SEE ATTACHED ADDENDUM

Emergency Use Authorization (EUA) for Kineret (Anakinra)
THE UNAPPROVED USE OF AN APPROVED PRODUCT
Center for Drug Evaluation and Research (CDER) Review

Identifying Information

Application Type (EUA or Pre-EUA) If EUA, designate whether pre-event or intra-event EUA request.	EUA
EUA Application Number(s)	109
Sponsor (entity requesting EUA or pre-EUA consideration), point of contact, address, phone number, fax number, email address	Swedish Orphan Biovitrum AB (Sobi) c/o Advyzom LLC. 335 Snyder Ave. Berkeley Heights, NJ 07922 Rula Ibrahim-Saker, PharmD US Agent Phone: (b) (6) Fax: (b) (6) (b) (6)
Manufacturer, if different from Sponsor	N/A
Submission Date(s)	February 10, 2022
Receipt Date(s)	February 10, 2022
OND Division / Office	Division of Rheumatology and Transplant Medicine (DRTM)/Office of Immunology and Inflammation (OII)
Reviewer Name(s)/Discipline(s)	Austin Anderson, DO, Clinical Reviewer Raj Nair, MD, Clinical Team Leader Lei He, PhD, Clinical Pharmacology Reviewer Jianmeng Chen, MD, PhD, Clinical Pharmacology Team Leader Ruihao Huang, PhD, Machine Learning Reviewer Qi Liu, PhD, Machine Learning Secondary Reviewer Hao Zhu, PhD, Machine Learning Tertiary Reviewer Suresh Doddapaneni, PhD, Division of Inflammation and Immune Pharmacology (DIIP) Acting Division Director Thomas Biel, Ph.D., Product Quality Reviewer Ashutosh Rao, Ph.D. Product Quality Team Leader Maria Gutierrez-Lugo, Product Quality Tertiary Reviewer Xiao Chen, PhD, Pharmacology/Toxicology Reviewer

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Integrated Review Completion Date	November 8, 2022
Proprietary Name	Kineret
Established Name/Other names used during development	Anakinra
Dosage Forms/Strengths	Injection 100 mg/0.67 mL (PFS)
Therapeutic Class	Interleukin-1 (IL-1) inhibitor
Intended Use or Need for EUA	Treatment of coronavirus disease 2019 (COVID-19)
Intended Population(s)	Hospitalized adults with positive results of direct SARS-CoV-2 viral testing with pneumonia requiring supplemental oxygen (low or high-flow oxygen) who are at risk of progressing to severe respiratory failure and are likely to have an elevated suPAR.
Product in the Strategic National Stockpile (SNS)	No
Distributor, if other than Sponsor	N/A

I. EUA Determination/Declaration

On February 4, 2020, Secretary of Health and Human Services determined pursuant to section 564 of the Federal Food, Drug and Cosmetic (FD&C) Act that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad and that involves a novel (new) coronavirus (nCoV) first detected in Wuhan City, Hubei Province, China in 2019 (2019-nCoV). The virus is named SARS-CoV-2, which causes the illness COVID-19.

On the basis of this determination, the Secretary of Health and Human Services declared, on March 27, 2020, that circumstances exist justifying the authorization of emergency use of drugs and biologics during the COVID-19 outbreak, pursuant to section 564 of the FD&C Act, subject to the terms of any authorization issued under that section.

II. Recommendations

A. Recommend EUA Issuance

The Division of Rheumatology and Transplant Medicine, Office of Immunology and Inflammation, Office of New Drugs, CDER recommends EUA issuance.

The EUA will authorize KINERET (anakinra) for emergency use for the treatment of COVID-19 in hospitalized adults with positive results of direct SARS-CoV-2 viral testing with pneumonia requiring supplemental oxygen (low or high-flow oxygen) who are at risk of progressing to severe respiratory failure and are likely to have an elevated suPAR.

B. Eligibility of the Product for an EUA

- COVID-19 is a serious or life-threatening disease or condition caused by SARS-CoV-2, as specified in the declaration of emergency.

- Based on the totality of the scientific evidence available to FDA, it is reasonable to believe that anakinra may be effective for the treatment of COVID-19 in hospitalized adults with positive results of direct SARS-CoV-2 viral testing with pneumonia requiring supplemental oxygen (low or high-flow oxygen) who are at risk of progressing to severe respiratory failure and are likely to have an elevated suPAR. Under such conditions, the known and potential benefits outweigh the known and potential risks of this product.

- There is no adequate, approved and available alternative to the emergency use of anakinra for the treatment COVID-19 in hospitalized adults with positive results of direct SARS-CoV-2 viral testing with pneumonia requiring supplemental oxygen (low or high-flow oxygen) who are at risk of progressing to severe respiratory failure and are likely to have an elevated suPAR:

  - Veklury (remdesivir), a SARS-CoV-2 nucleotide analog RNA polymerase inhibitor, is an FDA-approved alternative for the treatment of COVID-19 in hospitalized adults with pneumonia requiring supplemental oxygen (low or high-flow oxygen) who are at risk of progressing to severe respiratory failure. Veklury has demonstrated antiviral activity against SARS-CoV-2; whereas anakinra is an IL-1 inhibitor that blocks IL-1, which is involved in inflammatory diseases and thought to contribute to inflammation and worsening of COVID-19, thus offering a different mechanism of action.

  - Olumiant (baricitinib), a Janus kinase (JAK) inhibitor, is an FDA-approved alternative for the treatment of COVID-19 in hospitalized adults with pneumonia requiring supplemental oxygen and non-invasive ventilation. Anakinra offers an alternative mechanism of action as it targets IL-1, another component of the complex hyperinflammatory response thought to contribute to worsening of COVID-19. In addition, anakinra has a subcutaneous route of administration whereas, Olumiant is available as immediate-release tablets; thus, anakinra is

offering an alternative route of administration to some patients who are hospitalized (e.g., for patients who are unable to swallow).

III. Proposed Use and Dosing of the Product Under the EUA

Proposed use under EUA

The Division recommends the following for inclusion in the EUA:

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of anakinra for the treatment of COVID-19 in hospitalized adults with positive results of direct SARS-CoV-2 viral testing with pneumonia requiring supplemental oxygen (low or high-flow oxygen) who are at risk of progressing to severe respiratory failure and are likely to have an elevated suPAR.

Anakinra is FDA-approved for several indications[1]; however, anakinra is not approved for the treatment of COVID-19.

Anakinra is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of anakinra under section 564(b)(1) of the Act, 21 U.S.C.

Proposed dosing regimens for use under EUA

Adult patients: 100 mg subcutaneous (SC) daily for 10-days.

Rationale for dosing regimen

The proposed dosing and treatment duration of anakinra are based on the regimen that was evaluated in the double-blind, randomized, placebo-controlled study SAVE-MORE. The same dose (100 mg administered once a day by SC injection) is also recommended for the treatment of patients 18 years of age or older with rheumatoid arthritis (RA) as described in the Kineret USPI.

IV. Product Information (Dose Preparation and Administration)

- Commercial Kineret will be provided and supplied in single-use, preservative free, prefilled glass syringes. Each prefilled glass syringe contains 100 mg of anakinra per 0.67 mL.

- Kineret is to be administered by subcutaneous injection.

[1] The currently approved labeling for KINERET may be found at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/103950s5189lbl.pdf

- According to the USPI, Kineret should be stored in the refrigerator at 2°C to 8°C (36°F to 46°F). Do not freeze or shake. Protect from light.

- SEE ATTACHED ADDENDUM Kineret is also dispensed in a 1 x 7 syringe dispensing pack containing 7 syringes (NDC 66658-234-07).

V. Background Information on the Disease/Condition and Available Therapeutic Alternatives

- Background information on the condition

  - Coronavirus disease 2019 (COVID-19) can cause severe disease which can result in pneumonia, respiratory failure, multi-organ failure, and death. On March 11, 2020, the WHO declared COVID-19 a pandemic.

  - Globally, according to the World Health Organization (WHO), approximately 593 million confirmed cases of COVID-19 caused by the 2019 novel coronavirus (SARS-CoV-2) have been reported as of August 23, 2022, including an estimated 6,446,547 deaths. In the United States, according to the Centers for Disease Control and Prevention (CDC), approximately 92,108,785 cases of COVID-19 have been reported with 1,028,619 deaths as of August 23, 2022.

  - Per the CDC COVID-19 data tracker, available demographic information demonstrates all age groups are affected by hospitalizations, ICU admissions, and deaths with the highest percentage in older individuals and unvaccinated individuals. Following infection with COVID-19, some patients develop severe disease that can progress to pulmonary failure, ARDS, and death. The understanding of the underlying immunopathology and natural history of the disease is rapidly evolving. The accumulating evidence indicates that in some cases the immune response results in a hyperinflammatory state that may contribute to organ injury and increased mortality.

- Therapeutic alternatives for the disease/condition

  There is no adequate, approved and available alternative to the emergency use of anakinra for the treatment of COVID-19 in hospitalized adults with positive results of direct SARS-CoV-2 viral testing with pneumonia requiring supplemental oxygen (low or high-flow oxygen) who are at risk of progressing to severe respiratory failure and are likely to have an elevated suPAR:

  - Veklury (remdesivir), a SARS-CoV-2 nucleotide analog RNA polymerase inhibitor, is an FDA-approved alternative for the treatment of COVID-19 in hospitalized adults with pneumonia requiring supplemental oxygen (low or high-flow oxygen) who are at risk of progressing to severe respiratory failure. Veklury has

demonstrated antiviral activity against SARS-CoV-2; whereas anakinra is an IL-1 inhibitor that blocks IL-1, which is involved in inflammatory diseases and thought to contribute to inflammation and worsening of COVID-19, offering a different mechanism of action.

- Olumiant (baricitinib), a Janus kinase (JAK) inhibitor, is an FDA-approved alternative for the treatment of COVID-19 in hospitalized adults with pneumonia requiring supplemental oxygen and non-invasive ventilation. Anakinra offers an alternative mechanism of action as it targets IL-1, another component of the complex hyperinflammatory response thought to contribute to worsening of COVID-19. In addition, anakinra has a subcutaneous route of administration; whereas Olumiant is available as immediate-release tablets, thus anakinra is offering an alternative route of administration to some patients who are hospitalized (e.g., for patients who are unable to swallow).

- There are other COVID-19 treatments currently authorized under EUAs that cover the same use as proposed for anakinra. These products include Actemra (tocilizumab) and convalescent plasma.[2]

VI. Related Regulatory Submission(s)

Related BLA (BLA 103950)

- Anakinra (Kineret) is FDA-approved for the following indications:
  - Reduction in signs and symptoms and slowing the progression of structural damage in moderately to severely active rheumatoid arthritis, in patients 18 years of age or older who have failed 1 or more disease modifying antirheumatic drugs
  - Treatment of Neonatal-Onset Multisystem Inflammatory Disorder (NOMID)
  - Treatment of Deficiency of Interleukin-1 Receptor Antagonist (DIRA)
- Approved dosage form:
  - Injection: 100 mg/0.67 mL solution in a single-use prefilled syringe for subcutaneous injection. Graduated syringe allows for doses between 20 mg and 100 mg.
- Approved dosing regimens:

[2] For more information on COVID-19 treatments authorized for emergency use, please refer to: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization

- The recommended dose of anakinra for the treatment of patients with rheumatoid arthritis is 100 mg/day administered by subcutaneous injection. Physicians should consider a dose of 100 mg of anakinra administered every other day for rheumatoid arthritis patients who have severe renal insufficiency or end stage renal disease (defined as creatinine clearance < 30 mL/min, as estimated from serum creatinine levels)

- The recommended starting dose of anakinra is 1-2 mg/kg daily for NOMID patients. The dose can be individually adjusted to a maximum of 8 mg/kg daily to control active inflammation. SEE ATTACHED ADDENDUM

- The recommended starting dose of anakinra is 1-2 mg/kg daily for patients with DIRA. The dose can be individually adjusted to a maximum of 8 mg/kg daily to control active inflammation. SEE ATTACHED ADDENDUM

  - Initial approval 2001

  - Applicant: Amgen

- Related INDs and Pre-INDs (IND 157769)

  - Sponsor: Swedish Orphan Biovitrum (Sobi)

  - This IND was referenced in the Applicant's EUA submission and pertains to pre-EUA meeting communications.

  - EUA 109 cross references BLA 103950 which includes the related Master Files.

VII. Summary of Clinical Data

Table 1: Clinical Trials Submitted in Support of the EUA Request

Study Identifier/ Country(ies)/ EudraCT Number[a]/ Status	Study Design	Study Treatments	Number of Subjects	Study Population
SAVE-MORE/ Greece and Italy/ 2020-005828-11/ enrollment closed	Pivotal, prospective, interventional, multicenter, double-blind, placebo-controlled, randomized	Arm 1: anakinra+SoC Anakinra injected s.c. as 100 mg q.d. for 10 days Arm 2: placebo+SoC. Placebo injected s.c.	606 subjects randomized 2:1 Arm 1: (anakinra+SoC): 412 Arm 2: (placebo+SoC): 194	Males and females ≥18 years of age hospitalized with confirmed infection by SARS-CoV-2 virus, lower respiratory tract infection
SAVE/Greece/2020-001466-11/	Open-label, single-arm, prospective, interventional	Anakinra+SoC Anakinra injected s.c. as 100 mg q.d. for 10 days	Target: 1000 subjects 1st period (April to September 2020): 130, anakinra+SoC; 130, matched SoC comparator (not enrolled in SAVE) 2nd period (October to December 2020): 587, anakinra+SoC; 141, matched SoC comparator (not enrolled in SAVE)	Males and females ≥18 years of age hospitalized with confirmed infection by SARS-CoV-2 virus, lower respiratory tract infection (radiologically confirmed), and plasma suPAR ≥6 ng/mL

The clinical efficacy and safety data package to support the EUA request is primarily based on the SAVE-MORE trial. This was a multicenter, prospective, randomized, double-blind, placebo-controlled phase 3 clinical trial comparing anakinra dosed with background standard of care (SOC, i.e., remdesivir and dexamethasone) to placebo with background standard of care. Patients were randomly assigned 2:1 to anakinra + SoC or placebo + SoC. Anakinra was administered at 100 mg/day qdaily for 10 days. The study was conducted at 37 sites in 2 countries (Greece and Italy). The study started in December 2020 and ended in June 2021.

The prospective, open-label, single-arm, interventional SAVE trial was also submitted by the Requester as supplemental efficacy and safety data. Patients received anakinra at 100 mg/day qdaily for 10 days. Results from the SAVE trial for the first 130 patients (April through September 2020) were published[3]. In this publication, comparisons of anakinra treated patients to propensity-matched controls on SoC were conducted. Given the rapidly evolving pace of treatment paradigms and differences in

[3] Kyriazopoulou E, Panagopoulos P, Metallidis S, Dalekos GN, Poulakou G, Gatselis N, et al. An open-label trial of anakinra to prevent respiratory failure in COVID 19. eLife. 2021a;10:e66125. DOI: 10.7554/eLife.66125.

access for COVID-19 treatments, there are concerns with relying on non-randomized controls for comparisons in this setting. Therefore, these results are not detailed in the efficacy section of this review though a description of clinical safety for anakinra including SAVE is provided (see Section IX).

In addition to the SAVE-MORE and SAVE trials, safety data from the use of anakinra for COVID-19 from the following sources were provided as supplemental information:

- Phase 2/3, randomized, open-label, parallel-group, 3-arm, multicenter trial (Immuno-101) 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. However, enrollment in the study was prematurely closed due to the evaluation of SoC treatment during the time frame of the study and its critical effect on recruitment. As a result, only 16 patients were enrolled.

- All postmarketing cumulative safety data with off-label use of anakinra for COVID-19, including solicited and spontaneous (health care providers, consumers, and literature) reports, along with adverse events reported to the safety data based on other Sponsor supported studies.

Study Immuno-101 and other randomized studies of IL-1 inhibitor therapies including anakinra are summarized in Table 2. These studies of IL-1 inhibitors differed in design, comparators (placebo, SoC), patient populations, and endpoints. For comparative purposes, mortality results are shown. There was not a consistent mortality benefit seen; however, the studies were small, investigated a different IL-1 inhibitor, or lacked a concurrently randomized control, making interpretation of the results difficult. The interpretability of the results of REMAP-CAP, the largest study in Table 2, were limited by a lack of concurrent randomization for most of the SoC controls and imbalanced baseline characteristics (use of steroids, remdesivir, non-invasive ventilation, and invasive mechanical ventilation). Additionally, the randomized studies of anakinra in Table 2 were all open-label which can introduce bias in the results. In summary, other randomized studies of IL-1 inhibitors including anakinra had limited interpretability because of their study designs, and therefore, these studies could not be used reliably to support or refute the results from the randomized, double-blind, placebo-controlled SAVE-MORE trial used to support the EUA request.

