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)	12/15/2023
Receipt Date(s)	12/15/2023
OND Division / Office	Division of Rheumatology and Transplant Medicine (DRTM)/Office of Immunology and Inflammation (OII)
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Integrated Review Completion Date	05/09/2024
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

1 EXECUTIVE SUMMARY

On November 8, 2022, the US Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for anakinra for the treatment of coronavirus disease 2019 (COVID-19) in hospitalized adults with positive results of direct severe acute respiratory syndrome-coronavirus 2 (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 (SRF) and likely to have an elevated plasma soluble urokinase plasminogen activator receptor (suPAR).

The clinical efficacy and safety data to support the EUA was primarily based on the SAVE-MORE trial (NCT04680949), a randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of anakinra in adult patients with COVID-19 pneumonia who were at risk of progressing to SRF, defined as a respiratory ratio (partial oxygen pressure/fraction of inspired oxygen) below 150 mmHg necessitating high-flow oxygen, noninvasive ventilation, or mechanical ventilation. All enrolled patients in the SAVE-MORE trial were required to have a suPAR level ≥ 6 ng/mL at baseline. Since suPAR testing is not commercially available in the USA, the FDA review team developed an alternative scoring rule named SCORE2 based on two Artificial Intelligence/Machine Learning approaches using the SAVE-MORE data to identify patients likely to have suPAR ≥ 6 ng/mL at baseline. SCORE2 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. Neutrophil-to-Lymphocyte ratio (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 positive for SCORE2 and considered highly likely to have suPAR ≥ 6 ng/mL. The FDA review team also requested that the EUA Requester submitted interim data from the SAVE trial (an uncontrolled phase 2 study of anakinra in COVID-19 pneumonia) for external validation of SCORE2. SCORE2 demonstrated good performance in both the training (SAVE-MORE trial) and external validation (interim data from SAVE trial) datasets. The development and validation of SCORE 2 were reflected in the Kineret integrated review dated on November 8, 2022.

As a post-authorization requirement, the Requester further validated the predictive performance of SCORE2 using the remain cohort (post interim cohort) from the SAVE study. The objective of this review is to provide assessment for this EUA post-authorization requirement study. The results are summarized as following:

1. SCORE2 demonstrated consistent performance with additional external validation data. 967 patients were included in the post interim analysis of SAVE study. A specificity of 95.1% (95% CI 83.9-98.7%) and Positive Predictive Value (PPV) of 99.6% (95% CI 98.4-99.9%) were observed, which is generally consistent with the specificity (91.5%) and PPV (93.4%) values of SCORE2 from the SAVE study interim analysis. This result is also consistent with the specificity (95.5%) and PPV (95.1%) values of SCORE2 that have been reported from the SAVE-MORE Study. The progression to SRF or death by day 14 was explored by comparing patents with SCORE2 ≥ 3 and patients with SCORE2 < 3. It indicated that SCORE2 ≥ 3 may be predictive of a subgroup of patients who progress to SRF or death, which is also consistent with the findings observed in the SAVE-MORE study.

2. The Requester provided an analysis based on a broader population who are solely defined by suPAR < 6 ng/mL and suPAR ≥ 6 ng/mL, regardless of other inclusion or exclusion criteria or treatment usage. A total number of 266 patients with COVID-19 pneumonia from the national registry of the Hellenic Institute were analyzed. A PPV of 85.3% and sensitivity of 88.7% was observed suggesting the SCORE2 ≥ 3 is still a good marker for suPAR even in this broader population of patients.

Based on the totality of the evidence, SCORE2 is a valid alternative to plasma suPAR for determining a suitable patient population for anakinra for the treatment of COVID-19 under the Emergency Use Authorization.

1.1 Recommendations

The results from the current report provide further validation of the predictive performance of SCORE2 as an alternative to plasma suPAR to determine a suitable patient population for anakinra for the treatment of COVID-19 under the Emergency Use Authorization.

