with moderate illness.

- Regular monitoring of vital signs, including pulse oximetry.
- Anticoagulant prophylaxis was as follows: Patients who were receiving anticoagulant or antiplatelet therapies for other underlying conditions had to continue these medications. For the other patients, pharmacological prophylaxis, such as low molecular weight heparin, should be used according to local standards to prevent venous thromboembolism, when not contraindicated.
- Remdesivir treatment was reserved at the discretion of the treating physicians.

For patients in need of oxygen support with severe illness.

• Immediate implementation of oxygen support.

• Application of positioning and airway clearance management, as needed, per the discretion of the treating physicians.

• Regular monitoring of vital signs, including pulse oximetry.

• Regular monitoring for signs or symptoms suggestive of venous or arterial thromboembolism, such as stroke, deep venous thrombosis, pulmonary embolism, or acute coronary syndrome. Further diagnosis (e.g., laboratory tests and/or imaging) and management was done according to hospital protocols.

• Cautious treatment with i.v. fluids.

• Dexamethasone 6 mg i.v. or orally for up to 10 days or until hospital discharge, whichever came first.

• Anticoagulant prophylaxis was as follows: Patients who were receiving anticoagulant or antiplatelet therapies for other underlying conditions had to continue these medications. For the other patients, pharmacological prophylaxis, such as low molecular weight heparin to be used according to local standards to prevent venous thromboembolism, when not contraindicated.

• Remdesivir treatment was reserved at the discretion of the treating physicians.

There were protocol deviations in a considerable number of patients, with higher frequency in the placebo arm and mainly regarding the corticosteroid regimen used. It is not expected that these deviations have affected the effect of anakinra substantially.

The MAH stated that the recruitment period was only three months and that there were no relevant changes in SOC or temporal trends in the prescription of remdesivir as SOC. The MAH also provided univariate and multivariate analyses for the primary endpoint including treatment with remdesivir as a covariate. The data provided did not support any modification of anakinra effect by remdesivir use.

Objectives

Primary objective:

To evaluate the efficacy of early start of anakinra guided by suPAR in patients with LRTI by SARS-CoV-2 in improving the clinical state of COVID-19 over 28 days as measured by the ordinal scale of the 11-point WHO-CPS.

Secondary objectives:

-Clinical efficacy of anakinra treatment guided by suPAR in patients with LRTI by SARS-CoV-2. This was assessed by i) the changes of the ordinal scale of the 11-point WHO-CPS at Days 14 and 28 from baseline Day 1; ii) the changes of the SOFA score at Days 7 and 14 from baseline Day 1; iii) the duration of hospital and ICU stay; and iv) 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 in patients with LRTI by SARS-CoV-2. This was assessed by the changes over time in CRP, IL-6, suPAR, ferritin, D-dimers, viral load, blood transcriptomics, and plasma proteomics.
-Safety of anakinra in COVID-19. This was assessed by Day 28 and was further followed up long-term (Days 60 and 90).

Outcomes/endpoints

Primary endpoint

For clinical research, common outcome measures of COVID-19 were developed by the WHO, the International Forum for Acute Care Trialists, and the International Severe Acute Respiratory and Emerging Infections Consortium to serve as a minimum set of outcome measures for studies on COVID-19. Investigators in the clinical research community have been urged, by the WHO Working Group, to include these common outcome measures in ongoing and future COVID-19 studies.

Therefore, the primary study outcome for the SAVE-MORE study was the comparative 11-point WHO-CPS (see Table below) between the two arms of treatment by Day 28. This was expressed as the distribution of the frequencies of each score of the scale in each arm of treatment by Day 28. The primary endpoint was changed as agreed with EMA COVID-19 ETF from a dichotomic assessment on respiratory failure to the 11 point WHO-CPS scale.

The primary endpoint that was originally proposed and agreed with EMA COVID-ETF was the comparative incidence of SRF between the two arms of treatment by day 14 as measured by the 11-point WHO CPS scale. Patients dying before study visit of day 14 are considered achieving the primary endpoint. SRF was defined as clinical progression into hypoxemia with pO2/FiO2 <150 mmHg necessitating MV or NIV or ECMO.

Table 1 The WHO Clinical Progression Scale

Patient state	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalized; moderate disease	Hospitalized; no oxygen needed	4
	Hospitalized; oxygen by mask or nasal prongs	5
Hospitalized; severe disease	Hospitalized; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation pO_2/FiO_2 ≥150 or SpO_2/FiO_2 ≥200	7
	Mechanical ventilation pO_2/FiO_2 <150 (SpO_2/FiO_2 <200) or vasopressors	8
	Mechanical ventilation pO_2/FiO_2 <150 and vasopressors, dialysis or ECMO	9
Dead	Dead	10

Abbreviations: ECMO, Extracorporeal membrane oxygenation; FiO_2, Fraction of inspired oxygen; NIV, Noninvasive ventilation; pO_2, Partial oxygen pressure; RNA, Ribonucleic acid; SpO_2, Oxygen saturation.

Secondary endpoints

Several secondary and exploratory efficacy and safety endpoints to support the primary endpoint were included (see below). In addition to the 11-point of WHO-CPS score, the SOFA (sequential organ failure assessment) score has also been evaluated. The SOFA score can be used to evaluate organ dysfunction in sepsis. Also, time to discharge, long-term safety by 60 and 90 days, changes in circulating biomarkers and viral load were evaluated. Mortality was not included as an endpoint. However, a post-hoc survival analysis has been conducted by the MAH.

The secondary outcomes included the comparison of the following between the 2 arms of treatment:

• Change of the measure of the 11-point WHO-CPS by Day 28 from baseline Day 1 (both absolute and relative changes).

• Change of the measure of the 11-point WHO-CPS by Day 14 from baseline Day 1 (both absolute and relative changes).

• Change of the SOFA score* by Day 14 from baseline Day 1 (both absolute and relative changes) for patients who remained hospitalized by that day.

• Change of the SOFA score by Day 7 from baseline Day 1 (both absolute and relative changes) for patients who remained hospitalized by that day.

• Time until discharge from hospital.

• Time until discharge from the intensive care unit (This was applicable only for patients who were admitted in the ICU).

• Safety by Day 28.

• Long-term safety by Day 60.

• Long-term safety by Day 90.

• Relative changes of circulating concentrations of suPAR, CRP, D-dimers, ferritin, and IL-6 by Day 7 from baseline Day 1.

• Relative changes of circulating concentrations of suPAR, CRP, D-dimers, ferritin, and IL-6 by Day 4 from baseline Day 1.

• Change of the viral load by Day 7 from baseline Day 1 (both absolute and relative changes).

• Change of the viral load by Day 4 from baseline Day 1 (both absolute and relative changes).

• Transcriptomic analysis that also allowed for lymphocyte cell subset analysis.

• Proteomic analyses.

• Relation of endpoints to duration of disease (from first symptoms) and timing of treatment initiation.

In addition, there are supportive comparative analyses to the primary endpoint based on the following:

- Being fully resolved (WHO CPS = 0) at day 28.
- Having severe disease (WHO CPS > 5) at day 28.
- Event of SRF during trial.

*The SOFA score is based on the 6 variables as mentioned in the table below. Each variable is scored between 0 and 4 points, and the SOFA score is the sum of the score of each variable.

Table 2 The SOFA score

Variable	0 points	1 point	2 points	3 points	4 points
pO_2/FiO_2(mmHg)	≥400	<400	<300	<200	<100
Platelets (per mm^3)	≥150	<150	<100	<50	<20
Hypotension	MAP≥ 70mmHg	MAP<70mmHg	Dobutamine whatever dose	Adrenaline ≤0.1* or Noradrenaline ≤0.1*	Adrenaline >0.1* or Noradrenaline >0.1*
Glasgow Coma Scale	15	13-14	10-12	6-9	<6
Bilirubin (mg/dL)	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	≥12
Creatinine (mg/dL) or Urine output	<1.2	1.2-1.9	2.0-3.4	35-4.9 or <500mL/day	≥5.0 or <200mL/day

Abbreviations: FiO_2, Fraction of inspired oxygen; MAP, Mean arterial pressure; pO_2, Partial oxygen pressure; SOFA, Sequential organ failure assessment.
* µg/kg/min

Exploratory outcome

The exploratory outcomes of the study included the comparison of the following between the 2 arms of treatment:

• The cost of hospitalization.

• The 11-point WHO-CPS by Day 60; this was expressed as the distribution of the frequencies of each score of the scale in each arm of treatment by Day 60.

• The 11-point WHO-CPS by Day 90; this was expressed as the distribution of the frequencies of each score of the scale in each arm of treatment by Day 90.

• The over-time curve of the measures of the 11-point WHO-CPS between Days 1 and 14.

Sample size

The calculation of the sample size was based on the results of the phase II study (SAVE). According to this calculation:

• The distribution of the frequencies of the main categories of the WHO CPS of SOC comparators of the SAVE study by Day 28 was: 21% death; hospitalized with severe disease 21%; hospitalized with moderate disease 13.7% and ambulatory mild disease 44.3%

• The distribution of the frequencies of the main categories of the WHO CPS of anakinra-treated patients of the SAVE study by Day 28 was: 10.9% death; hospitalized with severe disease 5.4%; hospitalized with moderate disease 6.2%; and ambulatory mild disease 77.5%

• 90% power at the 5% level of significance were used

• 1:2 randomization was applied (one patient allocated to treatment Arm 1; two patients allocated to treatment Arm 2)

Final calculation after adjusting for the design effect (DEFF): 600 patients needed to be enrolled in total (200 patients in Arm 1; and 400 patients in Arm 2).

Randomisation

Randomisation was made using a computer-generated randomisation chart applied for each country. The randomisation was made in blocks of 30 (20 for intervention and 10 for control) to achieve the pre-specified proportion of 2:1. Eligible patients were randomly assigned to either placebo+SoC or anakinra+SoC randomly assigned 1:2 to placebo and anakinra. Also, randomisation was stratified based on severity of disease per WHO classification (moderate vs severe), administration of dexamethasone as SoC therapy (No vs. Yes), BMI (≤30 vs. >30), and region (Italy vs. Greece).

Blinding (masking)

This study was double-blinded, with both the treating physicians and staff that evaluated study endpoints being blind for treatment or placebo arm allocation.

Statistical methods

Continuous variables following normal distribution were expressed by mean and SD. Continuous variables not following the normal distribution were expressed by median and interquartile range. Binomial variables were expressed as absolute and percentage frequencies with 95% CIs.

All the baseline continuous and binomial variables alongside comparisons of the two arms of treatment were provided, including demographics (sex and age), disease severity, baseline laboratory values, and co-administered treatment.

Analysis population

The full analysis set (FAS) included all patients who were randomly assigned to treatment. The following patients were excluded from the FAS:

- Patients with a major violation of the inclusion or exclusion criteria that took place before the patient was randomized and objectively assessed according to the ICH-E9 guideline.

- Patients who withdrew consent and requested withdrawal of data.

The Per-protocol (PP) set included all patients randomly assigned to treatment. The following patients were excluded from the entire randomized population in order to determine the PP patient population:

- Patients with a major violation of the inclusion or exclusion criteria that took place before the patient was randomized and objectively assessed according to the ICH-E9 guideline.

- Patients who withdrew consent and requested withdrawal of data.

- Patients with a major deviation of the SoC treatment that was captured and objectively assessed according to the ICH-E9 guideline.

Primary endpoint

The primary study outcome was the comparative 11-point WHO-CPS between the two arms of treatment by Day 28. This was expressed as the distribution of the frequencies of each score of the scale in each arm of treatment by Day 28.

Multivariate ordinal regression was the primary statistical analysis procedure followed. The basic assumptions of the model were the assumption of proportional odds (also called the assumption of parallel lines) that was checked by performing the relevant chi-square test and the goodness-of-fit test, reported through Pearson's chi-square test. The dependent variable was the 11-point WHO-CPS scale, and the primary independent variable was the arm of treatment. The primary statistical measure reported was the point estimate in terms of the OR with its 95% CI, denoting the magnitude of the treatment effect in the multivariate model (adjusted effect). The variables used for the stratified randomization were entered as factors in the analysis model (i.e., severity of illness per WHO classification [moderate vs. severe], intake of dexamethasone in the SoC [No vs. Yes], and BMI [≤30 vs. >30]). The region, in the form of the country (Italy vs. Greece) where the study was performed, was also included as a variable.

The primary endpoint was supported by the following three pre-specified analyses:

• Analysis of the patient's WHO-CPS score by Day 14 in the FAS population was performed using the same statistical models as for the primary endpoint.

• Contextualisation of the clinical benefit was performed with a logistic regression model run on two spectra of the WHO-CPS score by Day 28. The two spectra were as follows:

- Spectrum 1: Patients who were uninfected or not. To achieve this, the WHO-CPS was transformed into a binary variable of patients with fully resolved and persistent disease.
- Spectrum 2: Patients who remained with severe disease. To achieve this, the WHO-CPS was transformed into a binary variable of patients who remained severe and were classified to points of 6 or more (Yes) and of patients who did not remain severe and were classified to points of 5 or less.

Two multivariate logistic models were run, i.e., 1 for each spectrum. In each model, the spectrum as the dependent variable, including independent covariate treatment allocation (placebo vs. anakinra)

and the variables used for the stratified randomization, i.e., severity of illness per WHO classification (moderate vs. severe), intake of dexamethasone in the SoC (No vs. Yes), and BMI (≤30 vs. >30). The region, in the form of the country (Italy vs. Greece) where the study was performed, was also included as a variable.

- Analysis of the time to SRF up to Days 14 and 28 was also performed as a pre-specified confirmatory analysis to provide a comparison to the results of the SAVE study. This included a Cox proportional model of the time until progression into NIV/HFO or MV or death from the start of blind treatment until Days 14 and 28. In this model, the progression into NIV/HFO or MV or death was the dependent variable; the independent covariates were treatment allocation (placebo vs. anakinra) and the variables used for the stratified randomization (i.e., severity of illness per WHO classification [moderate vs. severe], intake of dexamethasone in the SoC [No vs. Yes], and BMI [≤30 vs. >30]). The region, in the form of the country (Italy vs. Greece) where the study was performed, was also included as a variable.

Five sensitivity analyses of the primary endpoint were performed, as follows:

- Analysis in patients receiving at least 7 doses of the study drug.
- Comparison of the treatment-effect provided by the unadjusted comparison and the adjusted model.
- Complete case analysis (i.e., ignoring incomplete data) and comparison to the FAS.
- Responder analysis treating all missing values as failures.
- Analysis including the PP population.

Any p-value below 0.05 was considered to be statistically significant.

Secondary Endpoints

Change of the measure of the 11-point WHO-CPS by Days 14 and 28 from baseline Day 1

The statistical analysis procedure followed was an ordinal regression analysis of the change of the 11-point WHO-CPS by Days 14 and 28 from baseline Day 1. The variables in the equation were allocated group of treatment (placebo vs. anakinra), WHO severity (moderate vs. severe), intake of dexamethasone (No vs. Yes), and BMI (≤30 vs. >30). The region, in the form of the country (Italy vs. Greece) where the study was performed, was also included as a variable.

Change of the SOFA score by Days 7 and 14 from baseline Day 1 (both absolute and relative changes)

This analysis was applicable only for patients who remained hospitalized by Days 7 and 14, respectively. The statistical analysis procedure followed was an ordinal regression analysis of the change of the SOFA score by Days 7 and 14 from baseline Day 1. The variables in the equation were allocated group of treatment (placebo vs. anakinra), WHO severity (moderate vs. severe), intake of dexamethasone (No vs. Yes), and BMI (≤30 vs. >30). The region, in the form of the country (Italy vs. Greece) where the study was performed, was also included as a variable.

Time until discharge from hospital

Comparisons were done by Cox regression analysis, and the HR and 95% CIs were provided. A multivariate model was applied, including the following as covariates: allocated group of treatment (placebo vs. anakinra), WHO severity (moderate vs. severe), intake of dexamethasone (No vs. Yes), and BMI (≤30 vs. >30). The region, in the form of the country (Italy vs. Greece) where the study was performed, was also included as a variable.

Time until discharge from the ICU

This analysis was applicable only for patients who were admitted in the ICU after enrolment. Comparisons were done by univariate Cox regression analysis, and the HR and 95% CIs were provided.

Relative changes of circulating concentrations of suPAR, CRP, D-dimers, ferritin, and IL-6 by Day 7 from baseline Day 1

This analysis excluded patients whose sampling on Day 7 was not performed because of earlier hospital discharge. All other missing variables were imputed by the LOCF principle. Comparison between groups was done by the Mann-Whitney U test.

Relative changes of circulating concentrations of suPAR, CRP, D-dimers, ferritin, and IL-6 by Day 4 from baseline Day 1

This analysis excluded patients whose sampling on Day 4 was not performed because of earlier hospital discharge. All other missing variables were imputed by the LOCF principle. The statistical analysis procedure followed was the Mann-Whitney U-test. Comparison between groups was done by the Mann-Whitney U test.

Change of the viral load by Day 7 from baseline Day 1 (both absolute and relative changes)

This analysis excluded patients whose sampling on Day 7 was not performed because of earlier hospital discharge. All other missing variables were imputed by the LOCF principle. The viral load was expressed as the Ct to positivity of the real-time PCR. Each measurement was done in the pharyngeal swab and in the blood, and it was done separately for the genes ORF 1ab and N. Comparison between groups was done by the Mann-Whitney U test.

Change of the viral load by Day 4 from baseline Day 1 (both absolute and relative changes)

This analysis excluded patients whose sampling on Day 4 was not performed because of earlier hospital discharge. All other missing variables were imputed by the LOCF principle. The viral load was expressed as the Ct to positivity of the real-time PCR. Each measurement was done in the pharyngeal swab and in the blood, and it was done separately for the genes ORF 1ab and N. Comparison between groups was done by the Mann-Whitney U test.

Relation of endpoints to duration of disease (from the first symptoms) and timing of treatment initiation

This analysis was performed for the primary endpoint. The quartiles of time between the start of the first symptoms of COVID-19 and the start of the study drug were calculated. Then, the primary efficacy endpoint was compared between the treatment arms within each quartile.

All statistical tests were done at 5% level. Consequentially there was no control of the family wise error rate, and the analyses of secondary endpoints are regarded as being supportive to the analysis of the primary endpoint.

The primary study endpoint is the patient's WHO CPS score by day 28 in the FAS population. The WHO CPS is a minimal but comprehensively collected outcome set that could facilitate study design and data sharing, and includes information on viral burden, clinical course, and survival measured. However, it is important to acknowledge that due to its very recent nature the CPS scale lacks validation. The developers of the scale state in the published paper that further testing and validation of the measure are needed and this process might result in further modifications to its structure. Although this might not prevent its use as a measure of treatment intensity within clinical trials with COVID-19, as stated

by the WHO group that developed the scale, results from this only primary outcome should be interpreted with caution.

The stand out factor in the approach proposed is the fact that, depending on the relative distribution across the primary 11-point scale outcome it is proposed that the scale is transformed to a 5-point scale or even to a binomial variable to compare patients in all other scales against the baseline scale of uninfected patients. In case the latter case it is stated that logistic regression will be applied. Due to the lack of validation of the scale there is enough evidence that aggregating categories will not affect the reliability of the scale. This should be considered when interpreting the results in case the need to aggregate categories of the scale is verified.

The MAH provided the outcome of the Kolmogorov-Smirnov test performed for several of the secondary endpoints and the consequent specification for the statistical analyses. Some endpoints analysed are conditioned by the presence/absence of specific events, such that only a proportion of the population is analysed, e.g. discharge from ICU or change in SOFA score at day 14. However, the MAH did not identified this as a joint endpoint (entering ICU together with leaving ICU or remain in hospital at day 14 together with SOFA score) and omitted the conditional event doing only a marginal analysis on the other part of the joint endpoint. Since efficacy is supposed to have an impact on the conditioned event, a proper analysis would in principle include both parts. Upon request from the CHMP, an updated analysis was provided by the MAH which allowed to better understand the treatment effects, but due to the conditional nature of these endpoints, there remains considerable unclarity on how the results are to be interpreted. However, it is unlikely that the B/R assessment will be impacted and therefore, the issue was not further pursued by the CHMP.

The MAH specified that in the time-to-event analyses data were censored at the end of the analysed period (Day 14, Day 28). However, the MAH should have specified the censoring strategy for each time to event analysis, e.g. in the analysis of "Time to hospital discharge" how were patients who died before Day 28 handled and how were data censored for withdrawals and dropouts. Upon request from the CHMP, the MAH explained that the number at risk of patients in each group at day 4,8,12,16,20,24 and 28 will be provided at the bottom of all survival curves as well as the standard output from time-to-event analysis, such as median time to event or equivalent in the final CSR, planned to be submitted by End of December 2021 via a type II variation, which is acceptable.

Handling of missing data

Imputation of missing data was done by the principle of Last Observation Carried Forward (LOCF). The only exclusion of the LOCF rule is for biomarkers not sampled on days 4 and 7 because of earlier hospital discharge. In all other cases, the LOCF principle was applied for the biomarker analysis as well. There has only been one patient for which the primary endpoint, WHO-CPS at Day 28, was missing. The patient was allocated to treatment with placebo. With the principle of last-observation carried forward for the primary analysis the WHO-CPS at Day 28, the value was considered 0 and can as such be considered conservative and it did not change the statistics of the comparative analysis.

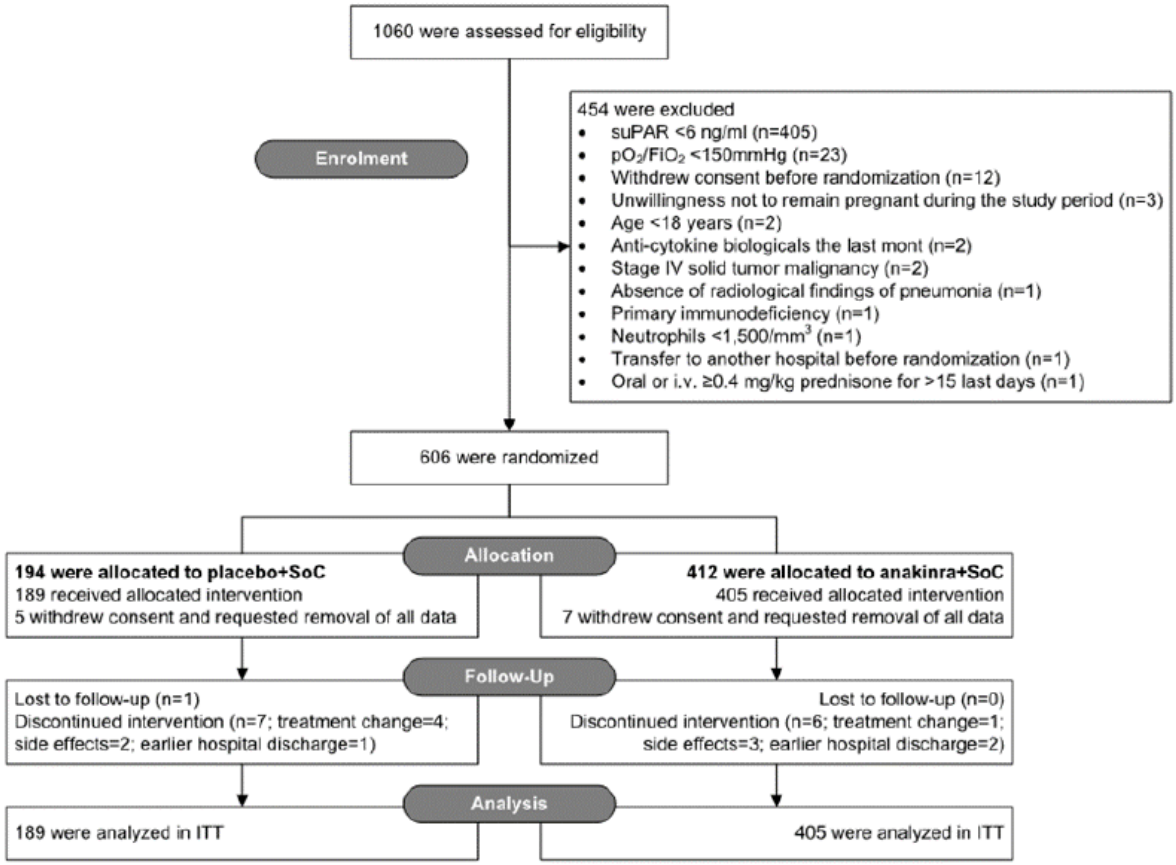
Further analyses of the primary endpoint have been completed to assess the impact of intercurrent events. The MAH made three sensitivity analyses to handle intercurrent events. One based on the population of patients who did not experience an intercurrent event and two using a hypothetical strategy for the intercurrent events (a "worst-case scenario" where patients with intercurrent events were imputed to have the worst-case outcome on the WHO-CPS, i.e. score=10, and a "LOCF scenario" using last available WHO-CPS score before the first intercurrent event).

Results

Participant flow

See disposition of patients below.

Figure 2 Disposition of patients



Recruitment

A total of 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) and randomized to one of the 2 treatment arms. 194 patients were allocated to the placebo+SoC arm and 412 patients were allocated to the anakinra+SoC arm. 12 patients withdrew consent and requested the removal of all data, leaving a final ITT (FAS) analysis set of 594 patients with 189 patients in the placebo+SoC arm and 405 patients in the anakinra+SoC arm. One patient allocated to the placebo+SoC arm was reported as lost to follow-up (but were still part of the FAS).

Extent of exposure

594 hospitalized patients with moderate and severe COVID-19 pneumonia (WHO classification) were exposed in this study. 27 patients with moderate pneumonia and 162 patients with severe pneumonia received placebo+SoC treatment. 82 patients with moderate pneumonia and 323 patients with severe pneumonia received anakinra+SoC treatment (see Table below). The mean number of administered doses of study drug for all the patients was 8.6. The mean number of administered doses was similar for both the treatment groups (placebo+SoC [8.7]; anakinra+SoC [8.4]). The median duration of

exposure (minimum, maximum) of anakinra was 10 (1,10) days and the same for placebo was 10 (2,10) days.

Patients (n=5 in the placebo arm and 7 in the anakinra arm) who withdrew consent and requested withdrawal of data (already obtained) were not part of the FAS.

Inclusion was guided by suPAR being noted that many patients (n=405) were excluded after screening based on suPAR<6 ng/ml.

Conduct of the study

Changes in the conduct of the study

The following changes from the schedule of assessments were included in the interim clinical study report:

• Measurements of the 11-point WHO-CPS were not marked in the schedule of assessments, but were recorded on Day 1, Day 28, and on Days 60 and 90.

• SOFA score was recorded only at Day 1, Day 7, and Day 14 and not recorded on Days 2, 3, 4, 5 ,6, 8, 9, 10.

• Blood sampling for suPAR, CRP, IL-6, ferritin, D-dimers, transcriptomic, and proteomic analysis was not performed at screening.

Changes in the planned analyses

The following changes from the analysis specified in the protocol v. 2.0 and SAP v. 4.0 were included in the interim clinical study report and were done prior to database lock and based on advice from the EMA COVID-19 ETF:

•Before database lock and unblinding, the analyses methods for the primary endpoint and secondary endpoints were updated and described in more detail in the SAP compared to the protocol.

•The patients who withdrew consent and requested withdrawal of data also were excluded from the SAS, although not defined that way in the SAP.

•The changes of the ordinal scale of the 11-point WHO-CPS and the SOFA score were unintentionally mentioned as "between Days 14 and 28" instead of "at Days 14 and 28" in the SAP.

•The analyses of treatment differences in biomarker and viral load endpoints (change from baseline) were performed by using the Mann-Whitney U test, not ANCOVA or ordinal regression analysis as stated in the SAP.

•The univariate Cox regression analysis of "Survival analysis/Time to death by Day 28" was added as a post hoc analysis, although not specified in the list of analysis.

•The secondary outcome "Time until discharge from the ICU" was analysed using the univariate model, not the multivariate model due to the low number of patients.

Protocol deviations

The rate of protocol deviations from the SoC treatment was significantly greater in the patients allocated to the placebo arm than in the patients allocated to the anakinra arm (14.3 % vs. 3.2 %). Significant differences were found for "administration of 6 mg/day dexamethasone for more than 10 days", "Administration of dexamethasone 6-18 mg daily with MTP for 10 days" and "Stop study drug, administration of TCZ+IVIG+ANA". It is unclear whether these differences affected the results

obtained, however these deviations are not expected to artificially inflate the anakinra's effect. Further, these patients were excluded from the PP analysis.

Study sites

In total patients were recruited from 37 different sites. The study recruitment was competitive between the participating sites and there were no limits to the number of included patients by each site/country nor an imbalance in the allocation.

Baseline data

Demographics, baseline characteristics and comorbidity are shown below.

Table 3 Baseline characteristics of FAS/SAS population

	SoC + placebo (N=189)	SoC + anakinra (N=405)	All patients (N=594)
Age, years, mean (SD)	61.5 (11.3)	62.0 (11.4)	61.9 (12.1)
Male sex, n (%)	108 (57.1)	236 (58.3)	344 (57.9)
Mean body mass index, kg/m^2 (SD)	29.8 (5.6)	29.4 (5.5)	29.5 (5.5)
Charlson's comorbidity index, mean (SD)	2.2 (1.5)	2.3 (1.6)	2.2 (1.6)
SOFA score, mean (SD)	2.5 (1.2)	2.4 (1.1)	2.4 (1.1)
WHO classification for COVID-19 at the time of screening, n (%)			
Moderate pneumonia	27 (14.3)	82 (20.2)	109 (18.4)
Severe pneumonia	162 (85.7)	323 (79.8)	485 (81.6)
WHO classification for COVID-19 before start of the study drug, n (%)			
Moderate pneumonia	12 (6.3)	39 (9.6)	51 (8.6)
Severe pneumonia	177 (93.7)	366 (90.4)	543 (91.4)
Days to start of study drug, median (Q1 to Q3)			
From symptom onset	9 (7-11)	9 (7-12)	9 (7-11)
From hospital admission	2 (2-3)	2 (2-3)	2 (2-3)
Laboratory values, median (Q1 to Q3)			
White blood cell count, cells per mm^3	5910 (4280-8300)	5980 (4320-8180)	5950 (4310-8200)
Lymphocyte count, cells per mm^3	730 (560-1090)	815 (570-1110)	800 (565-1100)
C-reactive protein, mg/L	51.4 (25.2-97.9)	50.5 (25.3-100.8)	50.6 (25.3-99.7)
Interleukin-6, pg/mL	20.1 (7.4-44.9)	15.5 (6.6-39.3)	16.8 (7.0-39.8)
Ferritin, ng/mL	628.6 (293.5-1062.3)	558.9 (294.1-1047.0)	585.2 (294.5-1047.0)
Serum soluble uPAR, ng/mL	7.5 (6.9-9.3)	7.6 (7.0-9.1)	7.6 (6.9-9.1)

	SoC + placebo (N=189)	SoC + anakinra (N=405)	All patients (N=594)
D-dimers, mg/L	0.51 (0.31-0.92)	0.52 (0.30-1.00)	0.52 (0.30-0.98)
PO_2: FiO_2, mmHg	215 (161-293)	235 (178-304)	230 (172-300)
Comorbidities, no. (%)			
Type 2 diabetes mellitus	28 (14.8)	66 (16.3)	94 (15.8)
Chronic heart failure	5 (2.6)	13 (3.2)	18 (3.0)
Chronic renal disease	1 (0.5)	9 (2.2)	10 (1.7)
Chronic obstructive pulmonary disease	9 (4.8)	15 (3.7)	24 (4.0)
Coronary heart disease	13 (6.9)	28 (6.9)	41 (6.9)
Atrial fibrillation	8 (4.2)	20 (4.9)	28 (4.7)
Depression	9 (4.8)	25 (6.2)	34 (5.7)
Administered doses of study drug, mean (SD)	8.7 (2.0)	8.4 (2.1)	8.6 (1.8)
Co-administered medications, n (%)			
Remdesivir	141 (74.6)	298 (73.6)	439 (73.9)
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)
Low molecular weight heparin	175 (92.6)	385 (95.1)	560 (94.3)
β-lactamases	10 (5.3)	23 (5.7)	33 (5.6)
Piperacillin/tazobactam	36 (119.0)	64 (15.8)	100 (16.8)
Ceftriaxone	85 (45.0)	155 (38.3)	240 (40.4)
Ceftaroline	32 (16.9)	75 (18.5)	107 (18.0)
Respiratory fluoroquinolone	24 (12.7)	53 (13.1)	77 (13.0)
Azithromycin	35 (18.5)	76 (18.8)	111 (18.7)
Any glycopeptide	19 (10.1)	24 (5.9)	43 (7.2)
Linezolid	22 (11.6)	45 (11.1)	67 (11.3)

Abbreviations: COVID-19, Coronavirus disease 2019; FAS, Full analysis set; FiO_2, Fraction of inspired oxygen; N, Total number of patients; n, Number of patients; pO_2, Partial oxygen pressure; Q, Quartile; SAS, Safety analysis set; SD, Standard deviation; SoC, Standard-of-care; SOFA, Sequential organ failure assessment; uPAR, Urokinase plasminogen activator receptor; WHO, World Health Organization.

The definition of the WHO classification on the severity of pneumonia according to the protocol is provided below:

- Moderate illness: clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) but no signs of severe pneumonia, including SpO_2 ≥90% on room air. These patients are not in need of oxygen.

- Severe disease: clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) plus one of the following: respiratory rate >30 breaths/minute; severe respiratory distress; or SpO_2 <90% on room air. These patients need oxygen.

Respiratory distress and need for oxygen supplementation are guiding severity.

Baseline viral load is provided below.

	SoC + placebo	SoC + anakinra	p-value
Mean	31.5	31.2	
SD	5.5	5.7	
95% CIs	30.6-32.4	30.6-31.8	
Viral load in blood measured as copies of the *ORF 1ab* SARS-CoV-2 gene; values in Ct			Student's t-test
Day 1 (baseline)			
n	181	391	0.321
Mean	39.4	39.6	
SD	1.9	1.6	
95% CIs	39.1-39.7	39.4-39.7	

Baseline WHO-CPS is provided below.

	SoC + Placebo (N=189) n (%)	SoC + Anakinra (N=405) n (%)
WHO-CPS=4	12 (6.3)	39 (9.6)
WHO-CPS=5	162 (85.7)	341 (84.2)
WHO-CPS=6	15 (7.9)	25 (6.2)

Abbreviations: N, Total number of patients; n, Number of patients; SoC, Standard of care; WHO-CPS, World Health Organization-Clinical Progression Scale.

The distribution of patients by treatment group and oxygen use is provided below; the p-value of the Pearson X2 test of the distribution of the frequencies between the 2 groups is 0.325.

	SoC + Placebo (N=189) n (%)	SoC + Anakinra (N=405) n (%)
Hospitalized without supplemental oxygen	12 (6.3)	39 (9.6)
Hospitalized with oxygen mask/nasal oxygen	162 (85.7)	341 (84.2)
Hospitalized at high-flow oxygen	15 (7.9)	25 (6.2)

Abbreviation: N, Total number of patients; n, Number of patients; SoC, standard of care.

The overall median time from symptom onset to enrolment was 9 days, and the median time from hospital admission to enrolment was 2 days. Upon request from the CHMP, the MAH provided a separate list of baseline medication and a separate list of co-administered treatment during the study. A marginally higher proportion in the anakinra arm received remdesivir whereas the opposite was the case for dexamethasone at baseline. In addition, more patients received antibiotics in the placebo arm. Pip/tazo was received in 19% in the placebo arm and 15.8% in the anakinra arm. Further, more patients in the placebo arm received cephalosporines with 58% in the anakinra arm and 63% in the placebo arm. Overall, baseline medications were equally distributed between the arms. However, during the study, more patients received furosemide in the placebo arm than in the anakinra arm

(19.6% vs 10.9%, respectively). Further, more patients received propofol in the placebo arm than in the anakinra arm (11.1 % vs 4.7%, respectively) and more received noradrenaline in the placebo arm than in the anakinra arm (11.6% vs 4.9%, respectively).