Table 2. Other Studies of IL-1 Inhibitor Therapies in COVID-19

Study	Design	Enrolled Population	Mortality Endpoint	Comparator	Investigational Product	Difference
Immuno-101	Open-label Randomized Anakinra + SoC (n=5) Emapalumab + SoC (n=5) SoC (n=6)	Hospitalized adults with confirmed SARS-COV-2 infection, respiratory distress, and hyperinflammation	Death by Week 10	0.0%	20%	Trial prematurely closed due to change in SoC which impacted recruitment

CORIMUNO ANA-1	Open-label Bayesian Randomized Anakinra + SoC (n=59) SoC (n=55)	Non-ICU hospitalized adults with mild-moderate COVID-19 pneumonia, at least 3 L/min of oxygen but without ventilation assistance, and CRP > 25 mg/L	Mortality at Day 28	24%	22%	Hazard ratio 0.77 95% CI 0.33-1.77 Trial terminated early due to futility
REMAP-CAP	Open-label Bayesian Adaptive platform Randomized Anakinra (n=378) SoC (n=418)	ICU hospitalized adults with COVID-19 and within 24 hours of receiving respiratory or cardiovascular organ support	In-hospital mortality by Day 21	36.9%	39.7%	OR 0.97 95% CI 0.66-1.40
ANA-CONDA	Open-label Randomized Anakinra + SoC SoC N = 71	Hospitalized adults with COVID-19, oxygen requirement, and CRP ≥ 50 mg/L	Terminated due to excess mortality in the anakinra arm Results not available			
COV-AID	Open-label Factorial design Randomized Anakinra (n=44) SoC (n=74)	Hospitalized adults with COVID-19, hypoxia, and signs of cytokine release syndrome	Mortality at Day 28	10%	16%	Not available
Kharazmi	Open-label Randomized Anakinra + SoC (n=15) SoC (n=15)	ICU hospitalized adults with confirmed diagnosis of COVID-19	Mortality at Day 14	46.7%	33.3%	P = 0.456
CAN-COVID	Double-blind Randomized Canakinumab (n=227) Placebo (n=227)	Hospitalized adults with COVID-19, hypoxia (not requiring MV), and systemic hyper-inflammation	Death by Day 29	7.2%	4.9%	OR 0.67 95% CI 0.30-1.50

ARDS, Acute respiratory distress syndrome; CI, Confidence interval; CID, Complex immune dysregulation; CRP, C-reactive protein; FiO2, Fraction of inspired oxygen; HR, Hazard ratio; ICU, Intensive care unit; MAS, macrophage activation syndrome; MV, Mechanical ventilation; O2, Oxygen, OR, Odds ratio; PaO2, Partial pressure of oxygen; PNA, Pneumonia; RA, Room air; SoC, Standard of care; SOFA, Sequential organ failure assessment score

VIII. Human Clinical Efficacy

SAVE-MORE

Study Design and Analysis Plan

The primary source of evidence of effectiveness of anakinra in the treatment of COVID-19 comes from the SAVE-MORE study. SAVE-MORE was a phase 3, prospective, multicenter, double-blind, placebo-controlled trial that compared anakinra + standard of care (SoC) to placebo + SoC. Anakinra was injected subcutaneously

(SC) as 100 mg once daily for 10 days and placebo was injected SC once daily for 10 days. Treatment randomization was 2:1 (anakinra:placebo). Randomization was stratified by severity of illness per World Health Organization (WHO) classification (moderate versus severe)[4], co-administration of dexamethasone as SoC therapy (No vs. Yes), BMI (≤30 vs. >30), and country (Italy vs. Greece). This study was conducted outside of an IND, and therefore, the study design and analyses were not reviewed by the Agency prior to study initiation.

The study population comprised hospitalized adults (≥18 years) with confirmed SARS-CoV-2 infection by real-time polymerase chain reaction of nasopharyngeal secretions, radiological findings compatible with lower respiratory tract infection, and plasma soluble urokinase plasminogen activator receptor (suPAR) level ≥6 ng/mL. Study visits took place on Days 1-10, 14, 28, 60, and 90 with WHO Clinical Progression Ordinal Scale (CPS) status collected at these timepoints.

Figure 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 pO2/FiO2 ≥150 or	7
	Mechanical ventilation pO2/FiO2 <150 (SpO2/FiO2 <200) or	8
	Mechanical ventilation pO2/FiO2 <150 and vasopressors, dialysis	9
Dead	Dead	10

Abbreviations: ECMO, Extracorporeal membrane oxygenation; FiO2, Fraction of inspired oxygen; NIV, Noninvasive ventilation; pO2, Partial oxygen pressure; RNA, Ribonucleic acid; SpO2, Oxygen saturation; WHO, World Health Organization.

The primary endpoint was the distribution of the 11-point WHO-CPS at Day 28. No multiplicity control was proposed, however, pre-specified secondary and supportive endpoints included:

- Distribution of WHO-CPS frequencies at Day 14
- WHO-CPS ≥1 vs 0 (uninfected vs. not) at Day 28
- WHO-CPS ≥6 vs ≤5 (severe disease vs. not) at Day 28
- Time to severe respiratory failure (SRF) by Day 14, Day 28, defined as death or pO2/FiO2 <150 mmHg necessitating HFO/NIV/MV
- Change in 11-point WHO-CPS by Day 28 from baseline
- Change in 11-point WHO-CPS by Day 14 from baseline

[4] Moderate illness was defined as clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) but no signs of severe pneumonia, including saturation of oxygen (SpO2) ≥90% on room air.
Severe illness was defined as clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) plus one of the following: respiratory rate >30 breaths/minute; severe respiratory distress; or SpO2 <90% on room air.

- Change in SOFA score by Day 14 from baseline
- Change in SOFA score by Day 7 from baseline
- Time until discharge from the hospital
- Time until discharge from the ICU
- Changes in suPAR, CRP, D-dimer, ferritin, and IL-6 by Day 7
- Changes in suPAR, CRP, D-dimer, ferritin, and IL-6 by Day 4
- Change of viral load by Day 7 from baseline
- Change of viral load by Day 4 from baseline

For the analysis of the primary endpoint, two different analyses were pre-specified in the statistical analysis plan (SAP): univariate (no covariate adjustment) and multivariate proportional odds models estimated the odds ratio (OR) for higher WHO-CPS (disease severity) comparing anakinra to placebo. The multivariate model adjusted for variables collected at time of screening and used in stratified randomization: dexamethasone use, moderate/severe disease, BMI, and country. For binary secondary endpoints, univariate and multivariate logistic regression models estimated the OR comparing anakinra to placebo. For time to event secondary endpoints, univariate and multivariate Cox proportional hazards regression models estimated the hazard ratio (HR) comparing anakinra to placebo. Logistic and Cox regressions adjusted for variables selected posthoc using forward step-wise regression. The variables selected differed depending on the endpoint. The study did not prospectively control the Type I error for number of endpoints tested or analyses conducted.

The Requester also analyzed the endpoints of all-cause mortality by Day 28 and Day 60, in a post hoc manner, using time to event methods as discussed above. Mortality percentage, risk difference, and corresponding CI were calculated from Kaplan-Meier estimates and their normal approximation. In addition, the review team performed analyses to estimate the difference in proportions and corresponding 95% confidence intervals of additional post hoc derived binary endpoints based on the WHO-CPS scale at Day 28 that included hospitalized status (WHO-CPS ≥4 vs. ≤3) and need for intubation, mechanical ventilation, or death (WHO-CPS ≥7 vs. ≤6) to further explore the SAVE-MORE data. The difference in proportions analyses did not adjust for covariates.

Among the secondary endpoints and those endpoints defined in post hoc analyses, the review team considered most clinically relevant endpoints for the EUA request the endpoints of all-cause mortality by Day 28 and Day 60 and time to SRF by Day 28. To avoid dependence on data driven variable selection, univariate Cox regression models were used for these endpoints. The multivariate Cox regression models adjusted for all variables (collected at the time of screening) and used in stratified randomization: dexamethasone, moderate/severe disease, BMI, and country are also provided. The difference in proportion and corresponding 95% confidence interval without covariate adjustment were also calculated for the binary endpoints of all-cause mortality at Day 28 and Day 60.

The pre-specified method for imputing missing outcomes was last observation carried forward (LOCF), which strongly assumes that a patient's outcome does not change after lost to follow-up (LTFU). LOCF is a single imputation approach that can result in a biased treatment estimate if this assumption is incorrect and underestimation of the estimate's variability. LOCF was applied to the analysis of the primary endpoint of WHO-CPS at Day 28. For the post hoc analyses of the time to event endpoints of mortality and SRF, censoring was assumed to be non-informative.

Baseline Patient Characteristics

A total of 1060 patients were screened for study eligibility, 405 patients were excluded because their suPAR was <6 ng/mL, 49 patients did not meet other inclusion/exclusion criteria, resulting in 606 patients randomized either to anakinra or placebo. With consent withdrawal and request for removal of all data from 12/606 (2%) patients, the primary analysis set had 189 patients in the placebo arm and 405 patients in the anakinra arm. Missing data from LTFU was low: 1 subject by Day 28, 20 patients by Day 60, and 27 patients by Day 90.

Baseline and demographic characteristics are shown in Table 3. The average age was 62 years, and 58% of patients were male. A higher percentage of patients had severe disease compared to moderate disease at screening (82% vs. 18%). Patients either had a WHO-CPS of 4 (8%), 5 (85%), or 6 (7%) at randomization. Dexamethasone (74%), remdesivir (86%), and heparin (94%) use were high at baseline. Most characteristics considered were approximately balanced between treatment arms, except for moderate/severe disease and certain medication use at baseline. A higher percentage of patients on placebo had severe disease compared to anakinra (86% vs. 80%) at the time of screening and before the start of study drug (94% vs. 90%). A higher percentage of patients on placebo received dexamethasone at baseline compared to anakinra (89% vs. 84%). Given randomization was stratified by disease severity and dexamethasone use, these imbalances are somewhat surprising. Other baseline use of medications that were potentially imbalanced included: low molecular weight heparin, piperacillin/tazobactam, and ceftriaxone.

Table 3. Demographics and Baseline Characteristics, SAVE-MORE

	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 disease	26 (13.8)	82 (20.2)	108 (18.2)
Severe disease	163 (86.2)	323 (79.8)	486 (81.8)

WHO classification for COVID-19 before start of the study drug, n (%)			
Moderate disease	12 (6.3)	39 (9.6)	51 (8.6)
Severe disease	177 (93.7)	366 (90.4)	543 (91.4)
WHO-CPS at randomization			
WHO-CPS=4 (no oxygen needed)	12 (6.3)	39 (9.6)	51 (8.6)
WHO-CPS=5 (need mask/nasal oxygen)	162 (85.7)	341 (84.2)	503 (84.7)
WHO-CPS=6 (need HFO)	15 (7.9)	25 (6.2)	40 (6.7)
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)
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)
Median (min, max) days of exposure	10 (2, 10)	10 (1, 10)	
Co-administered medications, n (%)			
Remdesivir	141 (74.6)	298 (73.6)	439 (73.9)
Dexamethasone	168 (88.9)	342 (84.4)	510 (85.9)
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 (19.0)	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	2 (1.1)	5 (1.2)	7 (1.2)
Linezolid	3 (1.6)	7 (1.7)	10 (1.6)

Source: Requester Clinical Study Report Table 10-2

Efficacy Results

Results for the primary endpoint, time to mortality, and time to SRF are shown in Table 4. The anakinra arm compared to placebo had lower odds for more severe disease (higher score) in the primary endpoint of WHO-CPS distribution at Day 28 in both univariate and multivariate proportional odds models (univariate OR=0.36, 95% CI 0.26, 0.49; multivariate OR= 0.37, 95% CI 0.26, 0.50). To aid in interpreting this comparison, Figure 2 shows stacked bar plots summarizing the ordinal scale status of patients in each treatment arm at Day 28. For additional information, refer to Appendix Table 17 for tabulations (n,%) of patients by WHO-CPS and timepoints. The model assumption of proportional odds was assessed by the Requester with a parallel lines test, and the result did not indicate that the assumption was violated.

The mortality risk by Day 28 and Day 60 was numerically lower in the anakinra arm compared to placebo (Figure 3) in both univariate and multivariate analyses (univariate analysis for Day 28, HR=0.45, 95% CI 0.21, 0.98; multivariate analysis for Day 28, HR=0.48, 95% CI 0.22, 1.04). By Day 28, there were 13 deaths (6.9%) in the placebo arm and 13 deaths (3.2%) in the anakinra arm. By Day 60, there were 18 deaths (9.7%) in the placebo arm and 21 deaths (5.3%) in the anakinra arm. The covariate adjusted HR estimates for all-cause mortality at Day 28 and Day 60 had wider confidence intervals that were potentially attributable to low event counts and small sample sizes.

The risk for SRF by Day 28 was lower in the anakinra compared to placebo in both univariate and multivariate analyses (univariate HR=0.61, 95% CI 0.44, 0.85; multivariate HR=0.66; 95% CI 0.48, 0.92). All other prospectively defined secondary/supportive endpoints based on the WHO-CPS scale (results not shown) were also in favor of the anakinra arm.

Subgroup analyses of the primary endpoint were performed using a univariate analysis by baseline remdesivir use, baseline dexamethasone use, and moderate/severe disease at time of screening. All of these univariate subgroup analyses of the primary endpoint showed lower odds for more severe disease in the anakinra arm compared to placebo (Figure 4). However, as discussed above, imbalances were observed between treatment arms in moderate/severe disease and certain medication use at baseline.

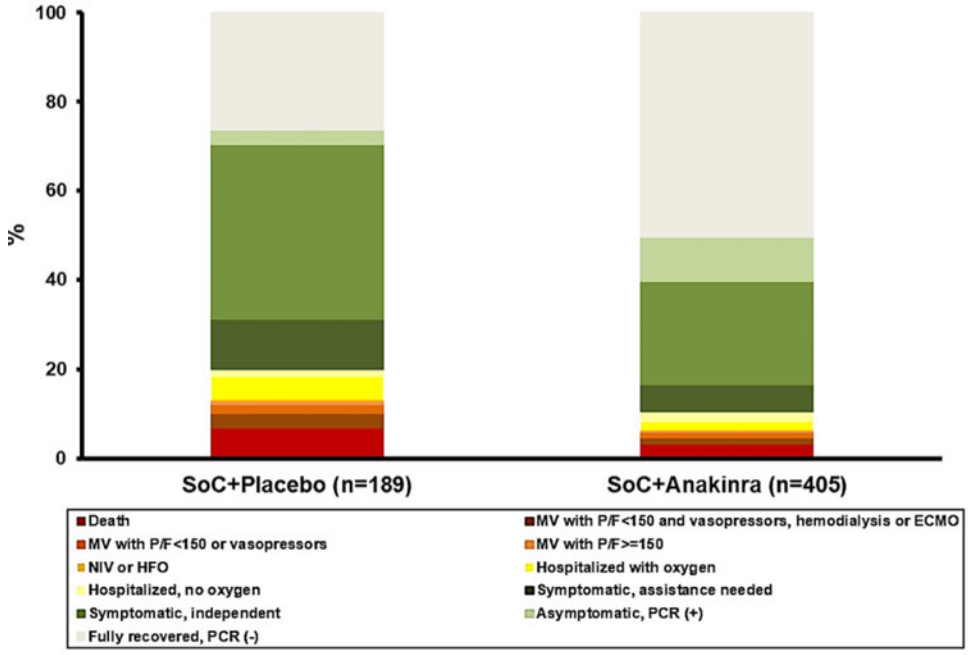
Reviewer-conducted post hoc derived binary endpoints of hospitalized status (WHO-CPS ≥4 vs. ≤3) and need for intubation, mechanical ventilation, or death (WHO-CPS ≥7 vs. ≤6) at Day 28 and Day 60 showed lower risk in the anakinra arm compared to placebo (Table 5).

Table 4. Efficacy Results, SAVE-MORE

Endpoints	Placebo #/N (%[c])	Anakinra #/N (%[c])	Risk Difference[c,d] (95% CI)	Univariate analysis[d] OR (95% CI)	Multivariate analysis[e] OR (95% CI)
WHO-CPS at Day 28 (primary)[a]	N=189	N=405	-	0.36 (0.26, 0.49)	0.37 (0.26, 0.50)
				HR (95% CI)	**HR (95% CI)**
Mortality by Day 28[b]	13/189 (6.9%)	13/405 (3.2%)	-3.7% (-7.7%, 0.3%)	0.45 (0.21, 0.98)	0.48 (0.22, 1.04)[f]
Mortality by Day 60[b]	18/189 (9.7%)	21/405 (5.3%)	-4.4% (-9.2, 0.4%)	0.52 (0.28, 0.98)	0.56 (0.30, 1.04)[f]
SRF by Day 28[a]	62/189 (32.8%)	86/405 (21.2%)	-11.6% (-19.4%, -3.8%)	0.61 (0.44, 0.85)	0.66 (0.48, 0.92)

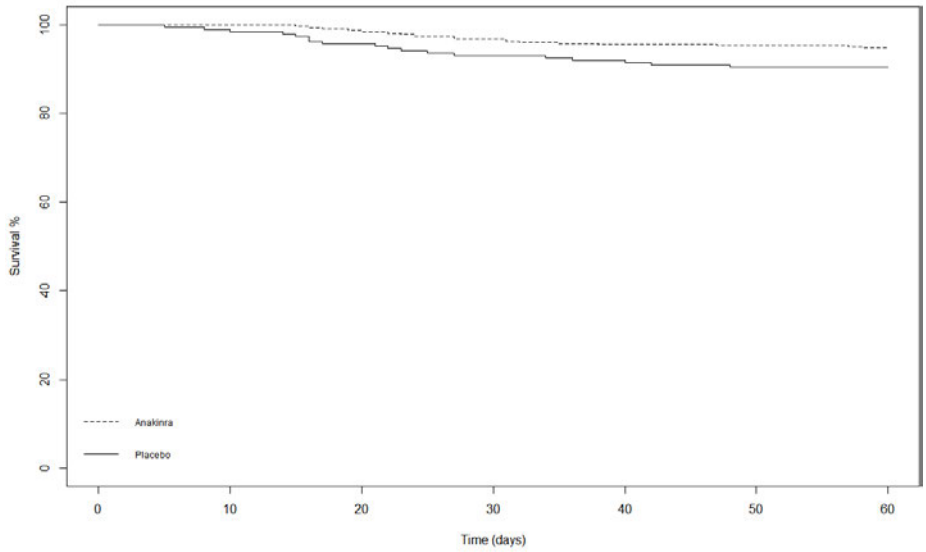
Abbreviations: CI, Confidence interval; HR, Hazard ratio; OR, Odds ratio; SRF, Severe respiratory failure; WHO-CPS, World Health Organization-Clinical Progression Scale
SRF: death or pO_2/FiO_2 <150 mmHg necessitating HFO/NIV/MV. OR: odds ratio for higher disease severity comparing anakinra to placebo. HR: hazard ratio for the endpoint comparing anakinra to placebo.
[a] Pre-specified analyses
[b] Post hoc analyses
[c] % and risk difference (95%CI) were based on Kaplan-Meier estimates
[d] Analysis did not adjust for baseline covariates
[e] Multivariate proportional odds model adjusted for variables used in stratified randomization: dexamethasone, moderate/severe disease, BMI, country
[f] Estimates for covariates dexamethasone use and moderate/severe disease could not be estimated because of data sparsity
Source: Statistical Reviewer Analysis

