Emergency Use Authorization (EUA) for Vilobelimab (IFX-1)
Center for Drug Evaluation and Research (CDER) Review

Table 1. Identifying Information

Application Type (EUA or Pre-EUA) If EUA, designate whether pre-event or intra-event EUA request.	EUA
EUA Application Number(s)	118
Sponsor (entity requesting EUA or pre-EUA consideration), point of contact, address, phone number, fax number, email address	InflaRx GmbH C/O Dunn Regulatory Associates Dana Dunn, MS 2709 Silkwood Court Oakton VA, 22124 phone: 703 577-8291 fax: 703 577-8291 (b) (6)
Submission Date(s)	September 29, 2022
Receipt Date(s)	September 29, 2022
OND Division / Office	Division of Pulmonology, Allergy, and Critical Care (DPACC)/Office of Immunology and Inflammation (OII)
Integrated Review Completion Date	March 29, 2023
Proprietary Name	Gohibic
Established Name/Other names used during development	Vilobelimab, IFX-1, CaCP29
Dosage Forms/Strengths	800 mg intravenous (IV)
Therapeutic Class	Chimeric monoclonal immunoglobulin G4 (IgG4) antibody, specifically binds to the soluble human complement split product complement factor 5a (C5a)
Intended Use or Need for EUA	Treatment of coronavirus disease 2019 (COVID-19)
Intended Population(s)	Adult patients with COVID-19 when initiated within 48 hours of receiving invasive mechanical ventilation or ECMO
Product in the Strategic National Stockpile (SNS)	No
Recommendation for Regulatory Action	Authorize

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Glossary

ADA	anti-drug antibodies
AE	adverse event
AESI	adverse events of special interest
ARDS	acute respiratory distress syndrome
AUC	area under the concentration-time curve
BSC	best supportive care
C_{avg}	average concentration
CDER	Center for Drug Evaluation and Research
COVID-19	coronavirus disease 2019
CMC	chemistry, manufacturing, and controls
C_{trough}	concentration at the end of the dosing interval
DP	drug product
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EUA	emergency use authorization
FAS	full analysis set
FDA	Food and Drug Administration
HR	hazard ratio
HS	hidradenitis suppurativa
ICU	intensive care unit
IRR	infusion-related reaction
IMV	invasive mechanical ventilation
NDA	new drug application
NOAEL	no observed adverse effect level
OI	oxygenation index
OR	odds ratio
PK	pharmacokinetics
popPK	populatin pharmacokinetics
PT	preferred term
Q2W	every 2 weeks
RRT	renal replacement therapy
SAF	safety analysis set
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOC	standard of care
VILO	vilobelimab
Vmax	maximum volume
VPC	visual predictive check
WHO	World Health Organization

1 EUA Determination/Declaration

On February 4, 2020, as amended on March 15, 2023, pursuant to Section 564(b)(1)(C) of the Act, the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency, or a significant potential for a public health emergency, that affects, or has a significant potential to affect, national security or the health and security of United States citizens living abroad, and that involves the virus that causes coronavirus disease 2019 (COVID-19).[1] On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Act (21 U.S.C. 360bbb-3), subject to terms of any authorization issued under that section.[2]

2 Recommendations

2.1 Recommend EUA Issuance

The Division of Pulmonology, Allergy and Critical Care in the Office of Immunology and Inflammation, Office of New Drugs, Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration (FDA or the Agency) recommends EUA issuance.

The EUA will authorize vilobelimab for the treatment of coronavirus disease 2019 (COVID-19) in hospitalized adults when initiated withing 48 hours of receiving invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

2.2 Eligibility of the Product for an EUA

- COVID-19 is a serious or life-threatening disease or condition caused by SARS-CoV-2.

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[1] U.S. Department of Health and Human Services, *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3.* February 4, 2020; U.S. Department of Health and Human Services, *Amended Determination of a Public Health Emergency or Significant Potential for a Public Health Emergency Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3(b)*. March 15, 2023. 88 FR 16644 (March 20, 2023) ("Amended Determination").

[2] U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, 85 FR 18250 (April 1, 2020). *See* Amended Determination ("The declarations issued pursuant to section 564(b)(1) of the FD&C Act that circumstances exist justifying the authorization of emergency use of certain in vitro diagnostics, personal respiratory protective devices, other medical devices and drugs and biological products, as set forth in those declarations, and that are based on the February 4, 2020 determination, remain in effect until those declarations are terminated in accordance with section 564 of the FD&C Act.").

- Based on the totality of the scientific evidence available to FDA, including data from an adequate and well-controlled clinical trial, it is reasonable to believe that vilobelimab may be effective for the treatment of coronavirus disease 2019 (COVID-19) in hospitalized adults when initiated within 48 hours of receiving invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO); and when used under such conditions, the known and potential benefits of vilobelimab outweigh the known and potential risks of the product.
- There is no adequate, approved, and available alternative to the emergency use of vilobelimab for the treatment of coronavirus disease 2019 (COVID-19) in hospitalized adults who are receiving IMV or ECMO.
- Remdesivir, a SARS-CoV-2 nucleotide analog RNA polymerase inhibitor, is an FDA-approved alternative for the treatment of COVID-19 in hospitalized adults when initiated within 48 hours of receiving IMV, or ECMO. Remdesivir has demonstrated antiviral activity against SARS-CoV-2; whereas vilobelimab acts by binding to C5a to block its interaction with the C5a receptor, both of which are components of the complement system thought to contribute to inflammation and worsening of COVID-19, offering a different mechanism of action.
- Baricitinib, a Janus kinase (JAK) inhibitor, is an FDA-approved alternative for the treatment of COVID-19 in hospitalized adults when initiated within 48 hours of requiring IMV, or ECMO. As noted, vilobelimab offers a different mechanism of action. In addition, vilobelimab has an intravenous route of administration; whereas, baricitinib is available as tablets, offering an alternative route of administration to adult patients who are mechanically ventilated or on ECMO.
- Tocilizumab, an interleukin-6 (IL-6) receptor antagonist, is also an FDA-approved alternative for the treatment of COVID-19 in hospitalized adults when initiated within 48 hours of receiving IMV, or ECMO. As noted, vilobelimab offers a different mechanism of action.

2.3 Proposed Use and Dosing of the Product Under the EUA

Proposed Use Under EUA

The Division recommends the issuance of an Emergency Use Authorization (EUA) for the emergency use of vilobelimab for the treatment of coronavirus disease 2019 (COVID-19) in hospitalized adults when initiated within 48 hours of receiving invasive mechanical ventilation (IMV), or extracorporeal membrane oxygenation (ECMO).

Vilobelimab is not FDA-approved for any indications, including for the treatment of COVID-19.

Proposed Dosing Regimen for Use Under EUA

The recommended dosage of GOHIBIC for the treatment of adults with COVID-19 is 800 mg administered by intravenous infusion after dilution [see Dosage and

Administration (2.2)] for a maximum of six doses over the treatment period as described below.

Treatment should be started within 48 hours of intubation (Day 1) followed by administration on Days 2, 4, 8, 15 and 22 as long as the patient is hospitalized (even if discharged from intensive care unit [ICU]).

Rationale for Dosing Regimen

The proposed dosing and treatment durations of vilobelimab are based on the regimen that was evaluated in the Phase 2/3 randomized, double-blind, placebo-controlled trial (PANAMO). Further details on the rationale for the dosing regimen are discussed in the section on Human Clinical Pharmacology.

3 Product Information (Dose Preparation and Administration)

Vilobelimab drug product is a clear, colorless, sterile, concentrated solution containing 10 mg/mL vilobelimab (200 mg vilobelimab per vial)] in a single-dose vial for intravenous administration after dilution. Vilobelimab is filled in 20 mL Type I glass vials, stoppered with (b) (4) rubber stoppers, and sealed with flip-off caps. The drug product is formulated at a nominal concentration of 10 mg/mL in (b) (4) (b) (4) sodium chloride, (b) (4) sodium phosphate, pH (b) (4)) with (b) (4) % polysorbate 80 (w/v).

Preparation

- Using aseptic technique, dilute and prepare vilobelimab for intravenous infusion before administration.
- For the recommended dose of 800 mg vilobelimab, dilute 80 mL of vilobelimab in 170 mL of 0.9% sodium chloride at room temperature.
- Use a 250 mL infusion bag of 0.9% sodium chloride solution USP and the follow steps below:
  - Withdraw 80 mL of 0.9% sodium chloride solution USP from the infusion bag and discard.
  - Withdraw the 80 mL of vilobelimab from the vials and add slowly to the 0.9% sodium chloride solution USP infusion bag to a final concentration of 3.2 mg/mL.
  - To mix the solution, gently invert the bag to avoid foaming.

Storage of Diluted Vilobelimab

- Diluted vilobelimab must be used within 4 hours when stored at room temperature 20°C to 25°C (68°F to 77°F).

- Diluted vilobelimab stored under refrigeration at 2°C to 8°C (36°F to 46°F) must be used within 24 hours.
- After removal of diluted vilobelimab from the refrigerator stored at 2°C to 8°C (36°F to 46°F), it must be left to acclimatize to room temperature prior to administration.

Administration

- Visually inspect for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if discoloration or visible particles are present.
- Administer diluted vilobelimab via intravenous infusion over 30 to 60 minutes.
- Avoid concomitant administration of vilobelimab with other drugs in the same intravenous line.

4 Background Information on the Disease/Condition and Available Therapeutic Alternatives

4.1 Background Information on the Condition

- Coronavirus disease 2019 (COVID-19) can cause severe disease which can result in pneumonia, respiratory failure, multiorgan failure, and death. On March 11, 2020, the World Health Organization declared the COVID-19 outbreak a pandemic.
- According to the World Health Organization, approximately 628 million confirmed cases of COVID-19 caused by the 2019 novel coronavirus (SARS-CoV-2) have been reported globally as of March 1, 2023, including ~6.86 million deaths. In the United States, according to the Centers for Disease Control and Prevention (CDC), approximately 103 million cases of COVID-19 had been reported with approximately 1.1 million deaths as of March 1, 2023.
- 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 75 years and older and unvaccinated individuals. Following infection with COVID-19, some patients develop severe disease that progresses to pulmonary failure, acute respiratory distress syndrome (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.
- Despite advances in vaccines and host- and non-host directed therapies, the mortality rate in patients who develop respiratory failure and require IMV or ECMO remains high, ranging from 64 to 85% in certain age groups, (Nicholson et al. 2021) and 54 to 100%, respectively. Higher mortality rates are observed in

patients who have been mechanically ventilated for 7 days or longer. (Lebreton et al. 2021; Kurihara et al. 2022)

4.2 Therapeutic Alternatives for the Disease/Condition

There is no adequate, approved, and available alternative to the emergency use of vilobelimab for the treatment of COVID-19 in hospitalized adults when initiated within 48 hours of receiving invasive mechanical ventilation or ECMO. Therapies that are FDA-approved, authorized for emergency use, and/or considered standard of care in hospitalized adult patients with COVID-19 disease are shown in the table below.

Table 2. Available Therapies for Hospitalized Patients With COVID-19

Drug	Dosing	Indication
Standard of Care per NIH COVID-19 Treatment Guidelines[1]		
Dexamethasone	Days 1 – 10: 6 mg IV	Hospitalized children and adults requiring conventional oxygen
FDA approved and authorized therapies		
Remdesivir	Day 1: 200 mg IV Days 2 – 10: 100 mg IV	Approved: Adults and pediatric patients (≥28 days of age and weighing at least 3 kg) hospitalized, or not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death
Tocilizumab	Single dose 8 mg/kg IV (max 800 mg)	Approved: Hospitalized adults who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO Authorized: Pediatric patients (≥2 years of age) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO

Drug	Dosing	Indication
Baricitinib	Days 1 – 14: 4 mg oral or enteral	Approved: Adults hospitalized requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO Authorized: Pediatric patients ≥ 2 years of age to 18) hospitalized requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO
Anakinra	Days 1 – 10: 100 mg subcutaneous	Authorized: Hospitalized adults with pneumonia requiring supplemental oxygen (low-or high-flow oxygen) who are at risk of progressing to severe respiratory failure and likely to have an elevated plasma suPAR

[1] https://www.covid19treatmentguidelines.nih.gov/ (NIH 2023)
Approved = Agent is approved via NDA/BLA approval; Authorized = Agent is authorized under Emergency Use Authorization for COVID-19. Table does not include dose adjustments. Time intervals correspond to the max.
Abbreviations: ECMO = Extracorporeal membrane oxygenation; IV = intravenous; kg = kilograms; mg = milligrams; MV = mechanical ventilation; suPAR = soluble urokinase plasminogen activator receptor.

5 Related Regulatory Submission(s)

Related INDs and Pre-INDs

- **IND 151995**
  - Phase 2/3 trial in COVID-19 (PANAMO)
  - Sponsor: InflaRx GmbH
- **IND 136470**
  - Treatment of adults with moderate to severe hidradenitis suppurativa (HS); treatment of adults with ulcerative pyoderma gangrenosum (PG)
  - Two Phase 2 clinical studies completed for HS; 1 Phase 2 clinical study completed for PG
  - Cross-reference for supportive pharmacology and toxicology studies
  - Sponsor: InflaRx GmbH

(b) (4)

(b) (4)

Related Drug Master Files

(b) (4)

6 Summary of Clinical Data

Table 3: COVID-19 Clinical Trials With Vilobelimab Submitted in Support of the EUA Request

Study Identifier NCT Number Countries Status	Study Design	Treatment Groups	Study Population	Primary Endpoint
Study IFX-1-P2.9 (PANAMO) NCT 04333420 France, Brazil, Germany, Mexico, Netherlands, Belgium, Peru, Russian Federation, South Africa March 2020 – December 2021	Phase 2, R, OL	Vilobelimab, N=15 Placebo, N=15 Vilobelimab 800mg IV or Placebo on Days 1, 2, 4, 8, 11/12/13 if needed and if still hospitalized, Days 15, and 22 (maximum of 7 doses)	≥18 years of age Hospitalized with COVID-19 Highly oxygen dependent	Relative change (%) from baseline to Day 5 in oxygenation index
	Phase 3, R, DB, PC	Vilobelimab, N=178 Placebo, N=191 Vilobelimab 800mg IV or Placebo on Days 1, 2, 4, 8, 15, and 22, while hospitalized (maximum of 6 doses)	≥18 years of age Hospitalized with COVID-19 Invasive mechanical ventilation or ECMO	28-day all-cause mortality

Source: Study Report 1
Abbreviations: DB = double-blind, ECMO = extracorporeal membrane oxygenation, IV = intravenous, NCT = National Clinical Trial, OL= open label, PC = placebo-controlled, R = randomized.

The clinical efficacy and safety data package to support the EUA request is primarily based on the PANAMO trial. This was a multicenter, randomized, double-blind, placebo-

controlled Phase 3 clinical trial comparing vilobelimab with background standard of care (SOC, i.e., dexamethasone) to placebo with background SOC. Subjects were randomly assigned 1:1 to vilobelimab + SOC or placebo + SOC. Vilobelimab was administered at 800 mg for a maximum of 6 doses while hospitalized.

The Phase 2 open-label portion of PANAMO was also submitted by the Requester as supplemental efficacy and safety data. Subjects received vilobelimab at 800 mg at a slightly different dosing interval. Thirty subjects were enrolled in this trial, and due to the different study design and small sample size, the study results did not substantially contribute to the evaluation of efficacy for the proposed population of IMV and ECMO patients; therefore, only summary level results are provided in this review.

In addition to the PANAMO trial, safety data in completed trials with vilobelimab for treatment of other disease indications were provided as supplemental information:

Table 4. Non-COVID-19 Clinical Trials With Vilobelimab Submitted in Support of the EUA Request

Study Number; Phase; Status	Study Design Patient Population Objectives	Number of Patients	Dose
IFX-1-P1.1 Phase I Completed	Dose escalation, placebo-controlled, double-blind in healthy volunteers S, PK, PD, I	Total: 26 Vilobelimab: 15 Placebo: 11	Single dose 0.02, 0.1, 0.5, 2, 4 mg/kg
IFX-1-P2.1 Phase II Completed	Randomized, placebo-controlled, double-blind study in patients with early septic organ dysfunction S, PK, PD, E	Total: 72 Vilobelimab: 48 (16 per cohort) Placebo: 24	Cohort 1: 2 doses of 2 mg/kg over 12 h Cohort 2: 2 doses of 4 mg/kg over 24 h Cohort 3: 3 doses of 4 mg/kg over 72 h
IFX-1-P2.2 Phase II Completed	Randomized, placebo-controlled, double-blind study in patients undergoing complex cardiac surgery E, S, PK, PD	Total: 104 Vilobelimab: 81 (Cohort 1: 23; Cohort 2: 18; Cohort 3: 21; Cohort 4: 20); Placebo: 22	Single dose: Cohort 1: 1 mg/kg Cohort 2: 2 mg/kg Cohort 3: 4 mg/kg Cohort 4: 8 mg/kg
IFX-1-P2.3 Phase II Completed	Open-label, single arm study in patients with HS S, PK, PD, E	Total: 12	9 doses of 800 mg (days 1, 4, 8, 15, 22, 29, 36, 43, 50)
IFX-1-P2.4 Phase II Completed	Randomized, placebo-controlled, double-blind study (with open-label extension phase) in patients with moderate to severe HS	Total: 177 Main Period Placebo (Cohort 1: 36) Vilobelimab: 141 (Cohort 2: 34; Cohort 3: 35;	Main Period Induction Phase (2 wk): Cohort 1: placebo, Cohort 2: vilobelimab 400 mg Day 1,4, Cohort 3: vilobelimab 800 mg Day 1,4,8, Cohort 4: vilobelimab 800 mg Day 1,4,8,15,

Study Number; Phase; Status	Study Design Patient Population Objectives	Number of Patients	Dose
	Dose response, E, S, PK, PD, PRO	Cohort 4: 36; Cohort 5: 36); Extension Period Responder: 72 Non-Responder: 84	Cohort 5: vilobelimab 800 mg Day 1,4,8, 1200 mg D15 Maintenance Phase (from Day 29 for 14 wks): Cohort 1: placebo, Cohort 2: vilobelimab 400 mg Q4W, Cohort 3: vilobelimab 800 mg Q4W, Cohort 4: vilobelimab 800 mg Q2W, Cohort 5: vilobelimab 1200 mg Q2W Extension Period (Induction phase day 127-140, Maintenance Phase day 141-281) Wk 16 HiSCR responders: OL vilobelimab 800 mg Q4W (from day 141 for 20 wks) Wk 16 HiSCR non-responders: 1-3 x vilobelimab 800 mg DB induction in 2 wk, OL Vilobelimab 800 mg Q2W (from day 141 for 20 wk)
IFX-1-P2.6 Phase II Completed	Randomized, double-blind, parallel group, placebo- controlled, in adult patients with GPA or MPA S, E, PK, PD	Total: 19 Vilobelimab: 13 Group A: 7 Group B: 6 Group C: 6	16-week treatment period: days 1, 4, 8, 15, 29, 43, 57, 71, 85, 99, 113 Group A: vilobelimab 400 mg + SoC Group B: vilobelimab 800 mg + SoC Group C: Placebo + SoC
IFX-1-P2.5 Phase II Completed	Randomized, double-blind, double-dummy, active controlled, 2-part in adult patients with GPA or MPA E, S, PK, PD	Total: 57 Vilobelimab: 33 Standard dose GC: 24 Group A: 15 Group B: 24 Group C: 18	16-week treatment period: days 1, 4, 8, 15, 29, 43, 57, 71, 85, 99,113 Group A: vilobelimab 800 mg + reduced dose GC Group B: Placebo-vilobelimab 800 mg + standard dose GC Group C: vilobelimab 800 mg + placebo ± GC

Source: Summary of Clinical Safety
Abbreviations: BSC = best supportive care, cSCC = Cutaneous squamous cell carcinoma, DB = double-blind, E = efficacy, GPA = granulomatosis with polyangiitis, h = hour, HiSCR = Hidradenitis Suppurativa Clinical Response, HS = hidradenitis suppurativa, I = immunogenicity, IV = intravenous, MPA = Microscopic polyangiitis, OL = open-label, PD = pharmacodynamics, PG = pyoderma gangrenosum, GC= glucocorticoids, PK = pharmacokinetics, PRO = patient-reported outcomes, qw = every week , Q2W = every 2 weeks, Q3W = every 3 weeks, Q4W = every 4 weeks, Q6W = every 6 weeks, S = safety, SoC = standard of care, wk = week(s).