The study drug compliance was determined from the empty syringes that were stored after the study drug administration. The mean number of administered doses of study drug for all the patients was 8.6.

Baseline characteristics

The baseline characteristics were overall equally distributed across treatment arms. However, based on the WHO classification, the majority of the patients (91.6%) were identified with severe COVID-19 pneumonia, and 8.4 % of patients were identified with moderate COVID-19 pneumonia. Numerically more patients in the placebo arm had severe pneumonia (94.2% vs 90.4% in the anakinra group), lower PO_2/FiO_2, slightly higher WHO-CPS and more patients received antibiotics. The only parameter pointing in a direction of the anakinra arm being slightly sicker is the fact that more patients in the anakinra arm progressed between screening and inclusion, as rapid progression is an important clinical measure for a more severe outcome. Further insight on the differences in baseline disease severity has been provided upon request from the CHMP. The MAH considered that the allocation of patients with severe COVID-19 is similar between arms despite the numeric differences observed. Further, the differences in baseline disease severity could potentially impact on differences in disease severity at day 28 in favour of the investigative drug. However, CHMP agreed that these differences (Severe COVID-19 by WHO) were taken in account in the multivariate analysis.

SOFA score was very similar in both groups 2.5 and 2.4 in the placebo and anakinra group respectively. Days from symptom onset (9 days) and from hospitalization (2 days) were similar in both groups.

Regarding laboratory values (WBC, Lymphocyte count, CRP, IL-6, Ferritin, and D-dimer) there were no differences between the two arms, except for a slightly higher IL-6 level in the placebo group (20.1 vs 15.5), which is assessed as not important. The included population had suPAR of median (IQR) 7.6 (6.9-9.1).

Comorbidity

The frequency of Type 2 diabetes mellitus, Chronic heart failure, Chronic renal disease, Chronic obstructive pulmonary disease, Coronary heart disease and Atrial fibrillation were well balanced between treatment arms. There is no information on asthma.

Baseline/Co-administered medication

A marginally higher proportion in the anakinra arm received remdesivir whereas the opposite was the case for dexamethasone at enrolment. This is not expected to have any clinical impact. However, as of March 31, 2021, the antiviral remdesivir and dexamethasone are the available SoC treatments that are recommended by the WHO for patients with COVID-19. For patients classified with moderate disease, SoC treatments include anticoagulation and remdesivir. For patients classified with severe disease, SoC treatments include anticoagulation, oxygen supply, dexamethasone, and remdesivir.

SAVE-MORE study had First Patient First Visit on 23 December 2020, and in total 606 patients were enrolled (194 patients in the placebo arm and 412 patients in the active arm). Of 20 February 2021, 225 patients had been enrolled, i.e. prior to the time that remdesivir and dexamethasone were introduced as SoC for COVID-19 treatment. Hence, a substantial number (> 1/3 of enrolled patients) of patients in SAVE-MORE were included in the study before the new SoC with remdesivir and dexamethasone was implemented. However, the MAH stated that the recruitment period was only

three months and that there were no relevant changes in SOC or temporal trends in the prescription of remdesivir as SOC in the period. The data provided in the table below does not support any modification of anakinra effect by remdesivir use.

Table 4 Univariate and multivariate ordinal regression analyses of the WHO-CPS at Day 28

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Group of treatment (Anakinra vs placebo)	0.36	0.26-0.49	3.6×10^{-10}	0.36	0.26-0.50	8.1×10^{-10}
Intake of dexamethasone (Yes/No)	1.90	1.28-2.83	0.002	1.74	0.67-4.56	0.258
Severe COVID-19 by WHO (Yes/No)	1.95	1.31-2.90	0.001	1.14	0.44-2.95	0.782
BMI >30 kg/m^2 (Yes/No)	1.27	0.87-1.61	0.27	1.10	0.81-1.50	0.525
Country (Italy vs Greece)	1.18	0.74-1.88	0.48	1.37	0.83-2.26	0.217
Intake of remdesivir (Yes/No)	1.00	0.72-1.41	0.97	0.94	0.66-1.33	0.737

Abbreviations: BMI, Body mass index; CI, Confidence interval; COVID-19, Coronavirus disease 2019; OR, Odds ratio; vs, Versus; WHO, World Health Organization; WHO-CPS, World Health Organization-Clinical Progression Scale.

A subgroup of patients did not receive dexamethasone at any time during the study. The table below show the univariate and multivariate analyses of the 84 patients not receiving dexamethasone. For clarification, the patients who had not commenced dexamethasone at baseline, did not receive dexamethasone at any time during the study.

Analysis on patients who have not received dexamethasone at any time during the study				
	SoC + Placebo (N=21) n (%)	SoC + Anakinra (N=63) n (%)	Odds Ratio (95% CI)	P-value
WHO-CPS Day 28			0.14 (0.05-0.39)	<0.0001
Fully recovered PCR(-)	4 (19.0)	40 (63.5)		
Asymptomatic PCR (+)	1 (4.8)	6 (9.5)		
Symptomatic independent	12 (57.1)	14 (22.2)		
Symptomatic assistance needed	3 (14.3)	1 (1.6)		
Hospitalized no need for oxygen	0 (0)	0 (0)		
Hospitalized with nasal/mask oxygen	0 (0)	0 (0)		
Need for HFO or NIV	0 (0)	0 (0)		
Mechanical ventilation with P/F >150	0 (0)	1 (1.6)		
Mechanical ventilation with P/F <150 or vasopressors	0 (0)	0 (0)		
Mechanical ventilation with P/F <150 and vasopressors or hemodialysis or ECMO	0 (0)	0 (0)		
Dead	1 (4.8)	1 (1.6)		

Abbreviations: ECMO, extracorporeal membrane oxygenation; HFO, high-flow oxygen; NIV, noninvase ventilation; PCR, polymerase chain reaction; P/F respiratory ratio; SoC, standard of care;WHO-CPS, World Health Organization Clinical Progression Scale

Univariate and multivariate ordinal regression analysis of the WHO-CPS at Day 28 for the 84 patients not receiving dexamethasone

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	P-value	OR_{adj}	95% CI	P-value
Group of treatment (Anakinra vs placebo)	0.14	0.05-0.39	<0.0001	0.14	0.05-0.39	<0.0001
Severe disease by WHO (Yes/No)	1.56	0.64-3.81	0.328	2.21	0.72-6.25	0.169
BMI >30 kg/m^2 (Yes/No)	0.83	0.32-2.15	0.707	0.71	0.25-1.96	0.514
Country (Italy vs Greece)	1.45	0.44-4.84	0.543	2.79	0.63-12.17	0.174

Abbreviations: BMI, body mass index; CI: confidence interval; OR, Odds ratio; OR_{adj}, Adjusted odds ratio; vs, Versus; WHO-CPS, World Health Organization Clinical Progression Scale

At baseline more patients received antibiotics in the placebo arm. This probably reflects that more patients in the placebo arm had severe pneumonia, as discussed above. Besides of that baseline medications were equally distributed between the arms. However, during the trial more patients received furosemide in the placebo arm 19.6% vs 10,9% in the anakinra arm. Further, more patients received propofol in the placebo arm 11.1 % vs 4.7% and more received noradrenaline in the placebo arm 11.6% vs 4.9% in the anakinra arm, reflecting that more patients in the placebo arm deteriorated to SRF.

Viral load in blood measured as copies of SARS-CoV-2 gene was equal in both groups. The MAH has not provided data and analyses on variants and argue that the hyperinflammatory consequences remain the same, which is agreed and acceptable.

As the study drug was an s.c. injection administered at the hospital, no issues are expected regarding study drug compliance.

Numbers analysed

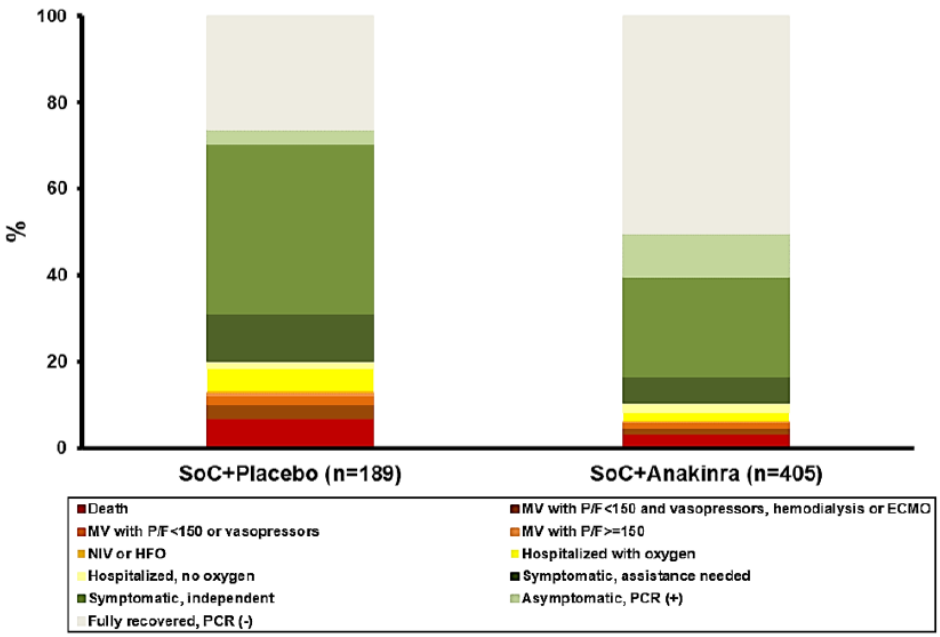
In total 1060 patients were screened and hereof 606 patients were randomized 1:2 to placebo+SoC n= 194 or to anakinra+SoC n=412. 12 patients withdrew consent leaving a final ITT (FAS) analysis set of 594 patients (n=189 in the placebo+SoC arm and n=405 in the anakinra+SoC arm). Patients (n=5 in the placebo arm and 7 in the anakinra arm) who withdrew consent and requested withdrawal of data (already obtained) were not part of the FAS.

Outcomes and estimation

Primary endpoint

The primary study endpoint, the comparative 11-point WHO-CPS between the two arms of treatment by Day 28, was expressed as the OR for allocation to lower severity after anakinra treatment compared to placebo. See Figure below. Covariates entered in the multivariate model were those used for stratified randomization. The unadjusted OR at Day 28 was 0.36 (95 % CI 0.26 to 0.49; P<0.001) (see Figure and Table below).

Figure 3 Study primary outcome – WHO-CPS at Day 28 – FAS population



Abbreviations: CPS, Clinical Progression Scale; ECMO, Extracorporeal membrane oxygenation; FAS, Full analysis set; HFO, High flow oxygen; MV, Mechanical ventilation; NIV, Noninvasive ventilation; Polymerase chain reaction; P/F, Respiratory failure; SoC, Standard-of-care; WHO, World Health Organization.

Table 5 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	<0.001	0.36	0.26-0.50	<0.001
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

Abbreviations: BMI, Body mass index; CI, Confidence interval; COVID-19, Coronavirus disease 2019; COVID-ETF, COVID-19 EMA pandemic Task Force; OR, Odds ratio; OR_{adj}, Adjusted odds ratio; WHO-CPS, World Health Organization Clinical Progression Scale.

The day 28 WHO-CPS distribution of patients is provided in the below table.

Table 6 WHO-CPS at Day 28 – FAS population

WHO-CPS	**SoC + Placebo (N=189)**	**SoC + Anakinra (N=405)**
Fully recovered PCR (-), n (%)	50 (26.5)	204 (50.4)
Asymptomatic PCR (+), n (%)	6 (3.2)	40 (9.9)
Symptomatic independent, n (%)	74 (39.2)	93 (23.0)
Symptomatic assistance needed, n (%)	21 (11.1)	25 (6.2)
Hospitalized no need for oxygen, n (%)	3 (1.6)	9 (2.2)
Hospitalized with nasal/mask oxygen, n (%)	10 (5.3)	8 (2.0)
Need for HFO or NIV, n (%)	1 (0.5)	1 (0.2)
Mechanical ventilation with P/F >150, n (%)	1 (0.5)	1 (0.2)
Mechanical ventilation with P/F <150 or vasopressors, n (%)	4 (2.1)	5 (1.2)
Mechanical ventilation with P/F <150 and vasopressors or hemodialysis or ECMO, n (%)	6 (3.2)	6 (1.5)
Dead, n (%)	13 (6.9)	13 (3.2)

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

The primary outcome

The prespecified primary endpoint was the comparative 11-point WHO-CPS between the two arms of treatment, and was expressed as the OR for allocation to lower severity after anakinra treatment compared to placebo at day 28 in the FAS population. This was assessed by ordinal regression analysis unadjusted and adjusted for other factors (administration of dexamethasone, severe COVID-19, BMI>30kg/m^2 and country). The unadjusted OR at Day 28 was 0.36 (95 % CI 0.26 to 0.49; P<0.001), hence the primary endpoint was met and statistically significant. Also, in the adjusted (multivariate) analysis anakinra+SoC was beneficial (OR 0.36; 95 % CI 0.26 to 0.50; P<0.001).

Based on the distribution of WHO-CPS at day 28, the proportion of patients with severe outcome needing oxygen supplementary WHO-CP score ≥ 5 is higher in the placebo arm than in the anakinra

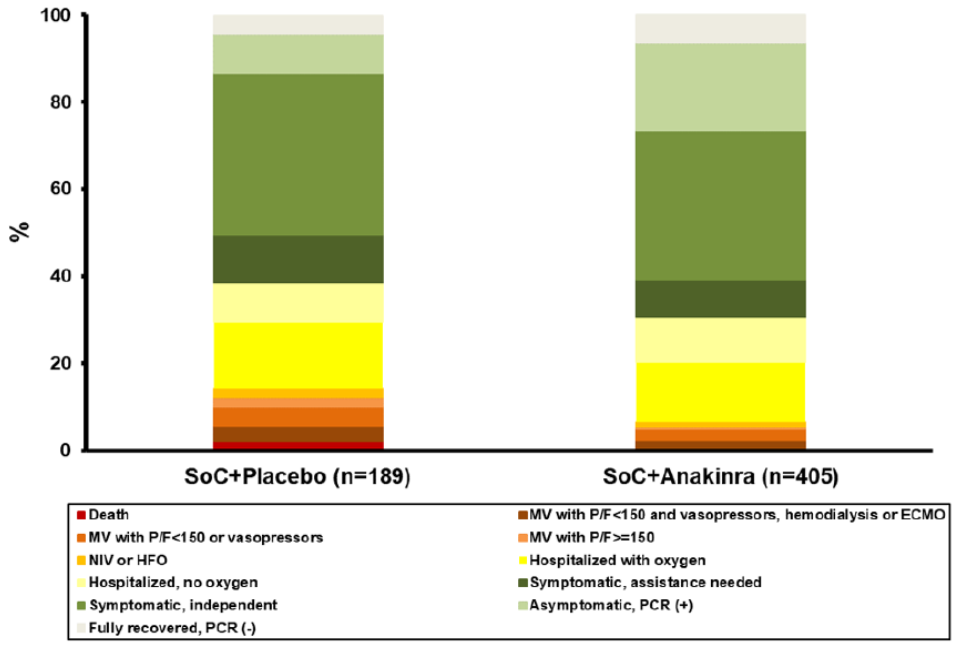
arm. This indicates an overall beneficial effect of anakinra treatment. However, there are few "events" in the severe groups, and numbers are low. The interpretation is eased by some of the supportive analysis of the primary endpoints such as "time to progression to severe respiratory failure", see below.

Supportive analyses of the primary endpoint

There were three supportive analysis of the primary endpoint:

1) The unadjusted OR of the ordinal regression analysis of the WHO-CPS by **Day 14** was 0.57 (95 % CI 0.44 to 0.77; P<0.001). See Figure below. The OR adjusted after multivariate analysis was 0.58 (95 % CI 0.42 to 0.79; P=0.001).

Figure 4: First supportive analysis of the study primary outcome, WHO-CPS by Day 14 – FAS population



2) The second supportive analysis to confirm the primary endpoint was designed to explain how the treatment benefit of anakinra may be associated with the two spectra of the WHO-CPS by Day 28. For the analysis of the first spectrum, patients were divided into those who were fully recovered by Day 28 with negative viral load and into those who had persistent disease ranging between points 1 to 10 of the WHO-CPS by Day 28. See Table below.

Table 7: Analysis towards fully resolved or persistent disease (first spectrum) – FAS population

	Analysis towards fully resolved or persistent disease					
	Fully resolved (n= 254)	Persistence (n= 340)	Univariate analysis		Multivariate analysis	
Variable			OR (95% CIs)	P-value	OR_{adj} (95% CIs)	P-value
Anakinra treatment, n (%)	204 (80.3)	201 (59.1)	0.35 (0.23-0.52)	<0.001	0.36 (0.25-0.53)	<0.001
Intake of dexamethasone, n (%)	198 (78.0)	288 (84.7)	1.56 (1.03-2.38)	0.036	*	
Severe COVID-19 by WHO, n (%)	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/m², n (%)	87 (34.3)	129 (37.9)	1.17 (0.84-1.65)	0.36	*	
Patients in Italy, n (%)	30 (11.8)	36 (10.6)	0.91 (0.55-1.52)	0.72	*	

Abbreviations: BMI, Body mass index; CI, Confidence interval; COVID-19, Coronavirus disease 2019; FAS, Full analysis set; n, Number of patients; OR, Odds ratio; OR_{adj}, Adjusted odds ratio; WHO, World Health Organization.
*Variables not included in the equation after two steps of forward analysis.

For the analysis of the second spectrum, patients were divided into those who by Day 28 were allocated to 6 or more points of the WHO-CPS (severe hospitalized and dead) and into those who were allocated into 5 or less points of the WHO-CPS. The multivariate logistic regression model for the second spectrum of the WHO-CPS are shown in the Table below.

Table 8: 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, n (%)	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, n (%)	435 (80.1)	51 (100)	*	<0.001	*	
Severe COVID-19 by WHO, n (%)	434 (79.9)	51 (100)	*	<0.001	**	
BMI >30 kg/m², n (%)	199 (36.6)	17 (33.3)	0.81 (0.44-1.50)	0.81	**	
Patients in Italy, n (%)	59 (10.9)	7 (13.7)	1.57 (0.70-3.49)	0.27	**	

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 odds ratio; WHO, World Health Organization.
* Cannot be computed because one value is zero

3) The third supportive analysis was a univariate and multivariate stepwise Cox regression analysis of respiratory failure progression during the first 14 and 28 days. SRF was defined as respiratory ratio-PF <150 necessitating HFO/NIV/MV or death by Day 14 or Day 28. See Table below.

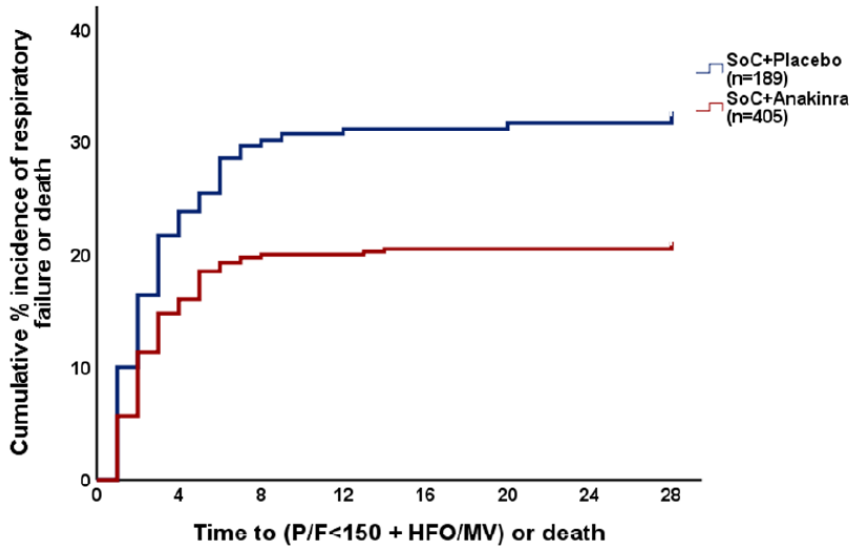
Table 9: Analysis of time to progression into SRF until Day 28 – FAS population

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

Abbreviations: BMI, Body mass index; CI, Confidence interval; COVID-19, Coronavirus disease 2019; HFO, High flow oxygen; HR, Hazard ratio; n, Number of patients; SRF, Severe respiratory failure; WHO, World Health Organization.;
*Variables not included in equation after 3 steps of forward analysis.

Time to progression to severe respiratory failure are shown in the Kaplan Meier curve in the Figure below.

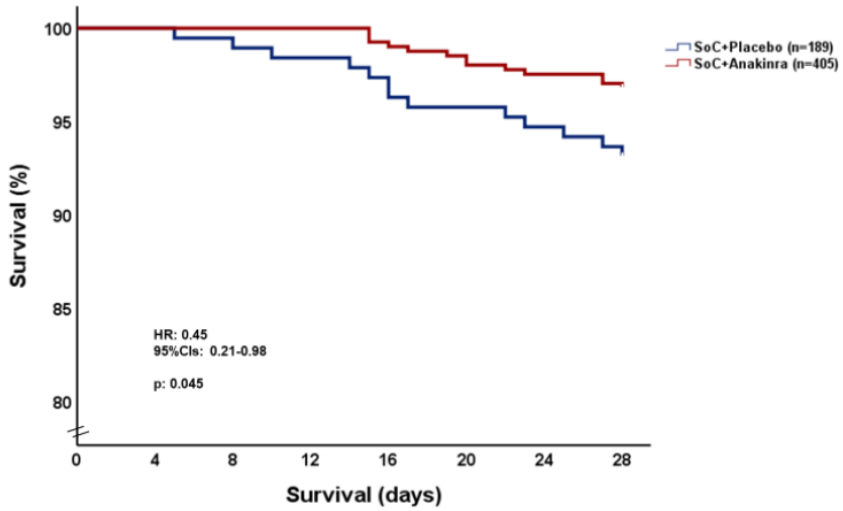
Figure 5: Time to progression into SRF until Day 28



Post hoc analysis (survival analysis)

The below Figure shows the Kaplan-Meier curve of time to death. 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); 6.9% of patients in the placebo+SoC group and 3.2% of patients in the anakinra+SoC group died by Day 28 (see also Table 6).

Figure 6: Survival analysis of enrolled patients in FAS population



Abbreviations: CI, confidence interval; FAS, Full analysis set; HR, Hazard ratio; SoC, Standard-of-care.

Sensitivity analysis of the primary endpoint

Five sensitivity analyses of the primary endpoint were performed (see Tables below). The first four sensitivity analyses were univariate and multivariate ordinal regression analyses of the primary study outcome (WHO-CPS) at Day 28. Covariates entered in the multivariate model were the same as those used for stratified randomization.

Table 10: Sensitivity analysis 1 – Per protocol population

	Sensitivity analysis 1: PP (SoC + placebo= 162; SoC + anakinra= 292)					
	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	<0.001	0.35	0.25-0.48	<0.001
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

Table 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	<0.001	0.38	0.27-0.53	<0.001
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

Abbreviations: BMI, Body mass index; CI, Confidence interval; COVID-19, Coronavirus disease 2019; n, Number of patients; OR, Odds ratio; OR_{adj}, Adjusted odds ratio; SoC, Standard-of-care; WHO, World Health Organization.

Table 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	<0.001	0.36	0.26-0.49	<0.001
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

Abbreviations: BMI, Body mass index; CI, Confidence interval; COVID-19, Coronavirus disease 2019; FAS, Full analysis set; n, Number of patients; OR, Odds ratio; OR_{adj}, Adjusted odds ratio; SoC, Standard-of-care; WHO, World Health Organization.

Table 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	<0.001	0.36	0.26-0.49	<0.001
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/m^2 (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

Abbreviations: BMI, Body mass index; CI, Confidence interval; COVID-19, Coronavirus disease 2019; FAS, Full analysis set; n, Number of patients; OR, Odds ratio; OR_{adj}, Adjusted odds ratio; SoC, Standard-of-care; WHO, World Health Organization.

Table 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	1.06

Abbreviations: CI, Confidence interval; OR, Odds ratio.

Upon request from the CHMP, the MAH provided results based on the originally proposed primary endpoint (dichotomic assessment on respiratory failure)**.** Univariate and multivariate stepwise analyses of the incidence and time to SRF progression at Day 14 were performed. SRF was defined as P/F <150 necessitating HFO/NIV/MV or death. In both analyses, anakinra treatment prevented the progression to SRF by Day 14. The adjusted OR for the incidence of SRF by Day 14 is 0.59 (95% CI: 0.40 to 0.89), and this is consistent with the analysis using the ordinal WHO-CPS scale at Day 14 (adjusted OR: 0.58, 95% CI: 0.42 to 0.79).

In order to handle intercurrent events three sensitivity analyses were completed. For the first sensitivity analysis, the treatment effect only in patients who did not experience an intercurrent event was estimated. Results are consistent with the primary analysis (primary analysis adjusted OR =0.36,

95% CI [0.26 to 0.50] versus OR = 0.35, 95% CI [0.25 to 0.50] for patients without intercurrent events). For the second patients with intercurrent events were imputed to have the worst-case outcome on the WHO-CPS, i.e. score=10 for the primary endpoint. The overall OR were consistent with the current primary analysis results (primary analysis adjusted OR: 0.36, 95% CI [0.26 to 0.50] versus OR=0.31, 95% CI [0.22 to 0.42] using this hypothetical estimand approach). For the third data beyond the intercurrent event was imputed with the patients' last available score before the event. Again, results are very consistent with the primary analysis (primary analysis adjusted OR = 0.36, 95% CI [0.26 to 0.50] versus OR=0.32, 95% CI: [0.23 to 0.44] using this hypothetical estimand approach).

Secondary efficacy endpoints

Analysis of the clinical secondary endpoints are shown in the Table below. The decrease of the WHO-CPS score from baseline to Days 14 and 28 and of the SOFA score from baseline to Day 7 were significantly greater in the anakinra+SoC arm compared to the placebo+SoC arm. Moreover, in the anakinra+SoC group, the average time until hospital discharge was 1 day shorter and the time until ICU discharge was 4 days shorter than in the placebo+SoC group.

Table 15: Secondary efficacy endpoints – FAS population

	SoC + Placebo	SoC + Anakinra	Unadjusted OR[a] (95 % CI)	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)	<0.001
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)	<0.001
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
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
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
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
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
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
Median (IQR) time to hospital discharge, days[c]	12 (8.5)	11 (7.8)	1.22 (1.02-1.47)[b]	0.033
Median time of ICU stay, days[c]	14 (22)	10 (21)	2.33 (1.11-4.92)[b]	0.026

Abbreviations: CI, Confidence interval; ICU, Intensive care unit; 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.
[b]Only for patients admitted in the ICU.
[c]Hazard ratio.

Regarding 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. Nevertheless, the SOFA score was only assessed in few

patients in each group (n= 66 in the placebo arm and n=120 in the anakinra arm), it is assumed to be because SOFA scores were only assessed in hospitalized patients.

Time until discharge from hospital

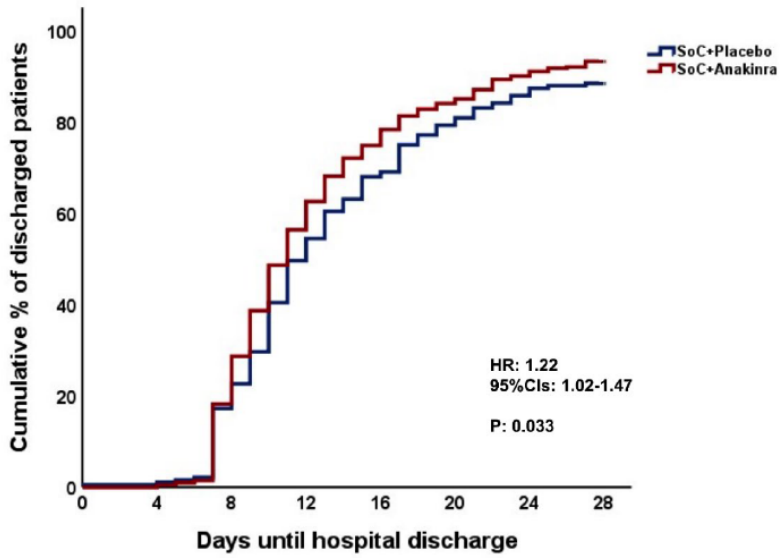
The multivariate Cox regression analysis showed that the time until hospital discharge was 1 day shorter in the anakinra+SoC group than in the placebo+SoC group (HR: 1.21; 95 % CI 1.01 to 1.45; P=0.042) (see Table and Figure below).

Table 16: Univariate and multivariate forward stepwise Cox regression of the time until hospital discharge, censored to 28 days

	Patients not discharged (n=44)	Patients discharged (n=550)	Univariate analysis		Multivariate analysis	
			HR (95 % CIs)	P-value	HR (95 %CIs)	P-value
Anakinra treatment, n (%)	24 (54.5)	381 (69.3)	1.22 (1.02-1.47)	0.033	1.21 (1.01-1.45)	0.042
Dexamethasone treatment, n (%)	43 (97.7)	443 (80.5)	0.66 (0.53-0.82)	<0.001	0.66 (0.53-0.82)	<0.001
Severe COVID-19 by WHO classification, n (%)	43 (97.7)	442 (80.4)	0.67 (0.54-0.83)	<0.001	*	
BMI >30 kg/m^2, n (%)	17 (83.6)	199 (36.2)	0.98 (0.83-1.18)	0.896	*	
Italian participants, n (%)	7 (15.9)	59 (10.7)	0.78 (0.59-1.02)	0.070	*	

Abbreviations: BMI, Body mass index; CI, Confidence interval; COVID-19, Coronavirus disease 2019; HR, Hazard ratio; n, Number of patients; WHO, World Health Organization;
*Variables excluded after two steps of forward regression analysis

Figure 7: Time until discharge from hospital

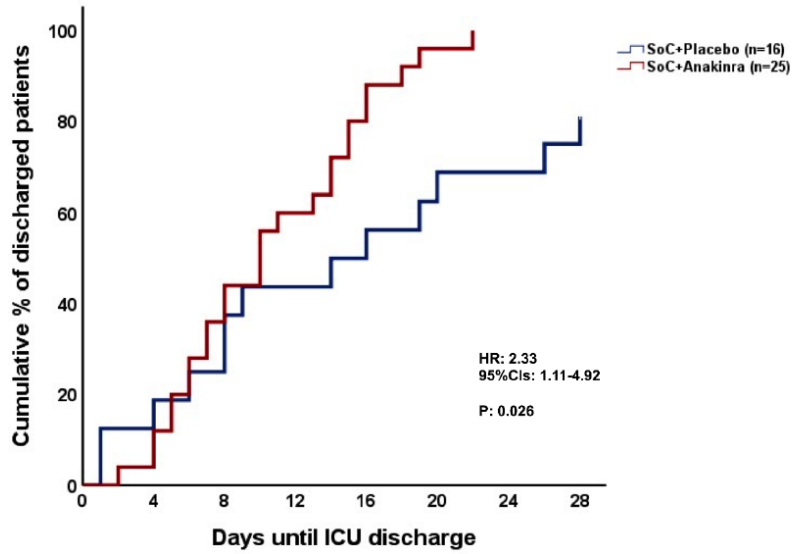


Abbreviations: CI, confidence interval; HR, Hazard ratio; SoC, Standard-of-care.

Time until discharge from the ICU

This analysis included only the patients who were admitted in the ICU. The univariate Cox regression analysis showed that the time until ICU discharge was 4 days shorter in the anakinra+SoC group than in the placebo+SoC group (HR: 2.33; 95% CI: 1.11-4.92; P=0.026) (see Figure below). Multivariate analysis was not performed because of the low number of patients.

Figure 8: Time until discharge from the ICU

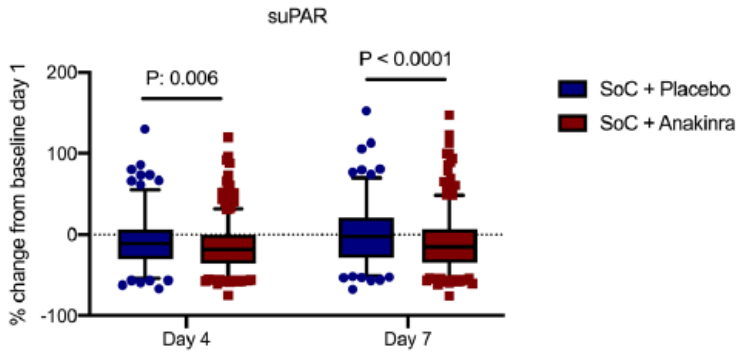


Time until discharge from ICU is a conditional analysis on entering ICU, and reporting the marginal only is not regarded as sufficient (see discussion on clinical efficacy). Time until discharge from ICU is shorter in the anakinra arm. The Kaplan-Meier curves separate from approximately day 9. Some clarity regarding censoring is still lacking. However, since this endpoint will be regarded as only supportive, this issue is not further pursued. Multivariate analysis was not performed because of the low number of patients, which is acceptable.

Relative changes of circulating concentrations of suPAR, CRP, D-dimers, ferritin, and IL-6 by Day 4 and 7 from baseline Day 1.

Concentrations of suPAR, CRP, D-dimers, ferritin, IL-6 and viral load were measured at three time points, baseline Day 1, on Days 4 and 7 for enrolled patients. The change from baseline at Days 4 and 7 in suPAR decreased significantly more in the anakinra+SoC group than in the placebo+SoC group (-21.0 % [41.3%] and -12.8% [43.3%], P=0.006 at Day 4; -17.1% [46.9%] and -2.5% [57.1%] at Day 7; P<0.001). See Figure below. CRP and IL-6 decreased more in the anakinra+SoC group than in the placebo+SoC group, while D-dimers and ferritin changes were similar in the 2 treatment groups. The changes of the viral gene expressions did not differ between the treatment groups.

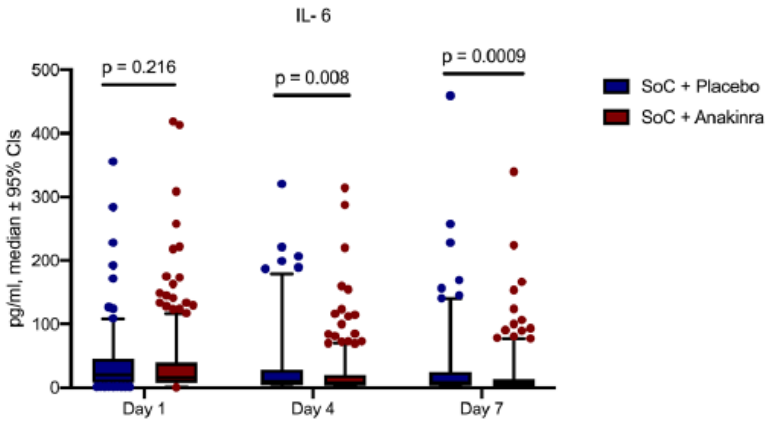
Figure 9: Relative % changes of suPAR from baseline Day 1



Abbreviations: SoC: Standard-of-care; suPAR, Soluble urokinase plasminogen activator receptor.
Analysis was performed using Mann-Whitney U test.