Figure 2. WHO-CPS Bar Plots at Day 28, SAVE-MORE



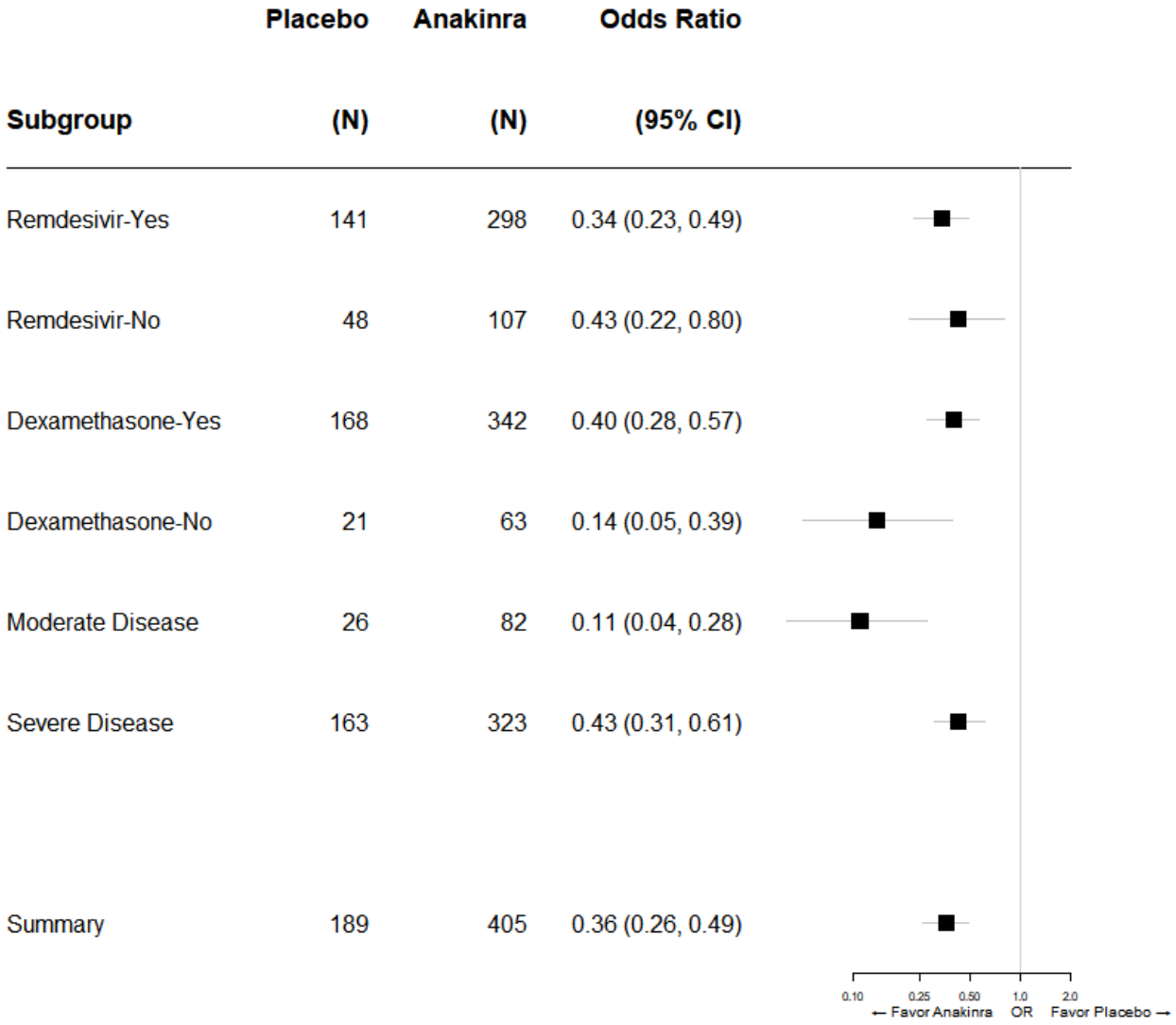
WHO-CPS: World Health Organization-Clinical Progression Scale
Source: Requester Clinical Study Report Figure 11-1

Figure 3. Kaplan Meier Curves for Mortality by Day 60, SAVE-MORE



Source: Statistical Reviewer Analysis

Figure 4. Subgroup Univariate Analysis-WHO-CPS at Day 28, SAVE-MORE



Source: Adapted from Requester Clinical Study Report Tables 11-57, 11-59, 11-61, 11-66, 11-68, 11-70, 11-72, 11-74,11-76

Table 5. Reviewer Analyses of Additional Endpoints based on WHO-CPS, SAVE-MORE

Endpoints	Placebo #/N (%)	Anakinra #/N (%)	% Difference* (95% CI)
WHO-CPS ≥4 vs. ≤3 at Day 28 (hospitalized vs. not)	39/189 (20.1)	43/405 (10.6)	-9.5 (-16.3,-3.4)
WHO-CPS ≥7 vs. ≤6 at Day 28 (intubation/MV/death vs not)	24/189 (12.7)	25/405 (6.2)	-6.5 (-12.4, -1.6)

Abbreviations: CI, Confidence interval; WHO-CPS, World Health Organization-Clinical Progression Scale
*Statistical Reviewer calculated using the Newcombe Hybrid Score CI

Early Study Withdrawal and Missing Data

In total, there were 13/606 (2%) randomized patients who had missing data by Day 28, and 32/606 (5%) randomized patients who had missing data by 60. There were 12 randomized patients who withdrew consent and requested removal of data (n=12/606 (2%), 7 anakinra-treated, 5 placebo-treated). As this study was conducted outside of an IND, the Agency could not provide feedback on the protocol and informed consent forms prior to study initiation and completion. No information other than randomized treatment was provided on these subjects because of this request. There was 1 patient (placebo-treated) LTFU by Day 28 who had a WHO-CPS of 0 (uninfected; no viral RNA detected) on the last recorded date of Day 14. There were a total of 20 (including the 1 patient LTFU after Day 14) randomized patients LTFU by Day 60 (20/606 (3%); 13 anakinra-treated, 7 placebo-treated). Of these 20 patients, 1/20 had a WHO-CPS of 5 (hospitalized; oxygen by mask or nasal prongs) and 19/20 had WHO-CPS ≤ 2 (not hospitalized, symptomatic, independent).

The Requester did not consider patients who withdrew consent and requested for removal of data to be missing. As such, only 1 patient who was LTFU by Day 28 was considered to have missing data in the Requester's analyses. This patient was in the placebo arm and was analyzed with an imputed WHO-CPS score of zero using last observation carried forward in the primary analysis. These assumptions resulted in treatment estimates for WHO-CPS distribution at Day 28 (univariate analysis, OR=0.36; 95% CI 0.26, 0.49) and all-cause mortality by Day 28 (univariate analysis, HR=0.45; 95% CI 0.21, 0.98) that were closer to the null of 1.0 than if the patient were assumed to have a worse outcome. Thus, regardless of missing data assumptions for this patient, the results for WHO-CPS distribution at Day 28 were robust and strongly supportive of a treatment effect. The same patient was assumed to be alive in the analysis of all-cause mortality by Day 28. If this patient was assumed to have died, the all-cause mortality risk would still be numerically lower in the anakinra arm compared to placebo.

The review team conducted additional missing data sensitivity analyses including all randomized patients with missing data: 12 patients who withdrew consent and 20 patients LTFU. For the 12 patients who withdrew consent, this analysis assumed that anakinra-treated patients had worse outcomes than placebo-treated patients, specifically that the 5 placebo-treated patients lived and the 7 anakinra-treated patients died by the timepoint of interest (e.g., Day 28 or Day 60). The review team applied this assumption about the withdrawn patients in addition to analysis-specific assumptions of patients LTFU to the sensitivity analysis of WHO-CPS at Day 28 and all-cause mortality by Day 28 and Day 60.

For the primary endpoint of WHO-CPS at Day 28, assuming that the 5 placebo-treated patients who withdrew had a score of 0, the 7 anakinra-treated patients who withdrew had a score of 10 (died), and the 1 placebo-treated patient LTFU had a score of 0 at Day 28 resulted in a (univariate analysis) OR=0.42 (95% CI 0.30, 0.57). For all-cause mortality by Day 28, assuming that the 5 placebo-treated patients who withdrew lived,

the 7 anakinra-treated patients who withdrew died, and the 1 placebo-treated patient LTFU was non-informatively censored resulted in a risk difference[5] of -1.9 (95% CI -6.0, 2.2). For all-cause mortality by Day 60, assuming that the 5 placebo-treated patients who withdrew lived, the 7 anakinra-treated patients who withdrew died, and the 20 patients LTFU were non-informatively censored resulted in a risk difference of -2.5 (95% CI -7.4, 2.3).

In summary, the sensitivity analysis of WHO-CPS at Day 28 produced an OR estimate that was supportive of a treatment effect when assuming that anakinra-treated patients with missing data had the worst possible outcome and placebo-treated patients with missing data had the best possible outcome. Sensitivity analyses of all-cause mortality by Day 28 and 60, which used all available data up to the time of LTFU, produced risk difference estimates that were attenuated compared to the risk difference estimates in Table 4 that excluded patients who withdrew. However, these results still indicated mortality was numerically lower in the anakinra arm. Notably, most of the patients who were LTFU (19/20) had mild COVID-19 and were no longer hospitalized (WHO-CPS ≤ 2) at the time of LTFU. Overall, these sensitivity analysis results do not change the overall conclusions of the primary analysis in the context of this Emergency Use Authorization.

Efficacy Conclusion

The efficacy results presented by the Requester from the SAVE-MORE study provided evidence that anakinra may be effective in this high-suPAR selected population. There were limitations to the results due to lack of multiplicity control across secondary endpoints and multiple analyses for the same endpoint. As the number of endpoints and analyses in a single trial increases, the likelihood of making false conclusions about a drug's effects with respect to one or more of those endpoints increases if there is not appropriate adjustment for multiplicity. However, a nominal treatment effect was observed across all the pre-specified efficacy endpoints and analyses, including the primary endpoint. While there is uncertainty around the post-hoc mortality estimates, the anakinra arm had numerically lower estimates of mortality risk compared to placebo across analyses and timepoints.

Furthermore, the observed imbalances between treatment arms in baseline disease severity and dexamethasone use were unexpected given these were factors used in stratified randomization. However, multivariate analyses that adjusted for disease severity, dexamethasone use, BMI, and country gave similar results to the univariate analyses for the primary endpoint, mortality, and SRF. The treatment effect was also consistently favorable across the subgroups of dexamethasone use and disease severity.

Additionally, there were limitations with the Sponsor's approach to handling missing data that (1) relied on unverifiable assumptions of included patients who had missing data and (2) excluded all data from withdrawn patients, a practice that is not generally

[5] Risk difference (95%CI) were based on Kaplan-Meier estimates.

recommended by FDA. Nonetheless, the percent of missingness was low in the SAVE-MORE study, and the primary endpoint analyses were robust to missing data assumptions.

An assessment of other randomized (either to placebo or SoC) studies of IL-1 inhibitor therapies including anakinra, summarized in Table 2, did not provide reliable efficacy results to either support or refute the SAVE-MORE study efficacy results. However, the review team notes that none of these studies have selected/enriched for patients based on criteria used in the SAVE-MORE study. Further, the other studies of IL-1 inhibitor therapies including anakinra had limitations in their study designs, e.g., open label, SoC controlled, non-concurrent randomization, and small sample sizes, that eluded consistent evidence for anakinra efficacy.

In summary, the efficacy results from the SAVE-MORE trial provided evidence that anakinra may be effective in the studied population.

Patient Selection Based on SCORE 2 to Address Unavailability of suPAR Test in the US

Patients in the SAVE-MORE and SAVE trials were selected based on a biomarker cut-off, suPAR ≥ 6 ng/mL, intending to enrich the trials with patients at risk for progressing to severe respiratory failure. At this time, the suPAR test is not commercially available in the United States. Given this enrichment strategy and the inconsistent results in the other studies in the broader population, it is unclear if the results seen in the SAVE-MORE trial can be generalized to the broader scope of the EUA, as proposed by the Requester (i.e., a population defined regardless of suPAR level). In order to identify a comparable population as in the SAVE-MORE trial, the review team worked with the Requester to explore ways to select patients most likely to have suPAR ≥ 6 ng/mL based on commonly measured patient characteristics.

On May 11, 2022, the FDA review team sent an Information Request (IR) to the Requester, strongly recommending that the Requester evaluate a path forward to develop suPAR as a companion diagnostic to identify patients who are most likely to benefit from treatment with anakinra. The IR also stated, “If you are unable to do so, we recommend that you investigate whether there are other combinations of clinical characteristics and/or laboratory tests that reliably identify the suPAR ≥ 6 ng/ml population.” In response to this IR, the Requester explored different combinations of baseline variables which may be predictive for suPAR ≥ 6 ng/ml using data from the SAVE-MORE trial. The Requester identified a potential scoring rule, referred to by the Requestor as “SURROGATE”, which included considerations of age (≥75 years), severe pneumonia by WHO criteria, current/previous smoking status, Sequential Organ Failure Assessment (SOFA) score ≥3, hemoglobin ≤10.5 g/dl, blood urea ≥50 mg/dl, medical history of renal disease and medical history of ischemic stroke. The Requester stated that patients meeting at least two of these criteria would be considered positive for SURROGATE score and highly likely to have suPAR ≥ 6 ng/mL.

The FDA review team evaluated the Requester's proposal of SURROGATE. In addition, the review team conducted additional analyses using data from SAVE-MORE trial to develop potentially improved scoring rule.

- The review team combined the criteria of "blood urea ≥ 50mg/dl" and "medical history of chronic renal disease," based on their similar biological relevance. In the SAVE-MORE trial dataset, seven out of nine of patients with history of chronic renal disease had blood urea ≥ 50 mg/deciliter. Therefore, the review team considered it reasonable to combine these variables into a single criterion.

- In addition to the baseline variables identified by the Requester and included in SURROGATE, the review team explored all baseline variables that were available in the dataset for the SAVE-MORE trial. In addition, FDA review team created and evaluated one additional composite variable (NLR) using two patient baseline variables from the dataset provided by the requester (the neutrophil absolute count and lymphocyte absolute count). This analysis included 837 out of 1060 patients whose data were available at screening from the SAVE-MORE trial database, containing 268 out of 454 patients who were screened but excluded from enrollment and 569 out of 606 patients who were enrolled for this trial.

  Two different artificial intelligence/machine learning (AI/ML) algorithms (artificial neural network and elastic net regression) were used to predict whether a patient has suPAR≥ 6 ng/mL based on his/her baseline characteristics (see Appendix **XXVI** for details of the machine learning analyses). Both algorithms produced similar results and suggested that an additional criterion "Neutrophil-to-lymphocyte ratio (NLR) ≥7" should be added. This is an inflammation and immune related biomarker. From a biological perspective, addition of this NLR based criterion is reasonable, as suPAR is an inflammation and immune related biomarker and none of the components of SURROGATE are clearly related to inflammation and immune system. This also appears to be a logical addition considering the mechanism of action of anakinra is related to the immune system. The cut-off of NLR, 7, was selected by the AI/ML algorithms. Interestingly, several literature papers suggested that the optimal cut-off value of NLR for predicting the severity/mortality risk of COVID-19 is around 7, which provides biological plausibility for this criterion (Onal et al. 2022; Asaduzzaman et al. 2022, PMC9172589; Li et al. 2020, PMC7667659). It is worth noting that while a continuous variable might have offered more power for predictive performance, for the purposes of this score, a dichotomized approach that might help guide physicians in identifying a similar patient population as was studied was considered preferable.

As a result, the FDA review team developed an alternative scoring rule, named "SCORE 2", to identify patients with suPAR ≥ 6 ng/mL. SCORE 2 includes considerations of the following:

1. age ≥75 years,
2. severe pneumonia by WHO criteria,
3. current/previous smoking status,
4. SOFA score ≥3,
5. NLR≥7,
6. hemoglobin ≤10.5 g/dl,
7. medical history of ischemic stroke, and
8. blood urea ≥50 mg/dl and/or medical history of renal disease

Patients meeting at least three of these eight criteria were considered positive for SCORE 2 and highly likely to have suPAR ≥ 6 ng/mL. As compared to SURROGATE, SCORE 2 had a higher positive predictive values and higher specificity (lower false positive rate), although lower sensitivity.

Based on the biological plausibility and the predictive performance, SCORE 2 was proposed to the Requestor by the FDA review team for validation. The Requester concurred with the FDA review team on the development of SCORE 2 and the addition of the criterion based on NLR (a biomarker for inflammation and immune status), considering the nature of suPAR and the mechanism of the drug (modulating the immune system).