2. Data Sources

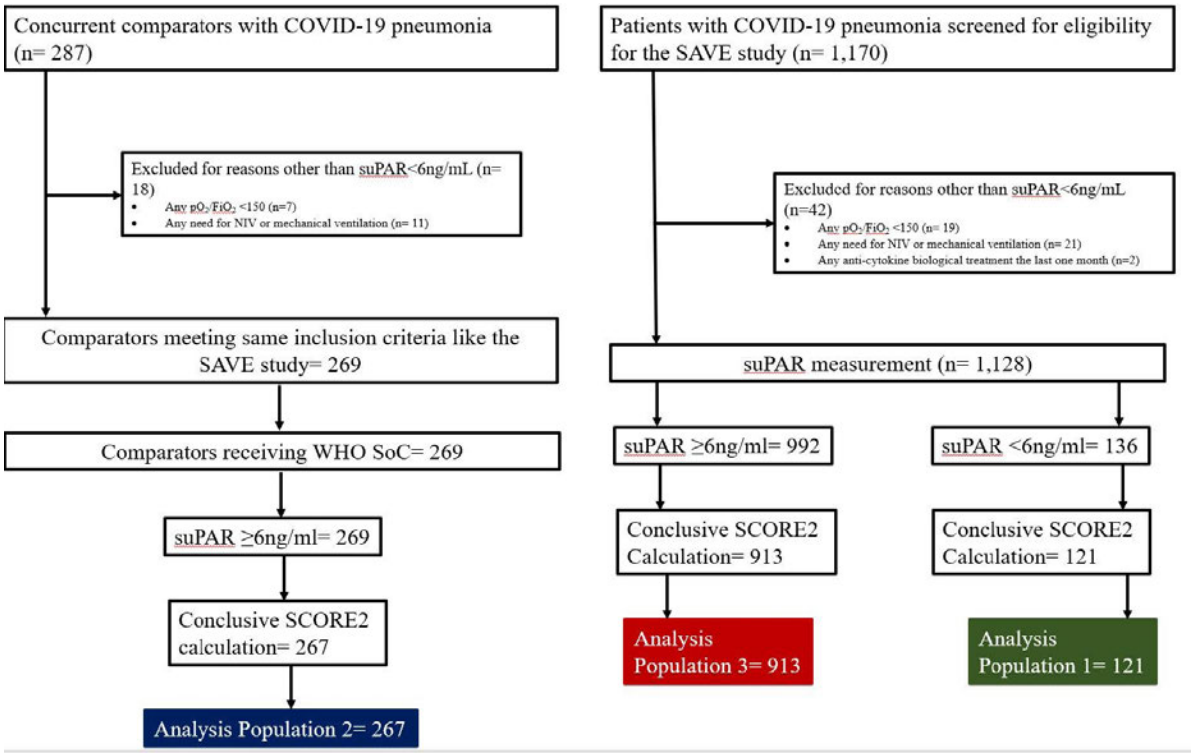
This analysis is conducted based on three patient populations, as described below.

- *Population 1, Patients with suPAR <6 ng/mL (n=136)*. The patients met all other enrollment criteria except their suPAR is less than 6 ng/mL. Note that for the patients to be eligible for suPAR measurements in the screening process they had to have met all inclusion and exclusion criteria beforehand.
- *Population 2, Concurrent comparators with suPAR ≥6 ng/mL (n=269)*. The patients met the same inclusion criteria and had suPAR ≥6 ng/mL, but did not meet any of the exclusion criteria and were treated with the same SoC as the SAVE study participants.
- *Population 3, Patients in the SAVE study with suPAR ≥6 ng/mL (n=992)*. The patients met all inclusion and exclusion criteria and received anakinra treatment.

The analysis includes all patients for whom SCORE2 could be reliably assessed (Figure 1). This means that:

- All patients for which information on all 8 elements was available were included in the analysis.
- All patients with at least 3 positive elements were included in the analysis as SCORE2-Positive, even if other elements were missing.
- All patients with at least 6 negative elements were included in the analysis as SCORE2- Negative, even if other elements were missing.