An overview of clinical studies evaluating other related C5 inhibitor products (ravulizumab, eculizumab, and zilucoplan) for the treatment of COVID-19 are summarized below. In contrast to vilobelimab, these products target inhibition of C5, which consists of the split products C5a and C5b. A recently published meta-analysis, including six studies evaluating C5 inhibition in COVID-19 subjects, demonstrated favorable results with respect to reducing mortality. (Tsai et al. 2023) Most recently, Annane et al. published the results of their study, in which treatment with ravulizumab (a C5 inhibitor) failed to meet statistical significance for the primary endpoint of 29 day all-

cause mortality. While the study by Annane et al. is not included in the meta-analysis, several important differences are notable, including: drugs with different mechanisms of action (ravulizumab is a C5 inhibitor and vilobelimab is a C5a inhibitor), an open-label study design, a relatively small number of subjects (N=201), a difference in baseline subjects mechanically ventilated (83% ravulizumab versus 100% in PANAMO), and an imbalance in the ravulizumab arm with a higher number of subjects having a history of septic shock, sepsis, or deep vein thrombosis at study entry than in the control group. Therefore, the degree of applicability to the findings with vilobelimab is uncertain.

Table 5. COVID-19 Clinical Studies With Other C5 Inhibitor Products

Study	Study Drug, Comparator	Study Design	Study Population	Primary Endpoint/ Outcome	N	Results
(Annane et al. 2023)	Ravulizumab IV weight-based dosing 2400 mg – 3000 mg on Day 1, 600 mg or 900 mg Day 5 and 10, and 900 mg Day 15 SOC	Phase 3, open-label randomized (2:1), controlled trial 31 hospitals in Japan, Spain, the UK, and the United States of America May 10, 2020 and January 13, 2021	COVID-19 patients with on IMV (<48hrs) or non-NIMV with severe pneumonia, acute lung injury or ARDs within 3 days of screening; Mechanical ventilated population: 84% Ravulizumab and 80% SOC	29 Day all-cause mortality	Ravulizumab = 135 Control = 66	74 (55%) of 135 patients in the ravulizumab group were alive at Day 29 and 37 (56%) of 66 patients in the SOC group Ravulizumab had an increased risk of Infections and Infestations and vascular disorders (DVT in 14 [11%] vs 2 [3%] and PE in 7 [6%] vs 0)
(Memon et al. 2022)	Ravulizumab IV (mean dose: 2800 mg) SOC	Phase 3, open-label randomized, controlled trial Single center in United States of America January 1, 2021 and July 30, 2021	COVID-19 patients with acute kidney injury	Not specified	Ravulizumab = 6 Control = 7	Ravulizumab increased platelet count and reduced number of anuric days in patients frequently requiring acute hemodialysis Safety data not reported in reference.
(De Leeuw et al. 2022)	Zilucoplan SC 32.4 mg for 14 days or until discharge plus ceftriaxone Ceftriaxone	Phase 2, prospective, randomized, open-label study 9 centers in Belgium Between August 15 and December 16, 2020	Hospitalized COVID-19 patients with systemic inflammation and hypoxemia (PaO2/FiO2 < 350 mmHg)	Change in oxygenation	Zilucoplan = 54 Ceftriaxone = 24	Day 28 mortality was 9% in the zilucoplan group and 21% in the control group No relevant safety differences between the zilucoplan and control group were identified

Study	Study Drug, Comparator	Study Design	Study Population	Primary Endpoint/ Outcome	N	Results
(Ruggenenti et al. 2021)	Eculizumab IV 900 mg x 2 SOC	Retrospective study	Hospitalized patients with COVID-19 receiving CPAP	Respiratory rate at one week of ventilator support	Eculizumab = 10 SOC = 65	Four eculizumab-treated patients died or had chronic complications versus 52 controls No treatment-related adverse events were reported.
(Annane et al. 2020)	Eculizumab IV1200 mg on days 1, 4, and 8 and 900 mg on days 15 and 22 SOC	Nonrandomized controlled study Single center in France Between March 10 and May 5, 2020	Severe COVID-19 required ICU admission, had severe pneumonia, ALI, or ARDS requiring supplemental oxygen	Survival (based on all-cause mortality) at day 15	Eculizumab = 35 Control = 45	Proportion of patients alive at day 15 was 82.9% for treatment with eculizumab and 62.2% for treatment without eculizumab Proportion of patients alive at day 28 was 80.0% with eculizumab and 51.1% without eculizumab Infectious complications were higher in the eculizumab group (57% versus 27%)

Source: (Annane et al. 2020; Ruggenenti et al. 2021; De Leeuw et al. 2022; Memon et al. 2022; Annane et al. 2023)

Abbreviations: ALI = acute lung injury; ARDS = acute respiratory distress syndrome; COVID-19 = coronavirus disease 2019; CPAP = continuous positive airway pressure; DVT: deep vein thrombosis; ICU = intensive care unit; IV = intravenous; PE: pulmonary embolism); SC = subcutaneous; SOC = standard of care (SOC and best supportive care [BSC] were used interchangeably in this table).

7 Human Clinical Efficacy

7.1 Overview

Clinical studies with eculizumab, ravulizumab, and zilucoplan (unapproved) have explored the effects of C5 blockade to treat COVID-19 (Table 5). Although these studies had several limitations (unblinded, small sample size, variable study population/disease severity and efficacy endpoints), there appears to be a favorable trend towards decreased mortality with C5 inhibitor treatment. (Tsai et al. 2023) Acknowledging the limitations of comparing results across agents, the positive trends in the available body of evidence suggest there is mechanistic plausibility for the role of C5 blockage in the treatment of COVID-19.

The primary evidence used to evaluate the efficacy of vilobelimab (referred to as "VILO" from this point forward) in patients with COVID-19 pneumonia who required mechanical ventilation or ECMO is from the Phase 3 portion of Study IFX-1-P2.9 (referred to as PANAMO from this point forward). The Phase 2 portion of PANAMO was small, open label and evaluated a different patient population and primary efficacy endpoint, and therefore, the results were reviewed but considered less relevant for supporting this authorization request. The results from the Phase 3 portion of the trial demonstrated that VILO reduced the risk of 28-day mortality in adult subjects with COVID-19 who required invasive mechanical ventilation or ECMO.

7.2 PANAMO Phase III Trial

7.2.1 Study Design

The Phase 3 portion of PANAMO was a double-blind, placebo-controlled, multi-center trial conducted between October 1, 2020 and December 1, 2021. The study randomized 369 mechanically ventilated COVID-19 subjects in a 1:1 ratio, stratified by study site, to receive either VILO or placebo. VILO 800 mg or placebo was administered at Days 1, 2, 4, 8, 15, and 22 so long as the subjects remained in the hospital. Subjects also received SOC which included venous thromboembolism (VTE) prophylaxis and the country-specific recommended treatments for COVID-19. The study was conducted at 46 sites in 9 countries.

7.2.2 Study Population

The inclusion and key exclusion criteria were as follows:

Inclusion criteria:

- 18 years of age or older
- On invasive mechanical ventilation

- PaO2 / FiO2 ratio between 60 and 200 at randomization (one representative measurement within 6 hours before randomization)
- SARS-CoV-2 infection confirmation (tested positive in last 14 days before randomization with locally available test system).

Key exclusion criteria:

- Intubated > 48 hours at time point of first investigational medicinal product (IMP) administration
- Anticipated discontinuation of mechanical ventilation or extubation in the next 24 hours
- History of chronic dialysis OR renal replacement therapy in past 14 days OR anticipated need for renal replacement therapy within 24 hours after randomization
- History of progressed chronic obstructive pulmonary disease (COPD) as evidenced by use of daily maintenance treatment with long-acting bronchodilators or inhaled/oral corticosteroids for more than two months
- Investigational antibody treatment(s) which were not approved or not included in locally adopted treatment guidelines (e.g., World Health Organization [WHO] guidance, National Institutes of Health [NIH] COVID-19 treatment guidelines) for COVID-19 in the past seven days (Antibody treatment for pre-existing diseases other than COVID-19 allowed)
- Cardio-pulmonary mechanical resuscitation in past 14 days
- Severe congestive heart failure (e.g., New York Heart Association [NYHA] Class III-IV, left ventricular ejection fraction <40%)
- History of chronic liver disease (Child-Pugh B or C).

Subjects randomized into the study were followed for 60 days. Survival status was assessed during the study and at Days 28 and 60. A single interim analysis to potentially stop the study for futility was performed after the first 180 subjects were followed through Day 28 or death. The study did not meet the prespecified stopping criteria at the interim analysis.

7.2.3 Primary Endpoint Analysis

The primary efficacy endpoint was 28-day all-cause mortality. The prespecified primary statistical analysis for the primary endpoint was based on a Cox proportional hazards regression model that included covariates for treatment group and age, and was stratified by study site. Given the primary analysis method, the primary endpoint was analyzed as time to death through Day 28. The primary analytic population was the Full Analysis Set (FAS) that included all randomized subjects except for those randomized in error who did not receive study treatment. Efficacy was assessed by the estimated Hazard Ratio (HR) and the p-value was based on the z-statistic defined as the estimated beta coefficient divided by its standard error. For the primary analysis, a subject was censored at the date of last contact or at Day 28 if death occurred after Day 28 or if there were more than 28 days of follow up.

A key review issue is that the prespecified primary statistical analysis used a Cox regression that stratified by site. However, an analysis that stratifies by site effectively drops subjects from those sites without an event and from those sites without subjects in both treatment groups. In studies such as PANAMO that have many sites with only a few subjects, stratification can lead to a substantial reduction in the effective sample size. Therefore, although it was not the prespecified analysis, this review will focus on the results from the Cox regression that does not stratify by site in order to evaluate a more precise estimate of the treatment effect. Of note, the Requester initially proposed an unstratified analysis. In the absence of details about target enrollment at each site, the FDA recommended that the Requester consider accounting for the stratified randomization in the analysis by stratifying by site in an Advice Letter dated July 13, 2021; however, FDA suggested that the Requester should first evaluate whether the sample size in each stratum was sufficient to avoid a significant loss in statistical power. The Requester modified their primary analysis in their SAP based on this recommendation.

Although the primary statistical analysis estimated a HR, a prespecified supplementary analysis estimated the risk difference (i.e., difference in rates of 28-day all-cause mortality). The risk difference (RD) was estimated by first obtaining an odds ratio (OR) using logistic regression adjusting for age and then converting the OR to an RD using the method described by Ge and colleagues. (Ge et al. 2011) Missing values were handled by multiple imputation, with age and treatment group included as covariates in the imputation model.

7.2.4 Secondary Endpoint Planned Analyses

The study included five multiplicity controlled secondary endpoints:

- 60-day all-cause mortality
- Proportion of subjects with improvement in the 8-point ordinal scale at Day 15
- Proportion of subjects with improvement in the 8-point ordinal scale at Day 28
- Proportion of subjects developing acute kidney failure by Day 28
- Proportion of subjects free of any renal replacement therapy (RRT) within 28 days

The 8-point ordinal scale refers to the World Health Organization (WHO) ordinal severity scale (Table 6). A subject was defined as having an improvement in the 8-point ordinal scale on a given day if the assessment on that day was lower than the baseline value or if the subject was already discharged from the hospital. A subject was defined as not having an improvement if the assessment on that day was at least as high as the baseline value or the subject died. Otherwise, a subject's value was set to missing. Additionally, acute kidney failure was defined as an estimated glomerular filtration rate (eGFR) < 15mL/min/1.73m^2. Subjects with eGFR < 15mL/min/1.73m^2 at baseline were excluded from the analysis and subjects without post-randomization eGFR values were set to missing.

Table 6. WHO 8-Point Ordinal Scale

0	**Uninfected, No Clinical or Virological Evidence of Infection**
1	Ambulatory, no limitation of activities
2	Ambulatory, limitation of activities
3	Hospitalized, mild disease, no oxygen therapy
4	Hospitalized, mild disease, oxygen by mask or nasal prongs
5	Hospitalized, severe disease, non-invasive ventilation or high-flow oxygen
6	Hospitalized, severe disease, intubation and mechanical ventilation
7	Hospitalized, severe disease, ventilation + additional organ support - pressors, RRT, extracorporeal membrane oxygenation (ECMO)
8	Death

Source: Clinical Study Report (page 52)
Abbreviations: RRT = renal replacement therapy; WHO = world health organization.

The 60-day all-cause mortality endpoint was evaluated similarly to the primary endpoint. The endpoints considering the proportion of subjects with an improvement in the WHO ordinal scale or developing kidney failure were evaluated by estimating the risk difference using the same method as used for the supplementary analysis of the primary endpoint.

The endpoint of the proportion of subjects free from RRT was evaluated using multiple time-to-event methods such as Gray's non-parametric test to compare the cumulative incidence of RRT between treatment groups and the cause-specific Cox proportional hazards regression model. (Gray 1988)

If the primary endpoint achieved statistical significance, the first secondary endpoint (i.e., 60-day all-cause mortality) was to be tested at a one-sided alpha of 0.025. If the first secondary endpoint achieved statistical significance, type I error would be controlled using a fallback procedure by which the alpha was to be attributed to the four remaining secondary endpoints at 0.02, 0.002, 0.002, and 0.001.

7.2.5 Efficacy Results

7.2.5.1 Subject Disposition

A total of 369 subjects were randomized into the study with 178 subjects randomized to receive VILO and 191 subjects randomized to receive placebo (Table 7). Among the 369 randomized subjects, one subject in the VILO group was randomized in error and did not receive study treatment, and was therefore excluded from the FAS. Of the 368 subjects in the FAS, four subjects did not receive study treatment, resulting in 364 (98.9%) subjects in the Safety Analysis Set (SAF), defined as all subjects who received at least one infusion of study treatment. See Table 7 for additional information on subject disposition.

Of the 369 randomized subjects, a total of 18 (4.8%, 9 [5.1%] in VILO and 9 [4.7%] in placebo) and 24 (6.5%, 13 [7.3%] in VILO, 11 [5.8%] in placebo) subjects prematurely discontinued the study for reasons other than death and could not be recontacted prior to Days 28 and 60, respectively. The reasons for these early study discontinuations included withdrawal by subject or legal representation (11), loss-to-follow-up (5), transfer to another hospital (6), unblinding due to breastfeeding (1), or randomized in

error (1). An additional 12 subjects transferred to another hospital during the study but were contacted and noted to be alive at Day 60 follow-up and could therefore be included in the primary analysis.

The percentage discontinuing study treatment due to AEs other than death was similar across treatment groups (2.2% in VILO, 1.6% in placebo).

Table 7: Subject Disposition (All Randomized Population)

Variable	VILO (N = 178)	Placebo (N = 191)	Total (N = 369)
Randomized in error and not treated, n (%)	1 (<1)	0	1 (<1)
Randomized and not treated, n (%)	2 (1.1)	2 (1.0)	4 (1.1)
Treated with at least one IMP dose (Safety Analysis Set), n (%)	175 (98.3)	189 (99.0)	364 (98.6)
Completed Day 60 follow-up alive[1], n (%)	103 (57.9)	93 (48.7)	196 (53.1)
Deceased, n (%)	62 (34.8)	87 (45.5)	149 (40.4)
Between randomization and Day 28, n (%)	54 (30.3)	77 (40.3)	131 (35.5)
Between Day 28 and 44, n (%)	7 (3.9)	8 (4.2)	15 (4.1)
Between Day 45 and 60, n (%)	1 (<1)	2 (1.0)	3 (<1)
Premature study termination, n (%)			
Reasons other than death	13 (7.3)	11 (5.8)	24 (6.5)
Lost to follow-up	4 (2.2)	1 (<1)	5 (1.4)
Randomized in error	1 (<1)	0	1 (<1)
Withdrawal by legal representative	5 (2.8)	3 (1.6)	8 (2.2)
Withdrawal by subject	1 (<1)	2 (1.0)	3 (<1)
Other[2]	2 (1.1)	5 (2.6)	7 (1.9)
Death	62 (34.8)	87 (45.5)	149 (40.4)
Premature treatment discontinuation without termination of study, n (%)	9 (5.1)	6 (3.1)	15 (4.1)
Reasons for premature treatment discontinuation, n (%)			
Adverse event	50 (28.1)	68 (35.6)	118 (32.0)
Fatal AE	46 (25.8)	65 (34.0)	111 (30.1)
Non-fatal AE	4 (2.2)	3 (1.6)	7 (1.9)
Clinical deterioration	0	2 (1.0)	2 (<1)
Physician decision	0	3 (1.6)	3 (<1)
Randomized in error	1 (<1)	0	1 (<1)
Recovery[3]	2 (1.1)	2 (1.0)	4 (1.1)
Withdrawal by legal representative	7 (3.9)	2 (1.0)	9 (2.4)
Withdrawal by subject	3 (1.7)	1 (<1)	4 (1.1)
Other[2]	8 (4.5)	9 (4.7)	17 (4.6)

Source: Clinical Study Report Table 9-1 (page 84); results reproduced by the reviewer using adsl.xpt
[1] Patients completing the study alive were defined as patients who completed the Day 60 follow-up visit or known alive on Day 60. Included 8 patients in VILO group and 4 patients in placebo group who completed the follow-up visit Day 60 alive (CSR listing 16.9.6) although their end of study reason was "other".
[2] A majority of these patients were transferred to another hospital.
[3] Patients who prematurely discontinued treatment for reason 'Recovery' were still in hospital at the timepoint of the scheduled IMP administration, but hospital discharge was anticipated very soon after and thus IMP was not given.
Abbreviations: A =: adverse event; IMP = investigational medicinal product, SOC = standard of care, VILO = vilobelimab,

7.2.5.2 Subject Demographics

The FAS included subjects from 46 sites across 9 countries (Table 8). One hundred and thirty-eight (37.5%) subjects were in the Netherlands, 74 (20.1%) subjects were in

Brazil, and the remaining subjects were spread across the remaining 7 countries. The FAS population was predominantly male (68.5%), ≤ 65 years old (69.8%), white (63.6%), and not Hispanic or Latino (38.9%). Vaccination status was not thoroughly captured in the trial and only available for three subjects; however, enrollment was not limited to unvaccinated patients. In general, baseline characteristics tended to be balanced across all groups. Although a slightly larger percentage of placebo subjects had diabetes (33.5% versus 25.4%), scored a 7 on the 8-point WHO scale (69.1% versus 59.3%), had an eGFR < 60 mL/min/1.73m^2 (31.9% versus 26.6%), and had severe ARDS with a $Pa0_2/Fi0_2$ ≤ 100 mmHg (28.8% versus 24.3%), the primary endpoint results remained significant after adjusting for baseline differences in disease severity (see Section 8.2.5.6).