The FDA review team also requested the Requester submit the dataset from the SAVE trial for external validation for SCORE 2. Table 6 summarizes the predictive performance of SCORE 2 in both the training dataset (SAVE-MORE trial) and the external validation dataset (SAVE trial). SCORE 2 demonstrated good performance in both the training and external validation datasets. With both datasets, SCORE 2 showed high positive predictive value, high specificity, and low false positive rate. This suggests that patients with suPAR<6 ng/mL are very unlikely to be incorrectly selected by SCORE 2 and given the anakinra treatment, therefore missing the chance to be treated by other medication(s). As a trade-off, SCORE 2 has a relatively low sensitivity, meaning some patients with suPAR ≥ 6 ng/mL will not be identified by SCORE 2. Despite this limitation, including the information on SCORE 2 in the fact sheet may help guide physicians to identify patients who are similar to the studied patient population in SAVE-MORE.

Table 6. Performance of SCORE 2 to predict suPAR levels of 6 ng/ml or higher in both the training dataset (SAVE-MORE trial) and the external validation dataset (SAVE trial).

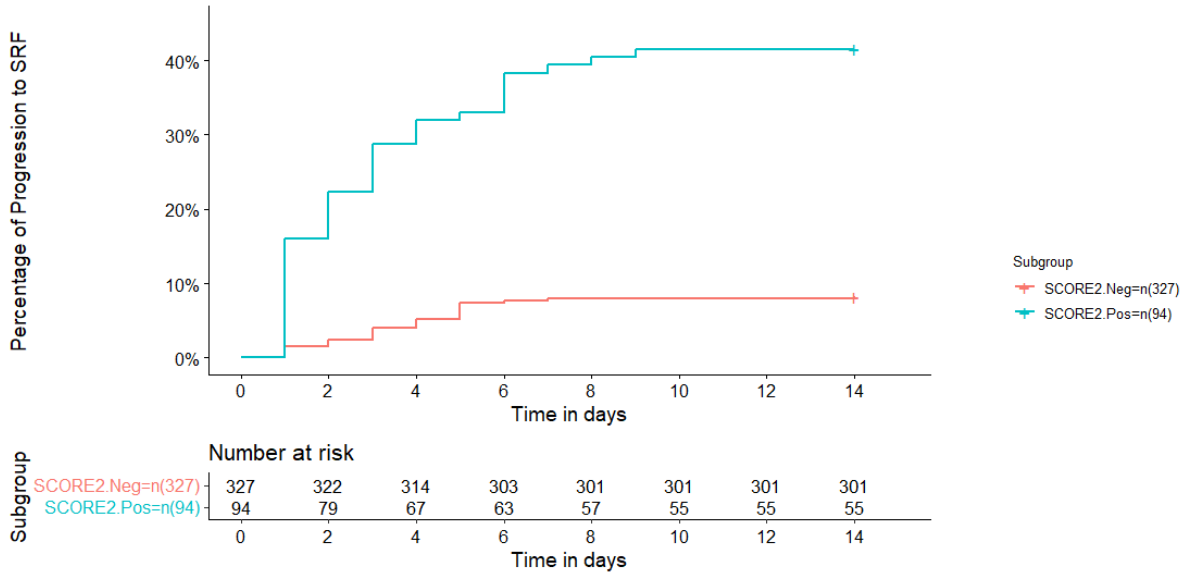
Training dataset (SAVE-MORE trial)				External validation dataset (SAVE trial)			
	suPAR≥6	suPAR<6	Total		suPAR≥6	suPAR<6	Total
SCORE 2 (+)	231 (PPV=0.95, sensitivity =0.41)	12 (FPR=0.04)	243	SCORE 2 (+)	95 (PPV=0.94, sensitivity =0.37)	6 (FPR=0.07)	101

SCORE 2 (-)	338	256 (NPV=0.43, specificity=0.96)	594	SCORE 2 (-)	159	76 (NPV=0.32, specificity=0.93)	235
Total	569	268	837	Total	254	82	336

*PPV: positive predictive value; NPV: negative predictive value; FPR: false positive rate.
Source: OCP Appendices (Technical documents supporting OCP recommendations) -MACHINE LEARNING REVIEW

As suPAR was intended to identify patients at risk for progressing to severe respiratory failure (SRF), the FDA review team used data from the SAVE-MORE trial to conduct an exploratory analysis to evaluate whether SCORE 2 can help identify patients at risk for progressing to SRF. The review team compared the prognosis for score-positive and score-negative subpopulations without anakinra treatment. For this analysis, the review team studied patients receiving only standard-of-care treatment (with or without placebo) during the same time period. This analysis included 421 patients who were screened for eligibility for the SAVE-MORE trial and for whom the 14-day outcome was known. These patients either had suPAR < 6 ng/mL and failed screening (n = 240) or they had suPAR ≥ 6 ng/mL and were enrolled in the SAVE-MORE trial and allocated to SoC + placebo treatment (n = 181). Figure 5 shows the time to progression to SRF by Day 14 for patients who are positive or negative for SCORE 2. Although there are limitations of this exploratory analysis, it appears that SCORE 2 is able to identify patients at risk for progressing to SRF.

Figure 5. Time to progression to severe respiratory failure (SRF) by Day 14 for patients who are positive or negative for SCORE 2.



Source: OCP Appendices (Technical documents supporting OCP recommendations) -MACHINE LEARNING REVIEW

At the request of the Agency, the Requester conducted efficacy analyses in the SAVE-MORE study of the primary endpoint WHO-CPS at Day 28, all-cause mortality by Day 28, and all-cause mortality by Day 60 comparing anakinra to placebo in the

subgroups: patients with SCORE 2 ≥ 3 and patients with SCORE 2 < 3 (Table 7). Only patients with suPAR ≥ 6 ng/mL were randomized to anakinra or placebo, and as such, there were no efficacy results in patients with suPAR < 6 ng/mL. In both the SCORE 2 ≥ 3 and SCORE 2 < 3 subgroups, the anakinra arm had lower odds for more severe disease compared to placebo. For the evaluation of mortality, a lower mortality risk in the anakinra group compared to the placebo group was observed only for the subgroup with SCORE 2 ≥ 3. However, the subgroup mortality results also had considerable uncertainty, i.e., with wide confidence intervals around point estimates, likely attributable to small subgroup sample size and few deaths (see Table 7).

Based on these subgroup results, patients in SAVE-MORE who met the SCORE 2 ≥ 3 criterion appeared to show beneficial efficacy results with treatment of anakinra consistent with the overall studied population. Given the uncertainty in the subgroup results and the exploratory nature of these analyses, it is unclear if patients who were SCORE 2 < 3 may also benefit. Consequently, identifying patients using SCORE 2 to treat with anakinra could potentially exclude patients who might benefit from treatment. However, identifying patients using SCORE 2 has the benefit of increasing the probability that the benefits seen in SAVE-MORE will apply to the patient. Other choices of treatment may be considered if a patient is not identified using SCORE2.

Table 7. Subgroup Univariate Analyses by SCORE 2 Cutoffs, SAVE-MORE

	SCORE 2 ≥ 3 (N=231)[a]				SCORE 2 < 3 (N=338)[a]			
Endpoints	**Placebo #/N (%)**	**Anakinra #/N (%)**	**% Difference[b] (95% CI)**	**OR[c] (95%CI)**	**Placebo #/N (%)**	**Anakinra #/N (%)**	**% Difference[b] (95% CI)**	**OR[c] (95%CI)**
WHO-CPS at Day 28 (primary)			NA	0.39 (0.23, 0.63)			NA	0.38 (0.24,0.58)
				HR[d] (95% CI)				**HR[d] (95% CI)**
Mortality by Day 28	12/83 (14.5)	8/148 (5.4)	-9.05 (-18.56, -1.32)	0.25 (0.14, 0.87)	1/98 (1.0)	5/240 (2.1)	1.06 (-3.63, 3.89)	2.04 (0.24, 17.47)
Mortality by Day 60[e]	16/79 (20.3)	14/141 (9.9)	-10.32 (-21.20, -0.78)	0.45 (0.22, 0.93)	2/96 (2.1)	7/235 (3.0)	0.90 (-4.52, 4.29)	1.44 (0.29, 6.91)

N: sample size associated with the primary endpoint WHO-CPS at Day 28
[a]Sample size corresponds to Day 28 analyses
[b]Percent difference (CI): difference in proportion (anakinra % - placebo %) with 95% confidence interval calculated using Newcombe Hybrid Score
[c]Odds ratio for higher disease severity comparing anakinra to placebo
[d]Hazard ratio for mortality comparing anakinra to placebo
[e]Subjects were excluded from analyses if they were lost to follow-up
Source: Statistical Reviewer

IX. Human Clinical Safety

Anakinra is approved for treatment of rheumatoid arthritis, cryopyrin-associated periodic syndromes (CAPS), and deficiency of interleukin-1 receptor antagonist (DIRA). The recommended dose for treatment of rheumatoid arthritis is 100 mg/day administered daily by subcutaneous injection. The recommended starting dose for treatment of CAPS and DIRA is 1-2 mg/kg daily, and the dose can be individually adjusted to a maximum of 8 mg/kg daily to control active inflammation. The approved

labeling for anakinra includes warnings and precautions for serious infections, decreased neutrophil counts, immunosuppression, and hypersensitivity reactions.

The safety profile of anakinra in the proposed COVID-19 use and dosing regimen is primarily derived from the SAVE-MORE trial. Supportive data sources include the SAVE trial, IMMUNO-101 trial, and postmarketing data on off-label use of anakinra for treatment of COVID-19. The SAVE-MORE, SAVE, and IMMUNO-101 trials are presented in Tables 1 and 2.

Supportive safety data was derived from the following:

1. The ongoing open-label, single-arm SAVE trial to investigate whether the use of anakinra in patients with lower respiratory tract infection due to SARS-CoV-2 and plasma suPAR ≥ 6 ng/mL may prevent the development of severe respiratory failure. Interim safety data up to 14-day follow-up, which included 130 patients, is presented for the EUA request.

2. The phase 2/3, randomized, open-label, parallel-group, 3-arm, multicenter IMMUNO-101 trial to investigate the efficacy and safety of anakinra and emapalumab versus standard of care in reducing hyperinflammation and respiratory distress in patients with SARS-CoV-2 infection. Only 16 patients were randomized due to a premature closure of enrollment in the trial due to evolution in the standard of care during the timeframe of the trial and its critical impact on patient recruitment. Of the 16 patients, 5 patients received treatment with anakinra and 6 patients received SoC.

3. Postmarketing safety data on the off-label use of anakinra for COVID-19 including solicited and spontaneous reports, literature reports, and adverse events reported to the safety database from other Sponsor-supported trials.

Human Exposure

As of May 1, 2021, the estimated exposure to anakinra in Sobi-sponsored clinical trials (encompassing all studied uses but excluding IMMUNO-101) is 6408 patient-years in 8631 patients.

SAVE-MORE

In the SAVE-MORE trial, 606 hospitalized patients with moderate and severe COVID-19 pneumonia and plasma suPAR ≥ 6 ng/mL were randomized 2:1 to subcutaneous treatment with anakinra 100 mg once daily for 10 days or subcutaneous treatment with placebo; 412 patients were allocated to the anakinra + SoC arm, and 194 patients were allocated to the placebo + SoC arm. Following the consent withdrawal from 12 patients, 405 patients received the allocated anakinra + SoC treatment, and 189 patients received the allocated placebo + SoC treatment.

The mean number of administered doses for all patients was 8.6. The mean number of administered doses was similar for both treatment arms (8.7 in the placebo + SoC arm; 8.4 in the anakinra + SoC arm).

Patients enrolled in the SAVE-MORE trial were required to have confirmed infection by SARS-CoV-2, findings on chest X-ray or chest computed tomography compatible with lower respiratory tract infection, need for hospitalization for COVID-19, and plasma suPAR ≥ 6 ng/mL. Patients were excluded for any stage IV malignancy, do-not-resuscitate decision, partial oxygen pressure to fraction of inspired oxygen ratio < 150 mmHg (irrespective if the patient is under mechanical ventilation, non-invasive ventilation, extracorporeal membrane oxygenation or not), less than 1500 neutrophils/mm^3, plasma sUPAR < 6 ng/mL, oral or intravenous intake of corticosteroids at a daily dose ≥ 0.4 mg/kg prednisone for a period greater than the 15 days, anticytokine biological treatment in the last month, severe hepatic failure (defined as Child-Pugh stage 3), or end-stage renal failure necessitating hemofiltration or peritoneal hemodialysis.

(b) (4)

SAVE

The SAVE trial interim analysis was based on 130 anakinra-treated patients and 130 propensity score matched I SoC comparators (hospitalized in the same time period at different departments). According to the study protocol, the treatment duration was up to 10 days. Exposure data are not available for the purpose of this submission.

Enrolled patients were hospitalized adults with confirmed SARS-CoV-2 infection by real-time PCR of nasopharyngeal secretions, radiological findings compatible with lower respiratory tract infection, and plasma suPAR level ≥ 6 µg/L. Exclusion criteria were: any stage IV malignancy, do-not-resuscitate decision, ratio of partial oxygen pressure to the fraction of inspired oxygen < 150 mmHg, need for mechanical ventilation or non-invasive ventilation under positive pressure, any primary immunodeficiency, neutropenia (< 1500/mm^3), intake of corticosteroids at a daily dose ≥ 0.4 mg/kg prednisone or equivalent the last 15 days, anticytokine biological treatment in the last month, and pregnancy or lactation.

(b) (4)

IMMUNO-101

A total of 16 patients completed screening and were enrolled in the trial. Five patients received treatment emapalumab, 5 patients received treatment with anakinra, and 6 patients received SoC.

A total of 5 patients were treated with anakinra in the IMMUNO-101 trial, with a mean (SD) daily dose of 391.9 (8.7) mg for a mean (SD) duration of 15.8 (0.4) days.

Enrolled patients were hospitalized adults with confirmed SARS-CoV-2 infection, presence of respiratory distress (defined as PaO2/FiO2 < 300 mmHg and > 200 mmHg, or respiratory rate ≥ 30 breaths per minute, or SpO2 < 93% on room air; patients given continuous positive airway pressure ventilator support were eligible for inclusion), and presence of hyperinflammation (defined as lymphocyte counts < 1000 cells/μL in patients who have not received systemic glucocorticoids for at least 2 days prior to assessment, < 1200 cells/μL in patients who have received systemic glucocorticoids for at least 2 days prior to assessment, and one of the following: ferritin > 500 ng/mL, LDH > 300 U/L, or D-Dimers > 1000 ng/mL). Exclusion criteria were: mechanical ventilation or modified early warning score > 4 with evidence of moderate or above ARDS, impairment of cardiac function, severe renal dysfunction (eGFR ≤ 30 or receive continuous renal replacement therapy, hemodialysis, or peritoneal dialysis), uncontrolled hypertension (systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg), administration of plasma from convalescent patients who recovered from SARS-CoV-2 infection, clinical suspicion of latent tuberculosis, history of hypersensitivity or allergy to any component of the study drug, pregnancy, existence of life-threatening comorbidity, liver dysfunction (defined as AST or ALT > 5 x ULN), or clinical suspicion of active mycobacteria, histoplasma capsulatum, herpes zoster, salmonella, or shigella infections.

(b) (4)

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Safety Overview and Summary

SAVE-MORE

All adverse events (AEs) in the SAVE-MORE trial were recorded from the first dose of study medication, through the 10-day treatment period, and up to the Day 90 follow-up.

Safety Overview

As shown in Table 9, the overall incidence of treatment emergent AEs (TEAEs) was similar in patients in the anakinra + SoC group (343 patients, 84.7%) compared to patients in the placebo + SoC group (161 patients, 85.2%). The proportion of patients with treatment-related TEAEs, serious TEAEs, TEAEs leading to study drug discontinuation, and TEAEs leading to death was slightly lower in the anakinra + SoC group.

Table 8. Overview of treatment-emergent adverse events reported in the SAVE-MORE trial (safety set)

	Placebo + SoC (N = 189) n (%)	Anakinra + SoC (N = 405) n (%)	Percent Difference (95% CI)
Any TEAE	161 (85.2)	343 (84.7)	0.5 (-6.1, 6.3)
Treatment-related TEAE	64 (33.9)	121 (29.9)	4.0 (-3.9, 12.2)
Serious TEAE	41 (21.7)	66 (16.3)	5.4 (-1.2, 12.6)
TEAE → study drug D/C	2 (1.1)	3 (0.7)	0.3 (-1.3, 3.1)
TEAE → death	17 (9.0)	18 (4.4)	4.5 (0.4, 9.7)

Source: SAVE-MORE CSR, Table 14.3.1, Table 14.3.2.1, Table 14.3.2.2. % difference and 95% CI were calculated by the review team.
Abbreviations: CI, Confidence interval; CSR, Clinical study report; D/C, Discontinuation; n, Number of patients with the event; N, Number of patients; SoC, Standard of care; TEAE, treatment-emergent adverse event

Common Adverse Events

The summary of most frequently reported TEAEs experienced by > 5% of patients is presented in Table 10. The TEAEs occurring more frequently in the anakinra + SoC group compared to the placebo + SoC group were transaminases increased, gamma-glutamyltransferase increased, hypernatremia, constipation, hyperkalemia, anxiety, acute kidney injury, and hypothermia. Of these events, transaminases increased and gamma-glutamyltransferase increased are expected with anakinra treatment as per the Kineret USPI. The TEAEs reported in the majority of patients were otherwise suggestive of advanced COVID-19 and its complications, along with worsening of patients' comorbid conditions.