In total, calculation of SCORE2 was determinable in 1301 patients and indeterminable in 91 patients. The baseline characteristics of the elements of SCORE2 for each of the three patient populations are presented in Table 1.



Note: All patients in this flow chart had COVID-19 pneumonia, i.e., positive radiological findings in chest X-ray or chest computed tomography and positive PCR of the nasopharyngeal swab for SARS-CoV-2.
Abbreviations – MV: mechanical ventilation; n: number of patients; NIV: non-invasive ventilation; pO_2/FiO_2: ratio of partial oxygen pressure to the fraction of inspired oxygen; SoC: standard-of-care; suPAR, soluble urokinase plasminogen activator receptor; WHO: World Health Organization
Source: Requester Data analysis report Version 2.0 Figure 1

Figure 1 Analysis flow chart

Characteristic	suPAR <6 ng/mL (Population 1) N=121	Concurrent comparators with suPAR ≥6 ng/mL (Population 2) N=267	Participants in the SAVE study with suPAR ≥6 ng/mL (Population 3) N=913
Age in years, mean (SD)	51.5 (13.5) (n = 121)	64.3 (14.3) (n = 267)	61.8 (13.5) (n = 898)
Age ≥75 years, m/n (%)	4/121 (3.3)	67/267 (25.1)	166/898 (18.2)
Severe by WHO classification, m/n (%)	58/121 (47.9)	168/267 (62.9)	711/913 (77.9)
SOFA score, mean (SD)	1.24 (1.06) (n =121)	2.63 (1.99) (n = 267)	2.20 (1.16) (n = 913)
SOFA ≥3, m/n (%)	11/121 (9.1)	118/266 (44.4)	348/913 (38.1)
Past or current smoker, m/n (%)	9/121 (7.4)	93/267 (34.8)	254/913 (27.8)
Absolute neutrophil count, /mm^3, mean (SD)	4342.3 (2801.5) (n = 99)	5438.4 (3257.5) (n = 263)	5306.7 (3014.7) (n = 744)
Absolute lymphocyte count, /mm^3, mean (SD)	1320.5 (607.8) (n = 99)	1014.9 (498.4) (n = 263)	1021.5 (592.2) (n = 744)
Neutrophil/lymphocyte ratio ≥7, m/n (%)	16/99 (13.2)	89/263 (33.8)	241/744 (26.4)
Hemoglobin, g/dL, mean (SD)	13.88 (1.60) (n = 105)	12.91 (1.94) (n = 261)	13.34 (1.63) (n = 880)
Hemoglobin ≤10,5 g/dl, m/n (%)	2/105 (1.9)	29/261 (11.1)	38/880 (4.3)
Urea, mg/dL, mean (SD)	36.1 (21.4) (n = 108)	58.2 (75.8) (n = 266)	40.9 (19.5) (n = 892
Urea ≥50mg/dL, m/n (%)	9/108 (8.3)	82/266 (30.7)	199/892 (21.8)
History of renal disease, m/n (%)	7/121 (5.8)	20/267 (7.5)	25/913 (2.3)
History of stroke, m/n (%)	0/121 (0)	18/267 (6.7)	26/913 (2.8)

Note: m represents the number of patients with the characteristic; n represents the number of patients with data available for each characteristic; N represents the total number of patients in the analysis population.