Overall, the study population was clearly defined and included a distinct population of critically ill patients requiring invasive mechanical ventilation or ECMO. Because eligibility criteria excluded patients who had been intubated for >48 hours prior to first study drug administration, there were minimal concerns regarding differences in hospitalization, disease course, and treatment prior to enrollment. Although the trial did not enroll any subjects at the US site, the trial did enroll subjects at Western European sites with presumed similar access to and standard of care as in the US and also enrolled patients at several geographic sites with subjects representative of US demographics. These factors were considered when assessing the clinical relevance of the vilobelimab data to the US population.

Table 8: Demographics and Baseline Characteristics (Full Analysis Set)

Demographics	VILO (N = 177)	Placebo (N = 191)	Total (N = 368)
Country, n (%)			
Belgium	8 (4.5)	7 (3.7)	15 (4.1)
Brazil	34 (19.2)	40 (20.9)	74 (20.1)
France	17 (9.6)	18 (9.4)	35 (9.5)
Germany	10 (5.6)	11 (5.8)	21 (5.7)
Mexico	18 (10.2)	19 (9.9)	37 (10.1)
Netherlands	68 (38.4)	70 (36.6)	138 (37.5)
Peru	6 (3.4)	9 (4.7)	15 (4.1)
Russian Federation	11 (6.2)	12 (6.3)	23 (6.2)
South Africa	5 (2.8)	5 (2.6)	10 (2.7)
Region, n (%)			
South Africa/Russian Federation	16 (9.0)	17 (8.9)	33 (9.0)
South America	58 (32.8)	68 (35.6)	126 (34.2)
Western Europe	103 (58.2)	106 (55.5)	209 (56.8)
Race, n (%)			
American Indian[1]	22 (12.4)	24 (12.6)	46 (12.5)
Asian	4 (2.3)	5 (2.6)	9 (2.4)
Black	5 (2.8)	8 (4.2)	13 (3.5)
Multiple	1 (<1)	0	1 (<1)
White	115 (65.0)	119 (62.3)	234 (63.6)
Other	16 (9.0)	19 (9.9)	35 (9.5)
Missing	14 (7.9)	16 (8.4)	30 (8.2)

Demographics	VILO (N = 177)	Placebo (N = 191)	Total (N = 368)
Ethnic, n (%)			
Hispanic or Latino	60 (33.9)	68 (35.6)	128 (34.8)
Not Hispanic or Latino	70 (39.5)	73 (38.2)	143 (38.9)
Not reported	28 (15.8)	35 (18.3)	63 (17.1)
Unknown	11 (6.2)	11 (5.8)	22 (6.0)
Missing	8 (4.5)	4 (2.1)	12 (3.3)
Sex, n (%)			
Female	52 (29.4)	64 (33.5)	116 (31.5)
Male	125 (70.6)	127 (66.5)	252 (68.5)
Age (years)			
Mean (SD)	56.7 (13.19)	55.9 (14.53)	56.3 (13.89)
Median	58	57	58
IQR	47.0, 67.0	46.0, 68.0	47.0, 68.0
Min, max	23.0, 81.0	22.0, 81.0	22.0, 81.0
Age group, n (%)			
≥ 18 years and < 40 years	22 (12.4)	30 (15.7)	52 (14.1)
≥ 40 years and < 50 years	32 (18.1)	31 (16.2)	63 (17.1)
≥ 50 years and < 60 years	43 (24.3)	39 (20.4)	82 (22.3)
≥ 60 years and < 70 years	47 (26.6)	55 (28.8)	102 (27.7)
≥ 70 years and < 80 years	31 (17.5)	35 (18.3)	66 (17.9)
≥ 80 years	2 (1.1)	1 (<1)	3 (<1)
BMI (kg/m^2)			
Mean (SD)	31.9 (6.08)	31.9 (7.11)	31.9 (6.63)
Median	31.1	30.8	30.9
IQR	27.8, 34.5	26.9, 36.5	27.5, 35.5
Min, max	22.1, 53.7	18.0, 55.2	18.0, 55.2
WHO 8-point ordinal scale evaluation, n (%)			
6 - Intubation and mechanical ventilation	72 (40.7)	59 (30.9)	131 (35.6)
7 - Ventilation + additional organ support– vasopressors, RRT, ECMO	105 (59.3)	132 (69.1)	237 (64.4)
Vasopressors[2]	115 (65.0)	136 (71.2)	251 (68.2)
RRT	1 (0.6)	2 (1.0)	3 (0.8)
ECMO	3 (1.7)	3 (1.6)	6 (1.6)
eGFR, n (%)			
< 60 ml/min/$1.73m^2$	47 (26.6)	61 (31.9)	108 (29.3)
≥ 60 ml/min/$1.73m^2$	129 (72.9)	130 (68.1)	259 (70.4)
Missing	1 (<1)	0	1 (<1)
Diabetes, n (%)			
Yes	45 (25.4)	64 (33.5)	109 (29.6)
No	132 (74.6)	126 (66.0)	258 (70.1)
Unknown	0	1 (<1)	1 (<1)
ARDS, n (%)			
Mild (200 mmHg < PaO_2/FiO_2 ≤ 300 mmHg)[3]	1 (<1)	1 (<1)	2 (<1)
Moderate (100 mmHg < PaO_2/FiO_2 ≤ 200 mmHg)	133 (75.1)	135 (70.7)	268 (72.8)
Severe (PaO_2/FiO_2 ≤ 100 mmHg)	43 (24.3)	55 (28.8)	98 (26.6)
Time between COVID-19 diagnosis and randomization (days)			
Mean (SD)	7.2 (4.81)	7.1 (4.76)	7.2 (4.78)
Median	7	7	7
IQR	3.0, 11.0	3.0, 10.0	3.0, 11.0
Min, max	0.0, 24.0	0.0, 30.0	0.0, 30.0

Demographics	VILO (N = 177)	Placebo (N = 191)	Total (N = 368)
Background therapies (prior[4] or concomitant use), n (%)			
Systemic corticosteroids			
Yes	176 (99.4)	188 (98.4)	364 (98.9)
No	1 (0.6)	3 (1.6)	4 (1.1)
Antithrombotic agents			
Yes	176 (99.4)	187 (97.9)	363 (98.6)
No	1 (0.6)	4 (2.1)	5 (1.4)
Anti-IL-6 (tocilizumab or levilimab)			
Yes	31 (17.5)	31 (16.2)	62 (16.8)
No	146 (82.5)	160 (83.8)	306 (83.2)
Remdesivir			
Yes	10 (5.6)	11 (5.8)	21 (5.7)
No	167 (94.4)	180 (94.2)	347 (94.3)
Baricitinib			
Yes	6 (3.4)	6 (3.1)	12 (3.3)
No	171 (96.6)	185 (96.9)	356 (96.7)

Source: Clinical Study Report Table 9-1 (page 84) and Table 9-3 (page 88); results reproduced by the reviewer using adsl.xpt
[1] Subjects were enrolled from sites in Mexico
[2] Note: Not all subjects on vasopressors at baseline were included as an WHO ordinal scale (OS) 7. Assigning of OS score by Investigator at baseline was done once in the 24 hours considered "baseline". Subjects assigned an OS 6 at baseline may have started on vasopressors after the score assignment, accounting for the higher number of subjects on vasopressors at baseline than recorded at OS 6.
[3] Two patients with values greater than 300 were included in the mild ARDS severity category.
[4] Prior medications were defined in the protocol as medications administrated 7 days before randomization.
Abbreviations: ARDS = acute respiratory distress syndrome, BMI = body mass index, COVID-19 = coronavirus disease 2019, ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate, ICU = intensive care unit, IMP = investigational medicinal product, IQR = interquartile range, Max = maximum, Min = minimum, RRT = renal replacement therapy; SD = standard deviation, SOC = standard of care, VILO = vilobelimab

7.2.5.3 Primary Endpoint Results

In the FAS, subjects in the VILO group were less likely to die before Day 28 than subjects in the placebo group (Table 9, Figure 1). Fifty-four of the 177 subjects in the VILO group and 77 of the 191 subjects in the placebo group died prior to Day 28. Eight subjects in the VILO group and 9 subjects in the placebo groups were lost to follow-up, withdrawn from study, or discontinued from the study due to other reason before Day 28 and were censored on the last day known to be alive. The Kaplan-Meier estimates of the mortality rate within 28 days were 31.7% in the VILO group and 41.6% in the placebo group. The Cox proportional hazards model stratifying by site produced an estimated HR of 0.728 (95% CI = 0.502, 1.056), indicating that VILO reduced the risk of death by 27.2%. However, the result was not statistically significant (p=0.0941). The analysis stratifying by site effectively excluded the 61 (16.6%) subjects from sites with no deaths and/or enrollment in only one treatment group. When considering a post-hoc analysis that used a Cox proportional hazards model without stratifying by site, the estimated HR was a statistically significant 0.674 (95% CI = 0.476, 0.955; p = 0.0266).

Ultimately the Agency used the post-hoc analysis (non-prespecified), which included all randomized subjects, as the primary basis of efficacy. The Requester originally proposed this non-site stratified method as the preferred analysis prior to study initiation, but subsequently changed to a site-stratified analysis based on comments from the Agency. However, the Agency would have recommended a non-site stratified

approach if the possibility of site dependent low enrollment had been more apparent. Because low enrollment at some sites leads to the exclusion of subjects in the pre-specified site-stratified analysis, the non-site stratified analysis is a more reliable and appropriate method to avoid the loss of statistical power. This is a rare instance of the Agency relying on a non-prespecified analysis as the primary analysis to support efficacy; however, in this particular case, the non-prespecified analysis is the more reliable method. Similar results were obtained in post-hoc supplementary analyses that used other methods to adjust for potential differences across countries or regions. For example, a Cox model stratified by country produced an estimated HR of 0.613 (95% CI = 0.430, 0.873) and a model stratified by geographic region produced an estimated HR of 0.644 (95% CI = 0.454, 0.914) shown in Figure 9 in the Appendices.

In addition to estimating HRs, the efficacy was also evaluated by estimating the difference in rates of 28-day mortality between the two treatment groups using the logistic regression model adjusting for age with multiple imputation for missing values. The estimated risk difference between the VILO and placebo groups was -11.2% (95% CI = -21.0%, -1.4%; p = 0.0293).

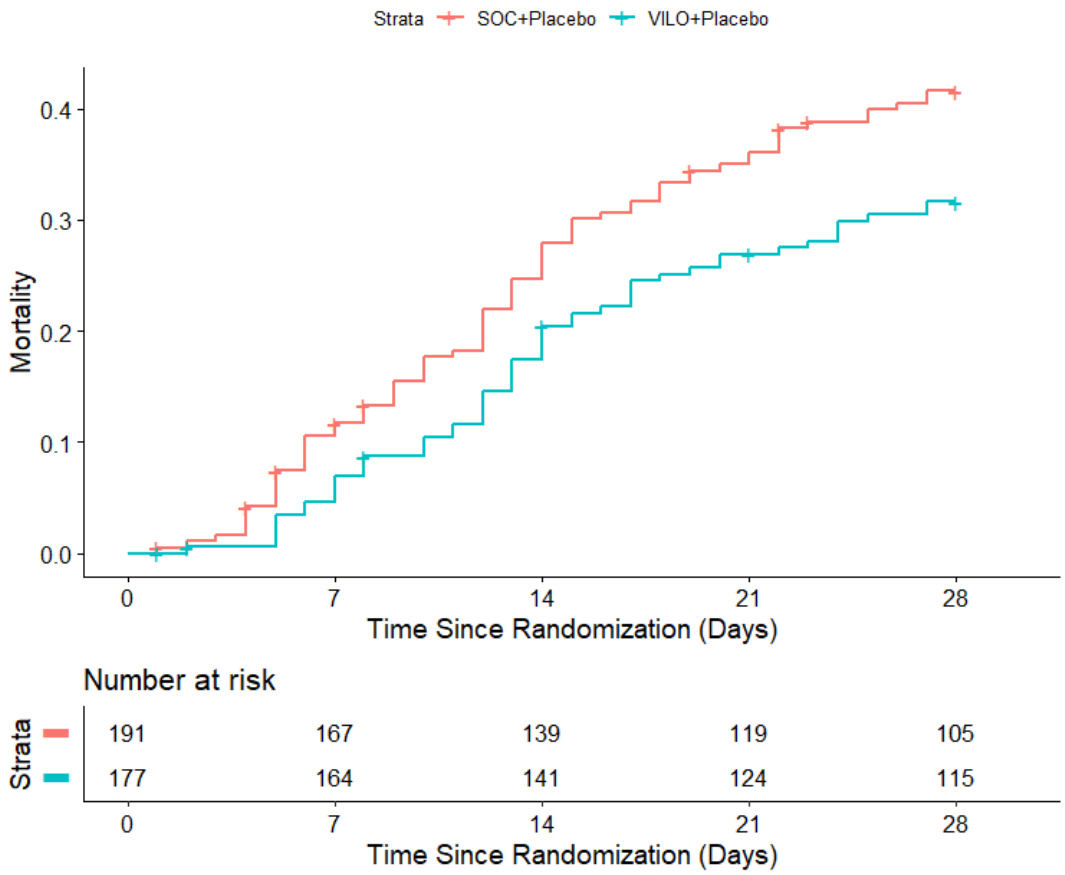
The mortality rate observed in the placebo group was consistent with mortality rates for patients with critical COVID-19 disease during the timeframe that the trial was conducted and with the available treatments. The placebo study drug was well-matched and there were no concerns about potential unblinding of treatment assignment due to differences in appearance or pharmacodynamic effects; therefore, this is not expected to be a major source of bias in this trial.

Table 9: 28-Day All-Cause Mortality, Cox Regression Analysis Adjusting for Age (Full Analysis Set)

Variable	VILO (N = 177)	Placebo (N = 191)
Proportion of patients with 28-day all-cause mortality[1] from Kaplan-Meier estimate, %	31.7%	41.6%
Hazard ratio for VILO versus placebo (95% CI); p-value[2] (stratified analysis)	0.728 (0.502, 1.056) p = 0.0941	
Hazard ratio for VILO versus placebo (95% CI); p-value[3] (unstratified analysis)	0.674 (0.476, 0.955) p = 0.0266	
Risk Difference[4], VILO-placebo (95% CI)	-11.2% (-21.0%, -1.4%)	

Source: Clinical Study Report Table 10-1 (page 99) and Table 10-5 (page 108); results reproduced by the reviewer using adeff.xpt
[1] Results from Kaplan-Meier estimate
[2] Results from Cox proportional hazards regression model with outcome 28-day all-cause mortality a time-to-event variable and explanatory variables of treatment and age, with stratification by site.
[3] Results from Cox proportional hazards regression model with outcome 28-day all-cause mortality a time-to-event variable and explanatory variables of treatment and age.
[4] Results from Fact Sheet for Healthcare Providers. Reviewer produced similar results (Risk Difference = -10.4%; 95% CI = -20.2%, -0.5%), but results were not identical due to use of multiple imputation.
Abbreviations: CI = confidence interval, SOC = standard of care, VILO = vilobelimab

Figure 1: Kaplan-Meier Graph for 28-Day All-Cause Mortality (Full Analysis Set)



Source: Clinical Study Report Figure 10-1 (page 99); results reproduced by the reviewer using adeff.xpt
Abbreviations: SOC = standard of care, VILO = vilobelimab

There was a small amount of missing data for the primary endpoint of 28-day mortality; 8 subjects in the VILO group and 9 subjects in the placebo group were censored in the full analysis set. Six subjects in the VILO group had fewer than 10 days of follow-up, 1 was censored on Day 14 and 1 was discharged from the hospital on Day 21. For the placebo group, 6 subjects had fewer than 10 days of follow-up, 3 were censored after Day 18 among which 2 were transferred to other hospitals and 1 was discharged. Sensitivity analyses showed that methods for handling missing data had minimal impact on the overall study result.

7.2.5.4 Secondary Endpoint Results

In the FAS, subjects in the VILO group were less likely to die before Day 60 than subjects in the placebo group. Sixty-two of the 177 subjects in the VILO group and 87 of the 191 subjects in the placebo group were reported to have died prior to Day 60. As seen in Table 10, the results were similar to the results seen at Day 28 (Table 9). As with the Day 28 results, the analysis stratified by site was problematic as it dropped subjects from those sites without an event and from those sites without subjects in both treatment groups. The results of the primary analysis without stratification by site as well as the assessment of the risk difference were both significant. Twenty-three subjects

were censored/had missing data prior to Day 60 (12 in the VILO group and 11 in the placebo group) in the FAS. Of the 6 subjects who were censored after Day 28, 4 were discharged from the hospital.

Table 10: Secondary Endpoints (Full Analysis Set)

Endpoint	VILO (N = 177)	Placebo (N = 191)
60 Day mortality		
Proportion of patients with 28-day all-cause mortality from Kaplan-Meier estimate, %	36.5%	47.2%
Hazard ratio for VILO versus placebo (95% CI); p-value (Stratified Analysis)	0.735 (0.519, 1.039) p = 0.0815	
Hazard ratio for VILO versus placebo (95% CI); p-value (Unstratified Analysis)	0.670 (0.484, 0.929) p = 0.0163	
Risk difference[1], VILO-placebo (95% CI); p-value	-12.2% (22.0%, -2.4%) p = 0.0162	
WHO 8-point scale at Day 15		
Proportion of patients with an improvement[2], n (%)	82 (46.3%)	77 (40.3%)
Proportion of patients without an improvement, n (%)	86 (48.6%)	104 (54.5%)
Not evaluable, n (%)	9 (5.1%)	10[3] (5.2%)
Risk difference[1] (95% CI); p-value	7.4% (-2.8%, 17.5%) p = 0.1553	
WHO 8-point scale at Day 28		
Proportion of patients with an improvement[2], n (%)	90 (50.8%)	85 (44.5%)
Proportion of patients without an improvement, n (%)	78 (44.1%))	96 (50.3%
Not evaluable, n (%)	9 (5.1%)	10[3] (5.2%)
Risk difference[1], VILO-placebo (95% CI); p-value	8.1% (-2.0%, 18.1%) p = 0.1181	
Acute kidney failure by Day 28		
Acute kidney failure, n (%)	8 (4.5%)	12 (6.3%)
No acute kidney failure, n (%)	158 (89.3%)	168 (88.0%)
Not evaluable, n (%)	11 (6.2%)	11[3] (5.8%)
Risk difference[1], VILO - placebo (95% CI); p-value	-2.1% (-6.9%, 2.8%) p = 0.4105	
Renal replacement therapy (RRT) within 28 days		
With RRT, n (%)	17 (9.6%)	30 (15.7%)
Gray's test for equality of cumulative incidence functions, p- value	p = 0.0779	
Cause-specific hazard ratio for VILO versus placebo (95% CI); p-value	0.539 (0.297, 0.978) p = 0.0422	

Source: Clinical Study Report Table 10-6 (page 111), Table 10-8 (page 117), Table 10.2.2 (page 119), Table 10-11 (page 121), Table 10-12 (page 121), Table 14.2.2.4.3.1 (page 1281), and Table 14.2.2.4.5.1 (page 1287); results reproduced by the reviewer using adeff.xpt and adeff2.xpt

[1] Results from clinical study report; reviewer produced similar results, but results were not identical due to use of multiple imputation.

[2] Patients with an improvement in the WHO 8-point scale include patients discharged from the hospital. See section 8.2.4 for definition.