Table 9. Treatment-emergent adverse events occurring in > 5% and more frequently in the anakinra group in the SAVE-MORE trial

	Placebo + SoC (N = 189) n (%)	Anakinra + SoC (N = 405) n (%)	Percent Difference (95% CI)
Transaminases increased	52 (27.5)	125 (30.8)	-3.4 (-10.8, 4.7)
GGT increased	22 (11.7)	56 (13.8)	-2.2 (-7.5, 4.0)
Hypernatremia	15 (7.9)	39 (9.6)	-1.7 (-6.2, 3.7)
Constipation	14 (7.4)	37 (9.1)	-1.7 (-6.1, 3.5)
Hyperkalemia	14 (7.4)	37 (9.1)	-1.7 (-6.1, 3.5)
Anxiety	12 (6.3)	33 (8.1)	-1.8 (-5.9, 3.2)
Acute kidney injury	10 (5.2)	26 (6.3)	-1.1 (-4.8, 3.5)

Hypothermia	8 (4.2)	30 (7.4)	-3.2 (-6.8, 1.3)

Source: SAVE-MORE CSR, Table 14.3.1. % difference and 95% CI were calculated by the review team.
Abbreviations: AE, Adverse event; CI, Confidence interval; CSR, Clinical study report; GGT, Gamma-glutamyltransferase; n, Number of patients with the event; N, Number of patients; SoC, Standard of Care

The majority of TEAEs were considered mild (Grade 1) or moderate (Grade 2) in severity. Overall, the Grade 3 severity TEAEs were few and balanced between the 2 treatment groups. Severe TEAEs occurring more frequently (by more than 2 patients) in the anakinra + SoC group compared to the placebo + SoC group were hyperglycemia (14 patients or 3.5% in the anakinra + SoC group vs 5 patients or 2.5% in the placebo + SoC group), gamma-glutamyltransferase increased (7 patients or 1.2% in the anakinra + SoC group vs 1 patient or 1.1% in the placebo + SoC group), hypernatremia (5 patients or 1.2% in the anakinra + SoC group vs 2 patients or 1.1% in the placebo + SoC group), and hyperkalemia (5 patients or 1.2% in the anakinra + SoC group vs 1 patient or 0.5% in the placebo + SoC group).

Overall, few TEAEs were considered related to study treatment. Related TEAEs of transaminases increased (53 patients or 13.1% in the anakinra + SoC group vs 20 patients or 10.6% in the placebo + SoC group), leukopenia (6 patients or 1.5% in the anakinra + SoC group vs 1 patient or 0.5% in the placebo + SoC group), neutropenia (6 patients or 1.5% in the anakinra + SoC group vs 0 patients in the placebo + SoC group), and injection site reaction (2 patients or 1.1% in the anakinra + SoC group vs 0 patients in the placebo + SoC group) were observed more frequently in the anakinra + SoC group compared to the placebo + SoC group. Related TEAEs of anemia, lymphopenia, and pneumonia were observed more frequently in the placebo + SoC group.

Serious Adverse Events

Serious TEAEs were reported in 107 (18.0%) patients overall, including 41 (21.7%) patients who received placebo + SoC and 66 (16.3%) patients who received anakinra + SoC. The most frequently reported serious TEAEs are presented in table 11.

Table 10. Most common serious treatment-emergent adverse events (safety set)

	Placebo + SoC (N = 189) n (%)	**Anakinra + SoC (N = 405) n (%)**	**Percent Difference (95% CI)**
At least one serious TEAE	41 (21.7)	66 (16.3)	5.4 (-1.2, 12.6)
Type of serious TEAE			
Infections and infestations	31 (16.4)	37 (9.1)	7.3 (1.7, 13.7)
Bacteremia	6 (3.2)	11 (2.8)	0.5 (-2.2, 4.2)
Nosocomial infection	7 (3.7)	10 (2.5)	1.2 (-1.5, 5.1)
Pneumonia	16 (8.5)	14 (3.5)	5.0 (1.1, 10.1)
Septic shock	7 (3.7)	6 (1.5)	2.2 (-0.3, 6.0)
Vascular disorders	4 (2.1)	9 (2.2)	-0.1 (-2.4, 3.3)
Pulmonary embolism	4 (2.1)	6 (1.5)	0.6 (-1.5, 3.9)

Source: SAVE-MORE CSR Table 14.3.2.2. % difference and 95% CI were calculated by the review team.

Abbreviations: CI, Confidence interval; n, Number of patients with the event; N, Number of patients; SoC, Standard of care; TEAE, Treatment-emergent adverse event

Serious infections occurred less frequently in the anakinra + SoC group (9.1%) than the placebo + SoC group (16.4%). The events within the infections and infestations SOC occurring at a higher frequency in the anakinra + SoC group compared to the placebo + SoC group were single cases of hepatitis B and skin and skin structure infection; all of which were considered unrelated by the investigator.

Overall, there were few treatment-related serious TEAEs in the two treatment groups as shown in Table 12. All treatment-related serious TEAEs reported in the anakinra + SoC group occurred in 1 patient each. In the placebo + SoC group, 2 patients reported treatment-related serious TEAEs of pneumonia; all other treatment-related serious TEAEs occurred in 1 patient each.

Table 11. Treatment-related serious treatment-emergent adverse events (Safety set)

	Placebo + SoC (N = 189) n (%)	**Anakinra + SoC (N = 405) n (%)**
Pneumonia	2 (1.1)	1 (0.2)
Nosocomial infection	1 (0.5)	1 (0.2)
Pyelonephritis acute	1 (0.5)	1 (0.2)
Transaminases increased	1 (0.5)	1 (0.2)
Septic shock	1 (0.5)	1 (0.2)
Neutropenia	0	1 (0.3)
Hepatitis B	0	1 (0.2)
GGT increased	0	1 (0.3)
Acute kidney injury	0	1 (0.3)
Hypernatremia	1 (0.5)	0

Source: SAVE-MORE CSR Table 14.3.2.2
Abbreviations: GGT, Gamma-glutamyltransferase increased; n, Number of patients with the event; N, Number of patients; SoC, Standard of care

Deaths

Forty one of 567 patients (7.2%) experienced an endpoint of death by Day 90; 19 (10.6%) patients received treatment with placebo + SoC, and 22 (5.7%) received treatment with anakinra + SoC. All deaths but one were considered by the investigator to be not related to study drug administration, and due to COVID-19 progression and complications and/or the patient's comorbidities.

A total of 35 (5.9%) patients in the trial had a serious AE (SAE) with an outcome of death up to 90 days; 17 (9.0%) patients received placebo + SoC and 18 (4.4%) patients received anakinra + SoC. Deaths were mostly attributed to SOC infections and infestations, either pneumonia (COVID-19 or bacterial superinfection), bacteremia, or septic shock.

Table 12. Serious treatment-emergent adverse events with an outcome of death by preferred term (safety set)

	Placebo + SoC (N = 189) n (%)	Anakinra + SoC (N = 405) n (%)
Patients with TEAE → death	17 (9.0)	18 (4.4)
Septic shock	7 (3.7)	6 (1.5)
Pneumonia	9 (4.7)	5 (1.2)
Bacteremia	2 (1.1)	4 (1.0)
Nosocomial infection	3 (1.6)	4 (1.0)
Pneumomediastinum	1 (0.5)	2 (0.5)
Pneumothorax	2 (1.1)	1 (0.2)
Acute kidney injury	0	2 (0.5)
Abdominal infection	0	1 (0.2)
Arterial thrombosis	0	1 (0.2)
Pyelonephritis acute	0	1 (0.2)
Thrombocytopenia	1 (0.5)	0
Subcutaneous emphysema	1 (0.5)	0
Transaminases increased	1 (0.5)	0
Creatine phosphokinase increased	1 (0.5)	0
Cardiac arrest	1 (0.5)	0
Hypernatremia	1 (0.5)	0
Lung empyema	1 (0.5)	0
Pulmonary embolism	1 (0.5)	0
Hemorrhagic diathesis	1 (0.5)	0
Candidemia	1 (0.5)	0

Source: SAVE-MORE Listing 16.2.7.2
Abbreviations: n, Number of patients with the event; N, Number of patients; SoC, Standard of care; TEAE, Treatment-emergent adverse event

Discontinuations due to Adverse Events

The percentage of patients where the study drug was stopped due to leukopenia (1 patient in the placebo + SoC group and 1 patient in the anakinra + SoC group) or due to increase of aminotransferase (1 patient in the placebo + SoC group and 2 patients in the anakinra + SoC group) was low and comparable between the 2 groups of treatment. No leukopenia events were reported as serious. Of the transaminases increased events, 3 (0.3%) were reported as serious in the anakinra + SoC group compared with 2 (0.5%) in the placebo + SoC group. The transaminase increase events were considered serious because they resulted in hospitalization or prolongation of hospitalization. No increases in hepatic enzymes were associated with clinical consequences such as drug-induced livery injury or non-infectious hepatitis.

Laboratory Findings

Laboratory measurements at Day 1 (baseline), Day 4, and Day 7 were reported for complete blood cell counting, biochemistry, and coagulation laboratory tests. The white blood cell count, neutrophil count, and lymphocyte count increased in both treatment groups from Day 1 to Day 7; however, these values were higher in the

placebo + SoC group. There were no imbalances in transaminase elevation > 3 x baseline. There were no events of drug-induced liver injury or Hy's law.

Table 13. Laboratory values

	Placebo + SoC	Anakinra + SoC
Total WBC (cells/mm^3)		
Day 1 (Baseline)		
N	184	392
Median (IQR)	5910 (4045)	5980 (3902.5)
Day 7		
N	172	381
Median (IQR)	8560 (4355)	7900 (3850)
Neutrophil count (cells/mm^3)		
Day 1 (Baseline)		
N	184	392
Median (IQR)	4780 (3657)	4535 (3857)
Day 7		
N	172	381
Median (IQR)	6620 (4860)	5785 (3950)
Lymphocyte count (cells/mm^3)		
Day 1 (Baseline)		
N	184	392
Median (IQR)	730 (552.5)	815 (540)
Day 7		
N	172	381
Median (IQR)	1200 (1020)	1330 (1120)

Source: SAVE-MORE Table 14.3.4.2
Abbreviations: IQR, Interquartile range; N, Number of patients; SoC, Standard of care; WBC, White blood cells

SAVE

The SAVE trial is an open-label trial with no comparison arm. However, the Requester provided propensity score matched patients receiving SoC treatment hospitalized during the same time period as a comparator to the 130 patients receiving anakinra + SoC. Given the rapidly evolving pace of treatment paradigms and access for COVID-19, there are limitations to using an external control in this setting and as such, these comparisons should be interpreted with caution.

TEAEs were collected from baseline up to 14 days of follow-up. The TEAEs are shown in table 15. The number of patients experiencing at least 1 TEAE was similar in the SoC comparators (68.5%) compared to the anakinra + SoC group (65.4%). The TEAEs occurring at a numerically higher proportion of patients in the anakinra + SoC group were gastrointestinal disturbances (11.5% vs 6.9%), leukopenia (8.5% vs 2.3%), thrombocytopenia (6.9% vs 5.4%), and headache (3.1% vs 1.5%). Of these events, leukopenia, thrombocytopenia, and headache are expected with anakinra treatment; however, these are also observed in COVID-19 infected patients.

Table 14. Treatment-emergent adverse events reported in the SAVE trial

	Propensity Score Matched SoC	Anakinra + SoC

	(N = 130) n (%)	(N = 130) n (%)
At least 1 TEAE by Day 14	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)
Thrombocytopenia	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)

Source: Kyriazopoulou et al 2021
Abbreviations: n, Number of patients with the event; N, Number of patients; TEAE, Treatment-emergent adverse event; SoC, Standard of care.

Serious Adverse Events

Serious TEAEs during the 14 days of follow-up are presented in Table 16. The number of patients experiencing at least 1 serious TEAE by Day 14 was higher in the SoC comparator group (48.5%) compared to the anakinra + SoC group (24.6%). The majority of serious TEAEs occurred at a higher rate in the SoC comparator group compared to the anakinra + SoC group with the exception of pulmonary edema, which occurred in 1 patient in the anakinra + SoC group.

Table 15. Serious TEAEs reported in the SAVE trial

	Propensity Score Matched SoC (N = 130) n (%)	Anakinra + SoC (N = 130) n (%)
At least 1 serious TEAE by Day 14	63 (48.5)	32 (24.6)
Extended hospitalization	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	1 (0.8)

Source: Kyriazopoulou et al 2021
Abbreviations: n, Number of patients with the event; N, Number of patients; SoC, Standard of care; TEAE, Treatment-emergent adverse event

Deaths

The proportion of all deaths in the anakinra + SoC group was lower than in the comparator group (4.6% vs 12.3% in the comparator group).

IMMUNO-101

Two patients (40.0%) in the anakinra + SoC group and 1 patient (16.7%) in the SoC group experienced TEAEs. Treatment-related (b) (6)

(b) (6)

Severe TEAEs were reported in 1 patient (20%) in the anakinra + SoC group and no patients in the SoC group. (b) (6) . The serious TEAE was not considered related to study drug.

One patient (20%) in the anakinra + SoC group experienced a TEAE (respiratory failure) leading to withdrawal of study drug compared to no patients in the SoC group.

(b) (6) . No patients in the SoC group experienced a fatal TEAE. The fatal TEAE was not considered related to study drug.

No severe TEAEs or serious TEAEs related to laboratory parameters were reported. (b) (6) The event was moderate in severity and considered related to the SoC treatment.

Postmarketing Safety Data

A total of 661 valid case reports for off-label use of anakinra for COVID-19 were received up to a data-lock period of October 31, 2021. Safety assessment was conducted on 1088 AEs from the 661 case reports. Off-label dosing of anakinra ranged from 1 mg up to 2400 mg every 6 hours. Out of the 1088 AEs, 364 AEs (33%) were serious and 724 AEs (67%) were non-serious. Event causality was reported as suspected in 67 events (6%), non-suspected (or no reasonable probability) in 314 events (29%), and not reported in 707 events (65%).

Within the global safety database, a total of 114 case reports with a fatal outcome were received through the data-lock period of October 31, 2021. Anakinra dosing ranged from 100 mg up to 600 mg every 6 hours. Review of fatal case reports showed that 73% of the population were elderly (mean age: 71 years and median age: 72 years). The most frequently reported fatal AE preferred terms (> 5) were death with cause unknown (14 events; 11.6% of all fatal AEs), multiple organ dysfunction syndrome (14 events; 11.6% of all fatal AEs), respiratory failure (11 events; 9.1% of all fatal AEs), acute respiratory distress syndrome (11 events; 9.1% of all fatal AEs), and septic shock (6 events; 5.0% of all fatal AEs).

X. Specific Populations

Pediatric Use

As of October 31, 2021, a total of 122 case reports with anakinra use were received for patients < 18 years of age. The age groups were reported as: neonate (n = 4; 2 of 4 involved exposure during pregnancy); infant (n = 10); child (n = 76); adolescent (n = 32). Of the 122 cases, 103 case reports involved off-label use with no AE. Of the events of off-label use, 95 events were coded with an unknown outcome.

Review of safety data in patients < 18 years showed the most frequent events were administration site reactions which are expected with any administration or injection procedure and listed for anakinra. The remaining events showed no trends and were most likely due to COVID-19 infection or concurrent clinical or background condition. The safety profile observed in pediatric patients was consistent with that observed in adult patients treated with anakinra for COVID-19 infection; and previous experience in approved pediatric anakinra indications.

The SAVE-MORE trial was conducted in adult patients with COVID-19 pneumonia with plasma suPAR ≥ 6 ng/mL and no PK data have been assessed in this trial. The role of suPAR is unclear in pediatric COVID patients. It is not clear if a similar suPAR high patient population could be identified in pediatric patients. In addition, since the suPAR assay is not commercially available in the United States, an alternative patient identification method (SCORE 2) was recommended to select patients most likely to have suPAR ≥ 6 ng/mL based on commonly measured patient characteristics. However, some of the patient characteristics may not be applicable to pediatric patients, such as age≥75 years, smoking history, and medical history of ischemic stroke. Therefore, the use of KINERET in pediatric patients (2 years of age and older) with COVID-19 pneumonia is not recommended.

Geriatric Use

In a placebo-controlled study in COVID-19 patients, 250/594 (42%) were 65 years of age and older (Anakinra 172/405, placebo 78/189). No differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly. Anakinra is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function.

According to the Kineret (anakinra) USPI, a total of 752 rheumatoid arthritis patients ≥ 65 years of age, including 163 patients ≥ 75 years of age, were studied in clinical trials. No differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treated the elderly.

Pregnancy

The use of anakinra in pregnant patients was not explicitly studied for COVID-19. According to the Kineret (anakinra) USPI, available data from retrospective studies and case reports on anakinra use in pregnant women are insufficient to identify a drug associated risk of major birth defects, miscarriage, and fetal adverse events. In animal reproduction studies, subcutaneous administration of anakinra to pregnant rats and rabbits during organogenesis demonstrated no evidence of fetal harm at doses up to 25 times the maximum recommended human dose (MRHD). The Sponsor notes 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.

Lactation

The use of anakinra in lactating women was not explicitly studied for COVID-19. According to the Kineret (anakinra) USPI, there are no data on the presence of anakinra in either human or animal milk or the effects on milk production. Available published data from a small retrospective study and postmarketing case reports do not establish an association between maternal anakinra use during lactation and adverse effects on breastfed infants. The limited clinical data during lactation precludes a clear determination of the risk of anakinra to an infant during lactation. Therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for anakinra, and any potential adverse effects on the breastfed infant from anakinra or from the underlying medical condition.

Renal Insufficiency

The use of anakinra in patients with renal insufficiency was not explicitly studied for COVID-19. Anakinra is known to be substantially excreted by the kidneys, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. According to the Kineret (anakinra) USPI, physicians should consider administration of the prescribed dose every other day for patients who have severe renal insufficiency or end stage renal disease (defined as creatinine clearance < 30 mL/min, as estimated from serum creatinine levels).