Source: Requester Data analysis report Version 2.0 Table 1

Table 1: Baseline characteristics of the analyzed patient populations

3. Evaluation of Sensitivity, specificity, PPV, and Negative Predictive Value (NPV)

The data from SAVE study were split into subgroups of data included in the interim and new data after the interim. The evaluation of data and its subgroups were provided in Table 2 and Table 3.

	suPAR ≥6 ng/mL,n	**suPAR <6 ng/mL, n**	**Total, n**	**Predictive values [95% CI]**
SCORE2 ≥ 3, n	541	9	550	PPV = 98.4% [96.9-99.1%]
SCORE2 <3, n	639	112	751	NPV = 14.9% [12.5-17.6%]
Total, n	1180	121	1301	
True rates [95% CI]	Sensitivity = 45.9% [43.0-48.7%]	Specificity = 92.6% [86.5-96.0%]		

CI: confidence interval; n: number of patients.
Source: Requester Data analysis report Version 2.0 Table 2

Table 2: Sensitivity, specificity, PPV, and NPV of SCORE2 ⩾3 to predict suPAR ⩾6 ng/mL

	suPAR ≥6 ng/mL,n	**suPAR <6 ng/mL, n**	**Total, n**
Data analysis including only new patients, post SAVE study interim analysis			
SCORE2 ≥ 3, n	442 Sensitivity= 47.8% (95% CI 44.5-50.9%) **PPV= 99.6%** **(95% CI 98.4-99.9%)**	2	444
SCORE2 <3, n	484	39 **Specificity= 95.1%** **(95% CI 83.9-98.7)** NPV= 7.5% (95% CI 5.5-10.0%)	523
Total	926	41	967
Data analysis of the prior validation including only patients from the SAVE study interim analysis			
SCORE2 ≥ 3, n	99 Sensitivity= 38.9% (95% CI 33.2-45.1%) PPV= 93.4% (95% CI 87.0-96.8%)	7	106

SCORE2 <3, n	155	73 Specificity= 91.5% (95% CI 83.0-95.7%) NPV= 32.0% (95% CI 26.3-38.3%)	228
Total, n	254	80	334

CI: confidence interval; n: number of patients
Source: Requester Responses to FDA Information Request of November 13, 2023 Table 1

Table 3: Sensitivity, specificity, PPV, and NPV of SCORE2 ≥3 to predict suPAR ⩾6 ng/mL for patients in SAVE study: Subgroup analysis.

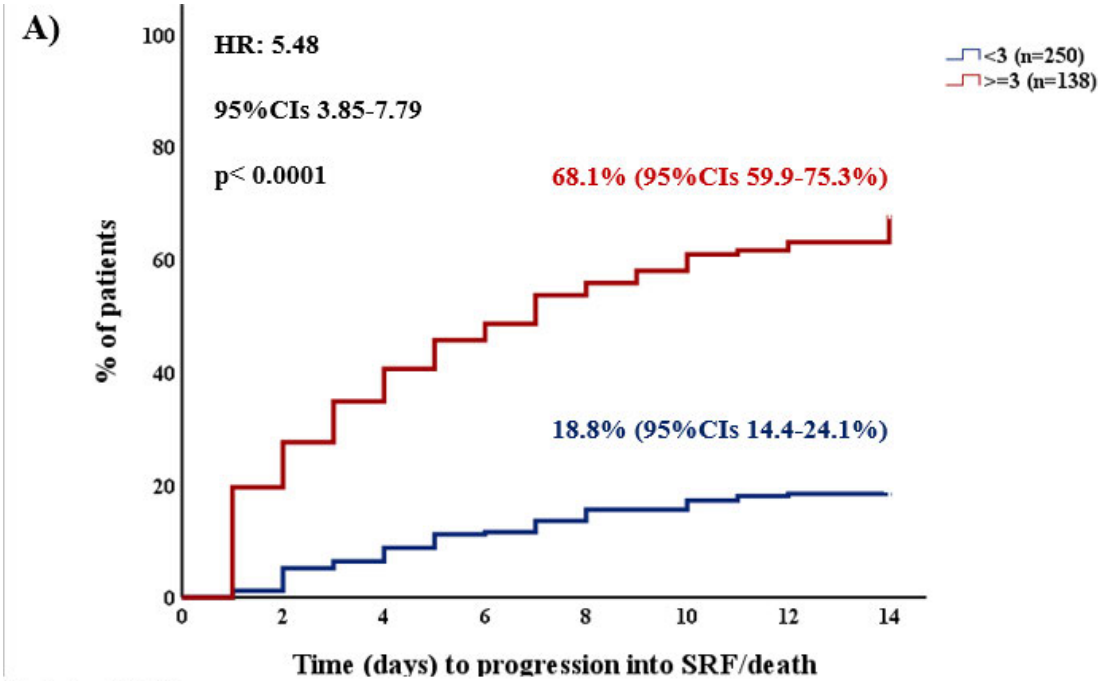
In the subgroup analysis on the remaining cohort (post interim analysis) from SAVE study, a specificity of 95.1% (95% CI 83.9-98.7%) and PPV of 99.6% (95% CI 98.4-99.9%) are observed, which is generally consistent with the specificity (91.5%) and PPV (93.4%) values of SCORE2 from the SAVE study interim analysis. This result is also consistent with the specificity (95.5%) and PPV (95.1%) values of SCORE2 that have been reported from the SAVE-MORE Study.