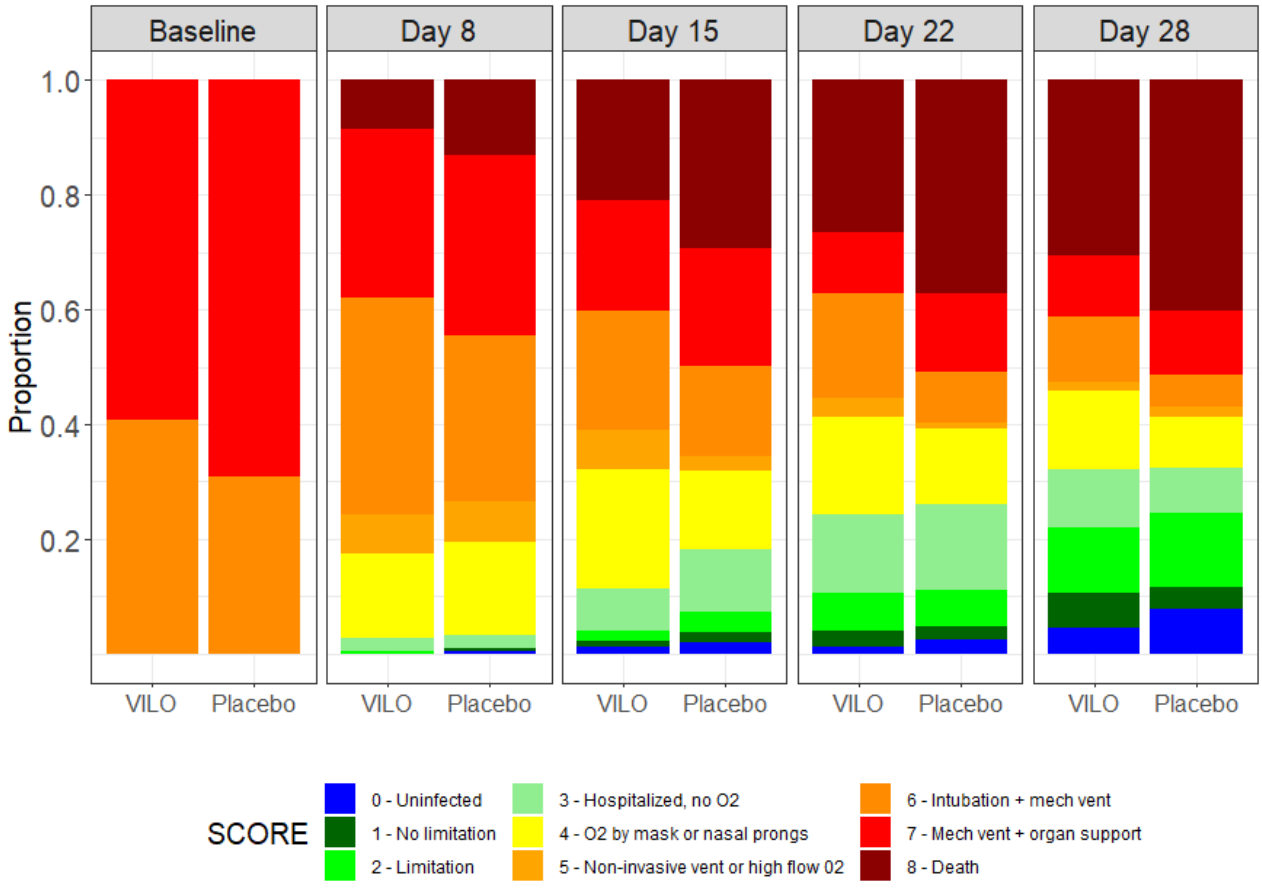
[3] For secondary endpoints, the Requester considered subject IFX-1-P2.9-(b) (6) to be non-evaluable. This subject discontinued the study at Day 10 when transferred to another hospital, but still provided results at Day 28 follow-up visit.

Abbreviations: CI = confidence interval, SOC = standard of care, VILO = vilobelimab; WHO = World Health Organization.

In the FAS, subjects in the VILO group were more likely to show an improvement in the WHO ordinal scale score as compared to subjects in the placebo group, although the differences were not statistically significant. The distribution of WHO ordinal scale scores by group and study visit is provided in Figure 2 using the method of last observation carried forward (LOCF). The details of the distribution are located in

Table33 in the Appendices. When descriptively comparing the baseline WHO scores of the two treatment groups, the placebo population had a higher proportion of subjects with a WHO 7 score compared to placebo. At Day 28, a similar proportion of subjects remained mechanically ventilated (WHO 6 and 7) in both the VILO and placebo groups, although a higher proportion of subjects in the placebo group had a WHO 8 score (death), consistent with the primary endpoint results. However, it is notable that improvement in WHO score at Day 28 appears to be driven by the higher number of deaths in the placebo group. At Day 28, a larger proportion of subjects in the VILO group continued to require respiratory support with low or high flow oxygen, noninvasive and invasive ventilation (WHO scores 4-7) as compared to placebo. Further, more placebo subjects had been discharged from the hospital (WHO score 0-2) by Day 28 than VILO-treated subjects. Given that this population of critically ill patients appears to have prolonged course of disease as evidenced by the number of subjects who continued to require substantial respiratory support at Day 28, additional exploratory analyses were performed at later timepoints (see Section 8.2.5.5 below).

Figure 2: WHO Ordinal Scale Score by Visit (Full Analysis Set, LOCF)



Source: Clinical Study Report Figure 10-9 (page 120); results reproduced by the reviewer using adsl.xpt and adqs.xpt
Abbreviations: LOCF = last observation carried forward, VILO = vilobelimab

Results for the final two endpoints related to acute kidney failure and renal replacement therapy also favored VILO, but the results were not statistically significant after

accounting for the multiple testing procedure, and low event rates produced large confidence intervals.

7.2.5.5 Exploratory Endpoints

Additional exploratory analyses evaluating the effect of VILO on recovery were performed estimating a risk difference using the method described in the Primary Endpoint Analysis Section. The first post-hoc reviewer-initiated analysis evaluated the percentage of subjects meeting the following criteria: alive without oxygen requirements (defined as a WHO ordinal score ≤ 3) or having been previously discharged from the hospital at Day 28 (Table 11). A similar percentage of subjects met these criteria in the VILO (35.0%) and placebo (36.1%) groups; the estimated difference was -0.8% (95% CI = -10.5%, 9.0%). The Requester had prespecified a similar analysis, but subjects discharged from the hospital without a Day 28 score were counted as missing.

A second post-hoc reviewer-initiated analysis evaluated the proportion of subjects meeting the following criteria: alive and not requiring MV or ECMO (defined as a WHO ordinal scale score ≤ 5) or having been previously discharged from the hospital at Day 28 (Table 11). A slightly higher percentage of subjects met these criteria in the VILO group (45.8% vs 42.9%); the estimated difference was 3.3% (95% CI = -6.8%, 13.3%). See Figure 2 for the full distribution of the WHO ordinal scale scores at Day 28.

The WHO ordinal scale score was not collected at Day 60, and therefore rates of recovery using the above definitions could not be compared at Day 60. In a prespecified analysis, the Requester evaluated the Glasgow Outcome Scale Score at Day 60 using the ordinal logistic regression model with covariates age and treatment group based on available data at Day 60. Missing Glasgow Outcomes Scale measurements were not imputed. The resulting OR was 1.504 (95% CI = 0.996, 2.272), indicating subjects in the VILO were more likely to have a better outcome. However, the difference in the proportion of subjects still in poor condition, defined as a Glasgow Score ≤ 3, at Day 60 was smaller than the difference in the proportion of subjects who died (10.5% vs 5.7%). We also note that the Glasgow Outcome Score is typically used to categorize the outcomes of patients after a traumatic brain injury and is a crude measure of recovery from COVID-19 infection.

Table 11: Exploratory Endpoints (Full Analysis Set)

Endpoint	VILO (N = 177)	Placebo (N = 191)
Recovery at Day 28 (OS ≤ 3 or discharged)		
Alive without oxygen requirement or discharged from hospital[1], n (%)	62 (35.0%)	69 (36.1%)
Requiring oxygen or died, n (%)	106 (59.9%)	113 (59.2%)
Not evaluable[2], n (%)	9 (5.1%)	9 (4.7%)
Risk difference[3], VILO – Placebo (95% CI)	0.8% (-10.5%, 9.0%)	
Recovery at Day 28 (OS ≤ 5 or discharged)		
Alive without IMV/ECMO or discharged from hospital, n (%)	81 (45.8%)	82 (42.9%)
Requiring IMV/ECMO or died, n (%)	87 (49.2%)	100 (52.4%)
Not evaluable[2], n (%)	9 (5.1%)	9 (4.7%)
Risk difference[3], VILO – Placebo (95% CI)	3.3% (-6.8%, 13.3%)	

Endpoint	VILO (N = 177)	Placebo (N = 191)
Glasgow Outcome Scale score at Day 60		
1 – Death, n (%)	62 (35.0%)	87 (45.5%)
2 – Persistent vegetative state, n (%)	1 (0.6%)	1 (0.5%)
3 – Severe disability (conscious but disabled), n (%)	16 (9.0%)	8 (4.2%)
4 – Moderate disability (disabled but independent), n (%)	22 (12.4%)	26 (13.6%)
5 – Good recovery, n (%)	60 (33.9%)	54 (28.3%)
Not evaluable[4], n (%)	16 (9.0%)	15 (7.9%)
Odds ratio (95% CI); p-value	1.504 (0.996, 2.272)	

Source: Clinical Study Report Table 10-15 , Table 10-6, (page 125), Table 10-17 (page 126), and reviewer analysis; results reproduced or generated using adsl.xpt, adqs.xpt, and adeff.xpt
[1] The Requester performed a similar analysis with the positive outcome defined as alive without oxygen requirement, but included all individuals without a WHO score, regardless of hospital discharge, as not evaluable. This analysis estimated a similar risk difference (Risk Difference = 0.8%; 95% CI = -9.2, 10.8%).
[2] The non-evaluable subjects include the 17 subjects who were censored and the one additional subject who did not have a WHO ordinal score.
[3] Risk difference and its confidence interval was estimated from a logistic regression model with multiple imputation for missing data.
[4] Glasgow Outcome Scale scores other than 1 (Death) were only included if they were assessed at or after study Day 53.
Abbreviations: CI = confidence interval, ECMO = extracorporeal membrane oxygenation; IMV = invasive mechanical ventilation; OS= WHO ordinal scale score, SOC = standard of care, VILO = vilobelimab

Finally, this review attempted to estimate the percentages of subjects who were dead, hospitalized with a tracheostomy, hospitalized, or discharged from their initial hospitalization by Day 60 using the Procedures dataset and the Healthcare Encounters Analysis dataset in a post-hoc analysis (Table 12). Among the 345 subjects who did not discontinue the study prematurely for a reason other than death, approximately 8.3% of subjects in placebo group and 14.4% of subjects in the VILO group were still hospitalized at Day 60. Collectively, these exploratory analyses suggest that these assessments may not have been reported for a sufficient duration or comprehensive enough to evaluate whether VILO increases the likelihood that a patient will fully recover from the illness or to assess the qualify life after the hospital discharge.

Table 12: Hospitalization at Day 60 (All Randomized Subjects)

Endpoint	VILO (N = 178)	Placebo (N = 191)
Death	62 (35.0%)	87 (45.5%)
Hospitalized with a tracheostomy	8 (4.5%)	2 (1.0%)
Hospitalized	16 (9.0%)	13 (6.8%)
Discharged alive[1]	79 (44.6%)	78 (40.8%)
Missing hospitalization information and mortality status	13 (7.3%)	11 (5.8%)

Source: Reviewer analysis using adho.xpt, adsl.xpt, and pr.xpt
[1] Discharged from the initial hospitalization.
Abbreviations: VILO = vilobelimab

7.2.5.6 Subgroup Analyses

The primary analysis of the primary endpoint was repeated in subgroups defined by demographics, baseline medical conditions, concomitant medications, country and region. Key results are reported in Table 13. In most subgroups with reasonable sample sizes, the estimated HR was < 1. In Brazil, however, the estimated HR was 1.268 (95% CI = 0.548 – 2.93), but in Latin America combined, the estimated HR was 0.940 (95% CI = 0.528 – 1.673). One potential explanation is that the placebo subjects in Brazil

tended to be younger than the VILO-treated subjects in Brazil, and adjusting for age as a linear term in the Cox model did not completely eliminate confounding. See Table 34 for age distribution in subjects from Brazil.

Post-hoc analyses of the mortality endpoint in subjects from Brazil that stratified by age as a categorical variable (≤ 30, 31-40, 41-50, 51-60, > 60 years of age) resulted in estimated HRs < 1; the estimated HR was 0.970 (95% CI = 0.414, 2.27) for the primary endpoint of all-cause mortality at 28 days and the estimated HR was 0.758 (95% CI = 0.342, 1.676) for the secondary endpoint of all-cause mortality at 60 days. Overall, there was no compelling evidence to suggest that VILO was less effective in subjects from Brazil.

Table 13: 28-Day All-Cause Mortality, Cox Regression Analysis Adjusting for Age by Subgroup (Full Analysis Set)

Variable	VILO n/N (%)	Placebo n/N (%)	HR (95% CI)
Sex			
Male	37/125 (29.6)	53/127 (41.7)	0.64 (0.42, 0.98)
Female	17/52 (32.7)	24/64 (37.5)	0.7 (0.37, 1.32)
Race			
White	35/115 (30.4)	42/119 (35.3)	0.75 (0.48, 1.17)
Other	15/48 (31.3)	27/56 (48.2)	0.6 (0.32, 1.13)
Ethnic			
Hispanic or Latino	22/60 (36.7)	24/68 (35.3)	0.96 (0.54, 1.71)
Not Hispanic or Latino	18/70 (25.7)	30/73 (41.1)	0.55 (0.3, 0.98)
Age Group			
≥ 18 years and ≤ 65 years	36/124 (29.0)	41/133 (30.8)	0.91 (0.58, 1.42)
> 65 years and ≤ 85 years	18/53 (34.0)	36/58 (62.1)	0.44 (0.25, 0.79)
Country			
Belgium	1/8 (12.5)	2/7 (28.6)	0.18 (0.01, 2.96)
Brazil	13/34 (38.2)	10/40 (25.0)	1.27 (0.55, 2.93)
France	0/17 (0)	5/18 (27.8)	0 (0, >100)
Germany	3/10 (33.3)	5/11 (45.5)	0.64 (0.15, 2.73)
Netherlands	17/68 (25.0)	26/70 (37.1)	0.57 (0.31, 1.04)
Mexico	7/18 (38.9)	13/19 (68.4)	0.39 (0.15, 0.99)
Peru	2/6 (33.3)	2/9 (22.2)	1.67 (0.23, 12.16)
Russia	8/11 (72.7)	11/12 (91.7)	0.37 (0.14, 0.97)
South Africa	3/5 (60.0)	3/5 (60.0)	0.94 (0.16, 5.43)
Region			
Western Europe	21/103 (20.4)	38/106 (35.8)	0.51 (0.3, 0.87)
Latin America	22/58 (37.9)	25/68 (36.8)	0.94 (0.53, 1.67)
South Africa/Russian Federation	11/16 (68.8)	14/17 (82.4)	0.62 (0.28, 1.38)
WHO 8 point ordinal scale evaluation			
6 - Intubation and mechanical ventilation	21/72 (29.2)	21/59 (35.6)	0.80 (0.44, 1.46)
7 - Ventilation + additional organ support (vasopressors, RRT, ECMO)	33/105 (31.4)	56/132 (42.4)	0.62 (0.4, 0.95)
eGFR			
< 60 mL/min/1.73m^2	19/47 (40.4)	34/61 (55.7)	0.55 (0.31, 0.96)
≥ 60 mL/min/1.73m^2	35/129 (27.1)	43/130 (33.1)	0.79 (0.5, 1.23)
Diabetes			
No	33/132 (25.0)	47/126 (37.3)	0.60 (0.38, 0.94)
Yes	21/45 (46.7)	29/64 (45.3)	0.89 (0.51, 1.56)

Variable	VILO n/N (%)	Placebo n/N (%)	HR (95% CI)
ARDS			
Mild	0/1 (0)	0/1 (0)	--
Moderate	37/133 (27.8)	45/135 (33.3)	0.75 (0.48, 1.16)
Severe	17/43 (39.5)	32/55 (58.2)	0.55 (0.3, 0.98)
Background therapies			
Systemic corticosteroids			
Yes	54/176 (30.7)	74/188 (39.4)	0.7 (0.49, 1.00)
No	0/1 (0)	3/3 (100)	--
Antithrombotic agents			
Yes	54/176 (30.7)	76/187 (40.6)	0.68 (0.48, 0.96)
No	0/1 (0)	1/4 (25.0)	--
Anti-IL-6 (tocilizumab or levilimab)			
Yes	3/31 (9.7)	13/31 (41.9)	0.21 (0.06, 0.75)
No	51/146 (34.9)	64/160 (40.0)	0.78 (0.54, 1.13)
Remdesivir			
Yes	5/10 (50.0)	5/11 (45.5)	0.71 (0.19, 2.62)
No	49/167 (29.3)	72/180 (40.0)	0.67 (0.47, 0.96)
Baricitinib			
Yes	0/6 (0)	2/6 (33.3)	--
No	54/171 (31.6)	75/185 (40.5)	0.69 (0.49, 0.98)

Source: Clinical Study Report Table 14.2.10.1 (page 762), Table 14.2.1.11.1 (page 775), Table 14.2.1.13.1 (page 771), Table 14.2.1.15.1 (page 591), Table 14.2.1.17.1 (page 810), Table 14.2.1.20.1 (page 819), Table 14.2.1.24.1 (page 831), and reviewer analysis; results reproduced by the reviewer using adeff.xpt and adsl.xpt
Abbreviations: ARDS = acute respiratory distress syndrome, ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate, HR = hazard ratio; RRT = renal replacement therapy; SOC = standard of care, VILO = vilobelimab; WHO = World Health Organization.

As we noted slight imbalances in medical conditions (i.e., diabetes, WHO ordinal scale, eGFR, ARDS) across treatment groups at baseline, it is important to note the HR < 1 in all subgroups defined by these variables. Furthermore, the estimated HR remained similar when using Cox models that stratified by WHO ordinal scale value (HR = 0.668, p-value=0.0236), eGFR category (HR = 0.683, p-value=0.032), ARDS category (HR = 0.687, p-value=0.0349), and diabetes status (HR = 0.699, p-value=0.056).

7.3 PANAMO Phase II Trial

The Phase 2 portion of PANAMO was a randomized, open-label, two-arm, multi-center trial conducted at three academic hospitals in the Netherlands between March 31, 2020 and July 8, 2020. The trial randomized 30 subjects (15 per group) to either VILO + Best Supportive Care (BSC) or BSC alone. The key inclusion criteria included (i) at least 18 years or older (ii) clinical evidence or otherwise confirmed severe pneumonia (iii) PaO_2 / FiO_2 ratio between 100 and 250, and (iv) SARS-CoV-2 infection confirmation. The primary endpoint was relative change (%) from baseline in Oxygenation Index (OI = PaO_2 / FiO_2) in supine position at Day 5, and the four secondary endpoints were all-cause 28 day mortality, percentage of subjects achieving an early response, percentage of subjects achieving a late response, and the relative change in OI on other study days. Definitions of early and late response were based on OI, body temperature, and white blood cell count at Days 7 and Day 28 respectively.