Hepatic Insufficiency

The use of anakinra in patients with hepatic insufficiency was not explicitly studied for COVID-19. According to the Kineret (anakinra) USPI, no formal studies have been conducted to examine the pharmacokinetics of anakinra administered subcutaneously in patients with hepatic impairment.

XI. Human Clinical Pharmacology

- Pharmacokinetics

  The PK of anakinra is not available in patients with COVID-19 in the EUA. The following PK information of anakinra is from the approved Kineret (anakinra) USPI under BLA103950:

  - The absolute bioavailability of KINERET after a 70 mg SC bolus injection in healthy subjects (n = 11) is 95%. In subjects with RA, maximum plasma concentrations of KINERET occurred 3 to 7 hours after SC administration of KINERET at clinically relevant doses (1 to 2 mg/kg; n = 18); the terminal half-life ranged from 4 to 6 hours. In RA patients, no unexpected accumulation of KINERET was observed after daily SC doses for up to 24 weeks.

  - The influence of demographic covariates on the pharmacokinetics of KINERET was studied using population pharmacokinetic analysis encompassing 341 patients receiving daily SC injection of KINERET at doses of 30, 75, and 150 mg for up to 24 weeks. The estimated KINERET clearance increased with increasing creatinine clearance and body weight. After adjusting for creatinine clearance and body weight, gender and age were not significant factors for mean plasma clearance.

  - In NOMID patients, at a median SC dose of 3 mg/kg once daily and a median treatment time of 3.5 years, the median (range) steady-state serum exposure of anakinra was Cmax 3628 (655–8511) ng/mL (n=16) and C24h 203 (53–1979) ng/mL (n=16). The median (range) half-life of anakinra was 5.7 (3.1–28.2) hours (n=12). There was no obvious gender difference.

- Immunogenicity

  The immunogenicity of anakinra has not been assessed in patients with COVID-19 in the EUA. The following information of anakinra is from the approved Kineret (anakinra) USPI under BLA103950:

  - Adult patients with RA: As with all therapeutic proteins, there is potential for immunogenicity. In Studies 1 and 4, from which data is available for up to 36 months, 49% of patients tested positive for anti-anakinra binding antibodies at one or more time points using a biosensor assay. Of the 1615 patients with available data at Week 12 or later, 30 (2%) tested positive for neutralizing antibodies in a cell-based bioassay. Of the 13 patients with available follow-up data, 5 patients remained positive for neutralizing antibodies at the end of the studies. No correlation between antibody development and adverse events was observed.

- NOMID: The immunogenicity of KINERET in NOMID patients was not evaluated.

- Drug-drug interaction

  KINERET is a therapeutic protein, consisting of 153 amino acids, and has a molecular weight of 17.3 kilodaltons. Per the approved Kineret (anakinra) USPI, “no drug-drug interaction studies in human subjects have been conducted. Toxicologic and toxicokinetic studies in rats did not demonstrate any alterations in the clearance or toxicologic profile of either methotrexate or KINERET when the two agents were administered together.” There is unlikely a drug-drug interaction between anakinra and any coadministered medications for treatment of COVID-19, such as remdesivir, corticosteroids, and others.

- Renal Impairment:

  Per the approved Kineret (anakinra) USPI, “the mean plasma clearance of KINERET in subjects with mild (creatinine clearance 50-80 mL/min) and moderate (creatinine clearance 30-49 mL/min) renal insufficiency was reduced by 16% and 50%, respectively. In severe renal insufficiency and end stage renal disease (creatinine clearance < 30 mL/min1), mean plasma clearance declined by 70% and 75%, respectively. Less than 2.5% of the administered dose of KINERET was removed by hemodialysis or continuous ambulatory peritoneal dialysis. Based on these observations, a dose schedule change should be considered for subjects with severe renal insufficiency or end stage renal disease”. It was recommended that physicians should consider administration of the prescribed KINERET dose every other day for patients who have severe renal insufficiency or end stage renal disease (defined as creatinine clearance < 30 mL/min, as estimated from serum creatinine levels).

  In SAVE-MORE trial, patients with end-stage renal failure necessitating hemofiltration or peritoneal hemodialysis were excluded. The proposed dosage adjustment in the EUA that “*physicians should consider a dose of 100 mg of KINERET administered every other day for COVID-19 patients who have severe renal insufficiency or end stage renal disease (defined as creatinine clearance < 30 mL/min, as estimated from serum creatinine levels)”* is reasonable and consistent with the approved KINERET label. To be explicit about the duration of treatment in COVID-19, the recommendation for patients with renal impairment in the final fact sheet is *“Consider administration of KINERET 100 mg every other day by subcutaneous injection for a total of 5 doses over 10 days in patients who have severe renal insufficiency or end stage renal disease (defined as creatinine clearance < 30 mL/min, as estimated from serum creatinine levels) [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]”.*

- Hepatic impairment:

Per the approved Kineret (anakinra) USPI, “no formal studies have been conducted examining the pharmacokinetics of KINERET administered subcutaneously in patients with hepatic impairment” and no dosage adjustment is recommended in patients with hepatic impairment.

Therefore, the proposed no dosage adjustment in patients with hepatic impairment in the EUA is reasonable.

- Pediatric patients

(b) (4)

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(b) (4)

XII. Nonclinical Data to Support Safety

- Nonclinical studies with anakinra were previously reviewed under BLA 103950 to support the approval of KINERET® (dated in DARRTS November 13, 2000; authored by Dr. Anne M. Pilaro) and the investigation of the impact of anakinra on neonatal/juvenile learning and memory (dated in DARRTS December 16, 2020; authored by Dr. Jessica A. Bonzo).

- Pharmacokinetics (PK), toxicokinetic (TK), absorption, distribution, metabolism, and excretion (ADME) for anakinra were assessed in rats, rabbits, and monkeys. Serum concentration levels and exposures for subcutaneous (SC) administration were comparable to intravenous (IV) administration in all species. The mean bioavailability for SC administration in rats was 75% to 100%. Anakinra was detected in cerebrospinal fluid (CSF) from rat pups given 200 mg/kg/day, SC for 6 weeks. Anakinra appears to be cleared by glomerular filtration in the kidney, followed by subsequent metabolism in the kidney tubules. The elimination half-life for SC administration was 1-3 hours. No sex differences were apparent in animals. A substantial accumulation (up to 48-fold) of plasma anakinra concentration was noted in rats after SC administration of 2, 20, and 200 mg/kg/day anakinra starting from Day 15 to Week 26. The accumulation in monkeys was not substantial (< 1-fold) after SC administration of 10, 100, and 200 mg/kg/day anakinra up to 1 month. Anti-anakinra antibody was detected in rats and monkeys after 2-4 weeks of treatment but diminished over time and did not appear to be neutralizing.

- Treatment with anakinra was well-tolerated in rats and monkeys by either SC or IV injection. In both species, drug-related local toxicity was noted at the injection sites as mild to moderate, gross and histologic evidence of dose-related inflammation, hemorrhage, and fibrosis. No systemic toxicity was noted in rats (up to 120 mg/kg/day, SC for 14 days; 30 mg/kg/day, IV for 14 days) or monkeys (up to 200 mg/kg/day, SC for 1 month). In rats given anakinra up to 200 mg/kg/day, SC for 6 months, drug-related systemic toxicity was noted in kidney (increased kidney weights, proteinuria, and chronic progressive nephropathy) at all levels with unknown clinical relevance. Both local (injection site) and systemic findings were reversible on discontinuation of drug treatment.

- Anakinra had no effects on fertility and early development, embryo-fetal development, or perinatal and postnatal development at doses up to 200 mg/kg/day in rats or rabbits.

- Anakinra up to 200 mg/kg/day, SC for 6 weeks did not affect juvenile rats' learning and memory.

- The nonclinical data provides coverage for the use anakinra as an SC injection for the treatment of COVID-19 in hospitalized adults at 100 mg/day.

XIII. Nonclinical Data to Support Efficacy

- IL-1α and IL-1β are potent pro-inflammatory cytokines. Upon the SARS-CoV-2 infection, IL-1α is released from virally infected lung epithelial cells undergoing pyroptosis. Together with other danger-associated molecular patterns (DAMPs), IL-1α recruits neutrophils and monocytes to the site of infection and induces IL-1β in monocyte/macrophages. This, in turn, will induce more IL-1 that will recruit and

activate more innate immune cells. Therefore, blocking IL-1 Receptor (IL-1R) is believed to help block the autoinflammation loop.

- Anakinra is a recombinant IL-1 Receptor antagonist (IL-1Ra) approved in US for the treatment of Rheumatoid Arthritis (RA), Neonatal-Onset Multisystem Inflammatory Disease (NOMID), and Deficiency of IL-1Ra (DIRA). It competitively inhibits the binding of IL-1 (IL-1α and IL-1β) to IL-1RI (100-fold selective *vs* IL-1RII), thereby blocking many IL-1 -mediated biological activities such as proliferation of C3H/HeJ mouse thymocytes, synthesis of prostaglandin E2 by human foreskin fibroblasts, and biological responses in human synovial cells and rabbit articular chondrocytes in vitro.

- The sponsor did not submit relevant animal studies showing the effectiveness of anakinra in the context of SARS-CoV-2 infection. SEE ATTACHED ADDENDUM [redacted].[6]

XIV. Supply Information

- Quantity of drug product needed for one treatment course per individual for proposed EUA use (adults)

- Patients will receive a single treatment course (consisting of Anakinra 100 mg subcutaneous daily for 10-days) for the proposed EUA use.

- At this time, there is no known shortage of anakinra supply.

- The dose of anakinra drug product proposed for treatment of COVID-19 is 100 mg daily for 10-days. An increase in the demand for anakinra drug product has been accounted for by the Sponsor. A new anakinra drug product manufacturing site at (b) (4) was recently approved. This expansion in anakinra drug product manufacturing was designed to meet the projected increase in demand.

XV. Chemistry, Manufacturing, and Controls Information

- This EUA will utilize licensed commercial anakinra (tradename: Kineret) at its approved dosage and route of administration. Anakinra drug substance is

[6] Renieris G, Karakike E, Xu Z, Gkavogianni T, Droggiti D, Schubert K, et al. IL-1α mediates tissue-specific inflammation and severe respiratory failure in COVID-19: clinical and experimental evidence. medRxiv. 2021;2021.04.09.21255190; doi: https://doi.org/10.1101/2021.04.09.21255190.

manufactured at two approved facilities located in [redacted]. Anakinra drug product is also manufactured at two approved facilities located in [redacted]. The increase in Kineret demand caused by the EUA was forecasted by the Sponsor, and the dual sourcing for anakinra drug substance and product is claimed to prevent any supply issues. There are no product quality concerns.

- There is no change from the approved product and each prefilled single use glass syringe for subcutaneous injection contains:
  - 100 mg anakinra
  - 1.29 mg citric acid
  - 5.48 mg sodium chloride
  - 0.12 mg disodium ethylenediaminetetraacetic acid (EDTA), dihydrate
  - 0.70 mg polysorbate 80
  - Water for injection

XVI. Manufacturing Site Inspections

Table 16 Manufacturing Sites

FDA Establishment Identifier	Drug Substances/ Drug Product/ Testing/Labeler/ Packager	Location	Associated NDA, BLA, or IND	Commercial Sponsor/ Applicant	Inspection Dates	GMP Status
[redacted]	[redacted]	[redacted]	BLA-103950	Swedish Orphan Biovitrum AB (Sobi)	Inspection Waived	Compliant
[redacted]	[redacted]	[redacted]	BLA-103950	Swedish Orphan Biovitrum AB (Sobi)	Not Applicable	Compliant

(b) (4)			
BLA-103950	Swedish Orphan Biovitrum AB (Sobi)	Inspection Waived	Compliant
BLA-103950	Swedish Orphan Biovitrum AB (Sobi)	Not Applicable	Compliant
BLA-103950	Swedish Orphan Biovitrum AB (Sobi)	Not Applicable	Compliant
BLA-103950	Swedish Orphan Biovitrum AB (Sobi)	Not Applicable	Compliant
BLA-103950	Swedish Orphan Biovitrum AB (Sobi)	Not Applicable	Compliant
BLA-103950	Swedish Orphan Biovitrum AB (Sobi)	Inspection Waived	Compliant
BLA-103950	Swedish Orphan Biovitrum AB (Sobi)	Inspection Waived	Compliant
BLA-103950	Swedish Orphan Biovitrum AB (Sobi)	Not Applicable	Compliant
BLA-103950	Swedish Orphan Biovitrum AB (Sobi)	Not Applicable	Compliant

Based on FDA's evaluation of the manufacturing process and control strategy, and the listed facilities, FDA considers the following condition(s) to the authorization as necessary to protect the public health[1]:

- SOBI will manufacture Kineret (anakinra) 100 mg/0.67 mL solution in a single-use prefilled syringe for subcutaneous injection to meet all quality standards and per the manufacturing process and control strategy as detailed in SOBI's EUA request. SOBI will not implement any changes to the description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy that assure process performance and quality of the authorized product, without notification to and concurrence by the Agency as described under

condition D.

- All manufacturing, packaging, and testing sites for both drug substance and drug product will comply with current good manufacturing practice requirements of the Federal Food, Drug, and Cosmetic Act Section 501(a)(2)(B).

- SOBI will submit information to the Agency within three working days of receipt concerning significant quality problems with drug product distributed under this emergency use authorization for Kineret (anakinra) 100 mg/ 0.67 mL pre-filled syringe that includes the following:

    - Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article; or

    - Information concerning any microbiological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet established specifications.

If a significant quality problem affects unreleased product and may also impact product(s) previously released and distributed, then information. should be submitted for all potentially impacted lots. SOBI will include in its notification to the Agency whether the batch, or batches, in question will be recalled.

If not included in its initial notification, SOBI must submit information confirming that SOBI has identified the root cause of the significant quality problems, taken corrective action, and provide a justification confirming that the corrective action is appropriate and effective. SOBI must submit this information as soon as possible but no later than 45 calendar days from the initial notification."

[1] See the evaluation documented in OMQ's EUA Recommendation Memo in CMS Case# 642274, OPMA's Product Quality Microbiology/Facility Assessment Memo associated with EUA 000109, and OBP's Chemistry, Manufacturing, and Controls Assessment Memo associated with EUA 000109 all dated (TBD)

XVII. Clinical Trial Site Inspections

No site inspections were performed or deemed necessary for the COVID-19 study supporting this request.

XVIII. Animal Study Site Inspections (Efficacy and PK/PD)

No site inspections were performed or deemed necessary.

XIX. Recommendations From Treatment Guidelines and Other Sources

As of September 26, 2022, the NIH COVID-19 Treatment Guidelines patients hospitalized due to COVID-19 are as follows:

Patient Disposition	Clinical Scenario	Recommendation for Antiviral or Immunomodulator	Recommendation for Anticoagulant Therapy
Hospitalized but does not require supplemental oxygen	All patients	Panel recommends against the use of dexamethasone or other systemic corticosteroids[b]	For patients without an indication for therapeutic anticoagulation: prophylactic dose of heparin unless contraindicated (AI); (BIII) for pregnant patients
	Patients who are at high risk of progressing to severe COVID-19[a]	Remdesivir[c] (BIII)	
Hospitalized and requires oxygen supplementation (not HFNC, NIV, MV, or ECMO)	Patients who require minimal oxygen	Remdesivir[e] (BIIa)	For nonpregnant patients with D-dimer levels above the ULN who do not have an increased bleeding risk: therapeutic dose of heparin[g] (CIIa) For other patients: prophylactic dose of heparin unless contraindicated (AI); (BIII) for pregnant patients
	Most patients	Use dexamethasone plus remdesivir[e] (BIIa). If remdesivir cannot be obtained, use dexamethasone (BI)	
	Patients who are receiving dexamethasone and have rapidly increasing oxygen needs and systemic inflammation	Add PO baricitinib[f] or IV tocilizumab[f] to 1 of the options above (BIIa)	
Hospitalized and requires HFNC oxygen or NIV	Most patients	Promptly start 1 of the following if not already initiated: dexamethasone plus PO baricitinib[f] (AI), or dexamethasone plus IV tocilizumab[f] (BIIa) If baricitinib, tofacitinib, tocilizumab, or sarilumab cannot be obtained: dexamethasone[h] (AI) Add remdesivir to 1 of the options above in certain patients[i] (CIIa)	For patients without an indication for therapeutic anticoagulation: prophylactic dose of heparin unless contraindicated (AI); (BIII) for pregnant patients For patients who are started on a therapeutic dose of heparin in a non-ICU setting and then transferred to the ICU, the Panel recommends switching to a

Patient Disposition	Clinical Scenario	Recommendation for Antiviral or Immunomodulator	Recommendation for Anticoagulant Therapy
			prophylactic dose of heparin unless there is another indication for therapeutic anticoagulation (BIII)
Hospitalized and requires MV or ECMO	Most patients	Promptly start 1 of the following if not already initiated: dexamethasone plus PO baricitinib[f] (AI), or dexamethasone plus IV tocilizumab[f] (BIIa) If baricitinib, tofacitinib, tocilizumab, or sarilumab cannot be obtained: dexamethasone[h] (AI)	For patients without an indication for therapeutic anticoagulation: prophylactic dose of heparin unless contraindicated (AI); (BIII) for pregnant patients For patients who are started on a therapeutic dose of heparin in a non-ICU setting and then transferred to the ICU, the Panel recommends switching to a prophylactic dose of heparin unless there is another indication for therapeutic anticoagulation (BIII)

Rating of recommendations: A = Strong; B = Moderate; C = Weak
Rating of evidence: 1 = one or more randomized trials without major limitations; IIa = other randomized trials or subgroup analyses of randomized trials; IIb = nonrandomized trials or observational cohort studies; III = expert opinion

Abbreviations: ECMO, Extracorporeal membrane oxygenation; HFNC, High-flow nasal cannula; ICU, Intensive care unit; IV, Intravenous; MV, Mechanical ventilation; NIV, Non-invasive ventilation; PO, Per os (oral administration); ULN, Upper limit of normal

A – for risk factors associated with higher risk of severe COVID, see the CDC webpage
B – corticosteroids that are prescribed for an underlying condition should be continued
C – evidence suggests that the benefit of remdesivir is greatest when the drug is given early in the course of COVID-19 (e.g., within 10 days of symptom onset)
D – conventional oxygen refers to oxygen that is not HFNC, NIV, MV, or ECMO
E – if these patients progress to requiring HFNC oxygen, NIV, MV, or ECMO, the full course of remdesivir should still be completed
F – if PO baricitinib and IV tocilizumab are not available or not feasible to use, PO tofacitinib can be used instead of PO baricitinib (BIIa) and IV sarilumab ca be used instead of IV tocilizumab (BIIa)

G – contraindications for the use of therapeutic anticoagulation in patients with COVID-19 include a platelet count < 50 x 10^9/L, Hgb < 8 g/dL, the need for dual antiplatelet therapy, bleeding within the past 30 days that required an ED visit or hospitalization, a history of bleeding disorder, or an inherited or active acquired bleeding disorder
H – if a JAK inhibitor or an anti-IL-6 receptor monoclonal antibody is not readily available, start dexamethasone while waiting for the additional immunomodulator to be acquired. If neither of the other immunomodulators can be obtained, use dexamethasone alone.
I – clinicians may consider adding remdesivir to 1 of the recommended immunomodulator combinations in patients who require HFNC oxygen or NIV, including immunocompromised patients. The Panel recommends against the use of remdesivir without immunomodulators in these patients (AIIa)

XX. Risk-Benefit Assessment and Recommendations for Emergency Use

The effectiveness and safety of anakinra in adult patients with COVID-19 infection was evaluated in the SAVE-MORE trial. This was a multicenter, prospective, randomized, double-blind, placebo-controlled phase 3 clinical trial comparing anakinra dosed with background standard of care (SOC, i.e., remdesivir and dexamethasone) to placebo with background standard of care.