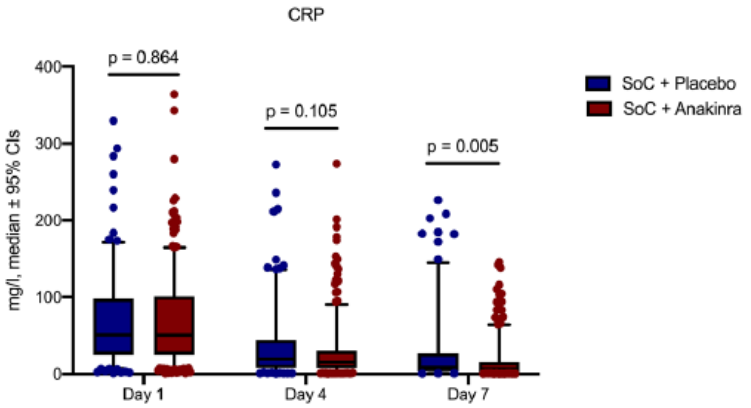
As shown in the Figures below, over-time follow-up of laboratory values showed that among patients treated with SoC and anakinra: a) circulating IL-6 was decreased by Days 4 and 7; and b) plasma CRP was decreased by Day 7.

Figure 10: Levels of IL-6 over days of follow-up



Abbreviations: CI, confidence interval; IL, Interleukin; SoC, Standard-of-care.
Day 1 sampling was done before start of administration of the study drug. The P-values of comparisons for each day of follow-up are provided.

Figure 11: Levels of CRP over days of follow-up



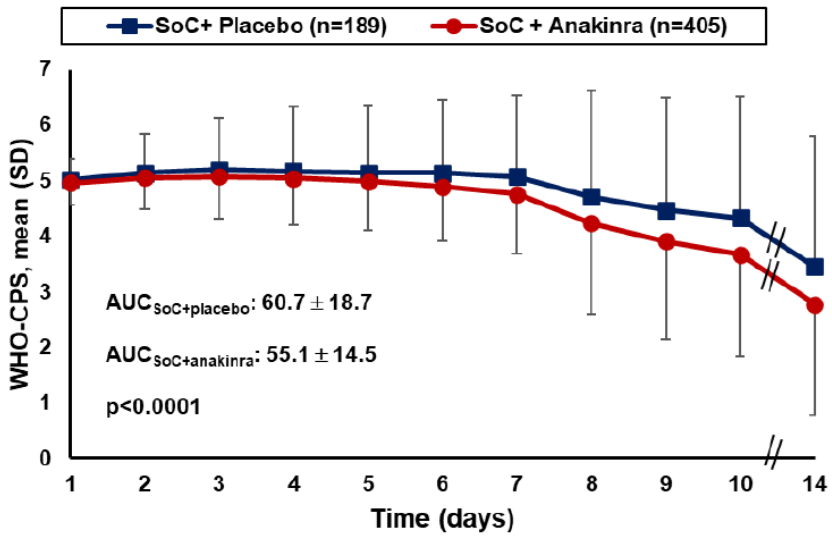
Abbreviations: CI, confidence interval; CRP, C-reactive protein; SoC, Standard-of-care.
Day 1 sampling was done before start of administration of the study drug. The P-values of comparisons for each day of follow-up are provided.

Ancillary analyses

Other efficacy endpoints

Time course of the 11-point of WHO-CPS between Days 1 and 14 is shown in the below Figure. The two treatment group scores begin to diverge at approximately Day 7; the mean (SD) AUCanakinra+SoC = 55.1 (14.5) and the AUCplacebo+SoC = 60.7 (18.7), P<0.001).

Figure 12: The over-time curve of the measures of the 11-point of WHO-CPS between Days 1 and 14



Summary of main study

The following table summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 17: Summary of Efficacy for study SAVE-MORE

Title: 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		
Study identifier	EudraCT Number: 2020-005828-11	
Design	Prospective, pivotal, confirmatory, randomized, double-blind, placebo-controlled, parallel, multi-centre	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	28 days and follow up until Day 90 Not applicable Not applicable
Hypothesis	Superiority	
Treatments groups	Placebo + Standard of Care (SoC)	Placebo + SoC, 10 days of treatment, 194 patients randomized
	Anakinra + Standard of Care (SoC)	Anakinra + SoC, 10 days of treatment, 412 patients randomized

Endpoints and definitions	**Primary endpoint:** 11-point WHO Clinical Progression ordinal Scale (CPS) by Day 28	**WHO-CPS Day 28**	The endpoint was expressed as the distribution of the frequencies of each score of the scale in each arm of treatment by Day 28, i.e., the primary endpoint was expressed as the OR for allocation to lower severity after anakinra+SoC treatment compared with placebo+SoC.
	Key Secondary endpoint: Change in the WHO-CPS by Day 28 from baseline Day 1 (absolute changes)	**WHO-CPS change Day 28**	See above for how the endpoint was expressed. Both absolute and relative changes from baseline were analysed and reported in the Clinical Study Report. The outcome showed very similar results. In this summary table absolute changes are shown.
	Spectrum 1: Binary endpoint based on 11-point WHO Clinical Progression ordinal Scale (CPS) by Day 28	**WHO-CPS Day 28 Spect 1**	Analysis towards fully resolved or persistent disease (first spectrum) Binary endpoint: 0: Fully recovered with negative viral load points 1 to 10 of the WHO-CPS Day 28. 1: Those who had persistent disease ranging between points 1 to 10 of the WHO-CPS Day 28.
	Spectrum 2: Binary endpoint based on 11-point WHO Clinical Progression ordinal Scale (CPS) by	**WHO-CPS Day 28 Spect 2**	Binary endpoint: Allocation into remains severe WHO-CPS ≥6 (Yes) or not WHO-CPS ≤5.
	Time until severe respiratory failure (SRF) up to Day 28	**TUSRF Day 28**	
	Time until death up to Day 28	**TUD Day 28**	
Database lock	18 August 2021		

Results and Analysis

Analysis description	**Primary Analysis (pre-specified)**
Analysis population and time point description	FAS (ITT) was the primary analysis population and treatment Day 28 was the primary timepoint. • **The FAS**: This included all patients who were randomly assigned to treatment. The following patients were excluded from the FAS: o Patients with a major violation of the inclusion or exclusion criteria that took place before the patient was randomized and objectively assessed according to the ICH-E9 guideline. o Patients who withdrew consent and requested withdrawal of data.

Descriptive statistics and estimate variability	Treatment group	Placebo + SoC	Anakinra + SoC	
	Number of subjects	189	405	
	WHO-CPS Day 28	0=Fully recovered PCR (-): 50 (26.5)	0=Fully recovered PCR (-): 204 (50.4)	

	Frequencies and percentage per item in the ordinal scale n (%)	1=Asymptomatic PCR (+): 6 (3.2)	1=Asymptomatic PCR (+): 40 (9.9)
		2=Symptomatic independent: 74 (39.2)	2=Symptomatic independent: 93 (23.0)
		3=Symptomatic assistance needed: 21 (11.1)	3=Symptomatic assistance needed: 25 (6.2)
		4=Hospitalized no need for oxygen: 3 (1.6)	4=Hospitalized no need for oxygen: 9 (2.2)
		5=Hospitalized with nasal/mask oxygen 10 (5.3)	5=Hospitalized with nasal/mask oxygen 8 (2.0)
		6=Need for HFO or NIV: 1 (0.5)	6=Need for HFO or NIV: 1 (0.2)
		7=Mechanical ventilation with P/F >150: 1 (0.5)	7=Mechanical ventilation with P/F >150: 1 (0.2)
		8=Mechanical ventilation with P/F <150 or vasopressors: 4 (2.1)	8=Mechanical ventilation with P/F <150 or vasopressors: 5 (1.2)
		9=Mechanical ventilation with P/F <150 and vasopressors or hemodialysis or ECMO: 6 (3.2)	9=Mechanical ventilation with P/F <150 and vasopressors or hemodialysis or ECMO: 6 (1.5)
		10=Dead: 13 (6.9)	10=Dead: 13 (3.2)
Effect estimate per comparison	Primary endpoint **WHO-CPS Day 28**	Comparison groups	Anakinra + SoC vs. Placebo + SoC
		Odds-ratio (OR) (adjusted)	0.36
		Confidence Interval (CI) (95%)	0.26 - 0.50
		P-value Ordinal regression analysis	p<0.001
Analysis description	**Secondary analysis (pre-specified)**		
Analysis population and time point description	FAS		

Descriptive statistics and estimate variability	Treatment group	Placebo + SoC	Anakinra + SoC	
	Number of subjects	189	405	
	WHO-CPS change Day 28 (absolute decrease) Median	3	4	
	IQR=InterQuartile Range	2.5	2.0	

Effect estimate per comparison	Key secondary endpoint: **WHO-CPS change Day 28** (absolute)	Comparison groups	Anakinra + SoC vs. Placebo + SoC
		OR (adjusted)	0.40
		95% CI	0.29-0.55
		P-value Ordinal regression analysis	<0.001

Analysis description	**Supportive analysis 2 for primary analysis (pre-specified)**
Analysis population and time point description	FAS

Descriptive statistics and estimate variability	Treatment group	Placebo + SoC	Anakinra + SoC
	Number of subjects	189	405
	WHO-CPS Day 28 Spect 1 Frequencies and percentage per category n (%)	Fully resolved: 50 (26.5) Persistence: 139 (73.5)	Fully resolved: 204 (50.4) Persistence: 201 (49.6)
	WHO-CPS Day 28 Spect 2 Frequencies and percentage per item in the ordinal scale n (%)	WHO CPS ≤5: 164 (86.8) WHO-CPS ≥6: 25 (13.2)	WHO CPS ≤5: 379 (93.6) WHO-CPS ≥6: 26 (6.4)

Effect estimate per comparison	**WHO-CPS Day 28 Spect 1**	Comparison groups	Anakinra + SoC vs. Placebo + SoC
		OR (adjusted)	0.36
		95% CI	0.25-0.53

		P-value Logistic regression analysis	<0.001
	WHO-CPS Day 28 Spect 2	Comparison groups	Anakinra + SoC vs. Placebo + SoC
		OR (adjusted)	0.46
		95% CI	0.26-0.83
		P-value Logistic regression analysis	0.010

Analysis description	**Supportive analysis 3 for primary analysis (pre-specified)**			
Analysis population and time point description	FAS			
Descriptive statistics and estimate variability	Treatment group		Placebo + SoC	Anakinra + SoC
	Number of subjects		189	405
	TUSRF Day 28 Frequencies and percentage per category SRF yes/no n (%)		SRF No: 127 (67.2) Yes: 62 (32.8)	SRF No: 319 (78.8) Yes: 86 (21.2)
	TUSRF Day 28	HR (adjusted)	0.66	
		95% CI	0.47-0.91	
		P-value Cox regression analysis	0.012	
Analysis description	**Post-hoc survival analysis (not pre-specified)**			
Analysis population and time point description	FAS			
Descriptive statistics and estimate variability	Treatment group	Placebo + SoC	Anakinra + SoC	
	Number of subjects	189	405	
	TUD Day 28 Frequencies and percentage n (%)	Deaths: 13 (6.9)	Deaths: 13 (3.2)	
Effect estimate per comparison	**TUD Day 28**	Comparison groups	Anakinra + SoC vs. Placebo + SoC	

		HR	0.45
		95% CI	0.21-0.98
		P-value Cox regression analysis	0.045

Clinical studies in special populations

Subgroup analyses were performed for the primary endpoints in three main subgroups of patients.

- Gender (male and female).
- Patients with suPAR of >9 ng/mL and ≤9 ng/mL before randomization.
- Patients with Charlson's Comorbidity Index (CCI) score of ≥2 and <2 before randomization. No subgroup analysis was performed for age since age was calculated with CCI.

Overall, results were consistent with the primary analysis showing unadjusted OR in favour of anakinra in all the subgroups. There were minimal differences between females and males; suPAR above 9 ng/mL or at 9 ng/mL or below; Charlson's Comorbidity Index (CCI) <2 or ≥2 as shown below.

Subgroup analysis for female patients showed in the univariate analysis OR 0.44 (0.27-0.72) p=0.001 and for male patients in the univariate analysis OR 0.30 (0.20-0.47) p<0.001.

Subgroup analysis for suPAR ≤ 9ng/mL in the univariate analysis OR 0.36 (0.25-0.5) p<0.001 and for suPAR > 9ng/mL OR 0.35 (0.18-0.65) p=0.001.

Subgroup analysis for CCI <2 in the univariate analysis OR 0.42 (0.24-0.73) p=0.003, and for CCI ≥ 2 OR 0.33 (0.23-0.49) p<0.001.

The effect of anakinra was similar in patients below and above 65 years of age as shown in the table below.

Univariate and multivariate analyses for the primary endpoint for patients <65 years

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Group of treatment (Anakinra vs placebo)	0.32	0.21-0.49	<0.0001	0.29	0.18-0.44	<0.0001
Intake of dexamethasone (Yes/No)	1.87	1.07-3.26	0.026	2.17	0.53-8.85	0.282
Severe COVID-19 by WHO (Yes/No)	1.97	1.13-3.44	0.017	1.00	0.24-4.09	0.999
BMI >30 kg/m^2 (Yes/No)	1.54	1.03-2.31	0.033	1.51	1.00-2.28	0.049
Country (Italy vs Greece)	2.59	1.17-5.71	0.018	3.45	1.50-7.92	0.003

Abbreviations: BMI, Body mass index; CI, Confidence interval; COVID-19, Coronavirus disease 2019; OR, Odds ratio; WHO, World Health Organization.

Univariate and multivariate analyses for the primary endpoint for patients ≥65 years

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Group of treatment (Anakinra vs placebo)	0.39	0.24-0.63	<0.0001	0.39	0.24-0.64	<0.0001
Intake of dexamethasone (Yes/No)	2.22	1.24-3.96	0.007	1.60	0.36-6.10	0.488
Severe COVID-19 by WHO (Yes/No)	2.25	1.24-4.07	0.007	1.33	0.42-4.92	0.666
BMI >30 kg/m^2 (Yes/No)	1.01	0.62-1.64	0.953	0.86	0.52-1.41	0.550
Country (Italy vs Greece)	0.86	0.46-1.62	0.646	0.86	0.45-1.65	0.669

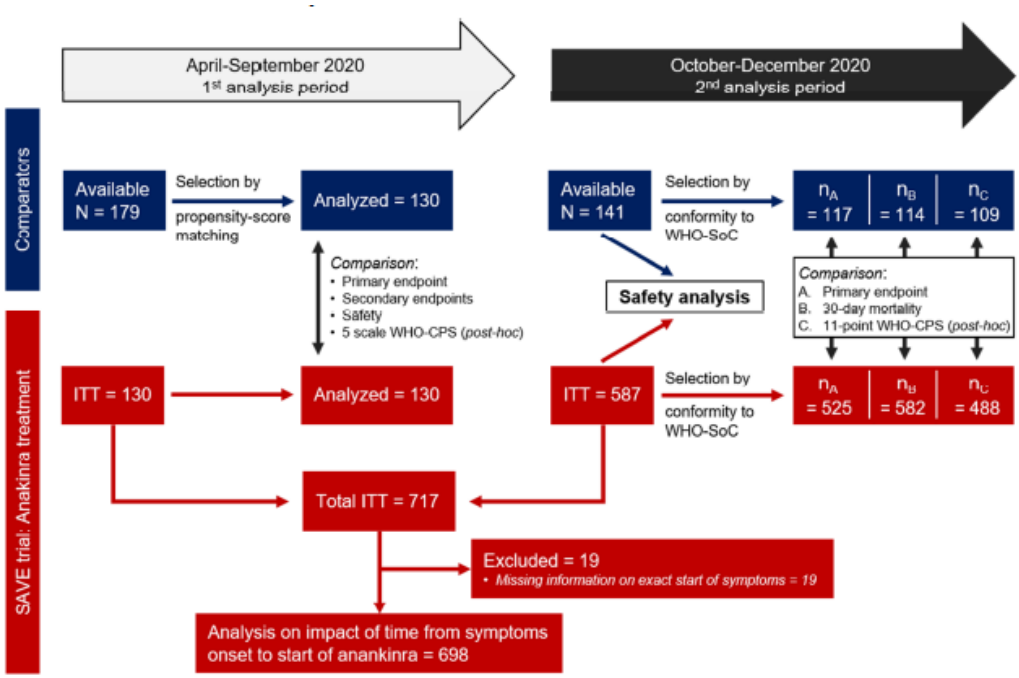
Abbreviations: BMI, Body mass index; CI, Confidence interval; COVID-19, Coronavirus disease 2019; OR, Odds ratio; WHO, World Health Organization.

Supportive study

The SAVE study

The SAVE study is an ongoing, prospective, open-label, single-arm study. Eligible patients in the SAVE study were the same as the patient population in the SAVE-MORE study (i.e., males and females ≥18 years of age hospitalized with confirmed infection by SARS-CoV-2 virus, LRTI [radiologically confirmed], and plasma suPAR levels ≥6 ng/mL). Patients were included in two periods. Eligible patients in the SAVE study received SoC and anakinra 100 mg s.c. q.d. for 10 days. See Figure below for study-flow.

Figure 13: SAVE study flow chart of patient selection of the 2 periods (SAVE study)



Abbreviations: CPS, Clinical Progression Scale; SoC, Standard-of-care; ITT, Intent-to-treat; WHO-CPS, World Health Organization Clinical Progression Scale.

In the first period from April to September 2020, 130 patients were included in the study and treated with anakinra+SoC and compared to a propensity matched control group of 130 patients receiving SoC treatment (in the same period and at same centers). Baseline data were comparative between the two groups. Results were in benefit for anakinra 22.3% (95 % CI: 16.0 to 30.2) receiving anakinra+SoC progressed to SRF by Day 14 (primary endpoint), whereas 59.2 % (50.6 to 67.3 %) among the

parallel SoC-treated patients progressed to SRF by Day 14 (adjusted HR=0.28; 95 % CI: 0.18 to 0.44, p<0.001).

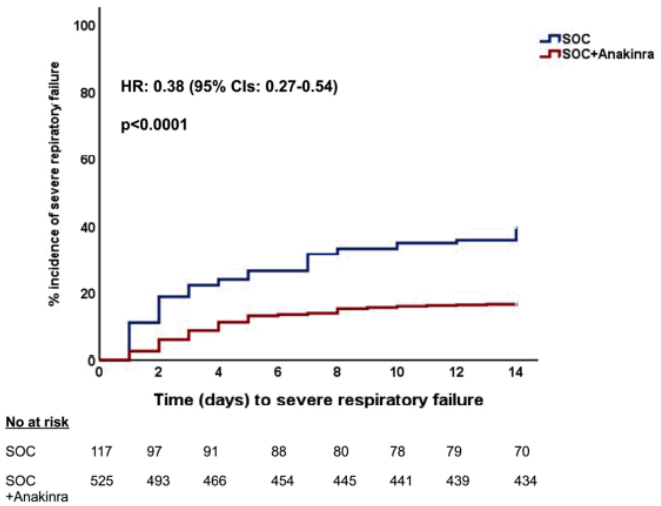
Table 18: Primary, secondary, and exploratory study outcomes of the first period (SAVE study)

	Parallel SoC (N=130)	Anakinra+SoC (N=130)	OR (95% CI)	p-value
SRF by Day 14, n (%)	77 (59.2)	29 (22.3)	0.19 (0.12-0.34)	<0.0001
Mechanical ventilation by Day 14	65 (50.0)	25 (19.2)	0.24 (0.14-0.42)	<0.0001
Non-invasive mechanical ventilation by Day 14	9 (6.9)	6 (4.6)	0.65 (0.23-1.88)	0.596
14-day mortality	16 (12.3)	6 (4.6)	0.35 (0.13-0.91)	0.043
SOFA score on Day 7, median (Q1-Q3)	2 (0 to 3)	1 (0 to 3)	NA	0.540
SOFA score on Day 14, median (Q1-Q3)	2 (0 to 9)	1 (0 to 3)	NA	0.191
Absolute change of SOFA score by Day 7 compared to baseline, median (Q1-Q3)	0 (-1 to 1)	0 (-1 to 0)	NA	0.356
Absolute change of SOFA score by Day 14 compared to baseline, median (Q1-Q3)	0 (-1 to 6)	-2 (-1 to 0)	NA	0.004
Absolute change of respiratory symptoms score by Day 7 compared to baseline, median (Q1-Q3)	0 (0 to 0.75)	-1 (-3 to 0)	NA	0.019
Absolute change of respiratory symptoms score by Day 14 compared to baseline, median (Q1-Q3)	0 (-0.75 to 0)	-2 (-4 to -1)	NA	0.016
Ventilator-free days, mean (SD)	18 (11)	25 (8)	NA	<0.0001
30-day mortality, n (%)	29 (22.3)	15 (11.5)	0.45 (0.23-0.90)	0.031
90-day mortality, n (%)	40 (30.8)	22 (16.9)	0.46 (0.25-0.83)	0.013

Abbreviations: CI, Confidence interval; N, Number of patients; NA, Non-applicable; OR, Odds ratio; Q, Quartile; SD, Standard deviation; SoC, Standard-of-care; SOFA, Sequential organ failure assessment; SRF, Severe respiratory failure.

In the SAVE study period 2; parallel SoC-treated patients and anakinra+SoC-treated patients (117 and 525 patients, respectively) were included. Due to the few available comparators, no propensity score matching was done. This means that the control group did not match the anakinra group in some essential ways e.g. the proportion having severe COVID-19 by WHO was 68.4% of the comparators and 82.7 % of the anakinra arm (p=0.0001) and diabetes type 2 in 12.8 % in the comparator arm vs 22.7% in the anakinra arm (p=0.017). However, since severe COVID-19 was more frequent in the anakinra arm this could not affect the effect positively and is thus acceptable. The incidence of SRF among the parallel SoC-treated patients was significantly greater compared to the patients treated with anakinra (adjusted HR=0.33; 95 % CI: 0.32 to 0.49; p<0.001). See Figure below. Further, Mortality Day 28 was decreased: Multivariate Cox regression analysis showed that survival was prolonged among the patients treated with anakinra (HRadj: 0.38; 95 % CI: 0.23 to 0.62; p<0.001).

Figure 14: Progression into SRF assessed in the second period (SAVE study)



Abbreviations: CI, Confidence interval; HR, Hazard ratio, SoC, Standard-of-care.
The time to SRF is compared among 117 parallel patients who were treated with SoC treatment according to the WHO recommendations and 525 patients in the SAVE study who were treated with SoC and anakinra.

In both periods of the SAVE study, secondary efficacy endpoints were supportive of the primary endpoint and demonstrated clinical improvement with anakinra treatment. However, the design of the SAVE trial does not facilitate a robust comparison of the treatment effects of anakinra towards a control. Even though a control group is established by the use of propensity scoring, the value of such a control is questionable. Furthermore, both the selection of subjects for intervention with anakinra, done at investigators discretion and the selection for the controls, which is not sufficiently described, could be the source of considerable biased treatment effects. It is agreed that results from the first two periods of the SAVE study, though not randomized nor blinded, provide support for the efficacy for the treatment of anakinra in patients with moderate-severe COVID-19 pneumonia who are at risk of progressing to SRF. It should be noted that this study was also suPAR guided and included only patients with suPAR>6 ng/mL as for SAVE MORE.

When analysing the two main secondary study outcomes of the SAVE study, i.e. the effect of anakinra treatment on circulating inflammatory biomarkers and function of peripheral blood mononuclear cell (PBMCs), it was noted that suPAR was increased among anakinra-treated patients on Day 7 from baseline. Nevertheless, one would expect suPAR to decrease in patients with beneficial effect of anakinra. Upon request from the CHMP, the MAH clarified that there was a difference between using suPAR as a prognostic marker and as a response marker. Additionally, data showed that suPAR increase or decrease by Day 7 is not relevant to predict the progression to SRF or 30 day-mortality. It is agreed that the evidence presented does not support the use of suPAR as a response biomarker.

Additional studies with anakinra in the treatment of COVID-19

Upon request from the CHMP, the MAH clarified that very few completed, randomized, controlled studies are available: SAVE-MORE, CORIMUNO-ANA-1, REMAP-CAP, COV-AID. Further, there are five ongoing/completed studies with no published results and four terminated. An overview of the three randomized controlled studies of IL1-RA agents in the treatment of COVID-19 (besides SAVE-MORE) is presented below:

The **CORIMUNO-ANA-1** was a randomized, open-label, controlled study of 116 patients with moderate COVID-19 pneumonia (requiring min 3 L/min, WHO-CPS at 5) randomized 1:1 to high-dose i.v. anakinra at 200 mg twice daily for 3 days, followed by lower dosing over 2 days or non-standardized SoC treatment at the discretion of the physician. In this study anakinra did not improve survival or need for MV or NIV. See table below.

Table 19: Primary and secondary efficacy outcomes (CORIMUNO-ANA-1, Lancet Respir Med 2021;9;295-304)

	Anakinra group (n=59)	Usual care group (n=55)	Treatment effect
Coprimary outcomes			
WHO-CPS score of >5 points at day 4	21 (36%)	21 (38%)	−2·5% (90% CrI −17·1 to 12·0)*
Posterior probability of any benefit	..	..	61·2%
Posterior probability of moderate or greater benefit	..	..	36·9%
Non-invasive ventilation, mechanical ventilation or death up to day 14	28 (47%)	28 (51%)	0·97 (90% CrI 0·62 to 1·52)†
Posterior probability of any benefit	..	..	54·5%
Posterior probability of moderate or greater benefit	..	..	31·7%
Secondary outcomes			
Overall survival			
Mortality at day 14	9 (15%)	13 (24%)	0·56 (95% CI 0·23 to 1·39)‡
Mortality at day 28	13 (22%)	13 (24%)	0·77 (95% CI 0·33 to 1·77)‡
Mortality at day 90	16 (27%)	15 (27%)§	0·97 (95% CI 0·46 to 2·04)‡
WHO-CPS score (10-point scale)			
Day 4	5 (5 to 6)	5 (5 to 6)	0·80 (95% CrI 0·38 to 1·68)¶
Day 7	5 (5 to 7)‖	5 (5 to 7)**	0·69 (95% CrI 0·33 to 1·43)¶
Day 14	5 (2 to 8)††	5 (3 to 8)**	0·70 (95% CrI 0·35 to 1·38)¶
Day 2 to 14 (longitudinal analysis)	..	..	0·92 (95% CrI 0·32 to 2·65)¶
Time to discharge			
Discharged at day 28	34 (58%)	34 (62%)	0·91 (95% CI 0·56 to 1·48)‡
Time to oxygen supply independency			
Independent from oxygen at day 28	37 (63%)	38 (69%)	1·01 (95% CI 0·64 to 1·61)‡

Data are n (%), median (IQR), or estimate with 90% or 95% CrI or 95% CI in parentheses. 95% CrIs are shown for Bayesian analyses, and 95% CIs for frequentist analyses. CrI=credible interval. WHO-CPS=WHO Clinical Progression Scale. *Median posterior absolute risk difference. †Median posterior hazard ratio adjusted for age and centre. ‡Hazard ratio, adjusted for age and centre. §One patient died on day 91 and is not counted here. ¶Median posterior odds ratio in a proportional odds model, adjusted for age and centre. ‖n=54 with available data. **n=53 with available data. ††n=56 with available data.

It is acknowledged that CORIMUNO-ANA-1 might have had an inadequate sample size. The study was ended prematurely due to futility, as the study did not show any difference in the primary endpoint between treatment arms after inclusion of 116 patients. Anakinra was administered in a higher dose but for a marginally shorter time than in the SAVE-MORE study, and the cumulative dose was higher. The included population reflects the included population in the SAVE-MORE study, with the exception that the SAVE-MORE study only included patients with a suPAR ≥6 ng/ml, whereas the COVIMUNO-ANA-1 included patients based on CRP >25 mg/ml.

REMAP-CAP was an open-label, randomized, adaptive platform study investigating multiple therapeutic approaches in critically ill COVID-19 patients, hereof also anakinra n=373. Patients enrolled in REMAP-CAP had already progressed to requiring intensive care and respiratory and/or cardiovascular support at baseline. The REMAP-CAP study (although not peer reviewed yet) showed no effect on the primary endpoint of anakinra compared with standard of care in critical ill patients.

COV-AID was a prospective, multicenter, open-label, randomized, controlled study. The COV-AID study has a 2 × 2 factorial design to evaluate IL-1 blockade vs no IL-1 blockade and IL-6 blockade vs no IL-6 blockade. Only 44 patients received anakinra alone. The studied population differ from the SAVE-MORE population in a tendency toward more severe disease. Patients in the COV-AID have lower PaO_2/FiO_2 median 135 (82-233) (PaO_2/FiO_2<150 excluded in SAVE-MORE), higher laboratory values (CRP, Ferritin, D-dimer) and fewer received remdesivir (5%) and dexamethasone (64%). In addition, the study design is complex and it seems that 2/3 of the patients assessed in the primary endpoint also received IL-6 blocker (in both the IL-1 group and in the comparator group). The study showed no benefit of anakinra.

4 terminated studies were also summarized by the MAH. **Sobi.IMMUNO-101** study was ended after inclusion of five patients in the anakinra group. The MAH explain that the trial was prematurely terminated for unknown reasons and data are not available. **JAKINCOV** a phase 2, open-label, randomized, controlled trial assessing the efficacy of anakinra and ruxolitinib in patients with severe and critical COVID-19. The study was ended after inclusion of two patients for unknown reason. **INFLAMMACOV** a phase 3, open-label, prospective, randomized trial assessing the efficacy of anakinra or tocilizumab alone or in combination with ruxolitinib in patients with severe COVID-19 (stages 2b and 3). Further details and reason for termination are not available. The fourth prematurely terminated study was **ANACONDA** a multicenter, open-label, randomized, controlled trial comparing the administration of optimized SoC and anakinra vs optimized SoC alone in patients with COVID-19 and worsening respiratory symptoms hospitalized in a medical unit. Due to a concern about an imbalance in the number of deaths in the anakinra arm compared to SOC the study was stopped after inclusion of 71 patients. The MAH clarified that the French Health Authority made further analysis of data from ANACONDA, as well as results available from other clinical studies and confirmed that there was no potential safety risk linked to the use of anakinra in COVID-19 patients. However, no data were made available.

In addition, the MAH referred to **3 systematic review/Meta-analyses** including both observational and RCT data of anakinra use in COVID-19. The study by, Kyriazopoulou et al included 9 studies of patients admitted to the hospital with pneumonia due to COVID-19: 8 studies were observational, and 1 was an RCT (i.e. CORIMUNO-ANA-1). Numbers of patients in the studies were 12- 130 treated with anakinra. Mortality was significantly lower in anakinra-treated patients (38/342 [11.1 %]) as compared with 137/553 (24.8 %) observed in patients receiving SoC and/or placebo on top of SoC. Barkas et al 2021 made a systematic review of 9 studies included, 7 studies overlapped with Kyriazopoulou's meta-analysis and numbers of patients in the studies were 12- 130 treated with anakinra. Anakinra reduced the need for invasive MV (OR: 0.38, 95% CI: 0.17 to 0.85, p=0.02, I2=67%; 6 studies, n=587) compared with SoC. Kyriakoulis et al 2021 made a systematic review of 6 studies including SAVE-MORE and SAVE. The pooled HR for death in patients treated with anakinra was 0.47 (95% CI: 0.34 to 0.65). The systematic reviews point in a direction of benefit of anakinra. However, the studies included are small and mostly controlled by historical cohorts, where the SoC was different as compared with today.

2.4.3. Discussion on clinical efficacy

Anakinra is a recombinant human IL-1Ra that blocks the activity of cytokine IL-1 (IL-1α and IL-1β) by competitively inhibiting its binding to the IL-1RI, thus controlling active inflammation. Anakinra is currently approved for the treatment of Rheumatoid Arthritis, all forms of Cryopyrin-associated periodic syndrome, Still's disease (including Systemic juvenile idiopathic arthritis and Adult-onset Still's disease) and for Familial Mediterranean fever in the EU. With this application, the MAH is proposing to add a new indication for the treatment of COVID-19. The MAH initially sought a broad indication as follows: *'Kineret is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adult patients with pneumonia who are at risk of developing severe respiratory failure.'* However, this was not considered acceptable by the CHMP and is further discussed below.

This application is primarily based on one single pivotal phase 3 study (SAVE-MORE), an investigator-sponsored study. The results discussed below are based on the interim CSR. Final CSR will be submitted by end of December 2021 as a Type II variation and will contain data by day 60 and day 90. Further, the MAH submitted results from the ongoing, open label phase 2 study (SAVE) which was considered as supportive by the CHMP. Upon request from the CHMP, the MAH also presented additional studies conducted with anakinra in the treatment of COVID-19, which are discussed below.

No dose response studies were performed in subjects with COVID-19. The posology proposed by the MAH is as follows: 100 mg s.c. once daily for 10 days. The supportive Phase 2 SAVE study was considered as a dose defining study and together with data available for other anakinra indications was sufficient to inform on the choice of the dose for COVID-19 patients. This was agreed by the CHMP.

Design and conduct of clinical studies

SAVE-MORE was a pivotal, confirmatory, prospective, multicenter, double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of anakinra guided by suPAR in patients with LRTI by SARS-CoV-2 in improving the clinical state of COVID-19 over 28 days. Patients were randomly assigned 1:2 to one of the two treatment groups placebo+SoC or anakinra+SoC. Anakinra was injected s.c. as 100 mg once daily for 10 days.

Patients were recruited from 37 sites. However, protocol deviations from the SoC treatment were not equally distributed and occurred significantly more often in the placebo group 14,3% than in the anakinra group 3.2%. Deviations consisted of increase of the corticosteroid or discontinuation of the study drug and administration of other anti-cytokines.

Bias in the comparative analyses related to intercurrent events are considered to favor the placebo group and thus are considered conservative with regards to the estimated treatment difference. This is supported by the requested post hoc analysis, in which bias due to intercurrent events were minimized by relevant means of imputation. Further, in the post hoc analysis submitted by the MAH, the difference to placebo remained significant, in line with what was seen in the pre-defined analyses. Furthermore, the estimated treatment difference (i.e. the placebo controlled anakinra effect) was more pronounced with a point estimate of the OR of 0.32 vs 0.36 in the pre-defined analysis in which bias of intercurrent events was not addressed. The issue on handling of intercurrent events was therefore considered to be sufficiently addressed by the CHMP.

As the study drug was an s.c. injection administered at the hospital, no issues were considered to be expected regarding study drug compliance.

Overall, the conduct of the study is acceptable by the CHMP.

Endpoints

The primary study endpoint was the comparative 11-point WHO-CPS between the 2 arms. This was expressed as the distribution of the frequencies of each score of the scale in each arm of treatment by Day 28. The primary endpoint was changed during the study conduct from a dichotomic assessment on respiratory failure to the 11 point WHO-CPS scale. Upon request from the CHMP, the MAH conducted a sensitivity analysis based on the original primary endpoint. The results are presented and discussed below. The MAH performed several sensitivity analyses on the primary endpoint, and supportive secondary and exploratory efficacy endpoints. In addition to the 11-point of WHO-CPS score, the SOFA (sequential organ failure assessment) sepsis score was also evaluated. Further, time to discharge, time to progression of disease and long-term safety by 60 and 90 days were also evaluated. Overall, the primary and secondary endpoints of the pivotal SAVE-MORE study are adequate for the objectives defined as part of the study.

Statistical analysis

All statistical tests were done at 5% level. Consequentially there was no control of the family wise error rate, and the analyses of secondary endpoints are thus regarded as being supportive of the primary endpoint.

Adjustment by factors used in the randomisation was not done according to the Guideline on adjustment for baseline covariates in clinical trials (EMA/CHMP/295050/2013), as these were included as main effects in the analyses, whereas any interactions have been excluded. Furthermore, 'country' also appeared to be a stratification factor but was not included in any of the analyses performed by the MAH. Due to the limited impact across the secondary endpoints and taking into account that those endpoints are only supportive, the issue on stratification factors was not pursued further by the CHMP.