Although results were not statistically significant, subjects randomized to VILO + BSC tended to have better outcomes, as compared to subjects randomized to BSC. A lower OI indicates improved oxygenation, and the relative change in OI at Day 5 was estimated to be 15.5% in the VILO + BSC group and 31.9% in the BSC group. The between-group difference was estimated to be –16.4% (95% CI = -53.2, 20.3; p=0.3677). However, at the May 20, 2020 meeting of the Expert Committee constituted by the Requester, the Requester noted multiple concerns with the primary endpoint, including high intra-individual variability of the measurement and difficulty in moving subjects into the supine position. Two subjects (13%) in the VILO + BSC group and 4 subjects (27%) in the BSC group died prior to 28 days; the adjusted hazard ratio for death 0.65 (95% CI 0.10–4.14, p=0.65). The Expert Committee noted that a "case by case assessment of the reason for deaths revealed that all patients in the BSC group died due to multiorgan failure including renal failure, whereas in the [VILO] group one patient died due to tube leakage that led to a sustained period of very low oxygenation / hypoxia and subsequent death and one patient had a medical history of progressed COPD and died of respiratory failure." The early response and late response endpoints could not be adequately assessed due to difficulties in obtaining needed measurements. Overall, the committee recommended continuing with the Phase 3 trial, but suggested using 28-day mortality as the primary outcome and focusing on more severely ill patients. That said, the small size and differences in patient population and efficacy endpoints limit the contribution of the Phase 2 data to the totality of evidence supporting the potential benefit of VILO for the proposed emergency use population.

8 Human Clinical Safety: Assessment of Risk and Risk Management

8.1 Potential Risks or Safety Concerns Based on Nonclinical Data

Because no test-article related toxicities were observed in the repeat-dose, reproductive or developmental toxicology studies in male and female cynomolgus monkeys (see Section 12), there are no safety concerns with vilobelimab based on the nonclinical data.

8.2 Adequacy of Clinical Safety Database

8.2.1 Previous Human Experience

VILO is not approved in the United States or marketed outside the United States for any indication. In addition to COVID-19, there are clinical trials with VILO in early septic organ dysfunction, patients undergoing complex cardiac surgery, moderate-to-severe hidradenitis suppurativa (HS), ANCA-associated vasculitis (AAV), granulomatosis with polyangiitis (GPA) and microscopic polyangiitis, and pyoderma gangrenosum. A total of

587 subjects have been exposed to at least one dose of VILO across all indications. Although vilobelimab has only been administered via the intravenous route of administration, clinical studies have evaluated a range of doses and dosing regimens including weight-based dosing (mg/kg) for septic organ dysfunction and fixed doses up to 1200 mg every 2 weeks for a maximum of 14 weeks in HS. Refer to Section 11 Human Clinical Pharmacology for additional details.

8.2.2 Safety Database for COVID-19

The safety of VILO in COVID-19 is derived entirely from the PANAMO trial, in which 190 total subjects were exposed (15 subjects in the Phase 2 portion and 175 in the Phase 3 portion). Given differences in disease severity between the study populations in Phase 2 and 3, the safety analysis focuses on data from Phase 3.

8.3 Safety Findings and Concerns Based on Review of Clinical Safety Database

8.3.1 Safety Overview of Phase III Trial

All safety analyses were conducted using the Phase 3 Safety Analysis Set (SAF), which included all subjects who received at least one dose of study drug. The SAF population included 175 subjects in the VILO group and 189 subjects in the placebo group for a total of 364 subjects. The SAF population excluded four subjects from the FAS population (two in the VILO group and two in the placebo group) who were randomized but did not receive study drug.

The definitions of adverse events (AEs) and serious adverse events (SAEs) were consistent with 21 CFR 312.32. Treatment emergent adverse events (TEAEs) were defined as any AE which occurred or worsened at or after the first administration of study drug. AEs were collected from the time of informed consent or documented decision timepoint of the responsible investigator and/or physicians to enroll patient until 30 days following the last study drug administration or until the end of study (Day 60) if the AEs were ongoing. Death and drug-related SAEs with onset during the follow-up period (after Day 30) were reported through Day 60. AEs were coded using MedDRA v24.1.

An overview of TEAEs is shown in Table 14. The high frequency of TEAEs observed in both treatment groups is to be expected in a critically ill, mechanically ventilated COVID-19 patient population. TEAEs overall were balanced in both treatment groups. The imbalance in SAEs in the placebo group is primarily driven by the higher number of deaths. Grade 3 and 4 TEAEs occurred in a higher proportion of subjects in the VILO group and are explored in more detail later in subsequent sections of the safety review.

Table 14. Treatment Emergent Adverse Events Summary (Safety Analysis Set)

Adverse Event Category	VILO (N = 175) n (%)	Placebo (N = 189) n (%)
Any subject with one or more SAE	103 (58.9)	120 (63.5)
Fatal SAEs	62 (35.4)	85 (45.0)
Non-fatal SAEs	82 (46.9)	88 (46.6)
Any TEAE leading to premature treatment discontinuation	5 (2.9)	3 (1.6)
Any TEAE leading to interrupted/omitted/postponed infusion	2 (1.1)	7 (3.7)
Any TEAE leading to premature study termination for reasons other than death	0	0
Any TEAE	159 (90.9)	172 (91.0)
Grade 1 (Mild)	14 (8.0)	12 (6.3)
Grade 2 (Moderate)	25 (14.3)	29 (15.3)
Grade 3 (Severe)	26 (14.9)	19 (10.1)
Grade 4 (Life-threatening)	32 (18.3)	27 (14.3)
Grade 5 (Fatal)	62 (35.4)	85 (45.0)

Source table: Study Report 1 Table 11-1
Grade categories as reflected by the NCI CTCAE v5.0.
Clinical reviewer produced table using JMP and adae.xpt Adam dataset, USUBJID: Unique Subject ID; TRT01A = "SOC + Vilobelimab, TRT01A = "SOC + Placebo, SAFFL (Y), AETRTEM (Y), AESER (Y/N), AESDTH (Y/N), ATOXGRN (1 – 5); 2 subjects not treated.
Abbreviations: TEAE: treatment emergent adverse Event; SAE: serious adverse event; VILO = vilobelimab.

8.3.1.1 Deaths

In the SAF population, the placebo group experienced more deaths (85/189, 45.0%) than the VILO group (62/175, 35.4%). Note that the number of deaths differs from the Day 60 all-cause mortality results because of the different analysis populations (SAF versus FAS). The most common causes of death by reported MedDRA preferred term (PT) were multiple organ dysfunction syndrome, respiratory failure, and septic shock, with more events occurring in the placebo group. The remaining fatal SAEs occurred with relatively equal frequency or as single events in both treatment groups. The types and pattern of events are consistent with progression of COVID-19 disease or complications from hospitalization and mechanical ventilation in an intensive care setting rather than being related to VILO treatment; therefore, for completeness, all adverse events leading to death are listed below.

Table 15. Treatment Emergent Adverse Events Leading to Death (Safety Analysis Set)

Preferred Term	VILO n=175 n (%)	Placebo n=189 n (%)
Unique subjects with treatment emergent SAEs leading to death	**62 (35.4)**	**85 (45.0)**
Multiple organ dysfunction syndrome	16 (9.1)	20 (10.6)
Respiratory failure	11 (6.3)	20 (10.6)
Septic shock	11 (6.3)	20 (10.6)
Pulmonary sepsis	5 (2.9)	5 (2.6)
Acute respiratory distress syndrome	3 (1.7)	3 (1.6)
Covid-19 pneumonia	2 (1.1)	0 (0.0)

Preferred Term	VILO n=175 n (%)	Placebo n=189 n (%)
Distributive shock	2 (1.1)	1 (0.5)
Hypoxia	2 (1.1)	3 (1.6)
Sepsis	2 (1.1)	0 (0.0)
Aspergillus infection	1 (0.6)	0
Bronchial obstruction	1 (0.6)	0
Candida sepsis	1 (0.6)	0
Cardiac arrest	1 (0.6)	2 (1.1)
Cardiac failure acute	1 (0.6)	0
Cardio-respiratory arrest	1 (0.6)	2 (1.1)
Cardiopulmonary failure	1 (0.6)	0
Enterococcal sepsis	1 (0.6)	1 (0.5)
Hemoptysis	1 (0.6)	0
Hyperthermia	1 (0.6)	0
Obstructive shock	1 (0.6)	0
Pneumomediastinum	1 (0.6)	0
Pneumonia	1 (0.6)	4 (2.1)
Pneumonia acinetobacter	1 (0.6)	0
Pneumonia aspiration	1 (0.6)	0
Pneumonia klebsiella	1 (0.6)	0
Pneumonia staphylococcal	1 (0.6)	0
Post procedural hemorrhage	1 (0.6)	0
Pulmonary necrosis	1 (0.6)	0
Severe acute respiratory syndrome	1 (0.6)	0
Staphylococcal infection	1 (0.6)	1 (0.5)
Stroke in evolution	1 (0.6)	0
Thrombosis	1 (0.6)	0
Urosepsis	1 (0.6)	2 (1.1)
Acinetobacter infection	0	1 (0.5)
Acute hepatic failure	0	1 (0.5)
Acute kidney injury	0	3 (1.6)
Acute myocardial infarction	0	1 (0.5)
Blood culture positive	0	1 (0.5)
Bronchopulmonary aspergillosis	0	1 (0.5)
Cardiac failure	0	1 (0.5)
Cardiac perforation	0	1 (0.5)
Cardiogenic shock	0	1 (0.5)
Hepatic failure	0	1 (0.5)
Herpes simplex pneumonia	0	1 (0.5)
Hyperkalemia	0	1 (0.5)
Klebsiella infection	0	1 (0.5)
Peritonitis	0	1 (0.5)
Pneumonia serratia	0	1 (0.5)
Pneumothorax	0	1 (0.5)
Pulmonary fibrosis	0	1 (0.5)

Preferred Term	VILO n=175 n (%)	Placebo n=189 n (%)
Shock	0	1 (0.5)
Superinfection bacterial	0	1 (0.5)
Ventricular arrhythmia	0	1 (0.5)
Ventricular fibrillation	0	1 (0.5)

Source: Clinical reviewer produced table using JMP and Analysis Studio Safety Explorer with adae.xpt Adam dataset.
Grade categories as reflected by the NCI CTCAE v5.0. USUBJID: Unique Subject ID, TRT01A = "SOC + Vilobelimab, TRT01A = "SOC + Placebo, SAFFL (Y), AETRTEM (Y), AESER: Y, ATOXGRN (5), AESDTH, AEDECOD.The listed PTs do not add up to the total number of subjects with SAEs leading to death due to one unique subject may have had multiple SAEs coded as a Grade 5 or AE associated with death. The following Preferred Terms were changed to American English for this Table: 'haemoptysis' 'haemorrhage', 'hyperkalaemia'.
Abbreviations: COVID-19 = coronavirus disease 2019; SAE = severe adverse event; VILO = vilobelimab.

8.3.1.2 Nonfatal Serious Adverse Events

Nonfatal SAEs that occurred in the safety analysis set population are shown in Table16. Events reported more frequently in the VILO group were primarily related to infections. This safety signal is described in more detail in the section on Adverse Events of Special Interest (AESI) below.

Table 16. Nonfatal Serious Adverse Events Reported in ≥1% Vilobelimab-Treated Subjects and More Frequently Than Placebo (Safety Analysis Set)

System Organ Class Preferred Term	VILO (N=175) n (%)	Placebo (N=189) n (%)
Infections and infestations	**58 (33.1)**	**55 (29.1)**
Pneumonia[1]	33 (18.9)	26 (13.8)
Sepsis[2]	26 (14.9)	14 (7.4)
Septic shock	16 (9.1)	14 (7.4)
Bronchopulmonary aspergillosis	6 (3.4)	5 (2.6)
Urinary tract infection	6 (3.4)	3 (1.6)
Acinetobacter infection	4 (2.3)	3 (1.6)
Enterococcal infection	2 (1.1)	1 (0.5)
Lung abscess	2 (1.1)	0
Stenotrophomonas infection	2 (1.1)	1 (0.5)
Respiratory, thoracic and mediastinal disorders	**29 (16.6)**	**30 (15.9)**
Respiratory failure	10 (5.7)	5 (2.6)
Hypoxia	3 (1.7)	0
Aspiration	2 (1.1)	0
Pneumomediastinum	2 (1.1)	0
Renal and urinary disorders	**21 (12.0)**	**30 (15.9)**
Renal failure	3 (1.7)	2 (1.1)
Nervous system disorders	**8 (4.6)**	**8 (4.2)**
Depressed level of consciousness	4 (2.3)	4 (2.1)
Autonomic nervous system imbalance	2 (1.1)	0
Cerebral infarction	2 (1.1)	1 (0.5)
Cardiac disorders	**7 (4.0)**	**11 (5.8)**
Cardiac arrest[3]	4 (2.3)	3 (1.6)

System Organ Class Preferred Term	VILO (N=175) n (%)	Placebo (N=189) n (%)
Vascular disorders	**7 (4.0)**	**2 (1.1)**
Shock hemorrhagic	3 (1.7)	1 (0.5)
Investigations	**5 (2.9)**	**3 (1.6)**
Bronchoalveolar lavage abnormal	2 (1.1)	1 (0.5)
Herpes simplex test positive	2 (1.1)	0 (0.0)
Blood and lymphatic system disorders	**3 (1.7)**	**3 (1.6)**
Thrombocytopenia	2 (1.1)	0

Source: Clinical reviewer produced table using JMP, JMP Safety Explorer and Analysis Studio with adae.xpt Adam dataset, USUBJID: Unique Subject ID, TRT01A = "SOC + Vilobelimab, TRT01A = "SOC + Placebo, SAFFL (Y), AETRTEM (Y), AESER (Y), ATOXGRN, AESOC, AEDECOD.
[1] "Pneumonia" includes the following PTs: Pneumonia, Pneumonia staphylococcal, Pneumonia klebsiella, Pneumonia acinetobacter, Pneumonia pseudomonal, Pneumonia Escherichia, Enterobacter pneumonia, Pneumonia bacterial, Pneumonia cytomegaloviral, Pneumonia serratia, Pneumonia streptococcal, Herpes simplex pneumonia, Pneumonia aspiration, Pneumonia haemophilus
[2] "Sepsis" includes the following PTs: Pulmonary sepsis, Staphylococcal sepsis, Enterococcal sepsis Sepsis, Acinetobacter sepsis Pseudomonal sepsis, Urosepsis, Device related sepsis, Klebsiella sepsis, Corynebacterium sepsis, Enterobacter sepsis
[3] Cardiac arrest" includes the following PTs: Cardiac arrest, Cardio-respiratory arrest
Grade categories as reflected by the NCI CTCAE v5.0
The following Preferred Terms were changed to American English for this Table: 'haemorrhage'.
Abbreviations: VILO = vilobelimab.

8.3.1.3 Dropouts and/or Discontinuations Due to Adverse Events

TEAEs leading to premature treatment discontinuation occurred with a slightly higher frequency in the VILO group compared to the placebo group. However, the PTs reported were single events with no particular pattern. The types of events leading to discontinuation appear more likely to be caused by the underlying COVID-19 disease than by VILO treatment. TEAEs leading to interrupted/omitted/postponed infusion occurred in two subjects in the VILO group (respiratory failure and hypotension) and seven subjects in the placebo group (septic shock, pulmonary sepsis, infection, multiple organ dysfunction, peripheral edema, renal failure, ventricular tachycardia, and skin swelling).

Table 17. Dropouts and/or Discontinuations Due to Treatment Emergent Adverse Events by Preferred Term (Safety Analysis Set)

Preferred Term	VILO N = 175 n (%)	Placebo N = 189 n (%)
Any subject with treatment discontinuation due to TEAE	**5 (2.9)**	**3 (1.6)**
Bronchopulmonary aspergillosis	1 (0.6)	0
Eczema	1 (0.6)	0
Hemodynamic instability	1 (0.6)	0
Multiple organ dysfunction syndrome	1 (0.6)	0
Thrombocytopenia	1 (0.6)	0
Rash	1 (0.6)	0
Acute kidney injury	0	1 (0.5)
Hyperkalemia	0	1 (0.5)
Organizing pneumonia	0	1 (0.5)

Source: Clinical reviewer produced table using JMP and Analysis Studio Safety Explorer with adae.xpt Adam dataset
TRT01A = "SOC + Vilobelimab, TRT01A = "SOC + Placebo, SAFFL (Y), AETRTEM (Y), AEACN = "DRUG WITHDRAWN".
Preferred terms do not add to total "any subject" total due to multiple unrelated reasons for discontinuation being attributed to one unique subject.
Abbreviations: TEAE: Treatment Emergent Adverse Events; VILO = vilobelimab.

8.3.1.4 Other Significant Adverse Events

As shown in Table 14, the overall frequency of Grade 3 and 4 TEAEs were higher in the VILO group. Because the majority of Grade 3 and 4 TEAEs were also SAEs, the review explored whether the difference was driven by the larger number of infection-related nonfatal SAEs in the VILO group as described in Table 16 or possibly due to another reason. To explore this question, the table below shows Grade 3 and 4 TEAEs that were not already captured as an SAE (Table 18). The non-serious, severe, or life-threatening TEAEs were similar across treatment groups or occurred at higher frequency in the placebo arm; no additional safety signals were detected in this assessment.

Table 18. Non-Serious Grade 3 and 4 TEAEs by Treatment Group With Frequency ≥ 1% in Vilobelimab-Treated Subjects and Greater Than Placebo (Safety Analysis Set)

System Organ Class Preferred Term	VILO (N=175) n (%)	Placebo (N=189) n (%)
Infections and infestations	**17 (9.7)**	**26 (13.8)**
Pneumonia	5 (2.9)	5 (2.6)
Bronchopulmonary aspergillosis	2 (1.1)	1 (0.5)
Staphylococcal bacteremia	2 (1.1)	1 (0.5)
Vascular disorders	**11 (6.3)**	**9 (4.8)**
Deep vein thrombosis	6 (3.4)	6 (3.2)
Hypertension	2 (1.1)	0
Renal and urinary disorders	**7 (4.0)**	**7 (3.7)**
Acute kidney injury	7 (4.0)	5 (2.6)
Respiratory, thoracic and mediastinal disorders	**7 (4.0)**	**6 (3.2)**
Pulmonary embolism	3 (1.7)	1 (0.5)
Investigations	**6 (3.4)**	**5 (2.6)**
Hepatic enzyme increased	2 (1.1)	0
Injury, poisoning and procedural complications	**2 (1.1)**	**0**
Endotracheal intubation complication	2 (1.1)	0

Source: Clinical reviewer produced table using JMP and Analysis Studio Safety Explorer, adae.xpt dataset
TRT01A = "SOC + Vilobelimab, TRT01A = "SOC + Placebo, SAFFL (Y), AETRTEM (Y), ATOXGRN Grade 3 and 4, AESER (N) AESOC, AEDECOD.
Grade categories as reflected by the NCI CTCAE v5.0.
Preferred Terms (PT); "bacteraemia" changed to spelling in American English spelling for table.
Abbreviations: VILO = vilobelimab

8.3.1.5 Common Adverse Events

TEAEs occurred in a high proportion of subjects in both treatment groups. The most commonly occurring TEAEs were pneumonia and sepsis, both of which occurred more frequently in the VILO group. As infection-related TEAEs appeared to be a consistent safety signal across analyses, infection risk will be further discussed below in the AESI subsection. Although pulmonary embolism and deep vein thrombosis events occurred at a slightly higher rate in the VILO group, the frequency was similar to placebo for events categorized as serious or severe/life-threatening (Grade 3 or 4). An assessment of a broad and narrow search for embolic or thrombotic events using the FDA MedDRA Query (FMQ) for 'Thrombosis Arterial', 'Stroke and TIA', and 'Thrombosis Venous' demonstrated a similar frequency of events between treatment groups and no

concerning safety signals. To explore the numerical difference in supraventricular tachycardia events, a broad and narrow search using the FMQ for 'arrythmia' and 'tachycardia', respectively, was performed; the analyses did not reveal an imbalance in other related PTs or new safety signals. Events such as pneumomediastinum and pneumothorax are not uncommon in a mechanically ventilated population and the numerical differences may be explained by increased survival and extended requirement for mechanical ventilation in the VILO group. The imbalance in thrombocytopenia TEAEs was not associated with an increase in bleeding events.