Patients in the SAVE-MORE trial were selected based on a biomarker cut-off, suPAR ≥ 6 ng/mL, intending to enrich the trial with patients at risk for progression to severe respiratory failure. At this time, suPAR is not an established measure to predict whether COVID-19 patients will progress to severe respiratory failure. In addition, the suPAR test is not commercially available in the United States.

The anakinra + SOC arm had lower odds compared to the placebo + SOC arm for more severe disease (higher score) in the primary endpoint of WHO-CPS distribution at Day 28. The mortality risk by Day 28 and Day 60 was lower in the anakinra + SOC arm compared to placebo + SOC. The risk for severe respiratory failure by Day 28 was lower in the anakinra + SOC arm compared to placebo + SOC. Subgroup analyses of the primary endpoint using a univariate analysis and by baseline remdesivir use, baseline dexamethasone use, and disease severity at screening showed lower odds for more severe disease in the anakinra + SOC arm compared to placebo + SOC.

An assessment of other randomized (either to placebo or SoC) studies of IL-1 inhibitor therapies including anakinra did not provide reliable efficacy results to either support or refute the SAVE-MORE study efficacy results. However, the review team notes that none of these studies have selected/enriched for patients based on criteria used in the SAVE-MORE study. Further, the other studies of IL-1 inhibitor therapies including anakinra had limitations in their study designs, e.g., open label, SoC controlled, non-concurrent randomization, and small sample sizes, that eluded consistent evidence for anakinra efficacy.

The overall incidence of treatment emergent AEs (TEAEs) was similar in patients in the anakinra + SoC arm (343 patients, 84.7%) compared to patients in the placebo +

SoC arm (161 patients, 85.2%). The proportion of patients with treatment-related TEAEs, serious TEAEs, TEAEs leading to study drug discontinuation, and TEAEs leading to death was slightly lower in the anakinra + SoC arm.

Based on the efficacy and safety information available, it is reasonable to believe that anakinra may be effective for the treatment of COVID-19 in hospitalized adults with positive results of direct SARS-CoV-2 viral testing with pneumonia requiring supplemental oxygen (low or high-flow oxygen) who are at risk of progressing to severe respiratory failure and are likely to have an elevated suPAR, as defined by the enrichment strategy used in SAVE-MORE, and that the potential benefits of anakinra outweigh its known and potential risks for this population. Therefore, the review Division recommends issuance of an EUA for anakinra for the treatment of COVID-19 in hospitalized adults with positive results of direct SARS-CoV-2 viral testing with pneumonia requiring supplemental oxygen (low or high-flow oxygen) who are at risk of progressing to severe respiratory failure and are likely to have an elevated suPAR, as detailed in the Fact Sheet.

Since the suPAR test is not commercially available in the United States, alternative scores were developed to identify the suPAR ≥ 6 population, patients who would be considered to be more at risk for progressing to respiratory failure. These alternative scores used a combination of clinical characteristics and laboratory data. Of the alternative scores that were developed, SCORE 2 was identified by the review team as having the most optimal performance metrics.

XXI. Considerations for Adverse Event (AE) Monitoring

This product will either be used in clinical trials or in clinical practice.

If used in clinical trials done under IND, FDA IND safety reporting regulations will apply. In the setting of a pandemic where practicing physicians will have many

competing priorities, adverse event reporting under this EUA will be streamlined through the MEDWATCH system.

The prescribing health care provider and/or the provider's designee will be responsible for reporting medication errors and adverse events (death, serious adverse events) considered to be potentially related to anakinra occurring during anakinra treatment within 7 calendar days from the onset of the event. The reports should include unique identifiers and the words "Anakinra Treatment under Emergency Use Authorization (EUA)."

XXII. Mandatory and Discretionary Requirements for Use of the Product Under the EUA

The suPAR lab test is not currently available in the United States. To identify patients who would benefit from use of anakinra and better validate the correlation between suPAR and the alternative identification method (SCORE 2), FDA and the Requester agree to the following post-authorization requirements:

1. Sobi will provide the necessary data and/or information validating the use of the alternative patient identification method to suPAR at baseline in patients with positive direct SARS-CoV-2 viral testing, who are hospitalized, requiring oxygen, with evidence of COVID-19 pneumonia. Sobi will pre-specify the analyses to examine the correlation, sensitivity, specificity, positive predictive value, and negative predictive value, between suPAR and the alternative patient identification method. Sobi must submit a data analysis plan no later than January 31, 2023. Sobi must submit a final analysis report no later than May 31, 2023.
2. Sobi will provide the data and/or information necessary to support the submission of a marketing application under the appropriate regulatory pathway, as determined by the Center for Devices and Radiological Health (CDRH), for a suPAR test for commercial use in the United States. Sobi has agreed to submit a marketing application to CDRH no later than January 31, 2025.

XXIII. Information to Be Conveyed to Health Care Providers and Recipients of the Product

Sobi will make available the authorized Fact Sheet for Health Care Providers (See Section XXVI. Appendices) and the authorized Fact Sheet for Patients and Caregivers (See Section XXVI. Appendices) through a dedicated website for the EUA covering anakinra at: www.KineretRx.com/Covid19_Update

XXIV. Outstanding Issues/Data Gaps

Refer to Section XXII, Mandatory and Discretionary Requirements for Use of the Product Under the EUA.

XXV. References

References are listed as footnotes in the relevant sections of the review, where applicable.

XXVI. Appendices

Pre-EUA Communications

A pre-EUA meeting was held with the Sponsor on September 15, 2021.

FDA provided the following notable feedback to the Sponsor:

- We recommend that your EUA request contain the source data to aid in the efficacy of the EUA review. You should work with the investigators to provide the raw patient data in the appropriate format.

- We note that the core clinical data you have proposed to support the EUA request are derived from a randomized controlled trial, SAVE-MORE, that selected patients based on a certain cut-off of a biomarker, suPAR (soluble urokinase plasminogen activator receptor). We note that this biomarker and the cut-off selected for the eligibility criteria are not widely accepted or available to define a clinically relevant patient population.

- While evidence provided from this trial upon review by the Agency may be sufficient to support the issuance of an EUA, it may not be sufficient to support approval of a supplemental BLA (sBLA). As stated in FDA's guidance entitled Emergency Use Authorization of Medical Products and Related Authorities (January 2017), an EUA is not a substitute for sponsor efforts to develop the product toward approval, including conducting clinical trials designed to determine whether the product is safe and effective for its intended use. Should an EUA be issued for your product, FDA will regularly assess the circumstances and appropriateness of the EUA, which will include its assessment of your progress toward submission of an sBLA.

- We have concerns that an EUA might compromise the ability to obtain timely and reliable results from ongoing or future studies that are critical to support a sBLA. In that light, you should consider how issuance of an EUA would ultimately fit into your overall development program, including a sBLA submission.

- In your EUA request, provide additional clarity on the baseline disposition of subjects who were screened and were not eligible to be randomized in the trial due to not meeting the suPAR eligibility criterion. Submit a table reflecting the breakdown of screened patients by WHO Clinical Progression Scale score and the number/percentage of patients in each category who were then randomized and not randomized in the trial. As you state that the suPAR test is not available as a diagnostic test in the US, we recommend that the eligibility criteria for future confirmatory trials does not include a criterion utilizing the suPAR test.

EUA Communications

An information request was sent to the Sponsor on May 11, 2022:

- We continue to note the difficulty of identifying an appropriate patient population in the absence of the suPAR test being commercially available in the United States. We also note that there are significant uncertainties with attempting to define a patient population based on post-hoc analyses. Given these considerations, we strongly recommend that you evaluate a path forward to develop suPAR as a companion diagnostic to identify patients who are most likely to benefit from treatment with anakinra.

- If you are unable to do so, we recommend that you investigate whether there are other combinations of clinical characteristics and/or laboratory tests that reliably identify the suPAR ≥ 6 population. You have suggested to use the SCOPE score instead of suPAR; however, we note that the SCOPE score had limited overlap with suPAR ≥ 6 patients, which suggests that the SCOPE score does not identify the same patients at risk for progression to severe respiratory failure.

- We would like to evaluate how the SCOPE score, or other methods can reliably predict patients' suPAR level to define the patient population where the benefit of anakinra can be expected and that can be adequately described, should an EUA be issued. For example, we recommend that you consider examining the individual components of the SCOPE score in alternative ways (e.g., provide the correlations for each component with suPAR and consider a score that uses the continuous scale of the components).

- In addition, we request that you submit datasets that contain the following baseline information for all subjects screened in SAVE-MORE and SAVE Study (including both suPAR greater than or less than 6 ng/mL).

An information request was sent to the Requester on July 20, 2022:

- We developed an alternative scoring rule (SCORE 2) in which patients must meet at least 3 of the following 8 criteria:

    - SOFA score ≥ 3
    - Smoking history (active or past)
    - Blood hemoglobin ≤ 10.5 g/dL
    - Medical history of ischemic stroke
    - Severe disease by WHO criteria
    - Age ≥ 75 years
    - Blood urea ≥ 50 mg/dL and/or medical history of chronic renal disease
    - Neutrophil-to-lymphocyte (NLR) ratio ≥ 7

- Conduct analyses to compare anakinra to control in the subgroup of patients who met both suPAR ≥ 6 ng/mL and "SCORE 2" ≥ 3 by analyzing the endpoints of WHO-CPS at Day 28 using the proportional odds model and mortality at Day 28, and mortality at Day 60 using the multivariate Cox proportional hazard model adjusting for variables used in stratified randomization. For mortality at Day 28 and mortality at Day 60, provide the unadjusted difference in proportion with 95% confidence interval calculated using the Newcombe Hybrid Score. Repeat the analyses for the subgroup of patients who met suPAR ≥ 6 ng/mL and "SCORE 2" < 3.

An information request was sent to the Requester on September 9, 2022:

- We note that an EUA is not a long-term alternative to approval, and issuance of an EUA is not an appropriate endpoint for new product development. Should an EUA be issued for your product, the statute requires FDA to periodically assess the appropriateness and circumstances of authorization, which includes our assessment of the progress being made toward the submission of a marketing application for the authorized use of the product under EUA. If you are not actively working to advance product development, FDA may reconsider the EUA status and may revoke the EUA.

- To have additional support for the authorization, we are considering the following as potential post-authorization requirements should your request be authorized:

- As the studies supporting the use of anakinra in COVID-19 were based on enrollment of patients with elevated suPAR, we continue to recommend you strongly consider development of suPAR for commercial use within the US to best inform prescribers in the selection of patients under the EUA. We recommend you engage with FDA CDRH on development of suPAR for commercial use within the US.

- As part of our review, we have attempted to find an alternate way to identify patient who would have elevated suPAR. At that time, we are considering at set of clinical and laboratory criteria (SCORE 2) to identify patients who would have elevated suPAR. Should your request be authorized, we would request a study in COVID-19 patients who are hospitalized, requiring oxygen, with evidence of COVID-19 pneumonia, and at risk of progressing to severe respiratory failure. This additional study should not be restricted to the suPAR high population. This study should collect suPAR and SCORE 2 at baseline and pre-specify analyses to examine the correlation, sensitivity, specificity, PPV, and NPV between suPAR and Score 2. To make the study further informative, patients may also be followed for the outcome of severe respiratory failure. Analyses should be pre-specified to assess suPAR and SCORE 2 as prognostic markers of progression to severe respiratory failure. The analyses of suPAR and SCORE 2 can be reported after baseline characteristics have been collected, and analyses on respiratory failure can be reported after completion of patient follow-up.

- In order to support a sBLA, it is likely you will need additional clinical data. We recommend a study in COVID-19+ patients who are hospitalized, requiring oxygen, with evidence of COVID19 pneumonia, and at risk to progress to severe respiratory failure. This additional study should not be restricted to the suPAR high population. This should be a randomized, double-blind, controlled trial of anakinra with appropriate access to standard of care. Outcomes of interest should include progression to severe respiratory failure and mortality. Baseline information to be collected should include suPAR and SCORE2.

The Requester responded to the September 9, 2022 IR comments as follows:

- Sobi agreed to collaborate with the manufacturer of the suPAR test, Virogates, and to engage with FDA CDRH to explore pathways for the development of the suPAR test for commercial use within the US. Sobi and Virogates expect that a pre-submission meeting with CDRH can be made within 5 months following issuance of an EUA.

- Sobi agreed to the post-EUA requirement to evaluate SCORE 2 as a substitute for identifying patients with suPAR ≥ 6 ng/mL, and if possible, to analyze the association of both methods with the risk to progress to severe respiratory failure. SEE ATTACHED ADDENDUM .

- To meet this commitment, Sobi proposed to use final data from the SAVE study to evaluate the correlation between suPAR and SCORE2 based on baseline characteristics, and to assess suPAR and SCORE2 as prognostic markers of progression to severe respiratory failure.

SAVE-MORE Study

Table 17. Number and percentage of patients by WHO-CPS and timepoints, SAVE-MORE

	SoC + Placebo n (%)					SoC + Anakinra n (%)				
	Baseline N=189	Day 14 N=189	Day 28 N=189	Day 60 N=183	Day 90 N=179	Baseline N=405	Day 14 N=405	Day 28 N=405	Day 60 N=392	Day 90 N=388
WHO-CPS=0		8 (4.2)	50 (26.5)	93 (50.8)	115 (64.2)		25 (6.2)	204 (50.4)	280 (71.4)	304 (78.4)
WHO-CPS=1		17 (9.0)	6 (3.2)	4 (2.2)	2 (1.1)		82 (20.2)	40 (9.9)	7 (1.8)	2 (0.5)
WHO-CPS=2		70 (37.0)	74 (39.2)	51 (27.9)	34 (19.0)		139 (34.3)	93 (23.0)	70 (17.9)	50 (12.9)
WHO-CPS=3		21 (11.1)	21 (11.1)	9 (4.9)	4 (2.2)		35 (8.6)	25 (6.2)	10 (2.6)	8 (2.1)
WHO-CPS=4	12 (6.3)	17 (9.0)	3 (1.6)	1 (0.5)	3 (1.7)	39 (9.6)	42 (10.4)	9 (2.2)	1 (0.3)	1 (0.3)
WHO-CPS=5	162 (85.7)	29 (15.3)	10 (5.3)	4 (2.2)	1 (0.6)	341 (84.2)	55 (13.6)	8 (2.0)	1 (0.3)	0 (0)

WHO-CPS=6	15 (7.9)	4 (2.1)	1 (0.5)	0 (0)	0 (0)	25 (6.2)	5 (1.2)	1 (0.2)	0 (0)	0 (0)
WHO-CPS=7		4 (2.1)	1 (0.5)	1 (0.5)	1 (0.6)		2 (0.5)	1 (0.2)	0 (0)	1 (0.3)
WHO-CPS=8		8 (4.2)	4 (2.1)	1 (0.5)	0 (0)		11 (2.7)	5 (1.2)	0 (0)	0 (0)
WHO-CPS=9		7 (3.7)	6 (3.2)	1 (0.5)	0 (0)		9 (2.2)	6 (1.5)	2 (0.5)	0 (0)
WHO-CPS=10		4 (2.1)	13 (6.9)	18 (9.8)	19 (10.6)		0 (0)	13 (3.2)	21 (5.4)	22 (5.7)

Abbreviations: n, number of subjects with score; N, total number of patients; WHO-CPS, World Health Organization-Clinical Progression Scale; %, n/N
Day 14, Day 28, Day 60, Day 90 tabulations assumed the one patient lost to follow-up by Day 14 had score 0
Day 60 and Day 90 tabulations excluded patients lost to follow-up
Source: Requester response, dated February 10, 2022, to FDA information request

OCP Appendices (Technical documents supporting OCP recommendations) - MACHINE LEARNING REVIEW

EXECUTIVE SUMMARY

The requester is seeking emergency use authorization (EUA) of anakinra, an interleukin 1 (IL-1) receptor inhibitor, for the treatment of COVID-19 in hospitalized patients with pneumonia requiring supplemental oxygen (low or high-flow oxygen) who are at risk of progressing to severe respiratory failure. The primary evidence to support the authorization request is from the SAVE-MORE trial, which is a randomized, double-blinded clinical trial in hospitalized patients with soluble urokinase plasminogen activator receptor (suPAR) ≥ 6 ng/mL at baseline. At this time, the suPAR test is not commercially available in the United States. It is unclear if the results seen in the SAVE-MORE trial can be generalized to the broader scope of the EUA as proposed by the Requester (i.e., a population defined regardless of suPAR level). In order to identify a comparable population as in the SAVE-MORE trial, the review team worked with the Requester to explore ways to select patients most likely to have suPAR ≥ 6 ng/mL based on commonly measured patient characteristics, as recommended by the medical policy and program review committee (MPPRC) in a meeting held on May 4, 2022.