Some endpoints analysed were conditioned by the presence/absence of specific events, such that only a proportion of the population was analysed, e.g. discharge from ICU or change in SOFA score at day 14. However, the MAH did not identify this as a joint endpoint (entering ICU together with leaving ICU; or remaining in hospital at day 14 together with SOFA score) and did omit the conditional event doing only a marginal analysis on the other part of the joint endpoint. Since efficacy is supposed to have an impact on the conditioned event, a proper analysis should have included both parts. Upon request from the CHMP, an updated analysis considering these endpoints to be joint was provided by the MAH, it provided further insight on the understanding of treatment effects, but due to the conditional nature of these endpoints, there remains considerable unclarity on how the results are to be interpreted. Nevertheless, the CHMP considers that it is very unlikely that the B/R assessment will be impacted. The issue was therefore not further pursued by the CHMP.

The MAH initially specified that in the time-to-event analyses data were censored at end of the analysed period (Day 14, Day 28). However, the MAH should have specified the censoring strategy for each time to event analysis, for example in the analysis of 'Time to hospital discharge' how were patients who died before Day 28 handled and how were data censored for withdrawals and dropouts. Upon request from the CHMP, the MAH explained that number at risk of patients in each group at day 4, 8, 12, 16, 20, 24 and 28 will be provided at the bottom of all survival curves as well as standard output from time-to-event analysis, such as median time to event or equivalent in the final CSR that will be submitted by End of December 2021 via a type II variation. This was accepted by the CHMP.

The estimation of the effect of the intervention in the outcomes was performed in accordance with the *a priori* statistical plan. In addition, due to the strong link between disease severity and use of dexamethasone, some uncertainty was raised on whether the effect of anakinra may be related to dexamethasone use. Upon request from the CHMP, a subgroup analysis for patients receiving or not receiving dexamethasone was provided. The magnitude of the effect was different in these subgroups but in both, anakinra had a beneficial effect independently of the administration of dexamethasone. In addition, for all analyses, the estimated treatment effect was adjusted for a potential effect of dexamethasone.

Study participants

Eligible patients were hospitalised patients with confirmed SARS-CoV-2, LRTI based on chest X-ray or computed tomography of the chest, and suPAR level ≥ 6 ng/ml.

Although eligible patients were hospitalised, hospitalisation is not included in the proposed wording of the therapeutic indication. This has been endorsed by the CHMP as the requirement for supplemental oxygen (low- or high-flow) usually required an hospital setting/hospitalisation.

The included population had suPAR of median (IQR) 7.6 ng/ml (6.9-9.1). Hence, anakinra was not studied in patients with a suPAR level < 6 ng/ml. Nevertheless, the indication that was initially proposed by the MAH did not restrict the use of anakinra in patients with a suPAR level ≥ 6 ng/ml. The MAH was therefore requested to further justify the proposed indication regardless of suPAR level. The MAH argued that patients with suPAR below 6 ng/ml are likely to benefit from treatment, however, this was not documented nor sufficiently justified, as no data in subjects with suPAR < 6 ng/ml have been provided. Therefore, in the absence of clinical efficacy established in patients with suPAR level < 6

ng/ml, the indication was ultimately restricted to patient with suPAR ≥ 6 ng/ml. This has been adequately reflected in SmPC sections 4.4 and 5.1.

There are some well-known risk factors for progression of the disease e.g. advanced age or COPD. However, not all of the included patients had such systemic comorbidities (39% placebo group 43% anakinra group). Nevertheless, this was not considered to be an issue as patients with moderate to severe COVID-19 pneumonia (WHO classification) are expected already to be at risk of progression to severe respiratory failure.

Efficacy data and additional analyses

In the single pivotal phase 3 SAVE-MORE study, a total of 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 allocated to the placebo+SoC arm, and 412 patients were allocated to the anakinra+SoC arm. 12 patients withdrew consent and requested the removal of all data, leaving a final intention-to-treat (ITT/FAS) analysis set of 594 patients with 189 patients in the placebo+SoC arm and 405 patients in the anakinra+SoC arm. 1 patient allocated to the placebo+SoC arm was reported as lost to follow-up. Except for one sensitivity analysis all analyses were made on the ITT population. The PP population consisted of: SoC + placebo= 162 patients; SoC + anakinra= 292 patients.

Baseline characteristics and disease severity

Slightly more patients in the placebo arm had severe pneumonia at the start of the treatment than in the anakinra group (93.7% vs 90.4%, respectively). In addition, slightly more patients in the placebo arm needed high flow oxygen and the P/F ratio was slightly lower at baseline than in the anakinra group. The MAH considered that the allocation of patients with severe COVID-19 was similar between the two arms despite the numeric differences observed. The CHMP did not fully agree with the MAH as the inability to exclude that this distribution could happen by chance is not synonymous of having equivalent or similar groups. Further, the differences in baseline disease severity could potentially impact on differences in disease severity at day 28 in favour of the investigative drug. However, the CHMP considered that severe COVID-19 by WHO were taken in account in the multivariate analysis and that the identified imbalance at baseline on signs of pneumonia, is expected to be correlated and to overall counterbalance potential bias on this regard.

Type 2 diabetes mellitus, Chronic heart failure, Chronic renal disease, Chronic obstructive pulmonary disease, Coronary heart disease and Atrial fibrillation were well balanced between treatment arms.

Viral load in blood measured as copies of SARS-CoV-2 gene was equal in both groups. The MAH did not provide data or analyses on variants and argued that the hyperinflammatory consequences would remain the same, which is agreed and acceptable by the CHMP.

Information on baseline characteristics and disease severity were adequately reflected into SmPC section 5.1, as requested by CHMP.

Co-administered medication

A marginally higher proportion in the anakinra arm received remdesivir, whereas the opposite was the case for dexamethasone at enrolment. In addition, there were more patients that received antibiotics in the placebo arm. This possibly reflects that more patients in the placebo arm had severe pneumonia. Overall, baseline medications were well balanced between arms. There were no relevant changes in SOC or temporal trends in the prescription of remdesivir as SOC. The MAH also provided univariate and multivariate analyses for the primary endpoint including treatment with remdesivir as a covariate, which did not show any modification of anakinra effect by remdesivir use. This is agreed.

Further, data from patients not treated with dexamethasone suggest that anakinra effect is not dependent on whether this was included in the SoC or not, as discussed above.

During the study, proportionally more patients received noradrenaline and propofol in the placebo arm. In addition, more patients in the placebo arm received furosemide than in the anakinra arm (19.6% vs 10.9%, respectively). It is agreed that this most likely reflects that worsening into SRF occurred more often in the placebo arm. The remaining relevant co-administered drugs provided upon request from the CHMP were equally distributed across treatment arms.

Primary endpoint

The pre-specified primary endpoint was the comparative 11-point WHO-CPS between the two arms of treatment; and was expressed as the OR for allocation to lower severity after anakinra treatment compared to placebo at day 28 in the FAS population. This was assessed by ordinal regression analysis unadjusted and adjusted for other factors (administration of dexamethasone, severe COVID-19, BMI>30kg/m^2 and country). The adjusted (multivariate) analysis anakinra+SoC was also beneficial (OR 0.36; 95 % CI 0.26 to 0.50; P<0.001), hence the primary endpoint was met and considered to be statistically significant. The unadjusted OR at Day 28 was 0.36 (95 % CI 0.26 to 0.49; P<0.001).

In addition, five sensitivity analyses of the primary endpoint were performed. 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. It is acknowledged that the first four sensitivity analysis on the primary endpoint were in favour of anakinra and did support the primary endpoint. The fifth sensitivity analysis showed the impact on the estimated treatment effect when adjusting for stratifying factors.

Three analyses of the primary endpoint were also made and supported the clinical benefit of anakinra treatment, though p-values were nominal as no hierarchy for analyses beside primary endpoint was predefined. In a multivariate logistic regression model of the WHO-CPS of 0 or ≥1 (the first spectrum) anakinra was protective (OR: 0.36; 95 % CI 0.25 to 0.53; P<0.001). The same was present when (the second spectrum) patients were divided into WHO-CPS ≥ 6 or ≤ 5 (OR: 0.46; 95 % CI 0.26 to 0.83; P: 0.010). Lastly, Kaplan Meier curve of time to progression to SRF illustrate an inhibitory effect of anakinra. Curves start to separate from approximately Day 3 and stay more or less parallel from Day 8 and onwards. Overall, the direction of anakinra effect was the same in all the analyses and therefore supportive of anakinra benefit. Further, an important post hoc analysis (not controlled for multiplicity) regarding time to death was made and showed that anakinra treatment reduced the mortality compared to placebo (HR: 0.45, 95% CI 0.21-0.98, P=0.045). 6.9% of patients in the placebo+SoC group and 3.2% of patients in the anakinra+SoC group died by Day 28. Separation of the survival curve occurred approximately from day 5.

As discussed, the MAH clarified that SoC did not change in the study period. The additive effect of dexamethasone is insignificant in the presence on anakinra (in the multivariable ordinal regression analysis), and so is the additive effect of remdesivir.

Upon request from the CHMP, the MAH also provided on treatment effects using the originally proposed primary endpoint; the comparative incidence of SRF between the two arms of treatment by day 14 as measured by the 11-point WHO-CPS scale. Patients dying before study visit of day 14 were considered achieving the primary endpoint. SRF was defined as clinical progression into hypoxemia with pO_2/FiO_2 <150 mmHg necessitating MV or NIV or ECMO. Univariate and multivariate stepwise analyses of the incidence and time to SRF progression at Day 14 were performed. In both analyses, anakinra treatment prevented the progression to SRF by Day 14. The adjusted OR for the incidence of SRF by Day 14 is 0.59 (95% CI: 0.40 to 0.89), and this is consistent with the analysis using the ordinal WHO-

CPS scale at Day 14 (adjusted OR: 0.58, 95% CI: 0.42 to 0.79). Overall, the CHMP agreed that the results presented by the MAH were in favour of anakinra and supported the primary endpoint.

Secondary endpoints

Several analyses (absolute and relative change in WHO CPS at days 14 and 28, SOFA score at days 7 and 14, suPAR at days 4 and 7 and others) were included as secondary endpoints. It is agreed that results are supportive of anakinra+SoC treatment. 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. However, the value of an absolute decrease of 1 additional point (4 points instead of 3 points) in the WHO-CPS can be discussed; and is dependent on where in the scale the decrease occurs. Regarding the absolute and relative change of the WHO-CPS at day 14 from baseline Day 1, results were also in favour of anakinra.

A multivariate Cox regression analysis showed that the time until hospital discharge was 1 day shorter in the anakinra+SoC group than in the placebo+SoC group (HR: 1.21; 95 % CI 1.01 to 1.45; P=0.042). However, the clinical importance of one day shorter for hospitalisation could be questioned. Time until discharge from ICU is significantly shorter in the anakinra arm, however some clarity regarding censoring was lacking. As this is a secondary endpoint and those are regarded as only supportive, this issue was not further pursued by the CHMP.

suPAR, CRP and IL-6 variation between baseline and days 4 and 7 showed a significantly larger decrease in anakinra + placebo when compared to SOC + placebo. However, the other biomarkers analysed such as ferritin and D-dimer did not show the same differences. While this information is considered to be relevant and supportive of the proposed mechanism of anakinra benefit, with an effect in decreasing inflammatory response, it should also be noticed that correlation with clinical improvement is not shown. Upon request from the CHMP, the MAH discussed the possibility to use biomarkers to guide an early stop of anakinra therapy. Nevertheless, it is agreed that the available data is insufficient to draw any conclusion and that additional prospective data would be necessary to validate any kind of stopping rule based on decreases in biomarkers Day 4 and 7.

Special populations

Three subgroups were analysed: females and males; suPAR above 9 ng/ml or at 9 ng/ml or below; and Charlson's Comorbidity Index (CCI) <2 or ≥2. There were significant results in favour of anakinra in all the subgroups. There were minimal differences between females and males; suPAR above 9 ng/mL or at 9 ng/mL or below; Charlson's Comorbidity Index (CCI) <2 or ≥2. About half of the included patients were above 65 years of age. In both patients below and above 65 years of age, the primary endpoint was met with OR in the multivariate analysis of 0.29 (0.18-0.44) and 0.39 (0.24-0.64), respectively. This information has been adequately reflected in SmPC section 4.4.

No paediatric pharmacokinetic or clinical data are available as this medicinal product is not recommended for use in paediatric patients with COVID-19.

Supportive study

The phase 2 SAVE study is an ongoing, prospective, open-label, single-arm study. Eligible patients in the SAVE study were the same as the patient population in the SAVE-MORE study (i.e., males and females ≥18 years of age hospitalized with confirmed infection by SARS-CoV-2 virus, LRTI [radiologically confirmed], and plasma suPAR levels ≥6 ng/mL). Patients were included in two periods.

In the first period, 130 patients were included in the study and treated with anakinra+SoC and compared to a propensity matched control group of 130 patients receiving SoC treatment (in the same period and at same centers). Results were in benefit for anakinra. In the second period, parallel SoC-

treated patients and anakinra+SoC-treated patients (117 and 525 patients, respectively) were included. The incidence of SRF among the parallel SoC-treated patients was significantly greater compared to the patients treated with anakinra. As the study has a single arm open label study design, the results should be interpreted with caution and can thus only be considered as supportive by the CHMP.

Additional studies with anakinra in the treatment of COVID-19

Upon request from the CHMP, the MAH presented results from published papers of three other completed randomized studies with anakinra conducted by academia (CORIMUNO-ANA-1, REMAP-CAP and COV-AID).

CORIMUNO-ANA-1 was a randomized, open-label, controlled study of 116 patients with moderate COVID-19 pneumonia (requiring min 3 L/min, WHO-CPS at 5) which was stopped prematurely because of an absence of effect of anakinra. In this study anakinra did not improve survival or need for MV or NIV (primary endpoints). The inclusion criteria and the studied population differed only slightly from the SAVE-MORE study (higher inflammatory markers, fewer received dexamethasone and levels of suPAR were unknown). The MAH argued that there was a tendency towards a positive benefit of anakinra, however, this was based on minor differences in the subgroups of the CPS score. Due to the differences in study population, comparisons between the two studies (CORIMUNO-ANA-1 vs SAVE-MORE) are difficult.

REMAP-CAP studied critically ill patients at baseline, that already had progressed to require intensive care, respiratory and/or cardiovascular support. There was no effect of anakinra compared with standard of care in this patient population. Although the study had an open label design, the results may indicate that the time window for the treatment of anakinra is of utmost importance.

COV-AID was a multicentre, open-label, randomized clinical trial with factorial design that allocated 112 patients for IL-1 blockade with anakinra. The study design had important differences when compared to SAVE-MORE, e.g. the median PaO2/FiO2 ratio at day of randomisation was 135, a value that would exclude an important part of the patients of SAVE-MORE. Also, patients already under NIV or MV could be included in COV-AID but not in SAVE-MORE, as patients on NIV other than HFNO and on MV were excluded in SAVE-MORE. Those are fundamental differences in the populations studied that make comparability of these studies difficult. Nonetheless, in COV-AID, no evidence for a treatment effect of IL-1 blockade could be found when analysing both primary and secondary endpoints and also no differences were apparent in the subgroup analysis.

Further, the MAH presented the results of three published meta-analysis including both observational and RCT data of anakinra use in COVID-19. All the metanalyses seem to support a beneficial effect for anakinra, however it should be stressed that all included studies with heterogeneous designs, different populations, different SoC, and different anakinra dosing schedules. Therefore, those meta-analyses as well as the RCTs presented above cannot be considered as supportive of anakinra for the treatment of COVID-19 and as such cannot be used as compelling evidence for the broad indication that was primarily sought by the MAH.

Overall, the MAH presented a thorough review of the available evidence about the use of anakinra in COVID-19 upon request from the CHMP. The evidence presented, particularly in the other RCTs, had contradictory results and did not provide robust support. It is acknowledged that the RCTs showing no effect included populations with substantial differences when compared with SAVE-MORE. Nonetheless, these discrepancies underline that patient selection is of utmost importance and that anakinra potential beneficial effects depend both on the type of patients selected and the timing of treatment initiation guided by suPAR level ≥ 6 ng/ml.

Therapeutic indication

The indication initially proposed by the MAH was as follows: *Kineret is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adult patients with pneumonia who are at risk of developing severe respiratory failure (see section 5.1).*

As also discussed above, this broad indication was not supported by the CHMP as it was considered not sufficiently justified from a scientific viewpoint in view of the population studied in the single pivotal phase 3 SAVE-MORE study supporting this application.

Patients who did not require supplemental oxygen were also included in the study. Upon request from the CHMP, the MAH provided subgroup analyses based on supplemental oxygen at screening during the study. However, the results in those who were not treated with supplemental oxygen at screening were not clinically relevant, and it is therefore agreed that the indication should be restricted to patients requiring supplemental oxygen, as proposed by the MAH. In addition, the MAH was requested to reflect the level of oxygen needed in the indication (i.e. low- or high- flow oxygen) as patients under MV or NIV or ECMO were not studied. Clinical efficacy has therefore not been established in those more severe patients. This has been adequately reflected in both SmPC sections 4.1, 4.4 and 5.1.

As the majority of the patients received corticosteroids (81.8%), the MAH was requested to further justify the efficacy of anakinra in patients not receiving corticosteroids. In a subgroup analysis focusing on patients that did not receive dexamethasone at baseline and during the study indicated that anakinra effect is not dependent on co-treatment with dexamethasone. Although the sample size was small and most of the patients in the SAVE-MORE study were under dexamethasone treatment, the CHMP ultimately considered that anakinra has shown benefit with or without corticosteroids.

The indication initially proposed by the MAH did not restrict the use of anakinra in COVID-19 to patients with a suPAR level $\geq$ 6 ng/ml. However, anakinra was not studied in patients with a suPAR level < 6 ng/ml and it is noted that 405 out of 1060 screened patients were excluded due to a suPAR below 6 ng/ml. Further, based on the responses submitted by the MAH, the CHMP concluded that an efficacy was not established in patients with suPAR level below 6 ng/ml. As such, the CHMP considered that only patients with suPAR level ≥6 ng/ml should be treated with anakinra as an efficacy was only demonstrated in those patients (i.e. suPAR ≥6 ng/ml).

Further, the inclusion of patients with suPAR level $\geq$ 6 ng/ml was chosen to identify a patient population in risk of disease progression to SRF. Based on a potential limited availability of suPAR testing in the EU, the MAH was requested to investigate whether other well-established biomarkers could identify a relevant target population. In a post-hoc analysis, the MAH tried to identify other biomarkers associated with progression to SRF (e.g. CRP, ferritin, IL-6 and D-dimer) and proposed a score for progression based on those biomarkers i.e. the SCOPE score. Based on this post-hoc analysis, the MAH initially stated in the SmPC section 5.1. that in the absence of suPAR, other biomarkers of inflammation (e.g. CRP, ferritin, IL-6, D-dimers, LDH) could provide similar clinical information. However, the SCOPE score only partly overlaps with patients identified with suPAR ≥6 ng/ml. The CHMP therefore considered that the SCOPE score did not identify the same patients at risk as suPAR does. As such, the SCOPE score was not considered as a valid tool to identify patients that may benefit from treatment with anakinra. Based on this, the MAH agreed to remove any claim referring to the SCOPE score in SmPC section 5.1.

Considering the decisive role of suPAR for the identification of patients that are suitable for treatment with anakinra in COVID-19 pneumonia, the MAH should ensure that an appropriate and validated test that reliably allows the distinction between patients with suPAR < 6 ng/ml and patients with suPAR ≥ 6 ng/ml is available for all European patients. Such test should be adequately CE-marked as a companion diagnostic under the In Vitro Diagnostic Medical Device Regulation framework.

Overall, the CHMP considered that the initially proposed indication did not fully reflect the patient population studied in the pivotal phase 3 SAVE-MORE study. Further, in the absence of a robust justification to extrapolate the indication to patients regardless of suPAR level, the CHMP considered that the indication should be restricted to the population of patients where a positive benefit/risk balance has been demonstrated i.e. suPAR level ≥ 6 ng / ml.

The final indication granted by the CHMP was thus restricted as follows: *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) ≥ 6ng/ml (see sections 4.2, 4.4 and 5.1).*

In SmPC section 4.4 the following was consequently included: '*The effect of treatment with Kineret has not been established in COVID-19 patients with suPAR < 6 ng/ml.'; and 'Kineret treatment should not be initiated in patients requiring non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) as efficacy has not been established in these patient populations*.'.

2.4.4. Conclusions on the clinical efficacy

The single pivotal phase 3 SAVE-MORE study met its primary endpoint and showed a statistically significant reduction in the 11-point WHO-CPS score. In addition, the study demonstrated that anakinra + SoC treatment had a beneficial effect on time to progression to severe respiratory failure, on time until hospital discharge and on mortality, as compared to placebo +SoC treatment. Based on the data submitted, the CHMP considered that a clinically relevant efficacy was only demonstrated in COVID-19 patients with pneumonia requiring supplemental oxygen (low- or high-flow oxygen) who are at risk of progressing to SRF determined by suPAR ≥ 6ng/ml.

2.5. Clinical safety

Introduction

As part of this application, the MAH proposed to add a new indication in COVID-19 pneumonia, where anakinra is administered as a daily s.c. injection at a dose of 100 mg for up to 10 days of treatment.

The safety profile of anakinra has been well established since its first use in company-sponsored studies and during almost 20 years of post-marketing experience across multiple indications.

The safety of anakinra in the proposed COVID-19 indication and dosing regimen was studied in 2 investigator-sponsored studies (SAVE-MORE and SAVE). The MAH provided safety data from the following sources:

-Primary safety data set: pivotal phase 3 SAVE-MORE study.

-Supportive safety data from:

- The open-label, single-arm phase 2 SAVE study.

- Company-sponsored Phase 2/3, randomized, open-label, parallel-group, 3-arm, multicenter study (Sobi.IMMUNO-101).

- Post marketing cumulative safety data with off-label use in COVID-19, including spontaneous (health care providers and consumers) and literature reports, including safety data from other Sobi-supported studies.

- Relevant findings from literature searches in PubMed and EMBASE performed to identify aggregated data from off-label use in COVID-19.

As part of their application, the MAH initially submitted information pertaining to TEAEs, serious TEAS, and aggregated data on laboratory values, medical history, and concomitant medications from the SAVE-MORE study (analysis of Day 28 only).

Patients in the phase 2 SAVE study were enrolled during 2 time periods (April to September 2020 and October to December 2020), considering the available SoC treatment that was recommended by the WHO for patients with COVID-19 before and after mid-September 2020. This included, for patients classified with moderate disease, anticoagulation and remdesivir (based on medical judgment) and, for patients classified with severe disease, anticoagulation, oxygen supply, dexamethasone, and remdesivir (based on medical judgment). Similarly, the SoC treatment was administered to all patients of the SAVE-MORE Phase 3 study. In both time periods of the phase 2 SAVE study, patients with COVID-19 who were concurrently treated with SoC alone were used as parallel SoC comparators; these parallel SoC comparators were hospitalized during the same time period. TEAE and serious TEAEs were reported, and the Common Terminology Criteria for Adverse Events (Version 4.03) was used for the classification of the events.

Interim safety data up to 14-day follow-up of 130 patients from the SAVE study from the 1st period (April to September 2020) have been published by Kyriazopoulou et al. 2021.

MAH-sponsored, Phase 2/3, randomised, open-label, parallel-group, 3-arm, multicenter study (Sobi.IMMUNO-101) was also initiated to investigate the efficacy and safety of anakinra and emapalumab versus SoC in reducing hyperinflammation and respiratory distress in patients with SARS-CoV-2 infection. Only 16 patients were randomized due to a premature closure of the enrolment in the study. Safety data related to the TEAEs, serious TEAEs, laboratory values, and vital sign results were collected and reported with the study report.

Summaries of TEAEs experienced by patients in studies SAVE-MORE, SAVE, and Sobi.IMMUNO-101 were presented sequentially for each category as common TEAEs, deaths, other serious TEAEs, other significant TEAEs, and analysis of TEAEs.

In addition, a search in the MAH's Global Safety Database was performed to retrieve all SAEs involving anakinra use in the SAVE-MORE study received after unblinding. Evaluation of SAEs, fatal and life-threatening case reports, serious infections, hepatic events, and Designated medical event (DME) summaries, in addition to an overall medical assessment of all case reports was performed. Of note, discrepancies in SAEs can be seen between the MAH's analysis and SAVE-MORE CSR, as no reconciliation has been performed yet. The MedDRA coding of SAEs was provided by the MAH as requested by the CHMP. In addition, the SAVE-MORE interim CSR presented serious TEAEs up to Day 28 whereas the Global Safety Database analysis is based on SAEs collected up to Day 28 and beyond. The final CSR for the SAVE-MORE study will be submitted in the post approval setting via a type II variation by End of December 2021. In addition, the CHMP recommends the MAH to provide the final CSR of the phase 2 SAVE study, once available.

Considering the lack of standardization between the different studies, it was not possible to pool or directly compare the TEAE frequencies. A high-level view of the data, however, indicated that the TEAE pattern was similar between the SAVE-MORE and SAVE studies and was primarily suggestive of the underlying disease and its complications.

Sobi.IMMUNO-101 study data were inconclusive due to a low patient number; the safety data are presented below.

Solicited SAEs from ISSs including the SAVE-MORE study are presented together with the COVID-19 off-label use data.

Patient exposure

As of May 1, 2021, the estimated exposure to anakinra in completed, company-sponsored, clinical studies (encompassing all studied indications, excluding Sobi.IMMUNO-101 study) was 6,408 patient-years in 8,631 patients.

Pivotal SAVE-MORE study

In the SAVE-MORE study, 594 hospitalized patients with moderate and severe COVID-19 pneumonia and plasma suPAR of ≥6 ng/mL or more and receiving SoC were randomized 1:2 to s.c. treatment with placebo or 100 mg anakinra once daily for 10 days; 194 patients were allocated to the placebo+SoC arm and 412 patients were allocated to the anakinra+SoC arm. Following the consent withdrawal from 12 patients, 189 patients received the allocated placebo+SoC treatment, and 405 patients received the allocated anakinra+SoC treatment. The mean number of administered doses of study drug for all the patients was 8.6. The mean number of administered doses was similar for both the treatment arms (placebo+SoC [8.7]; anakinra+SoC [8.4]). Upon request from the CHMP, updated safety data were provided up to Day 90.

Supportive studies

The analysis of the 1st period of the SAVE study was based on 130 anakinra-treated patients and 130 parallel SoC comparators (hospitalized the same time period at different departments). The 1st patient was enrolled on April 16, 2020 and the last on September 12, 2020. During the 2nd period of SAVE study (October to December 2020), 587 patients were enrolled for the treatment with anakinra in parallel with 141 patients treated with SoC. In both periods, COVID-19 patients who were concurrently treated with SoC alone were used as parallel SoC comparators. The treatment duration was up to 10 days during both periods.

A total of 16 patients completed screening and were enrolled in the Sobi.IMMUNO-101study. 5 patients received treatment with emapalumab, 5 patients received treatment with anakinra, and 6 patients received SoC. 12 patients (75%) completed the study, and 4 patients (25%) discontinued the study. The major reasons for early study discontinuation were death (1 patient each in the emapalumab and anakinra arms), TEAE (1 patient in the emapalumab arm), and lack of efficacy (1 patient in the SoC arm).

Demographic and other characteristics of study population

Pivotal SAVE-MORE study

The patients had a mean (SD) age of 61.9 years (12.1), with a similar distribution between treatment groups (placebo+SoC [61.5 years]; anakinra+SoC [62.0 years]). The distribution by sex was balanced between treatment groups, with the male sex accounting for 57.1% in placebo+SoC arm and 58.3% in anakinra+SoC arm. A total of 27 patients (14.3%) with moderate pneumonia and 162 patients (85.7%) with severe pneumonia received placebo+SoC treatment; 82 patients (20.2%) with moderate pneumonia and 323 patients (79.8%) with severe pneumonia received anakinra+SoC treatment.

Table 20: Baseline disease characteristics of patients in the SAVE-MORE study (safety analysis set)

	Placebo+SoC (N = 189)	Anakinra+ SoC (N = 405)	All Patients (N = 594)
Laboratory values, median (Q1 to Q3)			
White blood cell count, cells per mm^3	5910 (4280 to 8300)	5980 (4320 to 8180)	5950 (4310 to 8200)
Lymphocyte count, cells per mm^3	730 (560 to 1090)	815 (570 to 1110)	800 (565 to 1100)
C-reactive protein, mg/L	51.4 (25.2 to 97.9)	50.5 (25.3 to 100.8)	50.6 (25.3 to 99.7)
Interleukin-6, pg/mL	20.1 (7.4 to 44.9)	15.5 (6.6 to 39.3)	16.8 (7.0 to 39.8)
Ferritin, ng/mL	628.6 (293.5 to 1062.3)	558.9 (294.1 to 1047.0)	585.2 (294.5 to 1047.0)
Serum soluble uPAR, ng/mL	7.5 (6.9 to 9.3)	7.6 (7.0 to 9.1)	7.6 (6.9 to 9.1)
D-dimers, mg/L	0.51 (0.31 to 0.92)	0.52 (0.30 to 1.00)	0.52 (0.30 to 0.98)
pO_2: FiO_2, mmHg	215 (161 to 293)	235 (178 to 304)	230 (172 to 300)
Comorbidities, n (%)			
Type II diabetes mellitus	28 (14.8)	66 (16.3)	94 (15.8)
Chronic heart failure	5 (2.6)	13 (3.2)	18 (3.0)
Chronic renal disease	1 (0.5)	9 (2.2)	10 (1.7)
Chronic obstructive pulmonary disease	9 (4.8)	15 (3.7)	24 (4.0)
Coronary heart disease	13 (6.9)	28 (6.9)	41 (6.9)
Atrial fibrillation	8 (4.2)	20 (4.9)	28 (4.7)
Depression	9 (4.8)	25 (6.2)	34 (5.7)

Abbreviations: N, Number; Q, Quartile; SD, Standard deviation; SoC, Standard-of-care; uPAR, urokinase plasminogen activator receptor.

Supportive studies

In the SAVE study a total of 130 patients were enrolled during the 1st period and 130 parallel SOC comparators were identified after the propensity score matching within the same time frame. Overall, 62.3% patients in the anakinra+SoC arm and 64.8% patients in the SoC group were male, and the mean (SD) age was 63 (14) years in the anakinra+SoC arm and 66 (14) years in the SoC group. A total of 587 patients were enrolled during the 2nd period. When the results of the 1st period analysis of the SAVE study were announced, most of the medical departments managing patients with COVID-19 decided to join the study, which led to the 2nd protocol amendment (Version 3.0). This led to substantial reduction of the available parallel SoC comparators to only 141. No propensity score matching was done because the available comparators were far fewer than the treated patients. Overall, 59.8 % patients in the SoC group and 64.1% in the anakinra+SoC arm were male, and the mean (SD) age was 64.3 (14.6) years in the SoC group and 61.8 (13.2) years in the anakinra+SoC arm. Differences were observed between the 2 groups regarding the severity of COVID-19 and a few other baseline characteristics that includes Type 2 diabetes, coronary heart disease, and ceftaroline treatment.

In the Sobi.IMMUNO-101 study, all 16 patients that were randomized and treated were included in the safety population and in the modified intent-to-treat population. The patients had a similar distribution of the demographic and baseline characteristics in the safety population, with a mean (SD) age of 65 (14.8) years in emapalumab group, 62.4 (11.1) years in anakinra group, and 62.5 (13.4) years in SoC group and most patients were male (4 patients [80%] in emapalumab group, 4 patients [80%] in anakinra group, and 6 patients [100%] in SoC group).

Adverse events

The most common events reported overall with the primary safety data set were increased liver function tests, hyperglycaemia, and anaemia, along with other reported electrolyte abnormalities.

Although a consistent terminology was not presented across all safety results, a similar safety profile of anakinra was observed in the supportive SAVE study (both periods), which included elevated liver function tests, electrolyte abnormalities, and anaemia as the most commonly reported TEAEs.

Pivotal SAVE-MORE study

Overall, 170 (89.9%) patients treated with placebo+SoC and 352 (86.9%) patients treated with anakinra+SoC experienced at least one non-serious TEAE (see table below). The TEAEs occurring at a higher proportion in the anakinra+SoC arm compared to the placebo+SoC arm included the increase of liver function tests, hypernatremia, constipation, hyperkalemia, anxiety, rash at the injection site, neutropenia, 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 listed ADRs in the anakinra product information. The most frequent events overall were hyperglycaemia, increase of liver function tests, anaemia, and hypernatremia. The TEAEs reported in the majority of patients were suggestive of advanced COVID-19 and its complications along with the worsening of patients' concurrent clinical conditions.

Table 21: Most common (>2% of patients) non-serious TEAEs reported in the SAVE-MORE study

	Placebo+SoC (n = 189)	**Anakinra+SoC (n = 405)**
At least 1 nonserious TEAE, n (%)	170 (89.9)	352 (86.9)
Type of adverse event, n (%)		
Hyperglycemia	76 (40.2)	148 (36.5)
Increase of liver function tests	63 (33.3)	145 (35.8)
Anemia	37 (19.6)	58 (14.3)
Hypernatremia	17 (9.0)	46 (11.4)
Constipation	16 (8.5)	39 (9.6)
Bradycardia	19 (10.1)	36 (8.9)
Hyperkalemia	13 (6.9)	36 (8.9)
Anxiety	11 (5.8)	33 (8.2)
Hyponatremia	23 (12.2)	32 (7.9)
Hypocalcemia	20 (10.6)	32 (7.9)
Thrombocytosis	13 (6.9)	24 (5.9)
Creatinine increase	9 (4.8)	17 (4.2)
Headache	8 (4.2)	16 (4.0)
Injection site reaction	3 (1.5)	15 (3.7)
Diarrhea	8 (4.2)	14 (3.5)
Leukopenia	5 (2.6)	14 (3.5)
Neutropenia	1 (0.5)	12 (3.0)
Hypokalemia	12 (6.3)	11 (2.7)
Thrombocytopenia	4 (2.1)	9 (2.2)
Nausea, vomiting	1 (0.5)	9 (2.2)

Abbreviations: n, Number; SoC, Standard-of-care; TEAE, Treatment-emergent adverse events.
Note: the TEAEs were presented in descending order for anakinra+SoC arm.