Table 19. Common TEAEs With Frequency ≥3% by Treatment Group With Frequency ≥3% in Vilobelimab-Treated Subjects and 1% Greater Than Placebo (Safety Analysis Set)

Preferred Term	VILO n=175 n (%)	Placebo n=189 n (%)
At least 1 TEAE	**159 (90.9)**	**172 (91.0)**
Pneumonia[1]	55 (31.4)	44 (23.3)
Sepsis[2]	38 (21.7)	30 (15.9)
Delirium[3]	22 (12.6)	20 (10.6)
Pulmonary embolism	19 (10.9)	17 (9.0)
Hypertension	16 (9.1)	13 (6.9)
Pneumothorax	14 (8.0)	11 (5.8)
Deep vein thrombosis	11 (6.3)	9 (4.8)
Herpes simplex	11 (6.3)	5 (2.6)
Enterococcal infection	10 (5.7)	8 (4.2)
Bronchopulmonary aspergillosis	10 (5.7)	7 (3.7)
Hepatic enzyme increased	9 (5.1)	7 (3.7)
Urinary tract infection	9 (5.1)	6 (3.2)
Hypoxia	8 (4.6)	6 (3.2)
Thrombocytopenia	8 (4.6)	2 (1.1)
Pneumomediastinum	8 (4.6)	0
Respiratory tract infection	7 (4.0)	5 (2.6)
Supraventricular tachycardia	7 (4.0)	1 (0.5)
Constipation	6 (3.4)	3 (1.6)
Rash	6 (3.4)	0

Source: Clinical reviewer produced table using JMP Clinical and Analysis Studio Safety Explorer, adae.xpt dataset
TRT01A = "SOC + Vilobelimab, TRT01A = "SOC + Placebo, SAFFL (Y), AETRTEM (Y), AEDECOD.
[1] "Pneumonia" includes the following PTs: Pneumonia, Pneumonia staphylococcal, Pneumonia klebsiella, Pneumonia acinetobacter, Pneumonia pseudomonal, Enterobacter pneumonia, Pneumonia Escherichia, Herpes simplex pneumonia, Pneumonia aspiration, Pneumonia bacterial, Pneumonia cytomegaloviral, Pneumonia haemophilus, Pneumonia serratia, Pneumonia streptococcal, Organising pneumonia, Pneumonia viral; It does NOT include Covid-19 pneumonia (which is reflected in the footnote).
[2] "Sepsis" includes the following PTs: Pulmonary sepsis: Sepsis, Staphylococcal sepsis, Enterococcal sepsis, Urosepsis, Acinetobacter sepsis, Corynebacterium sepsis, Device related sepsis, Serratia sepsis, Enterobacter sepsis, Stenotrophomonas sepsis, Streptococcal sepsis.[3] "Delirium includes the following PTs: Delirium, Intensive care unit delirium
Abbreviations: TEAE = Treatment Emergent Adverse Events; VILO = vilobelimab

8.3.1.6 Adverse Events of Special Interest

AESIs that were pre-specified in the study protocol included infusion-related reactions (including hypersensitivity or anaphylaxis) during or after a VILO infusion, meningitis and meningococcal sepsis, and infections other than COVID-19 (SARS-CoV-2) infections.

8.3.1.6.1 Infusion-Related Reactions/Hypersensitivity

Events that were identified as potential infusion-related reactions (IRRs) were infrequent and reported in three VILO subjects (all Grade 1) and one placebo subject. The reactions consisted of mild, delayed onset rash; however, upon evaluation, none appear consistent with an IRR or hypersensitivity reaction. There were no reports of anaphylaxis in the PANAMO trial; however, plausible hypersensitivity reactions have occurred within one hour of VILO infusion in clinical trials for other indications (see Table 35 in Appendices for details) and are a potential risk with this product.

8.3.1.6.2 Meningitis/Meningococcal Sepsis

No meningococcal infections were reported in either treatment group.

8.3.1.6.3 Infections

Investigators identified any TEAE potentially related to infection and falling within the MedDRA system organ class (SOC) of 'Infections and infestations' or 'Investigations' as an AESI. Although Grade 5 (fatal) infections were reported more frequently in the placebo group, treatment-emergent infections that were considered serious or Grade 4 (life-threatening) occurred more frequently in the VILO group compared to placebo. Infections other than SARS-CoV-2 that required medical intervention (e.g., antibiotics) and/or were documented as serious by the investigator are shown in Table 20. Events in the table represent unique infections, rather than unique subjects; therefore, if a subject experienced more than one unique event, he/she may be counted more than once in a given category or row. Infections were based on clinical diagnoses, so pathogen data were not recorded for every infectious event; however, the table includes pathogen information where available.

The difference in number of infections between treatment groups is primarily due to an increase in bacterial infections and presumed clinical infections due to unknown etiology in the VILO group. Bacterial pneumonia appears to drive the imbalance in infections when analyzed by subject or by number of events. An assessment of causal pathogens, when available, show a higher incidence of staphylococcal pneumonia infections in the VILO group, with similar numbers of infections caused by other bacterial pathogens across treatment groups.

Although the clinical safety database is limited to a single trial, it is reassuring that the number of infections caused by encapsulated organisms was similar between treatment groups. Primary immunodeficiencies with defects early in the complement cascade, such as C1q, C1rs, C4, C2, C3, factors D, H and I, and/or properdin, are associated with increased risk of sepsis, meningitis, and respiratory tract infections caused by a vulnerability to encapsulated organisms (e.g., *acinetobacter*, *bacillus anthracis*, *enterococcus*. *haemophilus influenzae*, *klebsiella pneumoniae*, *streptococcus pneumoniae*, and *streptococcus agalactiae*, *neisseria meningitis*, *pseudomonas*, *yersinia pestis*, etc). In the case of vilobelimab, the target of inhibition is C5a, which

leaves C5b free to join with C6, C7, C8, C9 and subsequently form the Membrane Attack Complex (MAC) that can perform cell lysis of infected cells (see Figure 8).

Table 20: Unique Treatment-Emergent Infections Requiring Medical Intervention and/or Considered Serious (Safety Analysis Set)

Treatment-Emergent Infections	VILO (N = 175)	Placebo (N = 189)
Total number of treated or serious infection-related AESIs	**298**	**242**
SAE	163	125
Grade 3 (Severe)	58	70
Grade 4 (Life-threatening)	99	55
Grade 5 (Fatal)	19	28
Treated AESI	256	222
Type		
Bacterial[1]	177	153
Fungal[2]	22	21
Viral[3]	25	19
Unknown pathogen[4]	74	49
Location by infection type and pathogen		
Pneumonia	**92**	**58**
Bacterial	54	38
Gram positive organisms	17	7
Gram negative organisms	31	37
Encapsulated organism – yes	21	17
Encapsulated organism – no	24	24
Fungal	4	1
Viral	3	5
Sepsis/bacteremia	**95**	**84**
Bacterial	72	64
Gram positive organisms	41	39
Gram negative organisms	32	25
Encapsulated organism – yes	28	25
Encapsulated organism – no	42	37
Fungal	2	1
Viral	0	0
Respiratory infection, excluding pneumonia[5]	**40**	**35**
Bacterial	18	14
Gram positive organisms	4	5
Gram negative organisms	13	9
Encapsulated bacteria - yes	6	8
Encapsulated bacteria – no	27	23
Fungal	10	14
Viral	8	5
Urinary tract infection	**16**	**12**
Bacterial	11	11
Gram positive organisms	1	3
Gram negative organisms	10	8
Encapsulated bacteria – yes	4	4
Encapsulated bacteria – no	5	7
Fungal	0	0
Viral	0	0

Treatment-Emergent Infections	VILO (N = 175)	Placebo (N = 189)
Device-related infection	**12**	**19**
Bacterial	9	14
Gram positive organisms	9	13
Gram negative organisms	0	1
Encapsulated Bacteria - yes	1	2
Encapsulated Bacteria – no	9	11
Fungal	1	0
Viral	0	0
Other/unspecified infection[6]	**33**	**30**
Viral reactivation[8]	**10**	**4**

Source: Clinical reviewer produced table using JMP with aesi.xpt dataset, TRT01A = "SOC + Vilobelimab, TRT01A = "SOC + Placebo, AESER (Y) or AESITR=Y; ATOXGR , GRAM (pos/neg/na), CLASSINF, ENCAP (Y/N), ACAT1.
Events in this table were only included as onne Classification of Infection and are not included in multiple Location by infection type and pathogen.
[1] The most common bacterial genera reported included *staphylococcus, klebsiella, enterococcus, pseudomonas, acenitobacter, escheria*, and *streptococcus*, all which occurred at similar rates in both treatment arms.
[2] Fungal infections included aspergillus, and candida.
[3] Viral infections included herpes simplex virus (HSV), cytomegalovirus (CMV), and Epstein Barr virus (EBV).
[4] Pathogen data was not known for every infection, and so the values for gram stain and encapsulated organisms under Infection Type include only the pathogen data that was available.
[5]The final classification of “pneumonia” versus "respiratory infection” was based on the Requester’s medical review of Preferred Terms and additional data of the patient’s case report form (including elements such as culture from upper airway, deep bronchoalveolar lavage, chest Xray, etc), as available. Generally, the respiratory infection categorization included upper airway infections, and a pneumonia was considered an infection of the lung tissue. Unique events were not counted in both categories, each event was attributed to only one of the categories.
[6] Other/unspecified infections included the following PTs: Abscess jaw, Aspergillus infection, Bacterial disease carrier, Bacterial infection, Bronchoalveolar lavage abnormal, Candida infection, Cholangitis infective, Clostridium difficile colitis, Conjunctivitis, Cystitis, Cytomegalovirus infection, Cytomegalovirus infection reactivation, Dermatophytosis, Device related infection, Enterococcal infection, Fungal disease carrier, Herpes simplex, Herpes simplex reactivation, Herpes simplex test positive, Impetigo, Infective thrombosis, Klebsiella infection, Oral fungal infection, Oral infection, Otitis media, Parotitis, Pneumococcal infection, Postoperative wound infection, Proteus test positive, Pseudomonas infection, Sinusitis, Staphylococcal infection, Staphylococcus test positive, Streptococcal infection, Streptococcus test positive, Systemic bacterial infection, Systemic candida, Tinea pedis, Vascular device infection, Vulvovaginal mycotic infection, Wound infection.
Abbreviations: AESI = Adverse Events of Special Interest; SAE = Serious Adverse Event; VILO = vilobelimab

The Requester states that the increased infections observed in the VILO group are due to higher survival rates and prolonged hospitalization. To support this assertion, an exposure-adjusted analysis of infections was provided as shown in Table 21. However, adjusting for duration of hospital stay did not eliminate the numerical difference in infections, particularly pneumonia.

Table 21. AESI Infections and Infestations Per 100 Patient Days in Hospital for Infections Requiring Medical Intervention and/or Considered Serious (Safety Analysis Set)

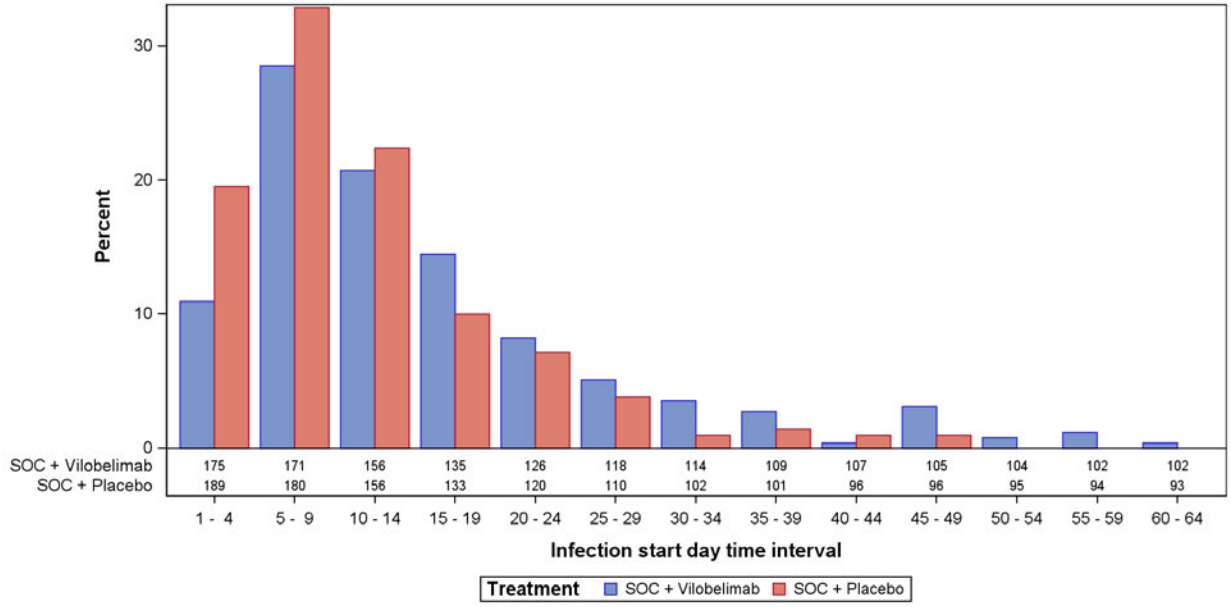
	VILO (N=175)		Placebo (N=189)			
Infections	Events, n	Events per 100 patient days	Events, n	Events per 100 patient days	Rate Ratio	95% CI
Any infection AESI	298	6.67	242	6.14	1.09	[0.92; 1.29]
Pneumonia	92	2.06	58	1.47	1.40	[1.01; 1.94]
Encapsulated bacteria	21	0.47	17	0.43	1.09	[0.58; 2.07]
Unencapsulated bacteria, virus, fungus, unknown	70	1.57	41	1.04	1.51	[1.02; 2.21]
Sepsis/bacteremia	95	2.13	84	2.13	1.00	[0.74; 1.34]
Encapsulated bacteria	28	0.63	25	0.63	0.99	[0.58 1.69]
Unencapsulated bacteria, virus, fungus, unknown	67	1.50	59	1.50	1.00	[0.71; 1.42]

Infections	VILO (N=175) Events, n	VILO (N=175) Events per 100 patient days	Placebo (N=189) Events, n	Placebo (N=189) Events per 100 patient days	Rate Ratio	95% CI
Respiratory infection	40	0.89	35	0.89	1.01	[0.64; 1.59]
Encapsulated bacteria	6	0.13	8	0.20	0.66	[0.23; 1.91]
Unencapsulated bacteria, virus, fungus, unknown	34	0.76	25	0.63	1.20	[0.72; 2.01]
Urinary tract infection	16	0.36	12	0.30	1.18	[0.56; 2.49]
Encapsulated bacteria	4	0.09	4	0.10	0.88	[0.22; 3.53]
Unencapsulated bacteria, virus, fungus, unknown	12	0.27	8	0.20	1.32	[0.54; 3.24]
Device-related infections	12	0.27	19	0.48	0.56	[0.27; 1.15]
Encapsulated bacteria	1	0.02	2	0.05	0.44	[0.04; 4.87]
Unencapsulated bacteria, virus, fungus, unknown	11	0.25	17	0.43	0.57	[0.27; 1.22]
Other/Unspecified infections	33	0.74	30	0.76	0.97	[0.90; 2.63]
Encapsulated bacteria	4	0.09	5	0.13	0.71	[0.19; 2.63]
Unencapsulated bacteria, virus, fungus, unknown	31	0.69	27	0.68	1.01	[0.60; 1.70]
Viral reactivation[1]	10	0.22	4	0.10	2.21	[0.69; 7.03]

Source: Table includes data from aesi.xpt dataset, TRT01A = "SOC + Vilobelimab, TRT01A = "SOC + Placebo, AESER (Y) or AESITR=Y; ATOXGR, CLASSINF, ENCAP (Y/N), ACAT1.
[1] Viral reactivation included the following PTs: Cytomegalovirus infection reactivation, Cytomegalovirus test positive, Epstein-Barr virus infection reactivation, Epstein-Barr virus test positive, Herpes simplex, Herpes simplex reactivation, Herpes simplex test positive, Sputum culture positive.
Abbreviations: AESI = Adverse Events of Special Interest; SAE = Serious Adverse Event; VILO = vilobelimab

The histogram in Figure 3 was provided by the Requester to provide an assessment of infection events over time and displays the day of onset of new infection-related AESIs (considered serious or required treatment) over the course of the trial while showing number of subjects still at risk. The placebo group clearly experienced more infections in the first two weeks of the trial. Although the higher number of infections in the VILO group occurring beyond Day 15 could be due to the greater number of subjects who remained alive and at risk, likely contributing to the overall imbalance in infections, there also appears to be more infections occurring in the trial when numbers at risk were roughly the same and study drug was still being administered (i.e., Days 15 to 24). As such, it cannot be concluded that the imbalance in infections can be entirely attributed to increased survival and prolonged hospitalization in the VILO group and an increased infection risk associated with VILO treatment cannot be ruled out.

Figure 3. New Infection-Related AESIs by Treatment Group and Onset Date (Safety Analysis Set)



Source: Requester provided histogram in response to an Information Request.
Abbreviations: AESI = Adverse Events of Special Interest.

8.3.2 Overview of Additional Safety Data

A review of the safety data for the 30 subjects included in the Phase II portion of PANAMO revealed no additional safety concerns for treatment with VILO. An overview of the clinical experience in other indications (Table 4) did not reveal any safety signals. Specifically, the SOC 'Infections and Infestations' did not appear to occur higher in frequency in the VILO group in these trials; however, it is important to note these non-COVID trials had different populations, dosing (days versus months), and did not all include placebo groups.

8.3.3 Summary of Safety Assessment

TEAEs, including events considered serious and/or severe/life-threatening/fatal, occurred with a high frequency in both treatment groups in the clinical trial; however, given the critically ill, mechanically ventilated, ICU study population, a high rate of TEAEs was not unexpected. Consistent with the all-cause mortality results, SAEs resulting in death occurred more often in the placebo group. The main safety signal observed in the trial was an increased risk of infections, particularly bacterial pneumonias and sepsis, with VILO treatment. Although nosocomial pneumonias are common in an ICU setting, the numerical difference in infections could not be completely attributed to increased survival and prolonged hospitalization in the VILO group. Based on the mechanism of action, there is a potential safety concern for risk of meningococcal infections or infections caused by encapsulated organisms; however, there was not an apparent safety signal for encapsulated bacterial or meningococcal infections observed in this trial. While the size and scope of the VILO safety database

are limited for a new biological product, the potential benefit of a substantial reduction in mortality in a critically ill population outweighs the known and potential risks of use.

9 Specific Populations

There is no information available regarding the use of vilobelimab in pediatric patients 0 to 17 years of age, pregnant or lactating women, or patients with renal or hepatic impairment. However, because vilobelimab is a monoclonal antibody, renal and hepatic impairment are not expected to significantly impact drug metabolism or clearance. Older adult patients 65 to 85 years of age were enrolled in the Phase III trial. The benefit/risk assessment in geriatric patients is favorable based on the available data.