There is a small difference in the SAVE study interim analysis in Table 3 as compared to the previous reported SAVE study interim analysis. Data corrections performed by the investigators as part of the final data cleaning cause some minor discrepancies for some variables. There are 2 fewer patients in the current version: (1) one patient was identified as a duplicate entry and therefore removed from the current report; (2) The other patient did not have all the necessary components for a conclusive risk score and was excluded from the current analysis, however previously this patient was considered SCORE2 negative. Despite the small difference, the conclusion of the interim analysis has not changed.

4. Progression to SRF or death by day 14 for patients with SCORE2

The Requester compared progression into SRF or death by day 14 between patients with SCORE2 ≥3 and patients with SCORE2 <3 using Cox-regression analysis.
Patients included in this analysis are patients defined above as Population 1 and Population 2. Population 3 is not included in this analysis as treatment with anakinra may confound interpretation of the results. Figure 2 shows an association between SCORE2 (≥3 vs. < 3) and the risk for SRF (hazard ratio [HR]: 5.48, 95% CI [3.85-7.79]).

Figure 2 : Time to progression to SRF or death according to the values of SCORE2



Patients at risk (n)

SCORE2≥3	138	100	82	71	61	54	51	44
SCORE2<3	250	237	228	221	211	207	204	203

Source: Requester Data analysis report Version 2.0 Figure 2A

5. Additional data analysis provided by the Requester

During the communication with the Requester, FDA recommended the Requester to conduct the analyses for the post interim analysis from SAVE study on broader population of subjects who are solely defined by suPAR < 6 ng/mL and suPAR ≥ 6 ng/mL, regardless of other inclusion or exclusion criteria or treatment usage. However, such analysis could not be performed on the SAVE or SAVEMORE populations because such patients would not have reached the suPAR measurement step if they failed other inclusion or exclusion criteria. Per Protocol procedure, suPAR testing was the last step prior to enrollment. Instead, the Requester provided a comparative analysis on broader populations who are solely defined by suPAR < 6 ng/mL and suPAR ≥ 6 ng/mL, regardless of other inclusion or exclusion criteria or treatment usage, a cohort of patients with COVID-19 pneumonia who were included in the national registry of the Hellenic Institute for the Study of Sepsis for patients with respiratory tract infections was used. These are patients with COVID-19 pneumonia diagnosed with a positive PCR test for SARS-CoV-2 and who were admitted to the hospitals between March 2022 and December 2022. The analyses were performed on data from the cohort of 274 patients. Among these patients, 266 were analyzed since they had all the needed variables allowing the conclusive calculation of SCORE2. A comparison between these patients with suPAR <6 ng/mL and patients with suPAR ≥6 ng/mL is presented in Table 4. The performance of SCORE2 is presented in Table 5.