Pivotal SAVE-MORE study by organ system and syndrome

Table 22: Most common (>2% of patients) non-serious TEAEs by SOC and PT (Safety set)

	Number (%) of patients		
	SoC+Anakinra (N=405)	SoC+Placebo (N=189)	Total (N=594)
Any adverse event	**320 (79.0)**	**161 (85.1)**	**481 (80.9)**
Blood and lymphatic system disorders	**144 (35.6)**	**79 (41.8)**	**223 (37.5)**
Leukopenia	14 (3.5)	5 (2.6)	19 (3.2)
Leukocytosis	39 (9.6)	19 (10.1)	58 (9.8)
Neutropenia	12 (3.0)	1 (0.5)	13 (2.2)
Lymphocytopenia	40 (9.8)	25 (13.2)	65 (10.0)
Anemia	58 (14.3)	37 (19.6)	95 (15.9)
Thrombocytopenia	9 (2.2)	4 (2.1)	13 (2.2)
Thrombocytosis	24 (5.9)	13 (6.9)	37 (6.2)
Skin and subcutaneous tissue disorders	**15 (3.7)**	**3 (1.5)**	**18 (3.0)**
Rash	15 (3.7)	3 (1.5)	18 (3.0)
Gastrointestinal disorders	**58 (14.3)**	**24 (12.7)**	**82 (13.8)**
Nausea, vomiting[b]	9 (2.2)	1 (0.5)	10 (1.7)
Constipation	39 (9.6)	16 (8.5)	55 (9.3)
Diarrhea	14 (3.5)	8 (4.2)	22 (3.7)
Investigations	**155 (38.3)**	**76 (40.2)**	**231 (38.9)**
Aminotransferase increase	145 (35.8)	63 (33.3)	208 (35.0)
Amylase increase	19 (4.7)	13 (6.9)	32 (5.4)
Cardiac disorders	**50 (12.3)**	**35 (18.5)**	**88 (14.8)**
Sinus bradycardia	36 (8.9)	19 (10.1)	55 (9.3)
Sinus tachycardia	16 (3.9)	7 (3.7)	23 (3.9)
Nervous system disorders	**16 (4.0)**	**8 (4.2)**	**24 (4.0)**
Headache	16 (4.0)	8 (4.2)	24 (4.0)
Psychiatric disorders	**35 (8.6)**	**13 (6.9)**	**48 (8.1)**
Anxiety	33 (8.2)	11 (5.8)	44 (7.4)
Renal and urinary disorders	**17 (4.2)**	**9 (4.8)**	**26 (4.4)**
Acute kidney injury	17 (4.2)	9 (4.8)	26 (4.4)
Metabolism and nutrition disorders	**222 (54.8)**	**106 (56.1)**	**328 (55.2)**
Hyperglycaemia	148 (36.5)	76 (40.2)	224 (37.7)
Hypoglycaemia	34 (8.4)	15 (7.9)	49 (8.3)
Hyponatremia	32 (7.9)	23 (12.2)	55 (9.3)
Hypernatremia	46 (11.4)	17 (9.0)	63 (10.6)
Hypokalemia	11 (2.7)	12 (6.3)	23 (3.9)
Hyperkalemia	36 (8.9)	13 (6.9)	49 (8.3)
Hypocalcemia	32 (7.9)	20 (10.6)	52 (8.8)
Vascular disorders	**13 (3.2)**	**5 (2.6)**	**18 (3.0)**
Epistaxis	10 (2.5)	2 (1.1)	12 (2.0)

Abbreviations: N, number; PT, preferred term; SoC, standard of care, SOC, system organ class; TEAE, treatment emergent adverse event.
[a] Patients with multiple events at the same level of summarization are counted only once at that level. Patients with events at more than one level of summarization are counted once at each of those levels.
[b] The reported PTs of nausea and vomiting have been grouped into one term (medical concept).
Note: MedDRA version 24.0

Upon request from the CHMP, the SAVE-MORE safety data up to Day 90 was provided, including all TEAEs combined, according to investigator causality; most common (>2%) serious and non-serious TEAEs; serious and non-serious TEAEs, according to investigator causality; and non-serious TEAEs, according to severity.

Overall, 156 (82.5 %) patients treated with placebo + SoC and 335 (82.7 %) patients treated with anakinra + SoC experienced at least 1 TEAE. The TEAEs, excluding single events, occurring at a higher proportion in the anakinra + SoC group compared to the placebo + SoC group, included Leukopenia,

Neutropenia, Injection site reaction, Fall, Rash, Nausea, Constipation, Transaminases increased, Gamma-glutamyl transferase increased, Alkaline phosphatase increased, Blood pressure decreased, Sinus tachycardia, Atrial fibrillation, Anxiety, Agitation, Acute kidney injury, Hyperglycemia, Hypernatraemia, Hyperkalaemia, Hypercalcaemia, Hypophosphataemia, Cystitis acute, Epistaxis, Chest pain, and Catheter bleeding. Of these, Neutropenia, Rash, Injection site reaction, and Hepatic enzyme increased, are listed ADRs in the anakinra product information. Few of these events were serious or led to premature treatment discontinuation (3 patients – 1 Leukopenia, 2 Transaminases increased, [0.7%] in the anakinra group and 2 patients – 1 Leukopenia, 1 Transaminases increased [1.0%] in the placebo group).

The TEAEs reported in the majority of patients were suggestive of advanced COVID-19 and its complications and/or worsening of patients' concurrent clinical/background condition and concomitant medication.

In the SAVE-MORE study, death was a component of the primary endpoint and in line with the study protocol; all deaths were considered by the MAH to be not related to study drug and due to COVID-19 progression/complications and/or the patient's concurrent clinical/background condition. A total of 35 patients (5.9%) in the study had an AE with an outcome of death up to 90 days; 17 patients (9.0%) received placebo + SoC and 18 patients (4.4%) received anakinra + SoC. Fatal events were reported in the SOCs of Infections and infestations (Bacteraemia, Pneumonia, Septic shock), Respiratory, thoracic and mediastinal disorders (Pneumothorax, Pneumomediastinum), and Vascular disorders (Arterial thrombosis, Pulmonary embolism).

Overall, 42 patients (22.2 %) treated with placebo + SoC and 66 patients (16.3 %) treated with anakinra + SoC experienced at least 1 serious TEAE. The most frequently reported (>2 %) serious TEAEs in both groups were Bacteremia, Nosocomial infection, Pneumonia, Septic shock, and Pulmonary embolism. Other serious TEAEs reported at a higher rate in the anakinra + SoC group than in the placebo + SoC group and in more than 1 patient were Acute kidney injury, Hypernatraemia, Hyponatraemia, and Lymphopenia.

The serious TEAEs were suggestive of advanced COVID-19 disease and its complications. Pulmonary infections, such as HAP/VAP with secondary bacterial infections, Sepsis, thromboembolic conditions, Acute kidney injury, electrolyte disturbances and Lymphopenia have been reported as complications of COVID-19 during the pandemic and reported in various reports.

Supportive studies

SAVE was an open-label study, and no comparison group was available. However, a group of parallel comparators receiving SoC treatments at the same period was used.

TEAEs were collected from baseline up to 14 days of follow-up. Investigators monitored the patients for TEAEs and were responsible for recording all TEAEs that occurred during the study.

The TEAEs captured during the 1st period (April to September 2020) are listed in the below table. The incidence of the same events was depicted among parallel SoC comparators. As shown in the table below, the number of patients experiencing at least 1 TEAE was similar in the parallel SoC comparators (68.5%) compared to the anakinra+SoC arm (65.4%). The TEAEs occurring at numerically higher proportion of patients in the anakinra+SoC arm compared to the parallel SoC comparators were gastrointestinal disturbances (11.5% versus 6.9%), leukopenia (8.5% versus 2.3%); thrombopenia (6.9% versus 5.4%), and headache (3.1% versus 1.5%), respectively. Of these events, leukopenia (neutropenia), thrombocytopenia, and headache are expected with anakinra treatment; however, these are also observed in COVID-19 infected patients. In addition, gastrointestinal disturbances are known to occur in COVID-19 patients, and although they were observed at a higher rate in the

anakinra+SoC arm, they are most likely due to the underlying COVID-19 medical condition in these patients.

Table 23: Treatment-emergent adverse events reported in the SAVE study (1st period – April to September 2020)

	Parallel SoC (N = 130)	Anakinra+SoC (N = 130)
At least 1 TEAE by Day 14, n (%)	89 (68.5)	85 (65.4)
Elevated liver function tests	51 (39.2)	40 (30.8)
Electrolyte abnormalities	41 (31.5)	35 (26.9)
Anemia	26 (20.0)	22 (16.9)
Gastrointestinal disturbances	9 (6.9)	15 (11.5)
Leukopenia	3 (2.3)	11 (8.5)
Thrombopenia	7 (5.4)	9 (6.9)
Any heart arrhythmia	22 (16.9)	9 (6.9)
Headache	2 (1.5)	4 (3.1)
Allergic reaction	7 (5.4)	4 (3.1)

Abbreviations: TEAE, Treatment-emergent adverse event; N, Number; SoC, Standard-of-care.
Note: The TEAEs were presented in descending order for anakinra+SoC arm.

Safety analysis was performed up to Day 14 for all 587 patients who were enrolled in the SAVE study during the 2nd period of October to December 2020. For reasons of comparison, the frequency of the same events was captured for all 141 patients who received SoC. The proportion of TEAEs in the anakinra group was lower than the SoC comparators for anaemia and any heart arrhythmia, and similar to that of the SoC comparators for thrombopenia, headache, gastrointestinal disturbances, electrolyte abnormalities, leukopenia, and allergic reactions, except for elevated liver function tests that were reported at a higher proportion in the anakinra group (43.8%) than in the SoC comparators group (36.9%) .

Table 24: TEAEs reported in SAVE study (2nd period – October to December 2020)

	SoC Comparators (N = 141)	Anakinra (N = 587)
At least 1 TEAE by Day 14, n (%)	91 (64.5)	420 (71.6)
Elevated liver function tests	52 (36.9)	257 (43.8)
Electrolyte abnormalities	42 (29.8)	159 (32.2)
Anaemia	22 (15.6)	71 (12.1)
Gastrointestinal disturbances	11 (7.8)	59 (10.1)
Thrombocytopenia	14 (9.9)	47 (8.0)
Any heart arrhythmia	17 (12.1)	45 (7.7)
Leukopenia	7 (5.0)	39 (6.6)
Allergic reaction	4 (2.8)	18 (3.1)
Headache	2 (1.4)	6 (1.0)

Abbreviations: N, Number; TEAE, Treatment-emergent adverse event.
Note: The TEAEs were presented in descending order for anakinra group.

The list of AEs captured until Day 90 follow-up are included in the table below for the 717 patients enrolled in SAVE and 271 comparators.

	Comparators (N=271) n (%)	Enrolled in SAVE and treated with anakinra (N=717) n (%)
Serious TEAEs		
Deaths	87 (32.1)	88 (12.3)
Infection-associated deaths	77 (28.4)	71 (9.9)
Deaths dues to COVID-19	10 (3.7)	17 (2.4)
Infections and infestations		
Pneumonia	48 (17.7)	50 (7.0)
Septic shock	93 (34.3)	65 (9.1)
Renal disorders		
Acute kidney injury	55 (20.6)	47 (4.6)
Vascular disorders		
Pulmonary embolism	9 (3.3)	13 (1.8)
Non-serious TEAEs		
Investigations		
Transaminases increased	103 (38.0)	297 (41.4)
Blood and lymphatic system disorders		
Leukopenia	10 (3.7)	50 (7.0)
Anemia	48 (17.7)	93 (13.0)
Thrombocytopenia	21 (7.7)	56 (7.8)
Gastronintestinal disorders		
Nausea	20 (7.4)	74 (10.3)
Nervous system disorders		
Headache	4 (1.5)	10 (1.4)
Cardiac disorders		
Sinus tachycardia	39 (14.4)	54 (7.5)
Skin and subcutaneous tissue disorders		
Rash at the injection site	Not reported	22 (3.1)

Abbreviations: COVID-19, Coronavirus disease 2019; N, Total number of patients; n, Number of patients; TEAEs, Treatment-emergent adverse events.

In the SAVE study, fatal events were all attributed to infections – either COVID-19 or secondary infections – by investigators.

There were relatively fewer deaths in anakinra-treated patients than comparators in the SAVE study up to Day 90 follow-up. Deaths due to underlying COVID-19 and secondary infections were both reported less frequently in the anakinra group than in the comparator group, as were other SAEs (infectious, renal, and vascular). Regarding non-serious AEs, increased transaminases, injection site rash, leukopenia, and nausea were more frequently reported in anakinra-treated patients than comparators. Given the non-randomized nature of the study, detailed analysis of the AE pattern is not feasible, but the data is compatible with the known safety profile of anakinra.

Overall, the review of TEAEs in SAVE MORE and SAVE up to Day 90 follow-up did not indicate any new safety signal identified with anakinra treatment in COVID-19, and indicated that the safety profile is

consistent with current approved product information, taking the underlying disease, dose, and duration of anakinra treatment in the studies into account.

In the Sobi.IMMUNO-101 study, 7 out of 16 patients experienced TEAEs in the safety population: 2 patients (40.0%) in the anakinra group, 4 patients (80.0%) in the emapalumab group, and 1 patient (16.7%) in the SoC group (see table 23). Treatment-related TEAEs were reported in 1 patient in each treatment group and included thrombocytopenia (1 patient [20.0%] in the anakinra group), atrial fibrillation (1 patient [20.0%] in the emapalumab group), hypertransaminasemia (1 patient [16.7%] in the SoC group).

Severe TEAEs were reported in 1 patient (20.0%) in the anakinra group and 2 patients (40.0%) in the emapalumab group each with SRF. No patients in the SoC group experienced a severe TEAE (see table 24). The most common TEAE by preferred term was respiratory failure (1 patient [20.0%] in the anakinra group and 2 patients [40.0%] in the emapalumab group). All other TEAE PTs were reported in single patients in each treatment group during this study.

Table 25: Overall summary of TEAEs during the study (Safety population)

	Number (%) of patients[a]		
	Emapalumab (N = 5)	**Anakinra (N = 5)**	**Standard of care (N = 6)**
Any TEAE	4 (80.0)	2 (40.0)	1 (16.7)
Any severe TEAE	2 (40.0)	1 (20.0)	0
Any treatment-emergent non-SAE	2 (40.0)	1 (20.0)	1 (16.7)
Any treatment-emergent SAE	2 (40.0)	1 (20.0)	0
Any related TEAE[b]	1 (20.0)	1 (20.0)	1 (16.7)
Any fatal TEAE	2 (40.0)	1 (20.0)	0
Any TEAE leading to study drug withdrawn	2 (40.0)	1 (20.0)	NA

Abbreviations: AE, Adverse event; N, Number; NA, Not applicable; SAE, Serious adverse event; TEAE, Treatment emergent adverse event.
[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
[b] Related to treatment (study drug or to standard of care), as judged by the investigator.

Table 26: Serious TEAEs by SOC and PT (Safety population)

	Number (%) of patients[a]		
	Emapalumab (N = 5)	**Anakinra (N = 5)**	**Standard of care (N = 6)**
Any AE	2 (40.0)	1 (20.0)	0
Respiratory, thoracic and mediastinal disorders	2 (40.0)	1 (20.0)	0
Respiratory failure	2 (40.0)	1 (20.0)	0

Abbreviations: AE, Adverse event; N, Number; PT, Preferred term; SOC, System organ class; TEAE, Treatment emergent adverse event.
[a] Patients with multiple events at the same level of summarization are counted only once at that level. Patients with events at more than one level of summarization are counted once at each of those levels.
Note: MedDRA version 23.0.

The Safety Data from the SAVE-MORE study was provided up to Day 90. TEAEs occurring at a higher proportion on the anakinra+SoC group included:

- Leukopenia, neutropenia, injection site reaction, fall, rash, nausea, increase of transaminases, γ-GT and alkaline phosphatase, blood pressure decreased, sinus tachycardia, atrial fibrillation, anxiety, agitation, acute kidney injury, hyperglycaemia, hypernatremia, hyperkalaemia, hypercalcemia, hypophosphatemia, cystitis, acute epistaxis, chest pain and catheter bleeding.

Already included in Kineret's SmPC are neutropenia, rash, injection site reaction and increased hepatic transaminases. According with the MAH the TEAEs reported in the majority of patients were suggestive of advanced COVID-19 and its complications and/or worsening of patients' concurrent clinical/background condition and concomitant medication; the same conclusion was adopted related with serious TEAEs.

To date the serious TEAEs reported can indeed be related to progression of COVID-19 infection.

The MAH has updated section 4.8 of the SmPC to include D90 data on safety:

"Adverse reactions data in COVID-19 are based on a randomized placebo-controlled study of 405 Kineret-treated patients with COVID-19 pneumonia (SAVE-MORE study). The incidence of serious adverse reactions in the anakinra-treatment group was comparable with the placebo group. Neutropenia, elevation of liver function test, rash and injection site reactions were reported more frequently in patients receiving Kineret compared with placebo. The overall safety profile in patients with COVID-19 treated with Kineret is similar to that in Kineret-treated patients with RA."

"In the clinical study in COVID-19, secondary serious infections were common, however less frequently observed in patients treated with Kineret compared to placebo-treated patients."

"In the clinical study in COVID-19, events of neutropenia were reported in 3.0% of Kineret-treated patients and 0.5% of patients receiving placebo. All adverse events of neutropenia were mild or moderate in severity."

"In patients with COVID-19 treated with Kineret, injection site reactions were reported with low frequency. "

Of note, for patients with COVID-19 that were treated with anakinra, injection site reactions (ISR) were reported with a frequency higher compared to the placebo treated patients. Nevertheless, the frequency of reported ISR in patient that received anakinra was still considered to be low by the MAH. Therefore, the addition of the following statement to SmPC section 4.8: 'In patients with COVID-19 treated with Kineret, injection site reactions were reported with low frequency' was agreed by the CHMP.

It is agreed that the data available up to Day 90 follow-up do not indicate any new safety signal identified with anakinra treatment in COVID-19, and also indicate that the safety profile is consistent with the current labelling, taking the underlying disease, dose, and duration of anakinra treatment in the studies into account.

The SmPC has been updated with the data available to the date. Any new follow up data should be provided as part of the final CSR for the SAVE-MORE and SAVE studies.

Serious adverse event/deaths/other significant events

Deaths

The proportion of patients with an outcome of death was lower in the anakinra-treated group than the placebo group in the primary SAVE-MORE study and was consistently lower in the anakinra-treated group than the comparator group in supportive studies.

Pivotal SAVE-MORE study

A total of 26 patients (4.3%) in the study experienced an outcome of death, up to 28 days; 13 patients (6.9%) received placebo+SoC and 13 patients (3.2%) received anakinra+SoC. All deaths were considered to be due to COVID-19 progression and the patient's concurrent medical conditions that were considered the risk factors for COVID-19 and may have contributed to fatal outcomes in these patients and considered to be not related to study drug. Secondary bacterial infections including associated septic shock and multiorgan failure are known complications of patients with COVID-19 hospitalized or in ICU and on ventilator respiratory support. Narratives for patients who experienced serious TEAEs and all TEAEs with an outcome of death were provided upon request from the CHMP.

In the SAVE-MORE study, death was a component of the primary endpoint and was excluded from reporting as an SAE according to the study protocol. All deaths but 1 were considered by the investigator to be not related to study drug and due to COVID-19 progression/complications and/or the patient's concurrent clinical/background condition. A total of 35 patients (5.9 %) in the study had an AE with an outcome of death up to 90 days; 17 patients (9.0 %) received placebo + SoC and 18 patients (4.4 %) received anakinra + SoC. Of the 18 fatal cases in the anakinra arm, 13 were in male patients and 5 in female patients. The median age of the patients was 75 years (age band range: 50 to 89 years). A list of all fatal event PTs is provided in the table below.

Table 27: Most frequently reported fatal events in the anakinra group in the SAVE-MORE study

Fatal event PT	**Event count**	**Median time to onset in days**
Septic shock	6	12 (range: 8-28 days)
Pneumonia	5	11 (range: 1–17 days)
Nosocomial infection	4	13 (range: 4–17 days)
Bacteraemia	4	38 (range: 11-69 days)
Acute kidney injury	2	8.5 (range: 8–9 days)
Pneumomediastinum	2	14.5 (range: 12-17 days)
Events occurring in 1 patient		
Fatal event PT	**Event count**	**Time to onset in days**
Abdominal infection	1	12
Arterial thrombosis	1	6
Pneumothorax	1	7
Pyelonephritis acute	1	23

Abbreviation: PT, Preferred term.

The most frequently reported fatal events (≥2 events) were Septic shock (6 events), Pneumonia (5 events), Nosocomial infection and Bacteraemia (4 events each), and Acute kidney injury and Pneumomediastinum (2 events each). The time to onset of the events occurring in ≥2 patients ranged from 1 to 69 days and showed no trend. The cases of arterial thrombosis, pneumothorax, and acute pyelonephritis were confounded by concurrent COVID-19 infection and concurrent clinical/background condition and/or concomitant medication. The case of abdominal infection had insufficient information to assess; however, the patient had medical history of possible intra-abdominal infection reported prior to anakinra start.

In the SAVE-MORE study, the most frequently reported fatal event was septic shock. The second most frequently reported fatal event was pneumonia (bacterial or fungal origin). Secondary pneumonia is recognized as a complication of severe COVID-19. In addition, these patients are at increased risk of infection due to prolonged ICU stays and broad-spectrum antibiotic use. The third most frequently reported fatal event was nosocomial infection and bacteraemia. Nosocomial infections were all reported

as hospital-acquired infections. A recent study found the nosocomial infection rate in the ICU was noted to be higher among COVID-19 patients compared to non-COVID-19 patients (Ong et al 2021). The events of bacteraemia had a median time to onset of 38 days (range: 11 to 69 days). The short duration of treatment of anakinra (10 days) along with its short half-life (4 to 6 hours) makes the role of anakinra in these cases unlikely. The most likely cause/contributing factor(s) is COVID-19, underlying severe clinical condition with possible pneumonia, and central venous catheters and other intravascular devices in these patients.

In the SAVE-MORE study, deaths were mostly attributed to the SOC Infections and infestations, either pneumonia (COVID-19 or bacterial superinfection), bacteremia, or septic shock. There were also single fatalities attributed to events in the 'Respiratory, thoracic and mediastinal disorders', and 'Vascular disorders' SOCs. The spectrum of fatal events was similar between anakinra- and placebo-treated patients.

In summary, all deaths in the SAVE-MORE study on the anakinra arm were considered by the MAH to be not related to study drug but related to COVID-19 progression/complications and/or the patient's concurrent clinical/background condition. The MAH performed a thorough review of all anakinra cases in the COVID-19 indication and, to date, no new signal/safety concern was identified.

For the SAVE-MORE study, deaths are provided in the table below (censored at Day 90).

MedDRA SOC/PT	SoC + Placebo (N=189) n (%)	SoC + Anakinra (N=405) n (%)
Infections and infestations, n (%)	18 (9.5)	19 (4.7)
Pneumonia	11 (5.8)	10 (2.5)
Bacteremia	1 (0.5)	2 (0.5)
Septic shock	6 (3.2)	7 (1.7)
Respiratory, thoracic, and mediastinal disorders, n (%)	0 (0)	2 (0.5)
Pneumomediastinum	0 (0)	1 (0.2)
Pneumothorax	0 (0)	1 (0.2)
Vascular disorders, n (%)	1 (0.5)	1 (0.2)
Pulmonary embolism	1 (0.5)	0 (0)
Arterial thrombosis	0 (0)	1 (0.2)

Abbreviatons: MedDRA, Medical Dictionary for Regulatory Activities; N, Total number of patients; n, Number of patients; PT, Preferred term; SoC, Standard of care; SOC, System organ class.
Note: In the SAVE MORE study, death is part of the primary endpoint and, as such, is exempt from safety reporting as an SAE by itself. There were 41 patients with an endpoint of death up to 90-day follow-up and 35 patients experiencing at least 1 SAE with fatal outcome up to 90-day follow-up.

Supportive studies

In the SAVE study the proportion of all deaths in the anakinra group was lower than in the comparator group for both the 1st period (4.6 % (n=6) in anakinra group and 12.3 % (n=16) in the comparator group) and the 2nd period (4.4 % (n=26) in the anakinra group and 14.2 % (n=20) in the comparator group). Narratives are not available yet. Those are expected to be provided once the final CSR will be ready.

An updated analysis reporting all deaths up to 90 days of follow-up in the SAVE study is included below. The table does not categorize events according to SOC and PT since the events have not been MedDRA-coded in the SAVE study.

Table 28: Fatal adverse events captured until day 90 among patients enrolled in SAVE and comparators

Serious TEAEs	Comparators (N=271) n (%)	Enrolled in SAVE and treated with anakinra (N=717) n (%)
Deaths	87 (32.1)	88 (12.3)
Infection-associated deaths	77 (28.4)	71 (9.9)
Deaths due to COVID-19	10 (3.7)	17 (2.4)

Abbreviatons: N, Total number of patients; n, Number of patients; TEAEs, Treatment-emergent adverse events.

In the Sobi.IMMUNO-101study, 1 patient (20.0 %) in the anakinra group and 2 patients (40.0 %) in the emapalumab group each experienced a serious TEAE of respiratory failure with a fatal outcome. No patients in the SoC group experienced a fatal TEAE. None of the fatal TEAEs was considered related to study drug. The patient that experienced a fatal outcome in the anakinra group was 60-69-year-old, hospitalized prior to enrolment in the study for interstitial lung pneumonia, secondary to COVID-19. Medical history of particular interest included SARS-CoV-2 infection (diagnosed 19 days before randomization), interstitial pneumonia, liver disease, and acute hepatitis C. Other relevant medical history included cirrhosis and chronic hepatitis C. The patient experienced severe respiratory failure on Day 14.

Other serious adverse events

The proportion of patients with at least 1 serious TEAE was lower in the anakinra-treated group than in the placebo group in the SAVE-MORE study and was consistently lower in the anakinra-treated group than in the comparator group in supportive studies. The most frequently reported serious TEAEs in both treatment groups in the SAVE-MORE study were VAP, bloodstream infection, probable nosocomial infections, and pulmonary embolism.

Pivotal SAVE-MORE study

Overall, 40 (21.2%) patients treated with placebo+SoC and 66 (16.3%) patients treated with anakinra+SoC experienced at least 1 serious TEAE. The most frequently reported serious TEAEs in both arms were VAP, bloodstream infection, probable nosocomial infections, and pulmonary embolism, see table below. Other serious TEAEs reported at a higher rate in the anakinra+SoC arm than in the placebo+SoC arm were AKI, pneumomediastinum, ischaemic stroke, hypernatremia, hyponatremia, increase of liver function tests, neutropenia, and lymphopenia.

These serious TEAEs were suggestive of advanced COVID-19 disease and its complications.

Pulmonary infections such as HAP/VAP with secondary bacterial infections, sepsis, and thromboembolic conditions have been reported as complications of COVID-19 during the pandemic and reported in various reports (i.e., by WHO).

Table 29: Most common (>2% patients) serious TEAEs in the SAVE-MORE study

	Placebo+SoC (n = 189)	Anakinra+SoC (n = 405)
At least 1 serious TEAE, n (%)	40 (21.2)	66 (16.3)
Type of serious TEAE, n (%)		
Infections and infestations, total	25 (13.0)	31 (7.5)
VAP	14 (7.4)	14 (3.5)
Bloodstream infection	6 (3.2)	12 (3.0)
Probable nosocomial infections	4 (2.1)	10 (2.5)
Pulmonary embolism	4 (2.1)	7 (1.7)

Abbreviations: CSR, Clinical study report; n, Number; SoC, Standard-of-care; TEAE, Treatment-emergent adverse event; VAP, Ventilator-associated pneumonia.

Table 30: Most common (>2%) serious TEAEs by SOC and PT (Safety set)

	Number (%) of patients		
	SoC+Anakinra (N=405)	SoC+Placebo (N=189)	Total (N=594)
Patients with at least one SAE	**65 (16.0)**	**41 (21.7)**	**106 (17.8)**
Infections and infestations	**34 (8.4)**	**30 (15.9)**	**63 (10.6)**
Bacteremia	11 (2.7)	5 (2.7)	16 (2.7)
Hospital-acquired infection	10 (2.5)	7 (3.7)	17 (2.9)
Ventilator-associated pneumonia	9 (2.2)	15 (7.9)	24 (4.0)
Hospital-acquired pneumonia	6 (1.5)	5 (2.6)	11 (1.9)
Vascular disorders	**9 (2.2)**	**4 (2.1)**	**13 (2.2)**
Pulmonary embolism	6 (1.5)	4 (2.1)	10 (1.7)

Abbreviations: N, number; PT, preferred term; SAE, serious adverse event; SoC, standard of care; SOC, system organ class; TEAE, treatment emergent adverse event.
[a] Patients with multiple events at the same level of summarization are counted only once at that level. Patients with events at more than one level of summarization are counted once at each of those levels.
SAE reconciliation with the safety database has not yet been performed.
Note: MedDRA version 24.0.

In the SAVE-MORE study *when classified by organ class or syndrome by organ system or syndrome*, the related TEAEs (as per investigator's assessment) of hypernatremia, hyperkalemia, hypercalcemia, elevation of liver function tests, constipation, nausea and vomiting, thrombocytosis, leukopenia, neutropenia, anxiety, rash, and reaction at injection site were observed more frequently in the anakinra+SoC arm than in the placebo+SoC arm. The related TEAEs of hyperglycemia, hypocalcemia, hyponatremia, hypokalemia, diarrhea, anaemia, thrombocytopenia, headache, and creatinine increase were observed more frequently in patients in the placebo+SoC arm than in the anakinra+SoC arm.

Events of neutropenia, rash, and elevated liver function tests are known ADRs for anakinra; while the events of nausea, vomiting, anxiety, hypernatremia, and hyperkalemia are known to occur in individuals with COVID-19 infection and are also in accordance with the comorbidities reported in this study population.

The classification by severity of non-serious TEAEs revealed that the majority of TEAEs were considered mild (grade 1) or moderate (grade 2) in severity. Grade 3 severity TEAEs were infrequent and balanced between the 2 arms.

The distribution of infections and infestations by MedDRA PT is shown in the table below. The distribution of the majority of infections is generally lower in the anakinra group than in the placebo group.

MedDRA SOC/PT	SoC + Placebo (N=189) n (%)	SoC + Anakinra (N=405) n (%)
Infections and infestations total, n (%)[a]	35 (18.5)	50 (12.3)
Pneumonia	18 (9.5)	19 (4.7)
Septic shock	7 (3.7)	6 (1.5)
Nosocomial infection	7 (3.7)	11 (2.7)
Pyelonephritis acute	4 (2.1)	5 (1.2)
Bacteraemia	6 (3.2)	13 (3.2)
Lung empyema	1 (0.5)	0 (0)
Clostridium difficile infection	2 (1.1)	2 (0.5)[b]
Cholecystitis acute	1 (0.5)	0 (0)
Diverticulitis acute	1 (0.5)	3 (0.7)
Herpes zoster infection	1 (0.5)	1 (0.2)
Cystitis acute	2 (1.1)	7 (1.7)
Latent tuberculosis	0 (0)	1 (0.2)

Abbreviations: N, Total number of patients; n, Number of patients; PT, Preferred term; SoC, Standard of care; SOC, System organ class.
[a]One infection occurred outside the infections and infestations system organ class.
[b]One event of *Clostridium difficile* infection in anakinra group and not 2 events. This will be corrected in the final CSR.

Overall, serious infections occurred less frequently in the anakinra + SoC group (9.1%) than in the placebo + SoC group (16.9%) in the SAVE-MORE study. The serious events (all causality) within the Infections and infestations SOC occurring at a slightly higher frequency in the anakinra + SoC group compared to the placebo + SoC group were single cases of diverticulitis, hepatitis B, and skin infection; all of which were considered unrelated by the investigator at the time of latest follow-up received.

The table below lists the causative organisms in the anakinra + SoC and placebo + SoC groups. Overall, the pattern of secondary infection pathogens was similar between treatment groups, and opportunistic agents were observed in both treatment groups.

The causative organisms occurring at a higher rate in the anakinra + SoC group compared to the placebo + SoC group were: Staphylococcus hominis, Enterobacter cloacae, Streptococcus pneumoniae, Escherichia coli, Aspergillus flavus, Candida spp., and Hepatitis B virus.

Table 31: Causative organisms according to treatment group for events of serious infection

Infection – causative organisms	SoC + Anakinra (N=405) n (%)	SoC + Placebo (N=189) n (%)
Bacteria		
Acinetobacter baumannii	13 (3.2)	9 (4.8)
Pseudomonas aeruginosa	5 (1.2)	5 (2.6)
Klebsiella pneumoniae	7 (1.7)	7 (3.7)
Staphylococcus aureus	1 (0.2)	1 (0.5)
Enterococcus faecalis	5 (1.2)	3 (1.6)
Staphylococcus hominis	1 (0.2)	0
Enterococcus faecium	0	1 (0.5)
Clostridium difficile	0	2 (1.0)
Stenotrophomonas maltophilia	1 (0.2)	1 (0.5)
Enterobacter cloacae	2 (0.5)	0
Acinetobacter lwoffi	0	1 (0.5)
Enterococcus	0	1 (0.5)
Serratia Marscecens	0	1 (0.5)
Streptococcus pneumoniae	1 (0.2)	0
Escherichia coli	1 (0.2)	0
Fungi		
Aspergillus flavus	1 (0.2)	0
Candida spp.	1 (0.2)	0
Candida parapsilosis	2 (0.5)	4 (2.1)
Candida albicans	1 (0.2)	4 (2.1)
Virus		
Hepatitis B virus	1 (0.2)	0

Abbreviations: N, Total number of patients; n, Number of patients; SoC, Standard of care.

In the SAVE-MORE study, serious infections, including pneumonia as a superinfection, were less frequent in the anakinra + SoC group than in the placebo + SoC group. This difference, compared to the current approved Kineret label, is not surprising, considering the different clinical setting of chronic treatment of ambulatory RA patients compared with hospitalized patients with ongoing viral SARS-CoV-2 associated pneumonia. In addition, as demonstrated by the efficacy results in the SAVE-MORE study, anakinra + SoC treated patients did clinically better overall, which could have contributed to fewer secondary infections. The types of infections and the causative micro-organisms reported in the SAVE-MORE study were due to gram-negative infections such as *A. baumannii*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *E. Faecalis*, which are frequently reported in hospitalized patients.

In conclusion, except for overall less frequent infections in anakinra-treated patients, the anatomic, as well as microbiological, patterns were similar between anakinra- and placebo-treated patients and appear congruent with the clinical setting.

In the SAVE-MORE study at Day 28 follow-up, 30 patients (15.9%) allocated to the placebo group worsened in clinical course due to infections, compared to 34 patients (8.4%) in the anakinra group (p=0.010 by the Fisher exact test), indicating that the incidence of infections aggravating the clinical course was lower in the anakinra group than in the placebo group. There were 12 cases of

neutropenia, both serious and non-serious, in the anakinra group. The table below shows the incidence of serious infections recorded as SAEs according to the presence of neutropenia. No infectious SAEs were recorded among patients developing neutropenia.

	No neutropenia (N=393)	Neutropenia (N=12)	p-value
At least one serious infection, n (%)	34 (8.7)	0 (0)	0.610

Abbreviation: N, Total number of patients; n, Number of patients.

Supportive studies

In the SAVE study the captured serious TEAEs during the 14 days of the 1st period are presented in the table below.

The number of patients experiencing at least 1 serious TEAEs by Day 14 was higher in the parallel SoC comparators group (48.5 %) compared to the anakinra+SoC arm (24.6 %). With the exception of pulmonary edema, which occurred in 1 patient in the anakinra+SoC arm, the majority of serious TEAEs observed by Day 14 occurred at a higher rate in the parallel SoC comparators group compared to the anakinra+SoC arm.

Table 32: Serious TEAEs reported in the SAVE study (1st period – April to September 2020)

	Parallel SoC (N = 130)	Anakinra+SoC (N = 130)
At least 1 serious TEAE by Day 14, n (%)	63 (48.5)	32 (24.6)
Extended hospitalization[a]	63 (48.5)	32 (24.6)
Death	16 (12.3)	6 (4.6)
Shock	56 (43.1)	27 (20.8)
Acute kidney injury	37 (28.5)	15 (11.5)
Any bacterial infection	30 (23.1)	9 (6.9)
Thromboembolic event	5 (3.8)	2 (1.5)
Pulmonary edema	0 (0)	1 (0.8)

Abbreviations: N, Number; SoC, Standard-of-care; TEAE, Treatment-emergent adverse event.
[a]Extended hospitalization proportion is based on the proportion of serious TEAEs of shock and any bacterial infections for each group.

The captured serious TEAEs during the 14 days of the 2nd period are shown in the table below.