10 Human Clinical Pharmacology

The proposed dosing regimen is six doses of 800 mg IV infusion on Days 1, 2, 4, 8, 15 and 22 as long as the patient is hospitalized. Initiation of dosing occurs within 48 hours of intubation (Day 1).

The clinical pharmacology information of VILO was collected from six clinical studies in healthy subjects and patients with various indications (Table 22), including one Phase 2/3 study (IFX-1-P2.9, PANAMO) in adults with severe COVID-19 pneumonia. In all the clinical studies, VILO has been administered as an intravenous (IV) infusion. In addition, one population pharmacokinetic (PK) analysis report entitled "*Abbreviated Population Pharmacokinetic/ Pharmacodynamic Modeling Report for IFX-1*" and bioanalytical assay validation reports were submitted.

Table 22. Summary of Clinical Pharmacology Studies in EUA 118

Study ID	Study Design and Objectives	Study Population	Study Treatment
IFX-1-P2.9	Phase 2: OL, R, 2-arm study for efficacy, safety, PK, PD	Phase 2: patients with COVID-19 highly oxygen dependent (n=30)	Phase 2: IV 800 mg or placebo on Days 1, 2, 4, 8, 11, 12, 13 if needed, 15, and 22, if in hospital, plus SOC
	Phase 3: DB, PC, R study for efficacy, safety, PK, PD, immunogenicity	Phase 3: patients with COVID-19 receiving invasive mechanical ventilation (n=369)	Phase 3: IV 800 mg or placebo on Days 1, 2, 4, 8, 15, and 22 if in hospital, plus SOC
IFX-1-P2.1	Phase 2, R, DB, PC study for safety, PK, PD, efficacy	Patients with early septic organ dysfunction (n=72)	2 doses of IV 2 mg/kg over 12 hours 2 doses of IV 4 mg/kg over 24 hours 3 doses of IV 4 mg/kg over 72 hours
IFX-1-P2.2	Phase 2, R, PC, DB study for efficacy, safety, PK, PD	Patients undergoing complex cardiac surgery (n=104)	Single IV dose: 1 , 2, 4, 8 mg/kg, or placebo
IFX-1-P2.3	Phase 2, OL study for safety, PK, PD, efficacy	Patients with HS (n=12)	9 doses of IV 800 mg on Days 1, 4, 8, 15, 22, 29, 36, 43, 50

Study ID	Study Design and Objectives	Study Population	Study Treatment
IFX-1-P2.4	Phase 2, R, DB study (OL extension) for dose-response, efficacy, safety, PK, PD	Patients with moderate to severe HS (n=177)	Induction phase (2 weeks): • IV 400 mg on Days 1, 4 • IV 800 mg on Days 1, 4, 8 • IV 800 mg on Days 1, 4, 8, 15 • IV 800 mg on Days 1, 4, 8, IV 1200 mg on Day 15 Maintenance phase (14 weeks): • IV 400 mg Q4W • IV 800 mg Q4W • IV 800mg Q2W • IV 1200mg Q2W
IFX-1-P1.1	Phase 1, dose escalation, PC, DB, for safety, PK, PD, immunogenicity	Healthy volunteers (n=26)	Single IV dose: 0.02, 0.1, 0.5, 2, 4 mg/kg

Source: Clinical pharmacology reviewer
Abbreviations: COVID-19 = coronavirus disease 2019; DB = double blind; HS = hidradenitis suppurativa; IV = intravenous; OL = open-label; PC = placebo-controlled; PD = pharmacodynamic; PK = pharmacokinetic; Q2W = every 2 weeks; Q4W = every 4 weeks; R = randomized; SOC = standard of care;

10.1 Pharmacokinetics

In healthy subjects, following single dose IV infusion of VILO ranged from 2 mg/kg to 4 mg/kg, VILO C_{max} increased dose proportionally while the area under the concentration-time curve (AUC) increased more than dose proportionally. The elimination half-life of VILO following 4 mg/kg single IV dose in healthy subjects is 95 hours (Table 23).

Table 23. Summary of PK Parameters in Healthy Subjects Following Single Dose IV Infusion of Vilobelimab (Study IFX-1-P1.1)

		Treatment Group				
		Single Dose of vilobelimab (mg/kg)				
		0.02 N=3	0.1 N=3	0.5 N=3	2.0 N=3	4.0 N=3
C_{max}	µg/mL	0.4 (0.1)	1.4 (0.2)	8.4 (1.1)	45.1 (10.6)	95.3 (12.5)
AUC_{0-t}	h*µg/mL	4.0 (2.7)	39.0 (6.9)	236.3 (52.8)	1969.3 (544.6)	6445.9 (575.3)
AUC_{0-inf}	h*µg/mL	5.9 (2.8)*	41.4 (6.7)	242.7 (49.7)	2028.6 (614.7)	6507.3 (629.6)
t_{max}[a]	h	1.00 (1.00-2.00)	2.00 (1.00-2.00)	2.00 (1.00-2.00)	2.02 (2.00-4.00)	2.00 (1.00-6.00)
$t_{1/2}$	h	10.9 (5.19)	38.5 (3.38)	49.7 (13.9)	101.3 (20.9)	94.9 (23.8)
MRT	h	NC	NC	61.8 (18.7)	111.0 (8.79)	138.4 (20.4)
CL	mL/min/kg	0.0635 (0.0304)*	0.0409 (0.0061)	0.0354 (0.0080)	0.0173 (0.0045)	0.0103 (0.0010)
V_z	L/kg	0.0572 (0.0055)	0.138 (0.0311)	0.148 (0.0275)	0.157 (0.0662)	0.0833 (0.0136)

AUC_{0-inf} = area under the plasma concentration vs time curve up to infinite time, AUC_{0-t} = area under the plasma concentration vs time curve up to the last quantifiable concentration, CL = clearance, C_{max} = maximum observed plasma concentration, MRT = mean residence time, NC=not calculated, $t_{1/2}$ = terminal half-life, t_{max} = time to reach C_{max}, V_z = volume of distribution during the terminal phase.

a median and range, other parameters are mean (standard deviation)

* N=2

Source: Table 22 on page 49 of Summary of Clinical Pharmacology

10.1.1 Study IFX-1-P2.9 Phase 2 Portion

Thirty patients requiring oxygen supplementation or being intubated were treated with either SOC alone or SOC plus up to 7 IV doses of VILO 800 mg over a period of 29 days. In VILO treatment group, the first 5 VILO treatments were administered to all patients on Days 1, 2, 4, 8, and 15. Treatment on Day 22 was only administered in the event that a patient had not previously been extubated and discharged from ICU. When a patient's clinical situation worsened after Day 8, one additional administration of 800 mg VILO between Days 11 and 13 could be given at the investigator's discretion. A total of 10 of 15 (66.7%) patients received all 5 infusions on Days 1, 2, 4, 8, and 15 and 3 of 15 (20.0%) patients received the maximum dose of 7 infusions. (Table 24).

Blood samples for PK assessment were collected up to 4 time points: pre-dose on Days 1, 2, 8, and 29 or day of hospital/ICU discharge. For some patients, additional pre-dose blood samples were also collected on Days 11, 15, and 22. VILO concentrations were measured in citrate plasma and analyzed using a validated enzyme-linked immunosorbent assay (ELISA). Results showed that geometric mean (CV%) VILO pre-dose concentration was 151,702 ng/mL (33.5%) on Day 2 and 139,503 ng/mL (23.1%) on Day 8,respectively (Table 25, Figure 4). The PK samples beyond Day 8 was too limited to be representative.

Table 24. Summary of Vilobelimab Administrations in Study IFX-1-P2.9 Phase 2 Portion

	IFX-1 + BSC (N=15) n (%)	BSC (N=15) n (%)
Administration of all 5 scheduled infusions at Days 1, 2, 4, 8, and 15 [n (%)]	10 (66.7%)	0 (0.0%)
Additional administration of IFX-1 [n (%)]		
Day 11	6 (40.0%)	0 (0.0%)
Day 22	3 (20.0%)	0 (0.0%)
Number of IFX-1 infusions received [n (%)]		
0	0 (0.0%)	15 (100.0%)
1	0 (0.0%)	0 (0.0%)
2	0 (0.0%)	0 (0.0%)
3	1 (6.7%)	0 (0.0%)
4	4 (26.7%)	0 (0.0%)
5	4 (26.7%)	0 (0.0%)
6	3 (20.0%)	0 (0.0%)
7	3 (20.0%)	0 (0.0%)
>7	0 (0.0%)	0 (0.0%)
Treatment duration (days)*		
n	15	
Mean (SD)	12.69 (5.57)	
Minimum-Maximum	2.9 – 20.7	
Median (Q1-Q3)	13.88 (6.94 – 14.28)	
Time to first IFX-1 administration (hours)**		
n	15	
Mean (SD)	4.47 (3.47)	
Minimum-Maximum	1.5 – 16.0	
Median (Q1-Q3)	3.58 (2.39 – 5.10)	

BSC = Best Supportive Care, N = total number of patients in the corresponding treatment group, n = number of patients with IFX-1 administration in the corresponding class and cohort, Min = Minimum, Max = Maximum, Q1 = first quartile, Q3 = third quartile, SD = Standard deviation,
Percentages are based on the number of patients in the respective cohort
*Treatment duration was calculated as start time of last IFX-1 administration minus start time of first IFX-1 administration
**since randomization

Source: Table 9-7 on page 77 of Study IFX-1-P2.9 Phase 2 Part CSR

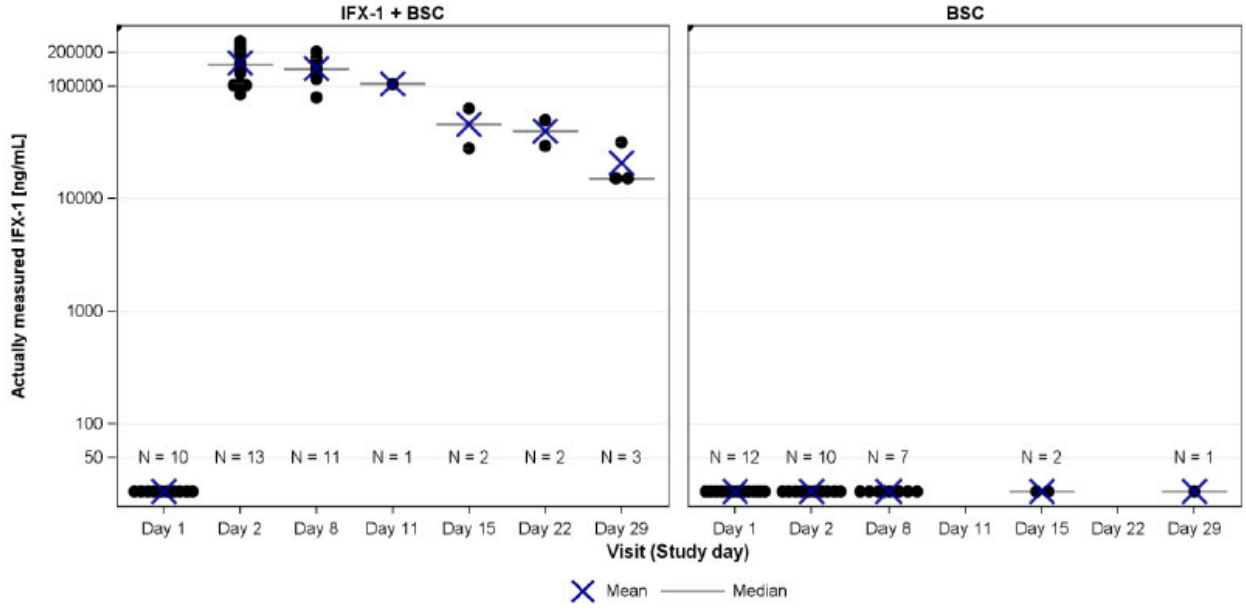
Table 25. Summary of Plasma Concentrations of Vilobelimab (IFX-1) in Vilobelimab Treatment Group of Study IFX-1-P2.9 Phase 2 Portion

	Trough IFX-1 [ng/mL] Concentrations		
Statistics	**Day 2**	**Day 8**	**Day 29**
n (%)	13 (86.7%)	11 (73.3%)	3 (20%)
Mean (SD)	160,259.52 (53706.11)	143,214.12 (33022.45)	20,707.39 (9546.90)
Min – Max	84,846.2 – 248,592.1	80,060.0 – 200,745.8	15,182.7 – 31,731.2
Median (Q1 – Q3)	154,201.80 (106,896.26 – 204,955.27)	141,364.96 (126,574.87 – 175,883.76)	15,208.25 (15,182.72 – 31,731.18)
CV %	33.51	23.06	46.10
Geom. Mean	151,701.94	139,502.83	19,422.50
Geom. CV %	36.15	25.09	44.51

BSC = best supportive care, CV = coefficient of variation, Max = maximum, Min = minimum, Q1 = first quartile, Q3 = third quartile, SD = standard deviation
Percentages are based on the number of patients in the respective cohort (IFX-1 + BSC: N=15; BSC: N=15)

Source: Table 12-1 on page 134 of Study IFX-1-P2.9 Phase 2 Part CSR

Figure 4. Dot Plot of Vilobelimab (IFX-1) Plasma Concentrations in Study IFX-1-P2.9 Phase 2 Portion



BSC = best supportive care
Values reported as being below the lower limit of quantification (LLOQ) are set to half of LLOQ.
Source: Figure 12-1 on page 135 of Study IFX-1-P2.9 Phase 2 Part CSR

10.1.2 Study IFX-1-P2.9 Phase 3 Portion

Three hundred sixty-nine patients with COVID-19 receiving invasive mechanical ventilation were randomized to receive a maximum of 6 IV doses of VILO 800 mg plus SOC or placebo plus SOC on Days 1, 2, 4, 8, 15, and 22, as long as the patient was still hospitalized. A total of 70 of 177 patients (39.5%) in the VILO treatment group and 56 of 191 patients (29.3%) in the placebo group received all 6 infusions (Table 26).

Blood samples for PK assessment were collected at up to 3 time points: pre-dose at screening and on Day 8, as well as on the day of hospital/ICU discharge. VILO concentrations were measured in citrate plasma and analyzed by a validated ELISA. Results showed that the VILO geometric mean (CV%) trough concentrations on Day 8 was 137,881.29 ng/mL (51.0%) in VILO treatment group (Table 27, Figure 5). Beyond Day 8, VILO concentrations were highly variable as the PK samples were sparse and collected on different days due to the hospital discharge.

Table 26. Summary of Vilobelimab Administrations in Study IFX-1-P2.9 Phase 3 Portion

	VILO+SOC (N = 177)	Placebo+SOC (N = 191)
Patients treated with at least one IMP dose (n [%])		
Overall	175 (98.9%)	189 (99.0%)
In ICU	161 (91.0%)	170 (89.0%)
In IMC	35 (19.8%)	29 (15.2%)
In normal ward	26 (14.7%)	37 (19.4%)
Administration of scheduled infusions at (n [%])		
Day 1	175 (98.9%)	189 (99.0%)
Day 2	174 (98.3%)	186 (97.4%)
Day 4	170 (96.0%)	179 (93.7%)
Day 8	152 (85.9%)	157 (82.2%)
Day 15	109 (61.6%)	90 (47.1%)
Day 22	70 (39.5%)	58 (30.4%)
Total number of IMP infusions received (n [%])		
0	2 (1.1%)	2 (1.0%)
1	1 (0.6%)	3 (1.6%)
2	4 (2.3%)	7 (3.7%)
3	18 (10.2%)	22 (11.5%)
4	42 (23.7%)	65 (34.0%)
5	40 (22.6%)	36 (18.8%)
6	70 (39.5%)	56 (29.3%)
> 6	0 (0.0%)	0 (0.0%)
Treatment duration (days)[a]		
n	175	189
Mean (SD)	14.63 (7.01)	12.80 (7.11)
Min – Max	1.0 – 23.0	1.0 – 23.0
Median (Q1 – Q3)	15.00 (8.00 – 22.00)	8.00 (8.00 – 22.00)
Time between randomization and first IMP administration (hours)		
n	175	189
Mean (SD)	1.98 (2.64)	1.86 (2.48)
Min – Max	0.0 – 21.2	0.0 – 22.1
Median (Q1 – Q3)	1.37 (0.77 – 2.17)	1.35 (0.88 – 2.05)
IMP treatment terminated prematurely before hospital discharge (n [%])	70 (39.5%)	87 (45.5%)
Reasons for premature treatment termination (n [%])		
Adverse event	50 (28.2%)	68 (35.6%)
Clinical deterioration	0 (0.0%)	2 (1.0%)
Other	8 (4.5%)	9 (4.7%)
Physician decision	0 (0.0%)	3 (1.6%)
Recovery[b]	2 (1.1%)	2 (1.0%)
Withdrawal by legal representative/relative	7 (4.0%)	2 (1.0%)
Withdrawal by patient	3 (1.7%)	1 (0.5%)

ICU = intensive care unit, IMC = intermediate care ward, IMP = investigational medicinal product, Min = minimum, Max = maximum, Q1 = first quartile, Q3 = third quartile, SD = standard deviation, SOC = standard of care, VILO = vilobelimab

a Treatment duration was calculated as end date of last IMP administration minus start date of first IMP administration + 1.

b Patients who prematurely discontinued treatment for reason 'Recovery' were still in hospital at the timepoint of the scheduled IMP administration, but hospital discharge was anticipated very soon after and thus IMP was not given.

Percentages were based on the number of patients in the respective treatment groups.