We found that a combination of multiple commonly measured patient characteristics can be used to reasonably identify patients with suPAR ≥ 6 ng/mL. We developed a scoring rule, named “SCORE 2”, to identify patients with suPAR ≥ 6 ng/mL. SCORE 2 includes considerations of the following:

1. age ≥75 years,
2. severe pneumonia by WHO criteria,
3. current/previous smoking status,
4. Sequential Organ Failure Assessment (SOFA) score ≥3,
5. NLR≥7,
6. hemoglobin ≤10.5 g/dl,
7. medical history of ischemic stroke, and
8. blood urea ≥50 mg/dl and/or medical history of renal disease

Patients meeting at least three of these eight criteria will be considered positive for SCORE2 and highly likely to have suPAR ≥ 6 ng/mL. We recommend using SCORE 2 to identify patients that should be treated with anakinra because of its predictive performance for identifying patients with suPAR ≥ 6 ng/mL (high positive predictive value and high specificity) and biological plausibility (including inflammation/immune related marker, neutrophil to lymphocyte ratio). In addition, SCORE 2 positive patients appear to be associated with higher risk to develop severe respiratory failure (SRF). With the capability to identify the patients to be treated with anakinra, we recommend that the EUA be issued for the treatment of COVID-19 in hospitalized adults with positive results of direct SARS-CoV-2 viral testing with pneumonia requiring supplemental oxygen (low or high-flow oxygen) who are at risk of progressing to severe respiratory failure and are likely to have an elevated suPAR.

METHOD AND RESULTS

Objectives

The objective for this analysis is to search for an alternative score based on commonly measured patient characteristics to identify patients with suPAR ≥ 6 ng/mL.

Datasets

Both SAVE-MORE and SAVE trials used suPAR ≥ 6 ng/mL as an inclusion criterion for patient enrollment. Hospitalized COVID-19 patients were recruited and screened. Alternative scores were developed based on patients (N=837) with measurement at screening from SAVE-MORE trial (training dataset). The developed alternative scores were externally validated using patients (N=336) with information collected at screening from SAVE trial (external validation dataset) (Table 18). A total of 30 patient characteristics, such as SOFA score, age, WHO severity, blood hemoglobin, blood urea, neutrophil absolute count, and lymphocyte absolute count, were available from each patient at screening, allowing subsequent score development and evaluation.

Table 18: Sample Size in Training and External Validation Datasets

Dataset	Trial	Total N	suPAR ≥ 6 ng/mL	suPAR < 6 ng/mL
Training Dataset	SAVE-MORE trial	837	569	268
Validation Dataset	SAVE trial	336	254	82

Source: Machine Learning Reviewer Analysis

SCORE *Development*

Two alternative scores, SURROGATE (from the requester) and SCORE 2 (from the FDA review team), have been developed and assessed (Table 19).

Table 19: Overview of Candidate Scores

SURROGATE (2 out of 8)	Score 2 (3 out of 8)
SOFA score ≥ 3	SOFA score ≥ 3
Smoking history (active or past)	Smoking history (active or past)
Blood hemoglobin ≤ 10.5 g/dL	Blood hemoglobin ≤ 10.5 g/dL
Medical history of ischemic stroke	Medical history of ischemic stroke
Severe disease by WHO criteria	Severe disease by WHO criteria
Age ≥ 75 years	Age ≥ 75 years
Blood Urea ≥ 50 mg/dL	Blood Urea ≥ 50 mg/dL and/or Medical history of chronic Renal disease
Medical history of chronic Renal disease	
*SOFA: Sequential Organ Failure Assessment	**Neutrophil-to-lymphocyte ratio (NLR)>=7

*Note: SURROGATE is developed by the requester. SCORE2 is developed by the review team as an improvement of SURROGATE. Patients meeting at least two of the eight listed criteria under SURROGATE will be considered positive for SURROGATE. Patients meeting at least three of the eight listed criteria under SCORE 2 will be considered positive for SCORE2.
Source: Machine Learning Reviewer Analysis

Development of SURROGATE Score

The SURROGATE score was developed by the Requester. The requester took a two-stage approach. First, patient features that can be applied to identify suPAR ≥ 6 ng/mL were determined at the feature selection stage. A total of 6 features were determined by forward stepwise logistic regression analysis. In addition, medical history of ischemic stroke and chronic renal disease were added since no patient failing screening had either of these 2 conditions. Next, the selected continuous patient features were dichotomized for easy use in medical practice. Each of the continuous patient features was used to generate a receiver operator characteristics (ROC) curve. Youden index was calculated for each of the coordinate points of the ROC curve. The peak of Youden index was identified and the corresponding value on the patient feature was selected as the cut off to provide the best trade-off between sensitivity and specificity. Based on the performance in SAVE-MORE trial, the requester determined that patients meeting at least 2 out of 8 baseline features are likely to be suPAR high (suPAR ≥ 6 ng/mL) patients.

Development of SCORE 2
SCORE 2 was developed as an improvement from SURROGATE score. The two scores share 6 items in common (SOFA score, smoking history, blood hemoglobin ≤ 10.5 g/dL, medical history of ischemic stroke, age ≥ 75, and severe disease by WHO criteria). In SCORE 2, we combined “blood urea ≥ 50 mg/dL” and “medical history of chronic renal disease” based on the biological relevance. In the SAVE-MORE trial dataset, seven out of nine of patients with history of chronic renal disease had blood urea ≥ 50 mg/deciliter.

The focus of our data analysis was to examine the potential contributions from the rest of the 22 patient baseline variables in identifying patients with suPAR ≥ 6 ng/mL. In addition, FDA review team created and evaluated one additional composite variable (NLR) using 2 of the 22 patient baseline variables (the neutrophil absolute count and lymphocyte absolute count).

A machine learning classification model with elastic net regularization (ref: Regularization and Variable Selection via the Elastic Net) was used to select additional contributing features. A sensitivity analysis of feature importance was conducted via exploring model penalty from 1 to 1000 and different l1_ratio values in sklearn package. The selected number of features increased as the model penalty in elastic net decreased. The potential of patient features being selected by the model with changes in penalty provides the order of feature importance. When the l1_ratio was 0.2 and the penalty was around 250 to 295, only baseline age, SOFA, hemoglobin, and blood urea were selected by the model. Decreased the penalty to 250, the corresponding ML model included 5 variables, adding baseline NLR on top of the existing 4 selected features. Moreover, the finding of NLR as additional contributing feature was robust with different l1_ratio values. The results suggested that baseline NLR is the next important feature.

A neural network-based model was applied to independently assess the importance of baseline NLR and its cut-off value. The neural network-based model is designed to simultaneously maximize sensitivity while maintaining positive predictive value (PPV) larger than or equal to 0.95 in model development. PPV is prioritized at the 0.95 level to ensure that patients selected by the determined score are more closely aligned with those in the SAVE-MORE trial. The cut-off value and the feature importance were assessed through the Gumbel-softmax technique (Ref: Categorical Reparameterization with Gumbel-Softmax). The neural network-based model confirmed that baseline NLR is an important feature, and the appropriate cut-off is around 7.

In summary, both neural network and elastic net regularization produced similar results, which suggested that an additional criterion of NLR ≥7 should be added. This is an inflammation and immune related biomarker. From a biological perspective, addition of this NLR based criterion is reasonable, as suPAR is an inflammation and immune related biomarker and none of the components of SURROGATE is clearly related to inflammation and immune system. This also appears to be a logical addition considering the mechanism of action of anakinra is related to the immune system. The cut-off of NLR, 7, was selected by the AI/ML algorithms. Interestingly, several literature reports suggest

that the optimal cut-off value of NLR in terms of predicting the severity/mortality risk of COVID-19 is around 7, which provides biological plausibility for this criterion (Table 20).

Table 20: References of NLR cut-off values

Reference	Finding	PMID for paper
Önal 2022	Among the geriatric patients with COVID-19 who have high risk for mortality, we found that NLR and LDH levels on admission might be useful prognostic factors. In addition to this, the optimal cut-off values were found as > 7.8 for NLR (83.33% sensitivity, 97.7% specificity and > 300 U/L for LDH (100% sensitivity, 79.31% specificity) regarding the prediction of 30-day mortality.	PMID: 35468761
Asaduzzaman 2022	To date, no cut-off value of the hematological ratio has been defined as optimal in COVID-19. The cut-off values of hemogram derived ratios for the prediction of mortality in this study are 7.57, 5.52, 3.87, 2.26, and 19.68, respectively, for NLR. d-NLR, NPR, PLR, and SII.	PMID: 35686199
Li 2020	Table 2 (cut-off value ≥ 6.5), disease severity prediction	PMID: 33198786

Source: Machine Learning Reviewer Analysis

SCORE Predictive Performance Evaluation

Evaluation Metrics

Based on the analysis objectives, the most critical metrics for evaluating the predictive performance of the selected scores are PPV and specificity. Sensitivity should also be considered as an additional important metric.

PPV, which is prevalence-dependent, is the probability that patients selected by a scoring rule (i.e., score positive) are patients with suPAR≥ 6 ng/mL at baseline. A high PPV is important to ensure that patients selected by a score rule are closely aligned with those enrolled in the SAVE-MORE trial.
Specificity, which is prevalence-independent, is defined as the probability that patients with suPAR < 6 ng/mL at baseline could be identified and rejected by a scoring rule (i.e., score negative). 1- specificity equals to false positive rate. A high specificity (or low false

positive rate) ensures that patients with suPAR<6 ng/mL at baseline are less likely to be selected for anakinra treatment by a defined score.
Sensitivity is the probability that patients with suPAR≥6 ng/mL at baseline could be identified by a scoring rule. High sensitivity is preferable, as low sensitivity means some patients with baseline suPAR ≥ 6 ng/mL may not be identified.

Performance Evaluation with SAVE-MORE Trial

The predictive performance of the two scores was assessed with SAVE-MORE trial data. The results are shown in Table 21.

Table 21: Predictive Performance of SURROGATE Score (A) and SCORE 2 (B) Based on SAVE-MORE Trial Data

SURROGATE	suPAR>=6	suPAR<6	Total
positive, n	356 (**PPV=0.90**,Sensitivity=0.63)	38 (FPR=0.14)	394
negative, n	213	230 (NPV=0.52, **Specificity=0.86**)	443
Total,n	569	268	837

(A)

SCORE 2	suPAR>=6	suPAR<6	Total
positive, n	231 (**PPV=0.95**,**Sensitivity=0.41**)	12 (FPR=0.04)	243
negative, n	338	256 (NPV=0.43, **Specificity=0.96**)	594
Total,n	569	268	837

(B)

Source: Machine Learning Reviewer Analysis

External Validation with SAVE Trial

The predictive performance of the two scores was validated with independent data from SAVE trial. The results are shown in Table 22.

Table 22: External Validation of SURROGATE Score(A) and SCORE 2 (B) by using Data from SAVE Trial

SURROGATE	suPAR>=6	suPAR<6	Total
positive, n	154 (**PPV=0.91,Sensitivity=0.61**)	15 (FPR=0.18)	169
negative, n	100	67 (NPV=0.40, **Specificity=0.82**)	167
Total, n	254	82	336

(A)

SCORE 2	suPAR>=6	suPAR<6	Total
postive, n	95 (**PPV=0.94,Sensitivity=0.37**)	6 (FPR=0.07)	101
negative, n	159	76 (NPV=0.32, **Specificity=0.93**)	235
Total, n	254	82	336

(B)

Source: Machine Learning Reviewer Analysis

Additional Analyses

As suPAR was intended to identify patients at risk for progressing to severe respiratory failure (SRF), the FDA review team used data from the SAVE-MORE trial to conduct an exploratory analysis to evaluate whether SCORE 2 can help identify patients at risk for progressing to SRF. The review team compared the prognosis for score-positive and score-negative subpopulation without anakinra treatment. For this analysis, the review team studied patients receiving only standard-of-care treatment (with or without placebo) during the same time period. This analysis included 421 patients who were screened for eligibility for the SAVE-MORE trial and for whom the 14-day outcome was known. These patients either had suPAR < 6 ng/mL and failed screening (n = 240) or they had suPAR ≥ 6 ng/mL and were enrolled in the SAVE-MORE trial and allocated to SoC + placebo treatment (n =

181). Figure 5 shows the time to progression to SRF by Day 14 for patients who are positive or negative for SCORE 2. Although there are limitations of this exploratory analysis, it appears that SCORE 2 is able to identify patients at risk for progressing to SRF.

CONCLUSION

As the suPAR test is not commercially available in the United States, we recommend the use of SCORE 2 to identify patients with suPAR ≥ 6 ng/mL. Our recommendation is based on the following reasons: (1) SCORE 2 has high PPV and high specificity in both the training and external validation datasets, which suggests that the risk of incorrectly selecting a patient for anakinra treatment is very low; (2) the sensitivity of 0.41 is not ideal, but it is reasonable, considering the fact that if we don't grant this EUA then no patient can benefit from the treatment; (3) As compared to SURROGATE, SCORE 2 includes a criterion which reflects the inflammation and immune status of the patient, which is biologically relevant considering the nature of suPAR and the mechanism of action for the drug; (4) additional analysis suggests that SCORE 2 positive patients appear to be associated with higher risk to develop severe respiratory failure (SRF).

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/s/

CINDY C CHEE
11/08/2022 09:53:50 AM

CAROL M GALVIS
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Xiaochun Chen, PhD, completed the nonclinical sections with my concurrence.

ASHUTOSH V RAO
11/08/2022 09:58:07 AM

QI LIU
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11/08/2022 10:04:03 AM
Sign on behalf of Clinical pharmacology primary reviewer Lei He and Clinical pharmacology team leader Jianmeng Chen.

HAO ZHU
11/08/2022 10:05:48 AM

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11/08/2022 10:13:47 AM
Signing for Van Tran and Rebecca Rothwell

KAREN M HIGGINS
11/08/2022 10:14:48 AM

AUSTIN M ANDERSON
11/08/2022 10:16:04 AM

RAJ NAIR
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JULIE G BEITZ
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RE: Emergency Use Authorization (EUA) for anakinra

Addendum: November 23, 2022

This addendum references the summary EUA review for anakinra, dated 11/8/2022.

Anakinra is authorized for the treatment of hospitalized adults with positive results of direct SARS-CoV-2 viral testing with pneumonia requiring supplemental oxygen (low or high-flow oxygen) who are at risk of progressing to severe respiratory failure and are likely to have an elevated suPAR.

The following amendments should be made to the summary EUA review:

- Page 5 - This statement should be removed because the NDC is inactive and the pack is not available in the US.

- Page 7, second bullet - This statement should be amended to “Physicians should consider administration of the prescribed anakinra dose every other day for NOMID patients who have severe renal insufficiency or end stage renal disease (defined as creatinine clearance < 30 mL/min, as estimated from serum creatinine levels).”

- Page 7, third bullet - This statement should be amended to “Physicians should consider administration of the prescribed anakinra dose every other day for DIRA patients who have severe renal insufficiency or end stage renal disease (defined as creatinine clearance < 30 mL/min, as estimated from serum creatinine levels).”

  Page 42 - The statement should be amended to “peer-reviewed publication” since the Requester submitted a peer-reviewed preference: Renieris G, Karakike E, Gkavogianni T, et al. IL-1 Mediates Tissue-Specific Inflammation and Severe Respiratory Failure in COVID-19 [published online ahead of print, 2022 May 11]. J Innate Immun. 2022;1-14. doi:10.1159/000524560 (submitted in eCTD to FDA in SN 0009).

- Page 55 – The statement should be amended to “Sobi agreed to provide the necessary data and/or information validating the use of the alternative patient identification method to suPAR at baseline in patients with positive direct SARS-CoV-2 viral testing, who are hospitalized, requiring oxygen, with evidence of COVID-19 pneumonia. Sobi will pre-specify the analyses to examine the correlation, sensitivity, specificity, positive predictive value, and negative predictive value, between suPAR and the alternative patient identification method. Sobi must submit a data analysis plan no later than January 31, 2023. Sobi must submit a final analysis report no later than May 31, 2023.”

These corrections replace the errors made in the 11/8/2022 summary EUA review. These corrections do not alter the conclusion of the review or alter the information presented in the authorized Fact Sheets for Healthcare Providers or for Patients, Parents, and Caregivers.

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