The incidence of all serious TEAEs in the anakinra group was 18.9% and in the SoC comparators group was 39.0%, including shock (anakinra 6.5% and SoC comparators 26.2%), AKI (anakinra 4.4% and 15.6% SoC comparators), any bacterial infection (anakinra 7.0% and SoC comparators 12.8%), and thromboembolic event (anakinra 1.9% and SoC comparators 2.8%).

Table 33: Serious TEAE reported in SAVE study (2nd period – October to December 2020)

	SoC Comparators (N = 141)	Anakinra (N = 587)
At least 1 serious TEAE by Day 14, n (%)	55 (39.0)	111 (18.9)
Death	20 (14.2)	26 (4.4)
Shock	37 (26.2)	38 (6.5)
AKI	22 (15.6)	26 (4.4)
Any bacterial infection	18 (12.8)	41 (7.0)
Thromboembolic event	4 (2.8)	11 (1.9)

Abbreviations: AKI, Acute kidney injury; N, Number; TEAE, Treatment-emergent adverse event.

Data analysis of adverse events by organ system or syndrome in the SAVE study are not available yet (those are expected to be provided once available).

In the SAVE study, serious infectious events (as a proxy of potentially aggravating secondary infectious events) reported up to 90 days of follow-up are 50 (7.0%) pneumonia events in anakinra treated patients and 48 (17.7%) pneumonia events in the comparator group, 65 (9.1%) septic shock events in anakinra-treated patients, and 93 (34.3%) septic shock events in the comparator group. No information on neutropenia in anakinra-treated patients in the SAVE study is available from the sponsor.

In the Sobi.IMMUNO-101study, serious TEAEs were reported in 1 patient (20.0%) in the anakinra group and 2 patients (40.0%) in the emapalumab group. No patients in the SoC group experienced a serious TEAE. None of the serious TEAEs was considered related to study drug. When classified by organ by organ system or syndrome the most common TEAE by organ system was respiratory, thoracic, and mediastinal disorders (anakinra: 1 patient [20.0%]; emapalumab: 2 patients [40.0%]).

Laboratory findings

Pivotal SAVE-MORE study

Over-time, follow-up of laboratory values showed that there were no statistically significant differences between the anakinra+SoC and placebo+SoC arms at Day 1, Day 4, or Day 7 except for white blood cells (WBC) (median 6710 versus 7250 cells/mm^3 at Day 4 and 7900 versus 8560 cells/mm^3 at Day 7, respectively), absolute neutrophil count (ANC) (median 5050 versus 5665 cells/mm^3 at Day 4 and 5785 versus 6620 cells/mm^3 at Day 7, respectively), absolute lymphocyte count (median 1330 versus 1200 cells/mm^3 at Day 7, respectively), and s-sodium (mean 141.7 versus 140.1 mmol/L at Day 4, respectively). Since treatment was continued past 7 days, the interpretation of these laboratory results is limited.

No data on vital signs, physical findings, and other observations related to safety were available.

Supportive studies:

Data from the SAVE study was not made available. Thus, there was no data on vital signs, physical findings, and other observations related to safety. Those are expected to be submitted once available.

In the Sobi.IMMUNO-101study no severe TEAEs or serious TEAEs related to laboratory parameters were reported. A non-serious TEAE of thrombocytopenia was reported for 1 patient in the anakinra group. The patient's platelet count was within the normal reference ranges (150 to 450 × 10^9/L) on

Days 1 through 10. The patient's platelet count was 94 × 10^9/L on Day 13 and 66 × 10^9/L on Day 15. The event was moderate and considered related to the study drug. The dose of study drug was not changed as a result of the event. At the time of reporting, the event was considered not recovered/not resolved. Of note, immune thrombocytopenic purpura can occur secondary to COVID-19. A non-serious event of hypertransaminasemia was reported for 1 patient in the SoC group. For this patient, ALT and AST levels were within the normal reference ranges on Day 1. From Days 4 through 10, the ALT and AST levels were above the normal range. On Day 15, AST had returned to the normal reference range, although ALT remained elevated. The event was moderate and considered related to the SoC. Action taken with the study drug was reported as not applicable. The event recovered/resolved after 22 days.

Vital signs, physical findings, and other observations related to safety

Mean values of systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature were similar across the treatment groups at baseline.

No relevant trends in vital signs over the course of the study were observed; however, the number of patients in each treatment group and overall was too small to allow for meaningful comparisons in vital signs between the treatment groups.

Overall, the majority of patients had normal physical examination findings at baseline. 1 patient had an abnormal skin examination, and 1 patient had an abnormal abdominal examination that were considered clinically relevant. At baseline, clinically relevant abnormal examination of the thorax/lungs was reported in 7 patients (3 [60.0%] in the emapalumab group, 2 [40.0%] in the anakinra group, and 2 [33.3%] in the SoC group). All 16 patients had clinically relevant abnormal chest imaging findings. In the emapalumab group, ECG changes from screening were reported for 2 patients, no clinically significant abnormal ECGs or ECG changes from screening to Day 15 were reported for patients in the anakinra group.

Safety in special populations

Intrinsic factors

Intrinsic factors have not explicitly been studied for COVID-19.

Studies in patients with hepatic and renal impairment have shown that anakinra is mainly excreted through the kidneys and that mean plasma clearance of anakinra after s.c. administration in patients with severe renal insufficiency and end stage renal disease (defined as creatinine clearance < 30 mL/min, as estimated from serum creatinine levels) was reduced by 70% and 75%, respectively. Anakinra is not eliminated by dialysis, removal of anakinra via hemodialysis or continuous ambulatory peritoneal dialysis is minimal (<2.5% of total clearance).

The approved anakinra product information recommends that physicians should consider administration of the prescribed dose of anakinra every other day for patients who have severe renal insufficiency or end stage renal disease. For patients with hepatic insufficiency, no dosage adjustment is warranted. It was confirmed that those dose adjustments also apply to patients with COVID-19.

Extrinsic factors

No extrinsic factors pertinent to individualizing therapy or patient management have been observed.

Safety related to drug-drug interactions and other interactions

Interactions between anakinra and other relevant medicinal products are described in the approved anakinra product information.

Interactions between Kineret and other medicinal products have not been investigated in formal studies. In clinical trials, interactions between Kineret and other medicinal products (including nonsteroidal anti-inflammatory medicinal products, glucocorticoids, and DMARDs) have not been observed.

Discontinuation due to adverse events

Pivotal SAVE MORE study

Overall, there were 5 patients who discontinued treatment due to an AE. The percentage of patients where the study drug was stopped due to leukopenia or due to increase of aminotransferase was low and comparable between the 2 groups of treatment (see table below) 2 patients from the placebo+SoC treatment group, one patient due to leukopenia and one patient due to derangement of liver function tests, were discontinued. 3 patients from the anakinra+SoC treatment group, one patient due to leukopenia and two patients due to derangement of liver function tests were discontinued. No leukopenia events were reported as serious. Three (3) (0.7%) Transaminases increased events were reported as serious in the anakinra group compared with 2 (1.1%) events assessed as serious in the placebo group. No increases in hepatic enzymes were associated with clinical consequences such as DILI or non-infectious hepatitis. The proposed treatment course of anakinra in COVID-19 is limited to 10 days.

Deviation	Decision taken by	SoC + Placebo (N=189) n (%)	SoC + Anakinra (N=405) n (%)	p-value
Premature stop of study drug due to leukopenia	Attending physicians	1 (0.5)	1 (0.2)	0.54
Premature stop of study drug due to increase of aminotransferases	Attending physicians	1 (0.5)	2 (0.5)	1.00

Abbreviations: N, Total number of patients; n, Number of patients; SoC, Standard of care.

Supportive studies

No data are available for the SAVE study. In the Sobi-IMMUNO-101 study, 1 patient (20.0%) in the anakinra group and 2 patients (40.0%) in the emapalumab group experienced TEAEs leading to withdrawal of study drug (see table below).

Table 34: TEAEs by SOC and PT leading to study drug withdrawn (Safety population

	Number (%) of patients[a]	
	Emapalumab (N = 5)	**Anakinra (N = 5)**
Any AE	2 (40.0)	1 (20.0)
Cardiac disorders	1 (20.0)	0
Atrial fibrillation	1 (20.0)	0
Respiratory, thoracic and mediastinal disorders	1 (20.0)	1 (20.0)
Respiratory failure	1 (20.0)	1 (20.0)

Abbreviations: AE, Adverse event; N, Number; PT, Preferred term; SOC, System organ class; TEAE, Treatment emergent adverse event.
[a] Patients with multiple events at the same level of summarization are counted only once at that level. Patients with events at more than one level of summarization are counted once at each of those levels.
Note: MedDRA version 23.0.

Use in pregnancy and lactation

No reports of pregnancies in patients with COVID-19 were received by the MAH up to May 1, 2021.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/fetal development, parturition or postnatal development. There are no adequate clinical study data from the use of anakinra in pregnant women since pregnant women were excluded from participation in anakinra clinical studies.

As a precautionary measure, it is preferable to avoid the use of anakinra during pregnancy and in woman of childbearing potential not using contraception. It is unknown whether anakinra/metabolites are excreted in human milk. Breast-feeding should be discontinued during treatment with anakinra.

Overdose, Drug abuse, Withdrawal and Rebound

No dose-limiting toxicities were observed during clinical studies. In studies of sepsis, 1015 patients received anakinra at doses up to 2 mg/kg/hour i.v. (approximately 35 times the recommended dose in RA) over a 72-hour treatment period. The safety profile of anakinra in these studies showed no overall difference from that seen in the RA or other studies.

Drug abuse

Currently, no evidence exists for potential abuse of anakinra. No reports of abuse of anakinra have been received.

Withdrawal and rebound

There have been no clinical studies specifically designed to evaluate withdrawal and/or rebound. However, there are no indications of withdrawal or rebound effects in clinical studies, or from post-marketing data, other than re-occurrence of the disease treated.

Effects on ability to drive or operate machinery or impairment of mental ability

No studies on the effects of anakinra on the ability to drive and use machines have been performed. There are no indications in clinical or preclinical data that anakinra would affect the ability to drive or operate machinery or impair mental ability.

Post marketing experience

As of May 1, 2021, the cumulative post-marketing exposure across multiple indications is estimated to be 142, 955 patient-years. The patient exposure was estimated based on the amount of product distributed and includes all preparations (i.e., both the non-graduated and graduated syringes, which were first launched in the US in August 2013 and in the EU in April 2014).

Review of MAH's global safety database for anakinra use in SAVE-MORE study

Serious AEs

A total of 112 SAEs in 76 case reports for SAVE-MORE study were retrieved up to the DLP of June 8, 2021, see table below.

The review of 112 SAEs in 66 patients (76 case reports) revealed a mean of 64 years and a median of 65 years (age band range: 30 to 89 years). The proportion of patients by age group was equal between adults and elderly patients (n=33 for each age group), of these 49 were male (74%) and 19 female (29%) patients.

The SAE outcomes were reported as favorable (recovered/ resolved/ recovering/ resolving) in 58 SAEs (52%); recovered/ resolved with sequelae in 3 SAEs (3%); not recovered/ not resolved in 3 SAEs (3%); and fatal in 27 SAEs (24%). The outcome of 21 SAEs (19%) were unknown. The reporter causality for the SAEs was reported as suspected in 12 SAEs (11%) and as not suspected in 100 SAEs (89%). The dose latency was reported in 99 SAEs with a mean of 13.5 days and median of 10 days (range: 1 day to 100 days). The distribution of the SAEs by SOC and PT from the case reports reported in the anakinra+SoC arm in SAVE-MORE study are shown in the below table.

Table 35: Distribution of the SAEs reported with the use of anakinra treatment arm in the SAVE-MORE study (safety database)

SOC/PT	Count of Event PT
Infections and infestations	**59**
Pneumonia	16
Nosocomial infection	7
Bacteraemia	5
Septic shock	4
Pyelonephritis acute	4
Staphylococcal bacteraemia	2
Bacterial infection	2
Sepsis	2
Klebsiella bacteraemia	2
Pneumonia pneumococcal	1
Diverticulitis	1
Clostridium difficile infection*	1
Urinary tract infection	1
Infection	1
Urosepsis	1
Chronic hepatitis B	1
Acinetobacter bacteraemia	1
Device related infection	1
Pneumococcal sepsis	1
Superinfection bacterial	1
Candida pneumonia	1
Pneumonia bacterial	1
Abdominal infection	1
Klebsiella infection	1
Respiratory, thoracic and mediastinal disorders	**13**
Pulmonary embolism	6
Pneumomediastinum	4
Pneumothorax	1
Respiratory failure	1
Pulmonary fibrosis	1
Metabolism and nutrition disorders	**11**
Hypernatraemia	4
Hypoglycaemia	2
Hyponatraemia	2
Hyperglycaemia	1

SOC/PT	Count of Event PT
Dehydration	1
Hypocalcaemia	1
Blood and lymphatic system disorders	**6**
Lymphopenia	3
Anaemia	2
Neutropenia	1
Investigations	**6**
International normalised ratio increased	1
Transaminases increased	1
Liver function test increased	1
Gamma-glutamyltransferase increased	1
Activated partial thromboplastin time prolonged	1
Hepatic enzyme increased	1
General disorders and administration site conditions	**5**
MODS	3
Pyrexia	1
Catheter site haemorrhage	1
Cardiac disorders	**5**
Atrial fibrillation	2
Sinus bradycardia	2
Bradycardia	1
Renal and urinary disorders	**3**
AKI	3
Immune system disorders	**1**
Anaphylactic shock	1
Vascular disorders	**1**
Arterial thrombosis	1
Musculoskeletal and connective tissue disorders	**1**
Haematoma muscle	1
Nervous system disorders	**1**
Ischaemic stroke	1
Grand Total	**112**

Abbreviations: AKI, Acute kidney injury; CSR, Clinical study report; MODS, Multiple organ dysfunction syndromes; SAE, Serious adverse event; SOC, System organ class; PT, Preferred term.
Note: These frequencies are different from those reported in the SAVE-MORE CSR, since no reconciliation has been performed yet, and the events in the CSR have not been MedDRA coded.

Following the review of all 76 case reports, which were all SAEs, from the SAVE-MORE study as identified in the MAH's global safety database, the outcome of the majority of the SAEs was favourable (52%). The AE outcome of 24% of AEs was reported as fatal and 42% as life threatening. Considering the inclusion criteria of the investigator-sponsored study included hospitalization for COVID-19 and the fact that a majority of patients (81.6%) were identified with severe COVID-19 pneumonia, this can be expected. The Investigator considered the majority of the reported AEs as not related (89%).

The mean age of COVID-19 patients at anakinra initiation was 64 years and the median was 65 years, with an age distribution of 1:1 of adults to elderly. The mean age of patients experiencing fatal outcomes was 71.1 years and the median was 74 years, with an age distribution of 1:2.8 of adults to elderly. According to the US Centers for Disease Control and Prevention (CDC), people in their 50s are

at higher risk for severe illness, than people in their 40s; meaning that a person with COVID-19 may require hospitalization, intensive care, or a ventilator to help them breathe, or they may even die.

Similarly, people in their 60s or 70s are, in general, at higher risk for severe illness than people in their 50s; with the greatest risk for severe illness from COVID-19 being among those aged 85 years or older. Thus, no unexpected shift in age distribution was seen with the use of anakinra for treating COVID-19 and its complications.

The most frequently reported AEs included pneumonia (16 AEs, 14.3% of all AEs); nosocomial infections (7 AEs, 6.3% of all AEs); pulmonary embolism (6 AEs, 5.4% of all AEs); bacteremia (5 AEs, 4.5% of all AEs); and pneumomediastinum, hypernatremia, pyelonephritis acute, and septic shock (each with 4 AEs, 3.6% of all AEs). The clinical presentation of the most frequently reported AEs can be explained by the underlying COVID-19, nosocomial causes, and the use of corticosteroids (74% of case reports involved concomitant use of corticosteroids at baseline).

The AE distribution for fatal and life-threatening AEs also followed a similar distribution with the events attributed to underlying COVID-19 pathogenesis and nosocomial factors.

Overall, 52 out of 76 case reports had sufficient case details, such as medical history, concomitant medication, and dose latency, for a comprehensive causal assessment. The dose latency had a mean of 13.5 days and a median of 10 days. All 52 case reports had at least 2 non-COVID-19 pre-existing morbidities at study baseline affecting different organ systems with 2 case reports having more than 5 organ systems affected, 12 case reports having more than 3 SOC affected, and 29 case reports having more than 3 organ systems affected. The most common non-COVID-19 medical histories reported were those affecting the cardiovascular system (e.g., hypertension, ischemic heart diseases, heart failure, arrhythmia, etc.), respiratory system (e.g., COPD, asthma), diabetes, infections, cancers, and obesity. As per the current understanding of COVID-19, adults with the conditions of cancer, chronic kidney disease, chronic lung diseases, dementia or other neurological conditions, diabetes mellitus, heart conditions (e.g., heart failure, coronary artery disease, cardiomyopathies, or hypertension), overweight and obesity, smoking (current or former), stroke, or cerebrovascular disease can be more likely to get severely ill from COVID-19 resulting in hospitalisation, intensive care, ventilator support, and even death.

Deaths

Within the global safety database, a total of 15 patients (27 AEs) with a fatal outcome were received by DLP on June 8, 2021, with anakinra used in the SAVE-MORE study, as shown in the table below.

Table 36: Distribution of fatal SAEs received in cases reporting the use of anakinra for treating COVID-19 in the SAVE-MORE study

MedDRA PT	Count of Event PT
Septic shock	4
MODS	3
Pneumonia	3
AKI	2
Nosocomial infection	2
Pneumonia pneumococcal	1
Bacterial infection	1
Respiratory failure	1
Klebsiella bacteraemia	1
Infection	1
Arterial thrombosis	1
Pneumothorax	1
Abdominal infection	1
Sepsis	1
Pneumococcal sepsis	1
Urosepsis	1
Pneumomediastinum	1
Bacteraemia	1
Grand Total	**27**

Abbreviations: AKI, Acute kidney injury; COVID-19, Coronavirus disease 2019; CSR, Clinical study report; MedDRA, Medical dictionary for regulatory activities; MODS, Multiple organ dysfunction syndrome; PT, Preferred term; SAE, Serious adverse event.
Note: These frequencies are different from those reported in the SAVE-MORE CSR, since no reconciliation has been performed yet, and the events in the CSR have not been MedDRA coded.

The review of 27 AEs from the 15 patients revealed a mean of 71.1 years and a median of 74 years (age band range: 50 to 89 years). The patients' age group ratio between adults and elderly was 1:2.8 (4 adults, 11 elderly). Of the 15 patients, 11 were male (73 %) and 4 female (27 %) patients. The dose latency was reported in 27 fatal AEs with a mean of 15.6 days and a median of 10.5 days (range: 1 to 100 days).

On review of the fatal cases, the majority (73%) were elderly patients (mean age: 71.1 years and median age: 74 years), which is consistent with the age distribution of mortality cases seen worldwide. The most frequently reported fatal AE PTs were septic shock (4 AEs [11.6% of all fatal AEs]); multiple organ failure syndrome (MODS) (3 AEs [11.1% of all fatal AEs]); pneumonia (3 AEs [11.1% of all fatal AEs]); Acute kidney injury (AKI) (2 AEs [7.4% of all fatal AEs]); and nosocomial infection (2 AEs [7.4% of all fatal AEs]). The remaining AEs PTs were singularly reported. Of the 27 fatal AEs, the most reported AEs were infections and infestations (18 AEs [67% of all fatal AEs]), wherein the most common systems affected were the circulatory system (including cause of septic shock) followed by the respiratory system. The main causative organisms reported were *Pneumococcus* and *Klebsiella*, which are commonly known respiratory pathogens or bloodstream infections in underlying COVID-19, underlying pneumonia, or hospitalized cases.

The clinical presentation of septic shock, MODS, pneumonia, AKI, nosocomial infection have been typically reported in critical COVID-19 and autopsies of COVID-19 mortality patients. Hence, the most frequently reported AEs identified as a clinical condition can be attributed to natural history and progression of the underlying COVID-19 or nosocomial causes.

Overall, all 15 case reports were confounded by COVID-19 progression, and/or medical history, and/or concomitant medication. The most common non-COVID-19 medical histories reported were those affecting the cardiovascular system identified in all 15 case reports with fatal AEs (such as hypertension, ischemic heart diseases, heart failure, arrhythmia, etc.), or diabetes or with comedication for diabetes (5 case reports [33%]), respiratory system in 4 case reports (27%) (e.g., COPD, asthma, etc.), extrapulmonary infections (2 case reports [13%]; septic shock, intraabdominal infection), and multiple co-morbidities (14 case reports [93%]). As per the current understanding of COVID-19, adults with the conditions of cancer, chronic kidney disease, chronic lung diseases, dementia or other neurological conditions, diabetes mellitus, heart conditions (such as heart failure, coronary artery disease, cardiomyopathies, or hypertension), overweight and obesity, smoking (current or former), stroke, or cerebrovascular disease are more likely to get severely ill from COVID-19 resulting in hospitalisation, intensive care, ventilator support, and even death.

Serious infections

Serious infections are considered important identified risks for anakinra. A total of 59 SAEs in 40 case reports of SOC infections and infestations were received up to the DLP on June 8, 2021, as shown in the table below.

Table 37: Distribution of SAEs in SOC infections and infestations reported with anakinra arm in the SAVE-MORE study (safety database reports)

MedDRA PT	Count of Event
Pneumonia	16
Nosocomial infection	7
Bacteraemia	5
Septic shock	4
Pyelonephritis acute	4
Staphylococcal bacteraemia	2
Bacterial infection	2
Sepsis	2
Klebsiella bacteraemia	2
Pneumonia pneumococcal	1
Diverticulitis	1
Clostridium difficile infection*	1
Urinary tract infection	1
Infection	1
Urosepsis	1
Chronic hepatitis B	1
Acinetobacter bacteraemia	1
Device related infection	1
Pneumococcal sepsis	1
Superinfection bacterial	1
Candida pneumonia	1
Pneumonia bacterial	1
Abdominal infection	1
Klebsiella infection	1
Grand Total	**59**

* Follow-up information received after data-lock point indicated the patient received placebo
Abbreviations: CSR, Clinical study report; MedDRA, Medical dictionary for regulatory activities; PT, Preferred term; SAE, Serious adverse event; SOC, System organ class.
Note: These frequencies are different from those reported in the SAVE-MORE CSR, since no reconciliation has been performed yet, and the events in the CSR have not been MedDRA coded.

On review of 59 AEs of infections, 18 (31%) were fatal. 41 % (n=24) of AE outcomes were reported as favourable (recovered/resolved/recovering/resolving) and 2% as non-recovered (n=1). The causality was reported as not suspected for the majority of AEs (88%, n=52) and suspected only in 7 AEs (12%).

The most frequently reported AE PTs in the life-threatening cases was pneumonia (16 AEs [14.3% of all AEs]); nosocomial infection (7 AEs [6.3% of all AEs]); bacteremia (5 AEs [4.5% of all AEs]); septic shock and pyelonephritis acute (each with 4 AEs [3.6% of all AEs]); and Staphylococcal bacteremia, bacterial infection, sepsis, and Klebsiella bacteremia (each with 2 AEs [1.8% of all AEs]). The remaining AEs were singularly reported. The most frequently reported AEs suggested respiratory involvement or bloodstream infection with the most common sources being *Staphylococcus* and *Klebsiella*, which are common with underlying COVID-19, underlying pneumonia, or hospitalised cases. However, considering the SAVE-MORE inclusion criteria "Need for hospitalization for COVID-19", and

the fact that a majority of patients (81.6%) were identified with severe COVID-19 pneumonia, this can be expected.

The dose latency was reported in 52 AEs with a mean of 18.3 days and a median of 10 days (range: 1 day to 100 days). Reasonable case details for comprehensive causal assessment was available in 57 out of 59 case reports, wherein confounders for predisposition to infections (in addition to pre-existing COVID-19 pneumonia) were identified such as the use of corticosteroids (29 case reports, 51%), diabetes (7 case reports, 3%), and serious cardiorespiratory comorbidity (100 % of case reports). About 51 % of patients were also on pre-existing higher antibiotics suggesting the possibility of a pre-existing infection prior to starting anakinra. Serious infections are listed as common ADRs for anakinra as per current reference safety information.

Life-threatening cases summary

A total of 33 life-threatening case reports with 38 AEs in 26 patients, were received up to the DLP of June 8, 2021, as shown in the table below. These case reports were considered life-threatening but were not fatal.

Table 38: Distribution of life-threatening SAEs reported with anakinra arm in the SAVE-MORE study (safety database reports)

MedDRA PT	Count of Event PT
Pneumonia	6
Pulmonary embolism	4
Bacteraemia	3
Lymphopenia	3
Hyponatraemia	2
Hypoglycaemia	2
Nosocomial infection	2
Superinfection bacterial	1
Pulmonary fibrosis	1
Pneumonia bacterial	1
International normalised ratio increased	1
Sepsis	1
Klebsiella bacteraemia	1
Klebsiella infection	1
Anaphylactic shock	1
Anaemia	1
Acinetobacter bacteraemia	1
Pyrexia	1
Neutropenia	1
Staphylococcal bacteraemia	1
Candida pneumonia	1
Haematoma muscle	1
Pneumomediastinum	1
Grand Total	**38**

Abbreviations: CSR, Clinical study report; MedDRA, Medical dictionary for regulatory activities; PT, Preferred term; SAE, Serious adverse event.
Note: These frequencies are different from those reported in the SAVE-MORE CSR, since no reconciliation has been performed yet, and the events in the CSR have not been MedDRA coded.

The patients' age was reported in all cases with a mean of 62.3 years and a median of 61 years (age band range: 40 years to 89 years) that comprised 16 adults (62%) and 10 elderly (38%) patients.

About 79% of the life-threatening AEs were reported in male patients. The dose latency identified in the 38 AEs had a mean of 13.8 days and a median of 10 days (range: 2 days to 67 days).

The most frequently reported AE PTs in the life-threatening cases were pneumonia (6 AEs, 15.8% of all life-threatening AEs); pulmonary embolism (4 AEs, 10.5% of all life-threatening AEs); bacteraemia and lymphopenia (each with 3 AEs, 7.9% of all life-threatening AEs); and hyponatremia, hypoglycaemia, and nosocomial infection (each with 2 AEs, 5.3 % of all life-threatening AEs). The remaining AEs were singularly reported.

Considering the clinical presentation of predominant severe respiratory involvement for the life-threatening cases identified, the most frequently reported AEs can be better attributed to natural history and progression of COVID-19, nosocomial causes (such as HAP, ventilator associated infections), co-morbidities (such as diabetes), and concurrent use of anti-coagulants, diuretics (for electrolyte disturbances). This clinical presentation has been typically reported in critical COVID-19 and patients on concomitant use of higher antibiotics at baseline (covering broad spectrum and antibacterial resistance usually seen in a nosocomial setting suggesting pre-existing systemic infections).

Overall, all the 33 life-threatening case reports (in 26 patients) were confounded by COVID-19 progression and/or medical history and/or concomitant medication. The most common non-COVID-19 medical histories reported were hypertension, ischemic heart diseases, heart failure, arrhythmia, diabetes, or concomitant diabetic medications. As per the current understanding of COVID-19, adults with the conditions of cancer, chronic kidney disease, chronic lung diseases, dementia or other neurological conditions, diabetes mellitus, heart conditions (such as heart failure, coronary artery disease, cardiomyopathies, or hypertension), overweight and obesity, smoking (current or former), stroke or cerebrovascular disease are more likely to become severely ill from COVID-19 resulting in hospitalisation, intensive care, ventilator support and even death.

Hepatic event case summary

Hepatic disorders are considered important identified risks for anakinra. Overall, in the SAVE-MORE study, few patients (4 patients) experienced SAEs: transaminases increased, liver function test increased, hepatic enzyme increased, and gamma-glutamyl transferase increased.

SAE of serum transaminases increased was reported in a 40-49-year-old patient who experienced an increase in transaminases (AST: 208 IU/L and ALT 447 IU/L) after 6 days of treatment with anakinra +SoC. This patient also received multiple medications (i.e., remdesivir and azithromycin) that were considered co-suspect concurrent medications. Following discontinuation of anakinra treatment, the patient's liver enzymes started to recover, and the patient was discharged in 4 days when positive de-challenge was noted. The event of serum transaminases increased was considered to be related to anakinra treatment, although the role of other concurrent treatments (i.e., remdesivir and azithromycin) cannot be ruled out.

SAE of liver function test elevated was reported in a 30-39-year-old patient who had mild elevated liver function tests at baseline, due to antibiotics while treated for COVID-19. The patient subsequently started treatment with anakinra and remdesivir. After finishing the remdesivir treatment and 7-day treatment with anakinra, the patient experienced further elevation of liver function tests (AST: 195 U/L, ALT: 321 U/L). Anakinra treatment was discontinued. The events resolved 4 days after discontinuation of anakinra treatment (i.e., positive de-challenge). The SAE of liver function test elevated was considered related to anakinra treatment, although confounding factors of remdesivir,

previous antibiotics, and pre-existing baseline liver function test elevations can be additional contributory factors.

SAE hepatic enzymes increased was reported in a 70-79-year-old patient who experienced the event after 5 days of anakinra treatment. Anakinra treatment was discontinued and the patient recovered completely in 5 days. The event was evaluated as related to study treatment with anakinra, although the role of concurrent antibiotics cannot be ruled out.

A SAE of gamma-glutamyl transferase increased was reported in a patient after 10 days of anakinra treatment. No medical history or details of concurrent treatments were provided. The event was evaluated as related to anakinra; however, there was minimal information available to complete a medical/causality assessment. It was noted that the patient was asymptomatic and that the event duration was approximately 40 days, which also casts doubt on the contribution of anakinra considering its short half-life (6 to 7 hours).

Overall, based on the review of the 4 case reports, there was no new safety signal reported for hepatic enzymes elevation. Hepatic enzymes elevation is a known complication of the antibiotic use, especially in infection. In addition, while patients are being treated in the hospital with other concurrent medications for COVID-19 (i.e., remdesivir), it is very difficult to differentiate which drug may have contributed to the hepatic events. All 4 patients remained asymptomatic and recovered completely after anakinra treatment discontinuation. The short duration (10 days) of anakinra treatment, along with the fact that the patients were treated concurrently with antibiotics and other COVID-19 treatments that may also affect hepatic enzymes, confounds the cases and suggests an alternate etiology.

Designated medical event (DME) case summary

On the evaluation of the MAH's database with SAVE-MORE case reports, 5 were identified as having events considered to be DMEs. These were events of anaphylactic shock (1 event), AKI (3 events), and pulmonary fibrosis (1 event). On further analysis of these patients, the anaphylactic shock was reported after completion of anakinra treatment in a patient who developed HAP while on ventilator support in the ICU. The event of anaphylactic shock was due to colistin treatment and was evaluated as unrelated to anakinra. The three AKI and pulmonary fibrosis events were evaluated as caused by the use of multiple antibiotics, as well as COVID-19-related complications. No new safety signal was identified on a review of the DME case reports.

Review of the investigator-sponsored dataset

A total of 171 case reports were received from 6 investigator-sponsored studies, of which 2 case reports were considered invalid. The breakdown of the 169 valid case reports by protocol number is provided in the table below.

Table 39: Investigator-sponsored study cases by protocol number

Study	Protocol Number	Number of Cases
SuPAR-Guided Anakinra Treatment for Validation of the Risk and Early Management of Severe Respiratory Failure by COVID-19: The SAVE Open-Label, Non-Randomized Single-Arm Trial	IMM-Gre-2020-009-Gia	55
CORIMUNO-ANA: Trial Evaluating Efficacy of Anakinra in Patients With COVID-19 Infection, Nested in the CORIMUNO-19 Cohort - 54	IMM-Fra-2020-001-Mar	52
Clinical Trial of the Use of ANAKINRA (ANTI-IL-1) in Cytokine Storm Syndrome (CSS) Secondary to COVID-19 (ANA-COVID-GEAS) - 26	IMM-Spa-2020-003-Fan	26
ANACONDA: Efficacy and safety of ANakinra during Adult «COroNa virus Disease-19» with Aggravative respiratory symptoms: a multicenter open controlled randomized trial - 21	IMM-Fra-2020-002-Aud	21
DAWn-Anticoc/ 2020-001739-28/ Belgium/ ongoing - 8	IMM-Bel-2020-004-Van	8
REMAP-CAP – A Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia - 7	IMM-Int-2020-006-Der	7
Total		**169**

Abbreviations: COVID-19, Coronavirus disease 2019; DAWn, Direct Antivirals Working against nCoV; REMAP-CAP, Randomized, embedded, multi-factorial, adaptive platform trial for community-acquired pneumonia; suPAR, Soluble urokinase plasminogen activator receptor.

The most frequently reported SOCs (>30 events) were respiratory, thoracic and mediastinal disorders (80 events); infections and infestations (76 events); blood and lymphatic system disorders (39 events); vascular disorders (33 events); and general disorders and administration site conditions (32 events). The most frequently reported PTs (≥10 events) were respiratory failure (27 events); shock and acute respiratory distress syndrome (23 events each); liver function test increased and anaemia (19 events each); electrolyte imbalance (18 events); AKI (15 events); leukopenia and septic shock (11 events each); and MODS (10 events).

Review of global safety database for anakinra use

A search of the MAH Global Safety Database was conducted up to DLP of May 1, 2021, to retrieve all cases involving anakinra use and any indication PT coded within the COVID-19 standardized MedDRA queries (narrow; MedDRA version 24.0).

Results

A total of 613 case reports (valid case reports: 455; invalid case reports: 158) were received through the DLP on May 1, 2021. A review of the invalid case reports did not identify any new signals or safety concerns.

The safety assessment for the COVID-19 indication was conducted on the 831 events in 455 valid case reports. The source of the 455 case reports is provided in the table below.

Table 40: Source of valid case reports

Source	Total Case Count	Medically Confirmed Case Count
Investigator-sponsored study	165	164
Literature	222	220
Spontaneous	45	33
Solicited	22	2
Clinical Study	1	1
Total	455	420

The review of 831 AEs from the 455 case reports revealed the following information:

- The off-label indication for anakinra for treatment of COVID-19, severe COVID-19 pneumonia or pneumopathy, or complications of COVID-19, such as severe COVID-19 with secondary haemophagocytic lymphohistiocytosis, cytokine storm syndrome due to COVID-19, ARDS, or paediatric multisystem inflammatory syndrome, are outside the product's marketing authorisation. Out of the 455 case reports, 216 case reports involved off-label use with no AE.

- The patients' age was reported in 337 case reports with a mean of 55 years and a median of 61 years (age band range: 0 to 99 years).

- The patients' age groups were reported in 369 case reports and comprised 18% in paediatric age group (i.e., neonate [N=1]; infant [N=6]; child [N=42]; adolescent [N=16]), 45% (N=167) as adults, and 37% (N=137) as elderly.

- The patients' gender was reported in 419 case reports with 274 male (65%) and 145 female (35%) patients.

- Out of 831 AEs, 476 AEs (57%) were serious and 355 AEs (43%) were non-serious.

- Anakinra dosing ranged from 2 mg up to 600 mg. No meaningful information could be gathered from the dose ranges concerning the COVID-19 outcome.

- The AE outcome was reported as favourable (either recovered, resolved, recovering, or resolving) in 192 AEs (23 %), recovered or resolved with sequelae in 6 AEs (0.7%), not recovered or not resolved in 39 AEs (4.7%), and fatal in 121 AEs (15%). The AE outcome of 473 AEs (57 %) was reported as unknown.

- About 90 % of the case reports were from studies and literature sources.

- The AEs causality was reported as suspected in 55 AEs (6.6 %), not suspected (or no reasonable probability) in 317 AEs (38.1%), and not reported in 459 AEs (55.2%).