Table 4: Comparison of patients with suPAR <6 ng/mL and patients with suPAR ≥6 ng/mL

Characteristic	**suPAR <6 ng/mL N=116**	**suPAR ≥6 ng/mL N=150**
Male gender, n (%)	76 (66.5)	89 (59.3)
Age (years), mean (SD)	69.6 (14.3)	78.9 (12.3)
Age ≥75 years, n/total available (%)	43/112 (38.4)	108/150 (72.0)
Severe COVID-19 by WHO classification, n/total available (%)	60/116 (51.7)	135/150 (90.0)
SOFA, mean (SD)	1.59 (1.25)	2.65 (1.46)
SOFA≥3, n/total available (%)	22/99 (22.2)	85/148 (57.4)
Smoking habit, n/total available (%)	36/96 (37.5)	67/149 (45.0)
Total white blood cell count, /mm^3, mean (SD)	7690.3 (3142.3)	8610.2 (5221.2)
Total neutrophil cell count, /mm^3, mean (SD)	5702.4 (2935.1)	6593.4 (4695.1)
Total lymphocyte cell count, /mm^3, mean (SD)	1239.3 (616.1)	1412.3 (2583.6)
Neutrophil/lymphocyte ratio ≥7, n/total available (%)	35/116 (30.2)	62/150 (41.3)
Hemoglobin g/dL, mean (SD)	13.11 (1.68)	12.13 (1.85)
Hemoglobin ≤10.5g/dL, n/total available (%)	8/115 (7.0)	31/147 (21.1)
Urea, mg/dL, mean (SD)	45.04 (23.80)	60.49 (36.67)
Urea ≥50mg/dL, n/total available (%)	27/110 (24.5)	79/144 (54.9)
History of renal disease, n/total available (%)	5/102 (4.9)	11/146 (7.5)

History of ischemic stroke, n/total available (%)	7/99 (7.1)	9/146 (6.2)

Abbreviations – n: number of patients; SD: standard deviation; SOFA: sequential organ failure assessment

suPAR: soluble urokinase plasminogen activator receptor; SRF: severe respiratory failure; WHO: World

Health Organization.

Source: Requester Responses to FDA Information Request of April 19, 2023 Table 1

Table 5: Evaluation of PPV, NPV, sensitivity, and specificity on additional data

	suPAR ≥6 ng/mL,n	**suPAR <6 ng/mL, n**	**Total, n**
SCORE2 ≥ 3, n	133 Sensitivity= 88.7% (95% CI 82.6-92.8%) PPV= 85.3% (95% CI 78.8-89.9%)	23	156
SCORE2 <3, n	17	93 Specificity= 80.2% (95% CI 72.0-86.4%) NPV= 84.6% (95% CI 76.6-90.1%)	110
Total	150	116	266

Source: Requester Responses to FDA Information Request of April 19, 2023 Table 2

The assessment of SCORE2 as alternative to suPAR in this dataset shows a PPV of 85.3% and a specificity of 80.2%. While the PPV is not as high as the one observed in the SAVE/SAVEMORE analysis, it should be acknowledged that this PPV remains high suggesting the SCORE2 ≥3 is still a good marker for suPAR even in this broader population of patients. This slightly lower PPV may be attributable to other confounding factors given the more heterogeneous patient population in this analysis.

5. Conclusion

The SCORE2 was previously developed on data from the SAVEMORE trial and validated based on the interim data from the SAVE trial. In this analysis report, the post interim data from the SAVE trial was analyzed as an additional external validation of SCORE2 as an alternative to the plasma concentration of suPAR at baseline in patients with positive direct SARS-CoV-2 viral testing with evidence of COVID-19 pneumonia and at risk of progression to SRF. The results from the current report are consistent with those from the analysis of SAVE-MORE data and the previous validation results based on the interim analysis of SAVE study. Therefore, this provides further validation of the predictive performance of SCORE2 as an alternative to plasma suPAR to determine a suitable patient population for anakinra for the treatment of COVID-19 under the Emergency Use Authorization.

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