- The dose latency was reported in 222 AEs with a mean of 9 days and a median of 7 days (range: 1 day to 55 days).

The SOC/PT distribution of the AE PTs (≥5 PTs) from valid case reports is shown in the table below.

Table 41: System organ class/preferred term distribution (≥5 events)

MedDRA SOC/PT	Count of Event
Injury, poisoning, and procedural complications	**293**
Off-label use	284
Incorrect route of product administration	7
Respiratory, thoracic, and mediastinal disorders	**100**
Respiratory failure	37
Acute respiratory distress syndrome	25
Pulmonary embolism	7
Respiratory distress	6
Infections and infestations	**86**
Septic shock	11
Pneumonia bacterial	8
Superinfection	7
COVID-19 pneumonia	5
Bacterial infection	5
Investigations	**63**
Liver function test increased	19
Blood triglycerides increased	8
Transaminases increased	8
Aspartate aminotransferase increased	5
Alanine aminotransferase increased	5
General disorders and administration site conditions	**58**
Multiple organ dysfunction syndrome	14
Death	14
Condition aggravated	10
Blood and lymphatic system disorders	**56**
Anaemia	20

MedDRA SOC/PT	Count of Event
Leukopenia	14
Thrombocytopenia	11
Splenomegaly	5
Vascular disorders	**40**
Shock	26
Haemodynamic instability	5
Renal and urinary disorders	**30**
Acute kidney injury	20
Renal failure	5
Cardiac disorders	**20**
Arrhythmia	7
Hepatobiliary disorders	**19**
Hepatic cytolysis	7
Hepatomegaly	5
Metabolism and nutrition disorders	**19**
Electrolyte imbalance	18
Gastrointestinal disorders	**17**
Gastrointestinal disorder	9

Abbreviations: MedDRA, Medical dictionary for regulatory activities; PT, Preferred term; SOC, System organ class.

Fatal cases reporting anakinra use for COVID-19 (off-label use)

Within the global safety database, a total of 80 case reports (121 AEs) with a fatal outcome were received through DLP on May 1, 2021, associated with anakinra use for COVID-19 treatment (off-label use) as shown in the table below.

Table 42: Distribution of fatal AEs received in cases reporting use of anakinra for treating COVID-19

MedDRA PT	Grand Total
Multiple organ dysfunction syndrome	14
Death	14
Respiratory failure	11
Acute respiratory distress syndrome	11
Septic shock	6
Shock	5
Condition aggravated	5
Respiratory distress	4
Disease complication	4
COVID-19 pneumonia	3
Pneumonia bacterial	3

MedDRA PT	Grand Total
Pneumonia	2
Sepsis	2
Cardio-respiratory arrest	2
COVID-19	2
Cardiac failure	2
Pulmonary embolism	2
Chest pain	1
Intestinal pseudo-obstruction	1
Candida sepsis	1
Cytomegalovirus infection reactivation	1
Aortic dissection	1
Acute respiratory failure	1
Bronchopulmonary aspergillosis	1
Circulatory collapse	1
Hypoxia	1
Acute myocardial infarction	1
Klebsiella infection	1
Renal injury	1
Oxygen saturation decreased	1
Arrhythmia	1
Cerebrovascular accident	1
Device related infection	1
Renal failure	1
Superior sagittal sinus thrombosis	1
Respiratory disorder	1
Upper gastrointestinal haemorrhage	1
Bacterial infection	1
Enterococcal infection	1
Brain stem syndrome	1
General physical health deterioration	1
Staphylococcal bacteraemia	1
Haemodynamic instability	1
Haemophagocytic lymphohistiocytosis	1
Acinetobacter infection	1
Enterobacter infection	1
Grand Total	**121**

Abbreviations: AE, Adverse event; COVID-19, Coronavirus disease 2019; MedDRA, Medical dictionary for regulatory activities; PT, Preferred term.

The review of 121 AEs from the 80 case reports revealed the following information:

- The patient's age was reported in 73 case reports with a mean of 71 years and a median of 72 years (age band range: 0 years to 99 years).

- The patients' age groups were reported in 74 case reports and comprised 1.4% of paediatric age group (child [1.4%, N=1]), 25.7 % (N=19) adults, and 73.0% (N=54) elderly.

- The patient's gender was reported in 53 case reports with 37 male (70.0%) and 16 female (30.0%) patients.

- Anakinra dosing ranged from 100 mg up to 600 mg. No meaningful information can be gathered from dose ranges concerning the severity or the outcome.

- Of the 80 patients with reported medical history or concomitant medications, 54 had at least 2 risk factors, 35 had at least 3 risk factors, and 27 had at least 4 risk factors, placing these patients in the higher risk category of getting severe COVID-19.

- The dose latency was reported for 52 of the fatal AEs with a mean of 11.3 days and a median of 9 days (range: 1 day to 55 days).

The most frequently reported fatal AE PTs (>5) were death (cause unknown for 14 events [11.6% of all fatal AEs]); MODS (14 events [11.6% of all fatal AEs]); respiratory failure (11 events [9.1% of all fatal AEs]); ARDS (11 events [9.1% of all fatal AEs]); and septic shock (6 events [5.0% of all fatal AEs]). The clinical presentation of MODS, respiratory failure, ARDS, and septic shock have been typically reported in critical COVID-19 and autopsies of COVID-19 mortality patients. Hence the most frequently reported AEs, identified as a clinical condition, can be attributed to the natural history and progression of the underlying COVID-19 disease.

A review of the case reports with fatal PTs occurring below ≤5 events and singular PTs at the MedDRA high-level term did not reveal any new safety trends.

Non-fatal case summary

A total of 33 life-threatening case reports (51 AEs) not reported with a fatal outcome were received through DLP of May 1, 2021, as shown in the table below.

Table 43: Distribution of life-threatening AEs in non-fatal case reports reporting use of anakinra for treating COVID-19

MedDRA PT	Count of Event
Lower respiratory tract disorders (excl obstruction and infection)	12
Bacterial infectious disorders	9
Infections - pathogen unspecified	6
Respiratory disorders NEC	6
Vascular disorders NEC	4
Ancillary infectious topics	3
Embolism and thrombosis	2
Pleural disorders	2
Decreased and nonspecific blood pressure disorders and shock	2
Procedural related injuries and complications NEC	1
Renal disorders (excl nephropathies)	1
Encephalopathies	1
Allergic conditions	1
Fungal infectious disorders	1
Grand Total	**51**

Abbreviations: AE, Adverse event; COVID-19, Coronavirus disease 2019; MedDRA, medical dictionary for regulatory activities; NEC, Not elsewhere classified; PT, Preferred term.

The review of the majority of life-threatening AEs for non-fatal case reports revealed the following information:

- The patient's age was reported in 30 case reports with a mean of 60 years and a median of 61 years (age band range: 20 years to 99 years).

- The patients' age groups comprised 60% (N=18) adults and 40% (N=12) elderly.

- About 77% of life-threatening AEs were reported in male patients.

- Anakinra dosing ranged from 1 mg up to 400 mg. No meaningful information could be gathered from the dose ranges concerning severity or outcome.

- The dose latency was reported for 46 AEs with a mean of 7 days and median of 6 days.

The most frequently reported AE PTs (≥2 events) in the life-threatening case reports were ARDS (23.5%; 12 events), haemodynamic instability (7.8%; 4 events), septic shock (5.9%; 3 events), nosocomial infection (5.9%; 3 events), pneumonia bacterial (5.9%; 3 events), shock (3.9%; 2 events), respiratory failure (3.9%; 2 events), dyspnoea (3.9%; 2 events), and pneumothorax (3.9%; 2 events).

The most frequently reported high-level group terms (≥3 events) were lower respiratory tract disorders (excluding obstruction and infection) (23.5 %; 12 events), bacterial infectious disorders (17.6 %; 9 events), infections - pathogen unspecified, and respiratory disorders NEC (11.8 %; 6 events each), vascular disorders NEC (7.8 %; 4 events), and ancillary infectious topics (5.9 %; 3 events). Most of the case reports were confounded by COVID-19 and/or medical history with the remaining cases having insufficient information to confirm a medical or causal association.

Serious infection summary

Serious infection is considered an important identified risk for anakinra. A search of the MAH Global Safety Database through May 1, 2021, for the COVID-19 off-label use cases, retrieved 61 case reports with 81 AEs. Events suggestive of COVID-19 or COVID-19 pneumonia were not included in the analysis of serious infection risk as they were considered as a disease under investigation. The table below shows the distribution of all SAE infection PTs (including events of COVID-19 and pneumonia) within the SOC of infections and infestations reported following the use of anakinra in COVID-19. This analysis is based on 54 case reports (73 AEs).

Table 44: Distribution of SAEs within the infection SOC in cases reporting use of anakinra for treating COVID-19

MedDRA PT	Count of Event
Septic shock	10
Pneumonia bacterial	8
Superinfection	7
COVID-19 pneumonia	5
Nosocomial infection	4
Pneumonia	4
Bacterial infection	4
Sepsis	4
COVID-19	3
Pneumonia pneumococcal	2
Enterobacter infection	2
Staphylococcal infection	2
Enterococcal bacteraemia	2

MedDRA PT	Count of Event
Device related infection	1
Pneumonia staphylococcal	1
Device related bacteraemia	1
Staphylococcal bacteraemia	1
Respiratory tract infection	1
Citrobacter infection	1
Candida sepsis	1
Corynebacterium infection	1
Pneumonia pseudomonal	1
Tracheobronchitis	1
Pseudomonas infection	1
Acinetobacter infection	1
Respiratory tract infection bacterial	1
Aspergillus infection	1
Enterobacter bacteraemia	1
Bronchopulmonary aspergillosis	1
Cytomegalovirus infection reactivation	1
Staphylococcal sepsis	1
Enterococcal infection	1
Superinfection bacterial	1
Haemophilus infection	1
Urinary tract infection pseudomonal	1
Klebsiella infection	1
Lower respiratory tract infection bacterial	1
Grand Total	**81[a]**

Abbreviations: COVID-19, Coronavirus disease 2019; MedDRA, medical dictionary for regulatory activities, PT, Preferred term; SAE, Serious adverse event; SOC, System organ class.
[a] including adverse events of COVID19 infections and pneumonia

Overall, 15 of 54 case reports reported a fatal outcome, including 6 elderly patients. The patients developed AEs of septic shock (6 events; 6 patients), pneumonia bacterial (3 events; 3 patients), pneumonia (2 events; 2 patients), and sepsis (2 events; 2 patients); the remaining events occurred singularly. Furthermore, 2 adult patients died due to VAP developed while they were on ventilator respiratory support in the ICU and had various superimposed bacterial infections such as *K. aerogenes*, *Pneumococcus* and MSSA, and *Enterobacter aerogenes*. These 15 cases with fatal outcomes had complex medical histories, with several debilitating concurrent medical conditions and advanced COVID-19 disease. This resulted in superimposed bacterial and viral infections in the ICU/ventilator-associated infections with fatal multiorgan failure. 1 patient died on Day 1, 1 patient died on Day 6, and 2 patients died on Day 9 of treatment with anakinra; the remaining 7 patients had a fatal outcome due to bacterial infections 15 to 41 days after the end of anakinra treatment. Advanced COVID-19 disease with progressive respiratory deterioration in these patients resulted in the development of bacterial infections, although anakinra treatment's role cannot be ruled out.

In 23 of the remaining 39 non-fatal case reports of serious infections, the patients had recovered completely, recovered with sequelae, or were recovering. Most of the non-fatal case reports (21 case reports) involving serious infections were reported in elderly patients. Patients who experienced infections had multiple COVID-19 related risk factors, including concurrent clinical conditions making them susceptible to secondary bacterial infections, which included pulmonary conditions like asthma, COPD, and diabetes. The patients were treated with anakinra for COVID-19 for a short duration

(mostly 10 days); thus, an increase in the secondary infections would be very unlikely. The infections experienced by patients were mostly due to ICU and ventilator-associated superimposed bacterial infections with advanced COVID-19; the incidence of such secondary infections is high in these clinical situations. Of note, 4 of the 39 non-fatal case reports involving serious infections were evaluated by treating physicians as related to anakinra treatment.

In summary, serious and severe superimposed and secondary bacterial, fungal, and viral infections were reported in patients with COVID-19, especially for patients with associated COVID risk factors such as immunocompromised patients, elderly, patients with diabetes mellitus, asthma, and COPD, etc. In COVID-19 patients, anakinra is used for a shorter duration (e.g., up to 10 days of treatment). In other approved indications, the risk of serious infections is reported in the context of long-term use of anakinra. In most of the case reports, the infections were treated with antibacterial or antifungal treatments, and the majority of patients recovered completely. Although biological plausibility and the time to onset of serious infections suggest the possible role of anakinra to potentially contribute to the serious infections, the scientific literature and SAVE-MORE data suggest that these infections are reported at a higher incidence in COVID-19 patients, especially when patients need to be treated in the ICUs, with most of the infections reported as pulmonary infections.

Hepatic event summary

The hepatic disorder is considered an important identified risk for anakinra. The search of the MAH's Global Safety Database up to May 1, 2021, for the COVID-19 off-label use case reports, retrieved 41 valid case reports with 59 hepatic events. The following PTs were reported: alanine aminotransferase increased (5 events), aspartate aminotransferase increased (5 events), cholestasis (1 event), gamma-glutamyl transferase increased (2 events), hepatic cytolysis (7 events), hepatomegaly (5 events), hepatitis (3 events), hepatic function abnormal (1 event), hypertransaminasemia (1 event), jaundice (1 event), liver function test increased (19 events), and transaminase increased (8 events).

A total of 22 events were reported as serious; all were reported by physicians, pharmacists, or other healthcare professionals; none of these were fatal or life-threatening. A total of 29 events from 26 case reports were from investigator-initiated studies, 24 events from 19 case reports were from literature, and 5 events from spontaneous case reports.

Age band ranged from 20 to 89 years (1 case did not have information on the age of the patient); 11 case reports with 14 events occurred in female patients. The outcome of the events was reported as not recovered/not resolved for 4 events in 3 patients; recovered/resolved for 7 events; recovering for 9 events in 6 patients; unknown for 38 events. Dose latency ranged from 1 to 21 days when reported (18 events). A total of 9 events were considered as related by the reporter and 23 events were considered not related. The dose of anakinra was maintained for 2 events, discontinued for 7 events, temporarily withheld for 1 event, not applicable for 1 event, and not reported for 1 event.

The results of liver function tests were evaluated in the case reports and showed normal range in 2 patients, increased with mild to moderate intensity in 34 patients, and severe elevations in 3 patients; no results were mentioned in 10 patients. The review of 3 case reports with severe intensity revealed the presence of many confounding factors and other concomitant medications; the relationship of the increase in liver function tests with the drug cannot be established clearly, but the causality cannot be excluded. The data were also analysed with Hy's law criteria.

Although the available data were limited, still no new safety signal was detected. The in-depth review of details provided in the case narratives did not reveal any new safety issues. A clear relationship between the drug and the hepatic events could not be established. The major confounding factor was the underlying COVID-19 disease. Other confounding factors in addition to the concomitant medications could also have contributed to the onset or worsening of the hepatic events. Few cases

had underlying HLH or secondary HLH based on the secondary HLH score criteria, which provided a strong alternate etiology. However, the relationship between the drug and hepatic events cannot be excluded.

PRES case summary

PRES (Posterior reversible encephalopathy syndrome) is a potential complication of severe COVID-19. This is increasingly recognized in a number of case reports and case series. A recent paper by Llansó et al. 2020 implied the occurrence of PRES a few days after anti-IL (IL-6 or IL-1) treatments which raised the possibility that these immunomodulatory agents may also favour PRES. Therefore, in order to ensure a comprehensive review of the safety data, the MAH performed an additional search of the safety database to identify all cases of anakinra with an AE coded to the PT of posterior reversible encephalopathy syndrome. The review of the MAH's Global Safety database identified a total of 3 reports with the off-label COVID-19, in patients aged 61 to 66 years.

The search retrieved a total of 7 case reports of PRES (including the 3 COVID-19 case reports), of which the 3 case reports from the literature, 2 spontaneous, and 1 case each originated from a solicited patient support program and investigator-sponsored study, respectively. The case reports involved 3 males and 4 females; 3 were paediatric patients aged <10 years (1 with juvenile RA; and 2 patients with a genetic inflammatory disorder with an overlap of Bechet's and Crohn's disease); 1 case involved a 30-39-year-old with familial Mediterranean fever.

There was insufficient evidence to suggest a causal relationship to anakinra in the treatment of COVID-19 at this point.

The MAH later conducted a search of the MAH's Global Safety database (data cut-off October 6, 2021) to identify all cases where Kineret was used in combination with an anti-IL-6 drug tocilizumab. A total of 176 cases were identified, of which 172 cases were considered valid. A review of the 4 invalid cases with no patient identifiers did not reveal any new signals of safety concerns. Of the 172 valid cases, 31 cases were in an unknown indication. The majority of the remaining 141 cases (>80%) were in patients with autoimmune or autoinflammatory disease. A review of the 141 valid cases, involving co-administration of Kineret and anti-IL-6, also did not reveal any new safety signals or safety concerns. An overview of the data from these 141 valid cases is provided below.

In 141 valid cases, the most frequently occurring MedDRA HLT (≥15 PTs) are presented in the table below.

Table 45: The most frequently occurring HLT (≥15 PTs)

MedDRA HLT	Count of Event PT
Therapeutic and nontherapeutic responses	144
Off label uses	70
General signs and symptoms NEC	46
Rheumatoid arthropathies	40
Joint related signs and symptoms	34
Product administration errors and issues	28
Arthropathies NEC	24
Musculoskeletal and connective tissue conditions NEC	20
Immune and associated conditions NEC	20
Joint therapeutic procedures	19
Liver function analyses	18
Medication errors, product use errors and issues NEC	17
Haematological analyses NEC	16
Nausea and vomiting symptoms	15

Abbreviations: HLT, Higher level term; MedDRA, Medical Dictionary for Regulatory Activities; NEC, Not elsewhere classified; PT, Preferred term.

A review of the events within the HLTs did not identify any new safety signals/concerns. The event PTs were in accordance either with the known safety profile of anakinra or with the background/concurrent clinical condition(s)/concomitant medication(s) of the patients in each case.

The most frequently occurring PTs in the 141 cases are presented in the table below.

The most frequently occurring PTs (≥10 PTs)

MedDRA PT	Count of Event PT
Off label use	70
Drug ineffective	67
Rheumatoid arthritis	30
Contraindicated product administered	28
Treatment failure	21
Joint swelling	19
Condition aggravated	17
Therapeutic product effect decreased	15
Arthropathy	15
Haemophagocytic lymphohistiocytosis	15
Drug intolerance	14
Arthralgia	14
Pain	12
Rash	11
Pyrexia	11
Drug hypersensitivity	10

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred term.

A similar review of the PTs did not identify any new safety concerns. The event PTs were in accordance either with the known safety profile of anakinra or with the background/concurrent clinical condition(s)/concomitant medication(s) of the patients in each case.

PRES individual case review

The MAH has provided a tabulated summary of the 7 cases of PRES in the table below.

Summary of the 7 PRES cases

Case number (Source)	Age (years)	Kineret regimen	Latency	Action taken with Kineret in response to event	Concomitant medication and medical history	Indication (PT)	Company comment
1 (Spontaneous)	1-9	100mg s.c. daily	13 days	Ongoing	Concomitant medication: Humira (adalimumab) (ongoing), Ilaris (canakinumab) (discontinued due to the event) and Actemra (tocilizumab) (discontinued due to the event). Medical history: NEMO A2 deletion	Behcet's syndrome; Crohn's disease.	Confounder: Behcet's syndrome. Autoimmune disorders are a common trigger for PRES.
2 (Spontaneous)	30-39	NR	NR	NR	NR	Familial Mediterranean fever	Insufficient information to make an assessment.

Case number (Source)	Age (years)	Kineret regimen	Latency	Action taken with Kineret in response to event	Concomitant medication and medical history	Indication (PT)	Company comment
3 (Literature)	1-9	NR	NR	NR	Concomitant medications: systemic corticosteroids (NOS), mesalamine, dapsone, methotrexate, azathioprine, colchicine, infliximab, adalimumab, certolizumab, canakinumab, tacrolimus, intravenous immunoglobulin and tocilizumab. Medical history: Behcet's syndrome; Crohn's disease; steroid-induced vertebral cempression fractures, cataracts, hyperglycaemia, and arterial hypertension.	Autoinflammatory disease (A20 haploinsufficiency, HA20)	Confounders: Behcet's syndrome, arterial hypertension, systemic corticosteroids. Autoimmune disorder, blood pressure fluctuations as well as immunosuppressive agents are common triggers for PRES.
4 (Solicited-PSP)	1-9	200mg s.c. daily	3 months	NR	NR	Juvenile idiopathic arthritis	Insufficient information to make an assessment.
5 (Literature)	60-69	100mg s.c. every 12 hours	Days	Temporarily discontinued; negative rechallenge	Concomitant medications: tocilizumab Medical history: Acute respiratory distress syndrome, pneumonia	COVID-19 pneumonia	Confounder: Severe COVID-19
6 (Solicited-ISS)	60-69	400mg i.v. daily	9 days	N/A – 7 day course; ended 3 days prior to event onset	Concomitant medications: tacrolimus Medical history: Renal transplant	COVID-19	Confounder: Severe COVID-19

Case number (Source)	Age (years)	Kineret regimen	Latency	Action taken with Kineret in response to event	Concomitant medication and medical history	Indication (PT)	Company comment
7 (Literature)	60-69	400mg i.v. daily	Approximately 2 weeks	Not reported	Concomitant medications: remdisivir Medical history: Not reported	COVID-19	Confounder: Severe COVID-19 and septic shock

Abbreviations: COVID-19, Coronavirus disease 2019; i.v., Intravenous; N/A, Not available; NEMO, NF-κB essential modulator; NOS, Not otherwise specified; NR, Not reported; PRES, Posterior reversible encephalopathy syndrome; PSP, Patient support program; PR, Preferred term; s.c., Subcutaneus.

PRES is an acute neurotoxic syndrome that is characterized by a spectrum of neurological and radiological features from various risk factors. Of the 7 cases of PRES, 2 cases had no concomitant medications or medical history reported; or information surrounding the occurrence of PRES, to make a medical or causal assessment. Of the remaining 5 cases, 2 cases involved paediatric patients with a medical history of Behcet's syndrome. In one case, which involved concomitant use of tocilizumab, the patient also had history of arterial hypertension and use of systemic corticosteroids, both of which, in addition to Behcet's syndrome, are known triggers of PRES. Common factors known to trigger PRES include abrupt elevations of blood pressure, impaired renal function, preeclampsia/eclampsia, autoimmune diseases, infection, transplantation, and chemotherapeutic agents (Hinduja 2020).

The remaining 3 cases involved use of Kineret in female patients over 60 years of age with severe COVID-19 infection. In one case, which involved concomitant use of tocilizumab, treatment with Kineret was temporarily interrupted in response to PRES, and then re-introduced at a lower unspecified dose with no re-occurrence of PRES; the patients concurrent condition confounds PRES. In the second COVID-19 case, the patient experienced PRES 3 days after a 7-day treatment course with Kineret was completed. Kineret has a half-life of 4 to 6 hours; therefore, the short half-life, in addition to the patient's history of renal transplant and use of tacrolimus (both known triggers for PRES), makes the PRES unlikely to be due to Kineret. The remaining COVID-19 case had no medical history reported. The event of PRES occurred approximately 2 weeks after initiation of Kineret and action taken with Kineret in response to the event was not reported. However, the patient's concurrent condition of septic shock (a known trigger for PRES), along with severe COVID-19 infection, confound the case.

In patients with severe COVID-19, PRES can be triggered by uncontrolled hypertension, or occur independently in the setting of systemic illness and certain medications. COVID-19 infection has an impact on multiple SOCs. Several reports have described significant procoagulant events (Sakr et al 2020), in addition to AKI (Nadim et al 2020) and gastrointestinal disturbances (Cha et al 2020; Trottein et al., 2020), both of which can lead to electrolyte disturbances (Pourfridoni et al 2021). Infection, renal disease, haematological disorders, and electrolyte disturbances are also all known triggers of PRES (Hinduja 2020). Current literature suggests that, like other infectious processes, critically ill patients with COVID-19 may be at greater risk of PRES because of impaired vasoreactivity (Lallana et al 2021). In summary, aside from the 2 cases of PRES with insufficient information, the remaining 5 cases were confounded by concurrent history/clinical condition/concomitant medication.

A review of all cases involving co-administration of Kineret and anti-IL-6, in licensed and unlicensed indications, including in patients with autoimmune disease, did not raise any new safety concerns. The MAH has a robust signal management process in place and reviews data from all sources routinely. Kineret has been marketed for over 19 years and has an established and well-characterized safety

profile. To date, aside from the known safety profile and risks associated with Kineret, no new safety signals or safety concerns have been identified from licensed or off-label use indications.

DME (Designated medical event) summary

A search of the MAH's Global Safety Database up to May 1, 2021, of the COVID-19 off-label use cases, retrieved 26 case reports with 27 events which included PTs on the EMA DME list of events. The DMEs included AKI (20 events), renal failure (5 events), pancytopenia (1 event), and pulmonary hypertension (1 event). A review of the 26 case reports, revealed the DMEs to be related to concurrent co-morbid clinical conditions along with COVID-19 related complications, and not related to anakinra treatment. The outcome was reported as recovered in 5 case reports.

A fatal outcome was reported in a 70-79-year-old patient, who experienced renal failure along with respiratory failure. This patient had a complex medical history of coronary artery disease and hemorrhagic cystitis along with reproductive organs cancer.

Literature search for off-label use of anakinra in COVID-19

A review of all the COVID-19 literature (as part of routine literature surveillance) up to the DLP on May 1, 2021, identified a total of 37 noteworthy articles (a mix of retrospective studies, case series, and reviews) reporting the positive benefits of anakinra in the COVID-19 indication.

2.5.1. Discussion on clinical safety

Introduction

The well-known safety profile of Kineret is based on the currently approved indications all with chronic long-term treatment. In COVID-19, Kineret treatment is limited to 10 days.

Kineret has a complex safety profile that has been well established with 20 years of post-marketing experience in multiple indications, and with ADRs that are similar to clinical manifestations observed in severe COVID-19. Kineret has been associated with an increased incidence of serious infections in RA patients and in a small number of patients with asthma. Overall, the approved SmPC includes warnings regarding allergic reactions, hepatic events, serious infections, renal impairment, neutropenia, pulmonary events, drug reaction with eosinophilia and systemic symptoms, immunosuppression, malignancies, vaccination, treatment in the elderly population ≥65 years of age, concurrent Kineret and TNF-α antagonist treatment and sodium content.

Design and exposure

The safety evaluation of anakinra for the treatment of COVID-19 pneumonia was primarily based on the safety data from the phase 3 SAVE-MORE study. In addition, supportive data were provided from the open-label phase 2 SAVE study and the company-sponsored Sobi.IMMUNO-101 study alongside supportive safety data from MAH's Global Safety Database, including other MAH-supported investigator-sponsored studies, post-marketing off label use data from spontaneous reports and literature, and a literature search.

The phase 2 SAVE study is still ongoing. The SAVE report covering Periods 1 and 2 was submitted by the MAH upon request from the CHMP. In addition, updated data on AEs were also provided.

In the pivotal phase 3 SAVE-MORE study, the placebo+SoC treatment group had fewer patients (14.3% vs. 20.2%) with moderate pneumonia and more patients (85.7% vs.79.8%) with severe pneumonia compared to the anakinra+SoC treatment group. In the anakinra + SoC treatment group there were also a higher percentage of patients with co-morbidities (43.4% versus 38.6%) including more patients with e.g. type 2 diabetes mellitus (16.3% versus 14.8%) and chronic renal disease

(2.2% versus 0.5%). The identified differences in disease characteristics are not expected to have a significant impact on the overall conclusion on safety.

No pooled safety data were provided due to a lack of standardization between the above-mentioned studies; thus, TEA frequencies could not be directly compared. MedDRA coded tables were not integrated in the safety summary but were provided during the procedure as requested by the CHMP. Overall, the mean ages in all the above studies above was 60 years, reflecting the age where the risk of a severe COVID-19 disease course is accentuated. For AEs, frequencies listed by organ system and syndrome where available, and were in alignment with the adverse event listings. The extent of the provided data from 1134 anakinra treated COVID19 patients is sufficient for the safety evaluation of this new indication.

Adverse events (AEs)

The most frequently reported AEs across groups in the SAVE-MORE study were hyperglycemia, increase of liver function tests, anaemia, and hypernatraemia. There were comparable proportion of patients experiencing at least one non-serious TEAE's in the anakinra and placebo treatment groups, 86.9% vs. 89.9% respectively. Most commonly reported non-serious TEAEs by SOC and PT occurring at numerical higher proportion in the anakinra+SoC arm compared to the placebo+SoC arm included the increase of liver aminotransferases (35.8% vs. 33.3%), hypoglycaemia (8.4% vs. 7.9%), electrolyte abnormalities (hypernatraemia (11.4% vs. 9.0%), hyperkalaemia (8.9% vs. 6.9%)), constipation (9.6% vs. 8.5%), nausea/vomiting (2.2% vs. 0.5%), anxiety (8.2% vs. 5.8%), rash (3.7% vs. 1.5%), neutropenia (3.0% vs. 0.5%), leukopenia (3.5% vs. 2.6%) and thrombocytopenia (2.2% vs. 2.1%). Of these, the increase of liver function tests (hepatic enzyme increased), rash at the injection site (injection site reaction), neutropenia, and thrombocytopenia are listed ADRs in the anakinra PI; hypernatremia, constipation, hyperkalemia, and anxiety are not. None of the enrolled patients showed signs of bone marrow suppression (all three cell lines affected). It is acknowledged that there is only limited information on medical history, however a higher frequency of depression could indicate an existing imbalance in predisposition for mental disorders/vulnerability. Overall the safety profile is acceptable singling out hyperglycemia and elevated aminotransferase increase as the most frequent TEAs, with elevated aminotransferase at a higher frequency in the anakinra + SoC treatment group (35.8% vs. 33.3%). It is acknowledged that some of the numerical imbalances in the given TEASs can indeed reflect different manifestations of underlying disease. SmPC section 4.8 was updated to reflect that '*in the clinical study in COVID-19, events of neutropenia were reported in 3.0% of Kineret-treated patients and 0.5% of patients receiving placebo. All adverse events of neutropenia were mild or moderate in severity.'*

Serious adverse events and deaths

In the phase 3 SAVE-MORE study, the frequency of patients with at least 1 serious TEAE was lower in the anakinra-treated group (16.3 %, n=66) than in the placebo group (21.2 %, n=40) and likewise in supportive studies with lower frequencies in the anakinra-treated group than in the comparator group. In the SAVE-MORE study the most frequently reported serious TEAEs in both treatment groups were ventilator associated pneumonia, bloodstream infection, probable nosocomial infections, and pulmonary embolism. Infections and infestations were fewer in the anakinra treatment group (8.4% vs. 15.9%). Bacteraemias were evenly distributed 2.7% in both groups, but hospital acquired infections (2.5% vs. 3.7%) and ventilator associated pneumonias (2.2% vs. 7.9%) were fewer in the anakinra treatment group. Overall the safety data on serious adverse events are acceptable.

In the pivotal phase 3 SAVE-MORE study the frequency of death was lower in the anakinra-treated group than the placebo group (3.2% vs. 6.9%) and was also lower in the anakinra-treated group than the comparator group in supportive studies: 4.6% vs. 12.3% in the SAVE study and 20.0% vs. 40% in

the Sobi.IMMUNO-101 study. All deaths were considered to be due to COVID-19 progression and the patient's concurrent medical conditions that were considered the risk factors for COVID-19 and may have contributed to fatal outcomes in these patients and considered to be not related to study drug. Overall, the safety data on deaths are acceptable. There were two more deaths (15 vs 13) within the global safety database. No reconciliation was performed as the 13 cases of deaths included in the primary endpoint and the 15 patients with STEAEs with fatal outcomes belong to partly different data subsets and cannot be directly compared.

Serious infection as an Adverse Event of Special Interest

In the PI currently approved for Kineret, it is stated in the SmPC section 4.4 that "Kineret has been associated with an increased incidence of serious infections (1.8%) vs. placebo (0.7%) in RA patients. For a small number of patients with asthma, the incidence of serious infection was higher in Kineret-treated patients (4.5%) vs. placebo-treated patients (0%), these infections were mainly related to the respiratory tract" and "Kineret treatment should not be initiated in patients with active infections".

The CHMP agreed that the clinical presentation of the most frequently reported AEs can to some extent be explained by the underlying COVID-19, nosocomial causes, and the use of corticosteroids. The MAH provided data on the distribution of infections and infestations by SOC/PT in the SAVE-MORE study, raising no concerns of specific risk of infection in anakinra treated patients. The distribution of the majority of infections was in general lower in the anakinra group than in the placebo group apart from single cases of diverticulitis, hepatitis B, and skin infection (considered unrelated by the investigator) occurring at a slightly higher frequency. Also, there were higher frequencies of *Staphylococcus hominis*, *Enterobacter cloacae*, *Streptococcus pneumoniae*, *Escherichia coli*, *Aspergillus flavus*, *Candida spp.*, and Hepatitis B virus, however numbers were low.

In off-label use of Kineret in Covid-19, of the 112 SAE's reported, 59 of them were infections and infestations, whereof pneumonia accounted for 16 of them. About 51 % of patients were on pre-existing higher antibiotics and predisposing factors for infection including the use of corticosteroids (29 case reports, 51%), diabetes (7 case reports, 3%), and serious cardiorespiratory comorbidity (100 % of case reports) were identified.

Infections and infestations were fewer in the anakinra treatment group (8.4% vs. 15.9%). Bacteremias were evenly distributed 2.7% in both groups, but hospital acquired infections (2.5% vs. 3.7%) and ventilator associated pneumonias (2.2% vs. 7.9%) were fewer in the anakinra treatment group.

In the SAVE-MORE study the incidence of infections aggravating the clinical course was lower in the anakinra group than in the placebo group and among the 12 cases of neutropenia in the anakinra group, no infectious SAEs were recorded. In the SAVE study, serious infectious events were registered as a proxy of potentially aggravating secondary infectious events with fewer cases with septic shock in the anakinra treated group (9.1% vs. 34.3%). In the Sobi-IMMUNO-101 study, there were no infections reported. No information on neutropenia in anakinra-treated patients in the SAVE or SOBI-IMMONO-101 studies are available. Overall, the incidence of infections aggravating the clinical course was lower in the anakinra group than in the placebo group. No concerns are raised with regards to potential study drug induced secondary infections that may have aggravated the clinical course, including patients with neutropenia. The following information was added to SmPC section 4.4: 'Treatment with Kineret for COVID-19 can be continued despite (secondary) infections.' The SmPC section 4.8 was also updated to reflect that 'In the clinical study in COVID-19, secondary serious infections were common, however less frequently observed in patients treated with Kineret compared to placebo-treated patients.'

In line with the currently approved product information, Kineret treatment must not be initiated in patients with neutropenia (ANC<1.5 x 109/l). Further, the existing warning included into SmPC section 4.4 is also applicable to patients with COVID-19.

Discontinuations

4 patients in the anakinra treatment group (n=3 in the SAVE-MORE and n=1 in Sobi-IMMUNO-101) studies discontinued, of these two were due to liver function test, one due to leukopenia and one due to respiratory failure. Data were not provided for the SAVE study. Overall the frequency of discontinuations in the anakinra treatment group were higher in the pivotal SAVE-MORE study compared to the placebo-group. It is unclear whether the impact on liver parameters and leukopenia was evaluated as related to the study product, however this cannot be ruled out. Nevertheless, neutropenia and derangement of liver function tests are well-known adverse drug reactions to anakinra and are already described in the SmPC.

The proposed treatment course of anakinra in COVID-19 is limited to 10 days and there were only a few discontinuations of study-drug due to leukopenia or due to increase of aminotransferase; and those were comparable between the 2 groups of treatment in the SAVE-MORE study with no clinical consequences of the aberrant lab values.

Laboratory findings

No clinical meaningful trends were observed among laboratory findings.

Safety in special populations

Aminotransferase increase was one of the most frequent TEA in the SAVE-MORE study with a higher frequency in the anakinra + SoC treatment group (35.8% vs. 33.3%). It is included in the SmPC that no dose adjustment is required for patients with moderate hepatic impairment (Child-Pugh Class B). Kineret should be used with caution in patients with severe hepatic impairment. This is also applicable for the COVID-19 indication.

The MAH has provided a list of Serious TEAEs and Non-Serious TEAEs in patients not receiving dexamethasone. The incidence of serious TEAEs through Day 90 were similar in anakinra and placebo groups (12.7% and 14.3%, respectively).

No data are available on the effects of vaccination with other inactivated antigens, or COVID-19 vaccines, in patients receiving Kineret. This has been adequately reflected in section 4.4 of the SmPC.

A total of 173 COVID-19 patients ≥ 65 years of age were studied in clinical study. No overall differences in safety or effectiveness were observed between these patients and younger patients. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating elderly patients. The SmPC section 4.4 has been updated accordingly.

Safety related to drug-drug interactions and other interactions

The potential for DDIs with Kineret is limited.

Pregnancy and lactation

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development. As pregnant women were excluded from participation in anakinra clinical studies, no adequate clinical study data from the use of anakinra are available in pregnant women. It is included in the SmPC that it is preferable to avoid the use of anakinra during pregnancy and in woman of childbearing potential not using contraception and

that breast-feeding should be discontinued during treatment with anakinra. This is also considered appropriate for the COVID-19 indication.

Overdose, Drug abuse, Withdrawal and Rebound

No concerns are raised with regards to re-occurrence of COVID-19 as this has not been observed (up to Day 28 or in the follow-up period up to Day 90) in the SAVE-MORE study.

Post marketing

No new relevant safety concerns were found in the data presented from post marketing off label use in the COVID-19 indication and literature.

Review of the investigator-sponsored dataset

A review by the MAH of the investigator-sponsored dataset with 169 valid case reports (377 events (103 unique PTs)) was provided; and did not reveal any new safety observations or concerns.

Off-label use

Review of off-label use (safety assessment for the COVID-19 indication conducted on 831 events in 455 valid case reports) showed that 57% of AEs reported were serious, but in 55% of cases the outcome was not reported. No apparent shift in age and gender distribution was seen on off-label use of anakinra for treating COVID-19, and it is acknowledged that the most frequently reported AEs (respiratory failure, shock, ARDS, AKI, anaemia, liver test derangements, electrolyte imbalance) identified could also be attributed to the course and progression of underlying COVID-19.

Posterior reversible encephalopathy syndrome (PRES)

The MAH identified 3 reports of PRES, a potential complication of severe COVID-19 in review of off-label use of Kineret. A review of the 141 valid cases, involving co-administration of Kineret and anti-IL-6 did not reveal any new safety signals or safety concerns, and no specific concerns are raised regarding the potential risk of PRES due to co-administration of anti-IL-1 and anti-IL-6, including patients with autoimmune diseases.

Overall, based on the data presented (including safety data provided from the SAVE-MORE study up to Day 90 upon request from the CHMP and presented below), the MAH considered that no new significant finding regarding safety was found.

TEAEs occurring at a higher proportion on the anakinra+SoC group included:

- Leukopenia, neutropenia, injection site reaction, fall, rash, nausea, increase of transaminases, gamma-GT and alkaline phosphatase, blood pressure decreased, sinus tachycardia, atrial fibrillation, anxiety, agitation, acute kidney injury, hyperglycaemia, hypernatremia, hyperkalaemia, hypercalcemia, hypophosphatemia, cystitis, acute epistaxis, chest pain and catheter bleeding.

Neutropenia, rash, injection site reaction (ISR) and increased hepatic transaminases are already included in Kineret's SmPC. Regarding ISR, for patients with COVID-19 that were treated with anakinra, ISR were reported with a frequency higher compared to the placebo treated patients. Nevertheless, the frequency of reported ISR in patient that received anakinra was still considered to be low by the MAH. Therefore, the addition of the following statement to SmPC section 4.8: 'In patients with COVID-19 treated with Kineret, injection site reactions were reported with low frequency' was agreed by the CHMP. According to the MAH, the TEAEs reported in the majority of patients were suggestive of advanced COVID-19 and its complications and/or worsening of patients' concurrent clinical/background condition and concomitant medication; the same conclusion was made regarding

serious TEAEs. The CHMP agreed that the serious TEAEs reported can be related to the progression of COVID-19 infection.

Overall, it is agreed that the data available up to Day 90 follow-up did not indicate any new safety signal identified with anakinra treatment in COVID-19. The data also supported that the safety profile is consistent with the other approved indications, taking the underlying disease, dose, and duration of anakinra treatment in the studies into account. The SmPC section 4.8 was updated to include D90 data on safety from the SAVE-MORE study. This is acceptable. Any new follow-up data should be submitted by the MAH i.e. as part of the final CSR of the SAVE-MORE study that will be submitted by end of December 2021 via a type II variation. In addition, the CHMP recommended the MAH to provide the final CSR of the phase 2 SAVE study, once available.

2.5.2. Conclusions on clinical safety

The safety evaluation of Kineret in COVID-19 pneumonia was mainly based on the pivotal phase 3 SAVE-MORE study. In addition, supportive data were provided from the open-label phase 2 SAVE study and the company-sponsored Sobi.IMMUNO-101 study alongside supportive safety data from MAH's Global Safety Database, including other MAH-supported investigator-sponsored studies, post-marketing off label use data from spontaneous reports and literature, and a literature search.

The overall occurrence of AEs, SAEs including infections discontinuations and deaths were lower in the patients treated with Kineret compared to the ones treated with placebo in the pivotal SAVE-MORE study.

No new safety signals were identified in the treatment of hospitalised adult patients with COVID-19 pneumonia. Relevant adverse reactions observed in COVID-19 treatment were adequately reflected in section 4.8 of the SmPC. The SmPC adequately reflects the safety profile of Kineret in this new indication. Overall, the safety profile is considered to be consistent with the known safety profile of Kineret in the other approved indications.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 5.9 is acceptable.

The CHMP endorsed the Risk Management Plan version 5.9 with the following content:

Safety concerns

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

Pharmacovigilance plan

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for the following important risks:

- Hepatic disorders
- Neutropenia
- Serious infections
- Macrophage activation syndrome (MAS)
- Pulmonary events (Interstitial lung disease, pulmonary hypertension, alveolar proteinosis)

Gathering of specific adverse event report information, including batch numbers, pertaining to a safety concern of special interest is pertinent. The targeted questionnaire is a method of follow-up used to collect structured data on a safety concern. Cumulative review of reports collected in this manner allows for further characterization of the nature of the risk and is used during the review process when considering the relationship between the drug and a safety concern.

Other forms of routine pharmacovigilance activities

The following important risks are monitored as Target medical events (TMEs):

- Serious infections
- Malignancies
- Neutropenia
- Allergic reactions
- Hepatic disorders
- Medication error/reuse of used syringe
- Macrophage activation syndrome (MAS)
- Pulmonary events (Interstitial lung disease, pulmonary hypertension, alveolar proteinosis)

Target medical events are certain AEs that are closely monitored for evidence of a possible association between Kineret and the events, regardless of the indication for Kineret treatment. TMEs are

established as a result of Sobi's own identification of potential safety signals for which a reasonable causal association has not yet been established, and also for post-marketing commitments or regulatory agency requests. Periodic assessment of these events and emerging safety observations, through synthesis of individual cases, aggregate analysis, and clinical study data, will be described in the PSURs.

There are no ongoing additional pharmacovigilance studies/activities.

Risk minimisation measures

Safety concern	Routine risk minimization measure	Pharmacovigilance activities
Injection site reactions	**Routine risk communication:** Information in SmPC section 4.8, and the following recommendations in section 4.2: Alternating the injection site, cooling of the injection site, warming the injection liquid to room temperature, use of cold packs (before and after the injection), and use of topical glucocorticoids and antihistamines after the injection. **Additional Risk Minimization Measure:** Guides describing how to prevent and manage ISRs for healthcare professionals treating patients with CAPS, FMF and Still's disease, and for patients. The guides describe ISRs and give tips on how to alleviate them.	None
Immunogenicity	**Routine risk communication:** SmPC section 5.1 refers to section 4.8 where the risk is described.	Evaluation of individual case safety reports (ICSRs) concerning suspected lack of effect.
Serious infections	**Routine risk communication:** Information in SmPC section 4.8 and the following information in section 4.4: Kineret treatment should not be initiated in patients with active infections. Kineret treatment should be discontinued in RA patients if a serious infection develops. In Kineret treated CAPS of FMF patients, there is a risk for disease flares when discontinuing Kineret treatment. With careful monitoring, Kineret treatment can be continued also during a serious infection. Available data is limited regarding whether Kineret can be continued during serious infections in patients with Still's disease. If Kineret treatment is continued during serious infections to reduce the risk for a disease flare, careful	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** AE follow-up form for adverse reaction Followed as TME

	monitoring is required. Physicians should exercise caution when administering Kineret to patients with a history of recurring infections or with underlying conditions which may predispose them to infections. Patients should be screened for latent tuberculosis prior to initiating Kineret. The available medical guidelines should be taken into account. Screening for viral hepatitis should also be performed in accordance with published guidelines before starting therapy with Kineret. **Additional Risk Minimization Measure:** Guides describing the risk of serious infections for healthcare professionals treating patients with CAPS, FMF and Still's disease, and a reminder card for patients with Still's disease describing serious infections.	
Neutropenia	**Routine risk communication:** Information in SmPC section 4.8 and the following information in sections 4.3 and 4.4: Kineret treatment must not be initiated in patients with neutropenia (ANC <1.5 x 10^9/l). It is recommended that neutrophil counts be assessed prior to initiating Kineret treatment, and while receiving Kineret, monthly during the first 6 months of treatment and quarterly hereafter. In patients who become neutropenic (ANC < 1.5 x 10^9/l) the ANC should be monitored closely and Kineret treatment should be discontinued. The safety and efficacy of Kineret in patients with neutropenia have not been evaluated.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** AE follow-up form for adverse reaction Followed as a TME
Allergic reactions	**Routine risk communication:** Information in SmPC section 4.8 and the following information in sections 4.3 and 4.4: Kineret is contraindicated in patients with hypersensitivity to the active substance, to any of the excipients or to E. coli derived proteins. If a severe allergic reaction occurs, administration of Kineret should be discontinued and appropriate treatment	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Followed as a TME

	initiated.	
Hepatic disorders	**Routine risk communication:** Information in SmPC section 4.8 and the following information in section 4.4: Routine testing of hepatic enzymes during the first month should be considered, especially if the patient has pre-disposing factors or develops symptoms indicating liver dysfunction. The efficacy and safety of Kineret in patients with AST/ALT ≥ 1.5 x upper level of normal have not been evaluated.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** AE follow-up form for adverse reaction Followed as a TME
Malignancies	**Routine risk communication:** Information regarding this potential risk is presented in SmPC section 4.4.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Followed as a TME
Macrophage activation syndrome (not applicable for RA, CAPS,FMF or COVID-19)	**Routine risk communication:** SmPC section 4.4 states that if MAS occurs, or is suspected, evaluation and treatment should be started as early as possible. Physicians should be attentive to symptoms of infection or worsening of Still's disease, as these are known triggers for MAS. **Additional Risk Minimization Measures:** Guides for healthcare professionals and a reminder card for patients with Still's disease describing the risk of MAS.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** AE follow-up form for adverse reaction Followed as a TME
Medication errors including reuse of syringe	**Routine risk communication:** SmPC section 6.6 states that the pre-filled syringe is for single use only and any unused medicinal product should be discarded. The syringe should not be shaken and should be allowed to reach room temperature before injecting. Before administration, the solution should be visually inspected for particulate matter and discolouration. Only clear, colourless to white solutions that may contain some product-related translucent-to-white amorphous particles, should be injected. **Additional Risk Minimization Measure:** Guides are employed to inform healthcare providers of their obligation to instruct patients with CAPS, FMF and Still's disease on correct injection procedures and disposal of used syringes and supplies, along with information material to patients.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Followed as a TME

Pulmonary events (Interstitial lung disease, pulmonary hypertension, alveolar proteinosis)	**Routine risk communication:** SmPC section 4.4 describes the potential risk.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** AE follow-up form for adverse reaction Followed as a TME
Use in pregnant women	**Routine risk communication:** SmPC section 4.6 states that as a precautionary measure, it is preferable to avoid the use of anakinra during pregnancy and in women of childbearing potential not using contraception.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Pregnancy follow-up questionnaire including questionnaire for neonatal, infant outcome and father information
Use in lactating women	**Routine risk communication:** SmPC section 4.6 states that breast-feeding should be discontinued during treatment with Kineret.	None
Use in patients with chronic infections	**Routine risk communication:** SmPC section 4.4 states that the safety and efficacy of Kineret treatment in patients with chronic and serious infections have not been evaluated.	None
Use in patients with pre-existing cancers	**Routine risk communication:** SmPC section 4.4 states that the use of Kineret in patients with pre-existing malignancy is not recommended.	None
Interaction with living vaccines	**Routine risk communication:** SmPC section 4.4 states that live vaccines should not be given concurrently with Kineret.	None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The package leaflet included in this submission is identical to the previously readability tested package leaflet for Kineret (indicated for RA and CAPS) with the only difference between the two leaflets being new indications (Still's disease, FMF previously approved and the current variation for COVID-19).

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The COVID-19 outbreak was declared a pandemic health emergency by the WHO on 11 March 2020 and presents a global healthcare challenge. COVID-19 is associated with high morbidity and mortality.

According to the WHO, as of 22 June 2021, there have been over 177 million confirmed cases of COVID-19, with approximately 3.9 million deaths reported to the WHO (WHO 2021a). As of 24 June 2021, a total of 33.0 million cases have been reported in EU/EEA, with over 736,000 deaths (ECDC).

The clinical spectrum of COVID-19 varies from asymptomatic or paucisymptomatic forms to clinical conditions characterized by respiratory failure that necessitates mechanical ventilation and support in an ICU, to systemic manifestations of sepsis, septic shock, and multiple organ dysfunction (Cascella et al. 2020).

Most people with COVID-19 develop only mild or uncomplicated illness, presenting with symptoms of an upper respiratory tract infection, including fever, cough, sore throat, nasal congestion, headache, muscle pain or malaise without evidence of viral pneumonia or hypoxia. Loss of taste (ageusia) and/or smell (anosmia) have also emerged as characteristic symptoms of COVID-19. Respiratory symptoms such as fever, cough, dyspnea and tachypnea without significant hypoxia are indicative of moderate pneumonia. Long-term symptoms have been reported even in non-hospitalized patients who have had mild COVID-19. Approximately 15% of COVID-19 patients develop severe pneumonia characterized by the same clinical signs as moderate pneumonia with the addition of one of the following: respiratory rate (>30 breaths/minute); severe respiratory distress; or hypoxia requiring hospitalization and oxygen support (WHO 2020; Cascella et al. 2020). In approximately 5% of infected patients, the severe form of interstitial pneumonia with alveolar damage may rapidly progress to critical manifestations of the disease characterized by respiratory failure associated with ARDS that necessitates mechanical ventilation and support in an ICU, sepsis, septic shock, and/or multi organ failure including acute kidney and cardiac injury, and even death (WHO 2020).

Mortality rate varies among regions and hospitals and with associated risk factors. In a cohort study of 64,781 patients with COVID-19 treated in 592 US hospitals during April and May 2020, the in-hospital mortality rate was 20.3% (Rosenthal et al. 2020). In a multicenter cohort study that included 3924 critically ill patients, 40.6% of patients not treated with TCZ within 2 days of ICU admission died (Gupta et al. 2021). Among patients admitted to ICU in a randomized platform trial (REMAP-CAP), the mortality in patients not receiving TCZ was 35.3% (REMAP-CAP Investigators et al 2021).

The therapeutic indication initially claimed by the MAH for this extension of indication for Kineret was 'treatment of coronavirus disease 2019 (COVID-19) in adult patients with pneumonia requiring supplemental oxygen who are at risk of developing severe respiratory failure (see section 5.1)'. See below sections for the final restricted indication granted by the CHMP.

3.1.2. Available therapies and unmet medical need

Prevention of infection by SARS-CoV-2 and clinical management of the disease are the 2 main strategies to fight the COVID-19 pandemic. Prevention with vaccines is expected to decrease the infection rate; however, emergent SARS-CoV-2 variants may constitute a threat, and the duration of

protection following immunization is still unclear. Because of these uncertainties, an effective clinical management of the disease to reduce COVID-19 morbidity and mortality is of great importance. As of March 31, 2021, the antiviral remdesivir became available. For patients classified with severe disease, treatments include anticoagulation, oxygen supply, dexamethasone, and remdesivir. Since the beginning of the COVID-19 pandemic, immunomodulators were suggested as one of the main strategies to attenuate the exaggerated immune response of the host. Also, two monoclonal antibodies Ronapreve (casirivimab/imdevimab) and Regkirona (regdanvimab) have been authorised for treating COVID-19 in adults and adolescents (from 12 years of age and weighing at least 40 kilograms) earlier in the course of the disease (patients who do not require supplemental oxygen and who are at increased risk of their disease becoming severe.) Besides these, two medicinal products are approved for the treatment of patients requiring oxygen supplementation, which is Veklury (remdesivir) and dexamethasone. Later phases of COVID-19 triggered by cytokine release syndromes are mainly treated with IL-6 inhibitors and dexamethasone. Recently, tocilizumab, targeting the IL-6 pathway was approved for treatment of adults with COVID-19 who are receiving systemic treatment with corticosteroids and require supplemental oxygen or mechanical ventilation, while Kineret is considered approvable in the treatment of adults COVID-19 pneumonia who require supplemental oxygen (low- or high- flow oxygen) who are at risk of progression to SRF. Several other therapeutics are currently under evaluation in Europe. Despite ongoing advancements in the development of vaccines and treatments for COVID-19, significant unmet medical need remains especially in hospitalised patients with COVID-19 pneumonia who are at risk of progressing to severe respiratory failure.

3.1.3. Main clinical studies

The submission was mainly based on one pivotal phase 3 study, SAVE-MORE, which was an investigator sponsored study.

SAVE-MORE was a double-blind, randomised pivotal phase 3 confirmatory study. In this study, a total of 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). Patients were eligible to the study if they had confirmed infection with SARS-CoV-2 virus, findings in chest X-ray or in chest computed tomography compatible with lower respiratory tract infection (LRTI), need for hospitalisation due to COVID-19 defined by the attending physician and suPAR level ≥ 6 ng/ml. Patients were randomized 2:1 with 412 patients were allocated to the anakinra+SoC arm and 194 patients were allocated to the placebo+SoC arm. The final intention-to-treat (ITT/FAS) analysis set consisted of 594 patients with 189 patients in the placebo+SoC arm and 405 patients in the anakinra+SoC arm.

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

Several secondary and exploratory efficacy and safety endpoints to support the primary endpoint were also included. In addition to the 11-point of WHO-CPS score, the SOFA (sequential organ failure assessment) score has also been evaluated. The SOFA score can be used to evaluate organ dysfunction in sepsis. Also, time to discharge, long-term safety by 60 and 90 days, changes in circulating biomarkers and viral load were evaluated. Mortality was not included as an endpoint, however, a supportive post-hoc survival analysis has been submitted by the MAH.

Further supportive data were also provided from the ongoing, open-label phase 2 SAVE study.

3.2. Favourable effects

The SAVE-MORE study met its primary endpoint and showed a statistically significant and clinically relevant reduction in the WHO-CPS score at Day 28 in patients treated with anakinra+SoC as compared to patients receiving placebo+SoC (adjusted OR at Day 28 was 0.36 (95 % CI 0.26 to 0.50; P<0.001)). The effect was already present at Day 14 (adjusted OR 0.58 (95 % CI 0.42 to 0.79).

More patients fully recovered by Day 28 in the anakinra arm in comparison to the placebo arm (50.5% vs 26.5 %, respectively). In a multivariate logistic regression model of the WHO-CPS of 0 or ≥1 anakinra was protective (adjusted OR: 0.36; 95 % CI 0.25 to 0.53). The same results were seen when patients were divided into WHO-CPS ≥ 6 or ≤ 5 (adjusted OR: 0.46; 95 % CI 0.26 to 0.83), and the proportion of patients with severe outcome (WHO-CP score ≥ 6) was higher in the placebo arm than in the anakinra arm.

Time to progression to serious respiratory failure (defined as PaO2/FiO2 <150, need for high flow oxygen, mechanical ventilation or death) also illustrated an effect of anakinra. Curves start to separate from approximately Day 3 and stay parallel from Day 8 and onwards (adjusted HR 0.66 (0.47-0.91), p=0.012).

The 28-day mortality was lower among patients allocated to the anakinra+SoC treatment (6.9 % vs. 3.2 %, respectively). Further, 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).

Treatment with anakinra, compared to placebo, had significant effect on the decrease of the WHO-CPS score from baseline by Day 28 and Day 14, and on the decrease of the SOFA score from baseline by Day 7. Anakinra treatment reduced time to hospital discharge. An increase in the number of patients fully recovered and reduction in the number of patients who progressed to SRF or death was also noticed. Anakinra treatment was associated with reduced mortality up to Day 28 compared to placebo.

A subgroup analysis based on patients not receiving dexamethasone treatment during the study (11% in placebo arm, 15% in anakinra arm) showed efficacy of anakinra. In addition, efficacy was demonstrated in subgroup analyses based on age, suPAR and gender; thus, supporting similar efficacy of anakinra across subgroups.

3.3. Uncertainties and limitations about favourable effects

This application was primarily based on interims results from a single pivotal phase 3 study (SAVE-MORE). Furthermore, the evidence presented, particularly in the other RCTs conducted with anakinra in COVID-19, had contradictory results and did not provide robust support for this application. Nevertheless, the CHMP considered that the RCTs showing no effect included populations with substantial differences when compared with SAVE-MORE. Consequently, the CHMP considered that the statistically significant and clinically relevant efficacy demonstrated in SAVE-MORE provided sufficient support for an approval of Kineret in this new indication.

Even though the study met most of the secondary endpoints, those were not controlled for multiplicity. Consequentially, the analyses of secondary endpoints can only be regarded as being supportive to the analysis of the primary endpoint. Even though, the clinical value of some of the secondary endpoints can be questioned e.g. the clinical value of a one-day shorter hospital stay and the median difference in CPS score of 1; they were considered to provide relevant information regarding the efficacy of anakinra in COVID-19 patients with pneumonia requiring supplemental oxygen and at risk of progressing to SRF.

Slightly more patients in the placebo arm had severe pneumonia, required more high flow oxygen and their P/F ratio was a bit lower at inclusion (baseline) than in the anakinra group. Further, at baseline more patients in the placebo group received antibiotics, probably reflecting that more patients in the placebo arm had severe COVID pneumonia. This could reflect that the placebo arm is somewhat sicker, which may have affected the endpoints in favour of anakinra. However, as this was accounted for in the multivariate analysis of the primary endpoint, this issue was not further pursued by the CHMP.

Since patients with suPAR level below 6 ng/ml were not included in the SAVE-MORE study, it is uncertain whether the treatment effect seen in patients with suPAR level above or equal to 6 ng/ml can be extrapolated to patients with suPAR level below 6 ng/ml. Therefore, the therapeutic indication was restricted to patients with suPAR ≥ 6 ng /ml only. This has been adequately reflected in SmPC section 4.1 and a corresponding warning statement was included in section 4.4 of the SmPC.

The clinical efficacy in patients critically ill (i.e. that have progressed to severe respiratory failure defined as i.e. in need of NIV, MV or ECMO) was not studied in the SAVE-MORE study. As such, it is uncertain whether an efficacy has been established in patients in need of NIV, MV or ECMO. While it could have been of interest to gain further insight on the efficacy of anakinra in patients that had progressed to SRF, this is not considered as an issue as the indication targeted an earlier stage of the disease i.e. patients that have not yet progressed to SRF. Nevertheless, a corresponding warning statement was included in section 4.4 of the SmPC.

A subgroup analysis based on supplemental oxygen at screening showed a statistically significant difference in the primary endpoint in favour of anakinra in both subgroups, however, the effect in the subgroup without need for supplemental oxygen was not considered clinically relevant, because none progressed to SRF. Therefore, the therapeutic indication was restricted to patients requiring supplemental oxygen (i.e. low- or high- flow oxygen). This has been adequately reflected in section 4.1 of the SmPC.

It is anticipated that only a few laboratories in EU are currently able to measure suPAR. In a post-hoc analysis, the MAH tried to identify other biomarkers associated with progression to SRF e.g. CRP, ferritin, IL-6 and D-dimer to define a score for progression. With this "SCOPE score", a score was given to each four biomarkers according to a determined level. The MAH claimed that a SCOPE score >6 could identify patients for treatment with anakinra in case suPAR would not be available. However, the score based on those biomarkers did not identify the same patients as suPAR ≥6 ng/ml did and therefore cannot replace suPAR in the selection of the patients at risk of SRF i.e. patients with suPAR ≥ 6 ng/ml. Considering the decisive role of suPAR for the identification of patients that are suitable for treatment with anakinra in COVID-19, the MAH should ensure that an appropriate and validated test that reliably allows the distinction between patients with suPAR < 6 ng/ml and patients with suPAR ≥ 6 ng/ml is available for all European patients. Such test should be adequately CE-marked as a companion diagnostic under the In Vitro Diagnostic Medical Device Regulation framework.

The final CSR of the SAVE-MORE study will be submitted by the MAH by Q4 2021, as agreed by the CHMP. It is expected to provide further insight on efficacy based on the following exploratory outcomes: the 11-point WHO-CPS score by Day 60 and the 11-point WHO-CPS score by Day 90.

3.4. Unfavourable effects

The well characterised safety profile of Kineret is based on the already approved indications, all with chronic long-term treatment. Kineret treatment for the treatment of COVID-19 pneumonia is limited to 10 days. The safety evaluation was primarily based on the safety data from the SAVE-MORE study. No new safety signals were identified in the patients studied. The safety profile is overall consistent with the known safety profile of Kineret in the other approved indications, including infections.

Slightly fewer patients in the anakinra treatment group experienced at least one non-serious TEAEs compared to the placebo in the SAVE-MORE study (86.9% vs. 89.9%, respectively). Most common non-serious TEAEs by SOC and PT occurring at numerical higher proportion in the anakinra+SoC arm compared to the placebo+SoC arm included the increase of liver aminotransferases (35.8% vs. 33.3%), hypoglycaemia (8.4% vs. 7.9%), electrolyte abnormalities (hypernatraemia, 11.4% vs. 9.0%, hyperkaliaemia, 8.9% vs. 6.9%), constipation (9.6% vs. 8.5%), nausea/vomiting (2.2% vs. 0.5%), anxiety (8.2% vs. 5.8%), rash (3.7% vs. 1.5%), neutropenia (3.0% vs. 0.5%), leukopenia (3.5% vs. 2.6%) and thrombocytopenia (2.2% vs. 2.1%). The increase of liver function tests (hepatic enzyme increased), neutropenia, and thrombocytopenia are listed ADRs in the anakinra label.

SAEs were lower in the anakinra-treated group (16.3 %,) than in the placebo group (21.2 %) in the SAVE-MORE study and in the supportive studies as well as lower frequencies in the anakinra-treated group were seen compared to the comparator group. In the SAVE-MORE study, the most frequently reported serious TEAEs in both treatment groups were ventilator associated pneumonia, bloodstream infection, probable nosocomial infections, and pulmonary embolism. Infections and infestations were lower in the anakinra treatment group (8.4% vs. 15.9%). Bacteraemia's were evenly distributed 2.7% in both groups, but hospital acquired infections (2.5% vs. 3.7%) and ventilator associated pneumonias (2.2% vs. 7.9%) were lower in the anakinra treatment group. In off-label use of Kineret in COVID-19, of the 112 SAEs reported, 59 of them were infections and infestations.

The occurrence of death was less frequent in the anakinra-treated group compared to the placebo group (3.2% vs. 6.9%) in the pivotal study and in supportive studies. All deaths were considered to be due to COVID-19 progression and the patient's concurrent medical conditions.

No clinical meaningful trends were observed regarding laboratory findings.

Overall, relevant adverse reactions data in COVID-19 based on the SAVE-MORE study were reflected into SmPC section 4.8: Neutropenia, elevation of liver function test, rash and injection site reactions were reported more frequently in patients receiving Kineret compared with placebo.

3.5. Uncertainties and limitations about unfavourable effects

There were no new or unknown unfavourable effects that could be discerned from the safety data submitted by the MAH to support this extension of indication in COVID-19.

Three reports of Posterior reversible encephalopathy syndrome (PRES), a potential complication of severe COVID-19, were identified following a review of off-label cases with Kineret. It is unclear whether to what extent co-administration of anti-IL-1 can induce safety event of PRES. However, the review of 141 valid cases involving co-administration of anakinra did not reveal any new safety signals or safety concerns.

This application was initially based on interim CSR from the SAVE-MORE study. Further safety data were provided during the procedure upon request from the CHMP. However, the final CSR of the SAVE-MORE study has not yet been submitted. Upon request from the CHMP, the MAH confirmed that the final CSR will be submitted as part of a type II variation by end of December 2021. Further long-term safety data are missing and are expected to be provided in the post-approval setting (e.g. as part of future PSURs).

3.6. Effects Table

Table 46: Effects table for anakinra 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) ⩾ 6ng/ml (data cut-off: 18 August 2021).

Effect	Short description	Unit	Treatment Anakinra +SoC	Control Placebo+SoC	Uncertainties / Strength of evidence	References
Favourable Effects						
WHO-CPS by Days 28 (FAS)	Primary endpoint; ordinal regression analysis	Absolute decrease (median). OR_{Adj} (95% CI)	4	3	The three supportive analyses and included sensitivity analyses supported the primary endpoint Clinical impact and patient benefit difficult to interpret	SAVE-MORE study
			0.36 (95% CI: 0.26 – 0.50) in favour of anakinra			
Absolute change WHO-CPS by Day 28 from baseline (FAS)	Key secondary endpoint; ordinal regression analysis	OR_{Adj} (95% CI)	0.40 (95% CI: 0.29 – 0.55)		The secondary endpoints were not controlled for multiplicity	SAVE-MORE study
WHO-CPS Spect 1 (FAS)	Supportive analysis 2 for primary analysis requested by the COVID ETF (pre-specified), n (%)	n (%); OR_{Adj}	Fully resolved: 204 (50.4)	Fully resolved: 50 (26.5)	The secondary endpoints were not controlled for multiplicity	SAVE-MORE study
			OR 0.36 (95% CI: 0.25 – 0.53)			
WHO-CPS Spect 2 (FAS)	Supportive analysis 2 for primary analysis requested by the COVID ETF (pre-specified), n (%)	n (%)	WHO-CPS≤5: 379 (93.6) WHO-CPS≥6: 26 (6.4)	WHO-CPS≤5: 164 (86.8) WHO-CPS≥6: 25 (13.2)	The secondary endpoints were not controlled for multiplicity	SAVE-MORE study
			OR_{Adj} 0.46 (95% CI: 0.26 – 0.83)			
Time until severe respiratory failure (TUSRF) Day 28	Supportive analysis 3 for primary analysis requested by the COVID ETF (pre-specified). Cox regression analysis	HR_{Adj}	0.66 (95% CI: 0.47 – 0.91)		The secondary endpoints were not controlled for multiplicity	SAVE-MORE study
Unfavourable Effects						
TEAEs Day 90	Proportion of TEAEs	%	84.7	85.2		SAVE-MORE study
Serious	Proportion of	%	16.3	21.7		SAVE-MORE

Effect	Short description	Unit	Treatment Anakinra +SoC	Control Placebo+SoC	Uncertainties / Strength of evidence	References
TEAEs	serious TEAEs					study
Deaths	Proportion of deaths in the SAVE-MORE study	%	5.7	10.6		SAVE-MORE study

Abbreviations: WHO-CPS: WHO clinical progression score; OR: Odds ratio; TEAE: treatment emergent adverse event;

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The SAVE-MORE study met its primary endpoint and showed a statistically significant reduction in the WHO-CPS score in patients treated with anakinra+SoC as compared to patients receiving SoC at Day 28. A robust and clinically relevant efficacy was therefore considered to be demonstrated with anakinra treatment in patients with COVID-19 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) ≥ 6ng/ml. Further, an effect was already observed at Day 14, although the difference was not statistically significant. A favourable effect of anakinra was also demonstrated by the secondary endpoints, as more patients fully recovered by Day 28 in the anakinra arm in comparison to the placebo arm (50.5% vs 26.5 %, respectively) and the proportion of patients with severe outcome (WHO-CP score ≥ 6) was higher in the placebo arm than in the anakinra arm. Nevertheless, these results were not controlled for multiplicity and should thus be interpreted with caution. The absolute decrease of the WHO-CPS score from baseline to Days 28 was significantly greater in the anakinra arm. Even though, the clinical relevance of an absolute decrease of 1 additional point (4 points with anakinra versus 3 points with placebo) can be debated the totality of the data are overall supporting a benefit of anakinra. Time to progression to serious respiratory failure until Day 28 also supported a benefit of anakinra. In addition, the lower 28-day mortality among patients allocated to the anakinra+SoC treatment in comparison to the placebo+SoC (6.9 % vs. 3.2 %, respectively) was considered clinically relevant. Time until hospital discharge was 1 day shorter in the anakinra+SoC group than in the placebo+SoC group; although the relevance of a 1-day shorter hospitalization is considered to be limited.

Overall, based on the data submitted to support this application, the CHMP considered that a clinical efficacy was only demonstrated in the population studied in SAVE-MORE. As such, the therapeutic indication was restricted as follows: 'treatment of adult COVID-19 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'.

The safety profile of Kineret is overall acceptable. No new or unknown unfavourable effects could be discerned from this COVID-19 pneumonia population who often had pre-existing co-morbidities. The risks thereof are adequately described in the SmPC.

3.7.2. Balance of benefits and risks

In the SAVE-MORE study, a statistically significant and clinically relevant efficacy has been demonstrated with anakinra in adult COVID-19 patients with pneumonia requiring supplemental

oxygen (low- or high-flow oxygen) who are at risk of progressing to SRF determined by suPAR ≥ 6 ng/ml. In addition, anakinra also had a beneficial effect on time to progression to severe respiratory failure, on time until hospital discharge and on mortality.

As no other biomarkers of inflammation could be reliably identified in recognising the same patients as suPAR ≥ 6 ng/ml did, the CHMP concluded that the data only supported the use of anakinra in patient with suPAR ≥ 6ng/ml.

The safety profile of Kineret in the studied population is overall consistent with the know safety profile of Kineret in the other approved indications. No new safety signals arose from the data submitted. The long-term safety in this patient population will be closely monitored in the post-approval setting as part of the regular PSURs submission.

3.8. Conclusions

The overall B/R of Kineret in the 'treatment of adult COVID-19 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' is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

C.I.6 - Extension of indication to include 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 for Kineret; as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP is updated to version 5.9.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

5. EPAR changes

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

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Kineret-H-C-000363-II-0086'

Attachments

1. Product Information as adopted by the CHMP on 16 December 2021.