Source: Table 9-7 on page 96 of Study IFX-1-P2.9 Phase 3 Part CSR

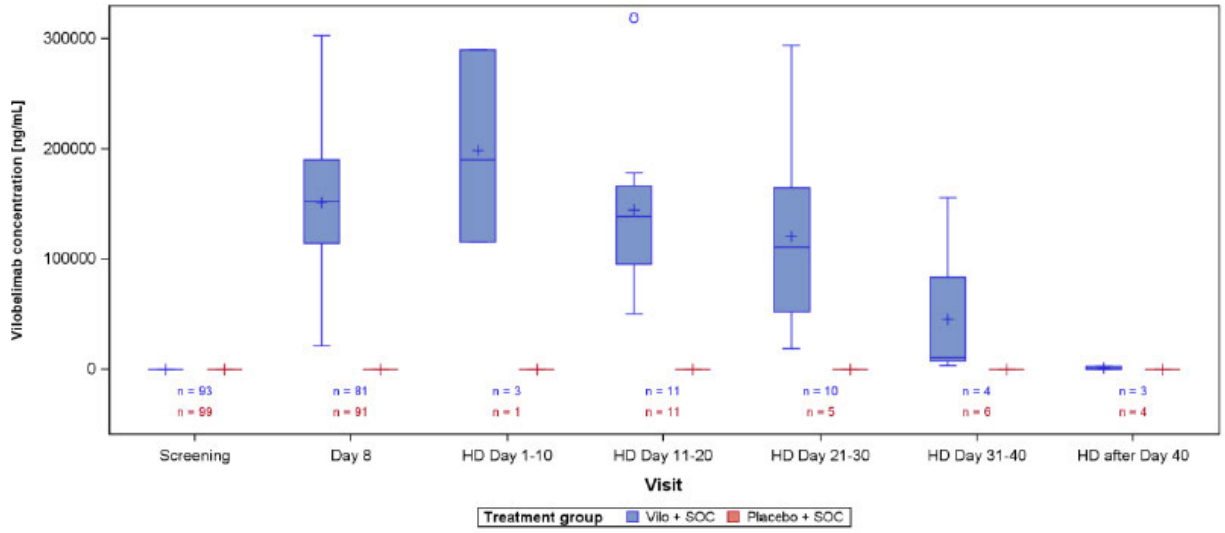
Table 27. Summary of Plasma Concentrations of Vilobelimab (IFX-1) in Vilobelimab Treatment Group of Study IFX-1-P2.9 Phase 3 Portion

	Trough Vilobelimab [ng/mL] Concentrations					
Statistic	**Day 8**	**HD Day 1-10**	**HD Day 11-20**	**HD Day 21-30**	**HD Day 31-40**	**HD After Day 40**
VILO+SOC (N = 175)						
n	81	3	11	10	4	3
Mean (SD)	151,236.35 (56,782.86)	198,506.84 (87,412.05)	144,856.82 (69,976.35)	121,030.00 (83,574.67)	45,638.49 (73,828.83)	1,235.72 (1,552.04)
Min – Max	21,799.3 – 302,972.1	11,581.7 – 289,803.4	50,495.0 – 318,129.1	18,893.8 – 293,685.4	3,834.7 – 156,257.9	61.7 – 2,995.4
Median (Q1 – Q3)	152,726.52 (114,606.15 – 190,052.48)	190,135.43 (115,581.66 – 289,803.43)	138,788.97 (95,706.28 – 166,271.94)	111,358.62 (52,598.46 – 164,688.82)	11,230.68 (7,434.23 – 83,842.76)	650.14 (61.66 – 2,995.36)
CV [%]	37.55	44.03	48.31	69.05	161.77	125.60
Geom. Mean	137,881.29	185,361.06	130,591.95	91,085.66	16,579.17	493.34
Geom. CV [%]	50.99	48.56	51.98	109.06	333.21	670.27

CV = coefficient of variation; Geom. = geometric, HD = hospital discharge, Max = maximum, Min = minimum, Q1 = first quartile, Q3 = third quartile, SD = standard deviation, SOC = standard of care, VILO = vilobelimab
Five values from VILO patients have been excluded from this summary table due to incorrect timing or implausible values.
Values below the lower limit of quantification were set to 0. Values above the upper limit of quantification were set to the upper limit of quantification.

Source: Table 12-1 on page 177 of Study IFX-1-P2.9 Phase 3 Part CSR

Figure 5. Box Plot of Vilobelimab (IFX-1) Plasma Concentrations in Study IFX-1-P2.9 Phase 3 Portion



HD = Hospital discharge, SOC = standard of care, Vilo = vilobelimab
Five values from VILO patients and one value from a Placebo patient have been excluded from this figure due to incorrect timing or implausible values. Values below the lower limit of quantitation were set to zero. Values above the upper limit of quantitation were set to the upper limit of quantitation.
Box plot: lower line of box =1st quartile, line inside box = median, upper line of box = 3rd quartile, + = mean, lower/upper whisker = minimum/maximum value below /above the lower/upper line of box + 1.5* (3rd quartile – 1st quartile), circle = values below/above whiskers.

Source: Figure 12-1 on page 178 of Study IFX-1-P2.9 Phase 3 Part CSR

Due to the different dosing regimen and PK sampling scheme, the observed VILO plasma trough concentrations obtained from the COVID-19 program cannot be directly compared to the plasma concentrations obtained from other clinical studies. Therefore, it is unclear if the systemic exposure of VILO in patients with COVID-19 is similar to healthy subjects or patients with other indications.

10.2 Pharmacodynamics

The plasma concentrations of C5a have been evaluated in patients with COVID-19 in Study IFX-1-P2.9 using a validated ELISA. However, the clinical relevance of C5a plasma concentrations is unclear.

10.2.1 Study IFX-1-P2.9 Phase 2 Portion

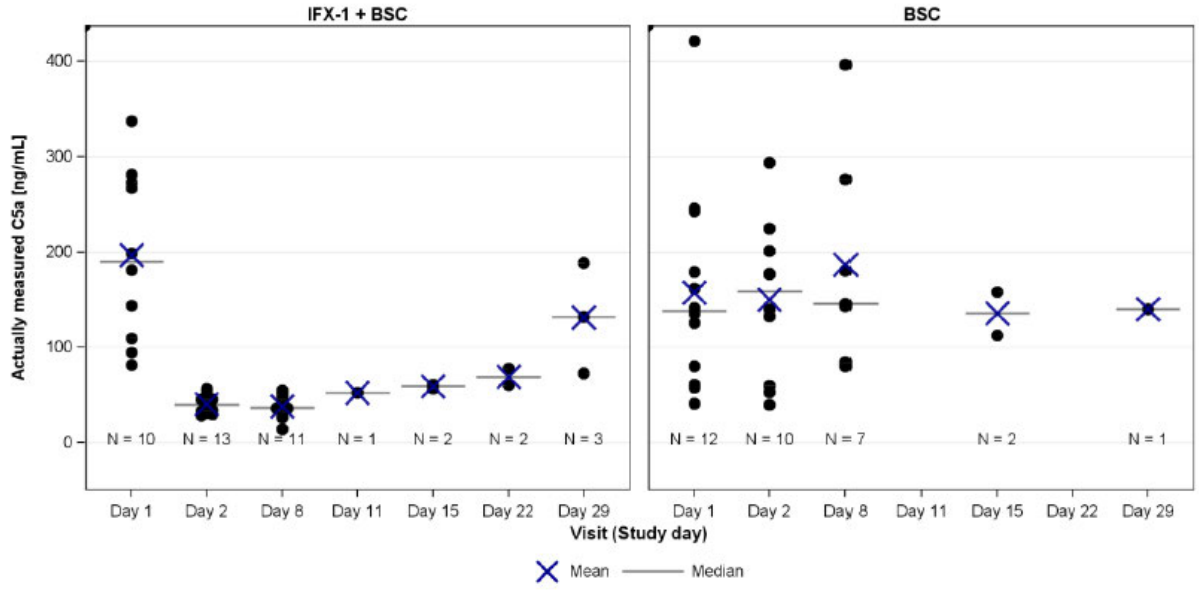
Blood samples for measuring C5a plasma concentration were collected at up to 4 time points: pre-dose on Days 1, 2, 8, and 29 or day of hospital/ICU discharge. Results showed that the median concentrations of C5a at baseline were comparable between the VILO group (189.98 ng/mL) and the placebo group (138.52 ng/mL) (Table 28, Figure 6).The median plasma concentration of C5a decreased to 39.70 ng/mL and 36.78 ng/mL in VILO group on Day 2 and Day 8, respectively; while no apparent change was observed in placebo group.

Table 28. Summary of Plasma Concentrations of C5a in Study IFX-1-P2.9 Phase 2 Portion

	C5a [ng/mL] Concentrations			
Statistics	**Day 1**	**Day 2**	**Day 8**	**Day 29**
IFX-1 group (N=15)				
n (%)	10 (66.7%)	13 (86.7%)	11 (73.3%)	3 (20%)
Mean (SD)	196.85 (89.35)	40.58 (9.27)	38.03 (11.23)	131.36 (57.91)
Min – Max	81.5 – 337.4	28.8 – 56.8	14.2 – 54.8	73.1 – 188.9
Median (Q1 – Q3)	189.98 (109.81 – 272.62)	39.70 (33.20 – 45.55)	36.78 (32.50 – 45.61)	132.14 (73.06 – 188.87)
CV %	45.39	22.83	29.54	44.08
Geom. Mean	177.15	39.63	36.09	122.17
Geom. CV %	53.43	22.95	38.19	50.87
BSC group (N=15)				
n (%)	12 (80%)	10 (66.7%)	7 (46.7%)	1 (6.7%)
Mean (SD)	157.83 (106.86)	149.92 (81.95)	186.73 (113.57)	140.39 (-)
Min – Max	41.1 – 421.4	39.7 – 294.0	80.1 – 396.4	140.4 – 140.4
Median (Q1 – Q3)	138.52 (70.81 – 210.84)	158.53 (60.03 – 200.89)	145.68 (84.73 – 276.49)	140.39 (140.39 – 140.39)
CV %	67.71	54.67	60.82	-
Geom. Mean	128.63	125.58	160.98	-
Geom. CV %	76.98	76.58	63.64	-

BSC = best supportive care, CV = coefficient of variation, Max = maximum, Min = minimum, Q1 = first quartile, Q3 = third quartile, SD = standard deviations
Percentages are based on the number of patients in the respective cohort (IFX-1 + BSC: N=15; BSC: N=15).
Source: Table 12-2 on page 136 of Study IFX-1-P2.9 Phase 2 Part CSR

Figure 6. Dot Plot of C5a Plasma Concentrations in Study IFX-1-P2.9 Phase 2 Portion



BSC = best supportive care
Values reported as being below the lower limit of quantification (LLOQ) are set to half of LLOQ.
Source: Figure 12-2 on page 137 of Study IFX-1-P2.9 Phase 2 Part CSR

10.2.2 Study IFX-1-P2.9 Phase 3 Portion

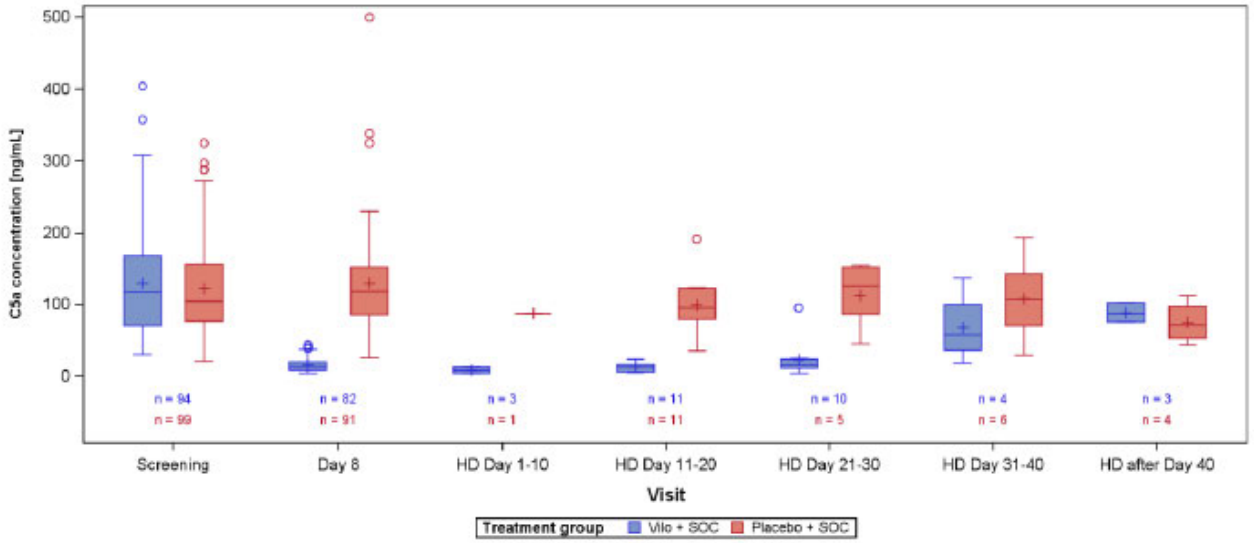
Blood samples for measurement of C5a plasma concentration were collected at up to 3 time points: pre-dose at screening and on Day 8, as well as on the day of hospital/ICU discharge. Results showed that the median plasma concentrations of C5a at baseline were comparable between the VILO group (118.29 ng/mL) and the placebo group (104.62 ng/mL) (Table 29, Figure 7). By Day 8, the median concentrations of C5a decreased to 14.53 ng/mL in VILO group while little change occurred in placebo group (119.18 ng/mL). From Day 8 to Day 30, C5a plasma concentrations in VILO group remained lower compared to placebo group regardless of the sparse samples. C5a plasma concentrations in VILO group slowly increased after Day 30 and became slightly higher than placebo group after Day 40.

Table 29. Summary of Plasma Concentrations of C5a in Study IFX-1-P2.9 Phase 3 Portion

	C5a [ng/mL] Concentrations						
Statistic	**Screening**	**Day 8**	**HD Day 1-10**	**HD Day 11-20**	**HD Day 21-30**	**HD Day 31-40**	**HD After Day 40**
VILO+SOC (N = 175)							
n	94	82	3	11	10	4	3
Mean (SD)	130.25 (71.45)	16.80 (9.15)	9.06 (4.32)	13.13 (6.30)	23.82 (26.19)	68.37 (49.74)	88.99 (13.82)
Min – Max	30.9 – 403.9	4.6 – 43.7	4.6 – 13.3	5.6 – 24.5	4.5 – 96.2	19.1 – 137.4	75.9 – 103.4
Median (Q1 – Q3)	118.29 (71.22 – 168.20)	14.53 (9.46 – 20.99)	9.28 (4.63 – 13.27)	12.93 (6.50 – 16.93)	16.05 (11.63 – 24.53)	58.52 (36.63 – 100.10)	87.68 (75.87 – 103.42)
CV %	54.86	54.47	47.70	48.02	109.97	72.76	15.53
Geom. Mean	112.83	14.54	8.29	11.74	17.23	54.65	88.28
Geom. CV %	59.31	59.30	57.56	54.16	91.59	96.61	15.59
Placebo+SOC (N = 189)							
n	99	91	1	11	5	6	4
Mean (SD)	123.15 (65.53)	129.81 (67.59)	87.70 (–)	99.93 (39.06)	113.20 (46.22)	108.75 (56.91)	75.27 (29.67)
Min – Max	21.5 – 324.6	26.4 – 500.0	87.7 – 87.7	36.4 – 192.0	46.2 – 154.6	29.6 – 193.6	43.8 – 113.2
Median (Q1 – Q3)	104.62 (77.54 – 156.64)	119.18 (85.89 – 152.05)	87.70 (87.70 – 87.70)	95.94 (80.07 – 122.41)	126.26 (87.16 – 151.84)	107.47 (71.31 – 143.06)	72.05 (52.99 – 97.56)
CV %	53.21	52.07		39.09	40.83	52.33	39.42
Geom. Mean	106.95	116.03	87.70	93.00	103.59	93.57	70.89
Geom. CV %	59.25	50.66	n.a.	43.02	54.14	73.41	42.04

C5a = complement component 5a, CV = coefficient of variation; Geom. = geometric, HD = hospital discharge, Max = maximum, Min = minimum, n.a. = not applicable, Q1 = first quartile, Q3 = third quartile, SD = standard deviation, SOC = standard of care, VILO = vilobelimab
Five values from VILO patients and one value from Placebo patients have been excluded from this summary table due to incorrect timing or implausible values.
Values below the lower limit of quantification were set to zero. Values above the upper limit of quantification were set to the upper limit of quantification.
Source: Table 12-2 on page 179 of Study IFX-1-P2.9 Phase 3 Part CSR

Figure 7. Box Plot of C5a Plasma Concentrations in Study IFX-1-P2.9 Phase 3 Portion



HD = Hospital discharge, SOC = standard of care, Vilo = vilobelimab
Five values from VILO patients and one value from a Placebo patient have been excluded from this figure due to incorrect timing or implausible values. Values below the lower limit of quantitation were set to zero. Values above the upper limit of quantitation were set to the upper limit of quantitation.
Box plot: lower line of box =1st quartile, line inside box = median, upper line of box = 3rd quartile, + = mean, lower/upper whisker = minimum/maximum value below /above the lower/upper line of box + 1.5* (3rd quartile – 1st quartile), circle = values below/above whiskers.
Source: Figure 12-2 on page 180 of Study IFX-1-P2.9 Phase 3 Part CSR

10.3 Immunogenicity

In the Phase 2 portion of Study IFX-1-P2.9, samples were not collected for an immunogenicity assessment.

In the Phase 3 portion of Study IFX-1-P2.9, samples for the immunogenicity assessment were collected at baseline and on the day of hospital discharge. Treatment-induced anti-drug antibodies (ADAs), defined as negative ADA results at screening with positive ADA results at hospital discharge, were observed in 1 of 95 patients in the VILO group and 1 of 98 patients in the placebo group. However, due to limitations in the immunogenicity assay used in the COVID-19 program, the immunogenicity results should be interpreted with caution.

10.4 Drug-Drug Interaction

No specific drug-drug interaction studies have been conducted with vilobelimab to date. Vilobelimab is a chimeric monoclonal IgG4 antibody with an approximate molecular weight of 148-149 kDa.

Drug-drug interactions between vilobelimab and any co-administered medications for treatment of COVID-19, such as remdesivir, corticosteroids, tocilizumab, and baricitinib are unlikely.

10.5 Renal Impairment

No dedicated PK study in subjects with renal impairment has been conducted with vilobelimab.

10.6 Hepatic Impairment

No dedicated PK study in subjects with hepatic impairment has been conducted with vilobelimab. Since vilobelimab is degraded by proteolytic enzymes widely distributed in the body and not metabolized by hepatic-specific enzymes, change in hepatic function is not expected to influence vilobelimab clearance.

10.7 Pediatric Patients

The pharmacokinetics, safety and effectiveness of vilobelimab have not been assessed in pediatric patients; therefore, the Division is not currently recommending pediatric use under the EUA.

11 Nonclinical Data to Support Safety

The nonclinical program with vilobelimab consisted of pharmacology, safety pharmacology (in vitro human-ether-a-go-go-related gene [hERG] assay), oral repeat-dose toxicity (2 weeks and 26 weeks in monkeys), reproductive toxicology (13-week male fertility study and enhanced pre- and postnatal development [ePPND] in monkeys), and tissue cross-reactivity studies. Animal studies have not been conducted to evaluate the carcinogenic potential of vilobelimab. Vilobelimab is also referred to as IFX-1 and CaCP29.

11.1 Safety Pharmacology

The safety pharmacology of vilobelimab was evaluated in vitro in a hERG assay. Central nervous system (CNS), cardiovascular, and respiratory parameter evaluation was incorporated into toxicology studies with monkeys. There were no effects on CNS, cardiovascular, and respiratory functions.

11.2 Repeat-Dose Toxicity

The repeat-dose toxicity of vilobelimab was evaluated in GLP-compliant 2-week and 26-week intravenous (IV) toxicity studies in cynomolgus monkeys. Key study findings for the toxicity studies with vilobelimab are described below.

Study Title: 2-Week Subchronic Toxicity Study of CaCP29 by Intravenous 1-H Infusion to Cynomolgus Monkeys (Study #25488): In the 2-week IV toxicity and toxicokinetic (TK) study in cynomolgus monkeys (42 to 46 months of age), male and

female animals (n = 3/sex/group) were treated on Days 1, 2, 8, and 15 via one-hour IV infusions (5 mL/kg volume) with vehicle (PBS with 0.05% Tween 80) or vilobelimab (1, 15, or 50 mg/kg) for 2-weeks. Two animals/sex/group were placed in 6-week recovery groups (control and HD).

No mortality occurred, and no clinical signs were observed. There were no effects observed on body weight, food and water consumption, electrocardiogram (ECG), blood pressure, respiratory rate, blood gas analysis, hematology and lymphocyte typing, clinical chemistry, immunotoxicology parameters (immunoglobulins, and cytokines), urinalysis, ophthalmology exam, auditory exam, organ weights, gross pathology, bone marrow, histopathology, or local tolerance (infusion site). CH50 (a measure of all major complement proteins) levels were reduced by up to 37% in animals receiving 15 or 50 mg/kg IFX-1. This reduction was time and dose-dependent. Female monkeys were more sensitive to IFX-1-mediated decrease in CH50. The decrease in CH50 was not considered adverse. No anti-drug-antibodies (ADA) were detected on Days 1 (pre-dose), 16, or 58. Plasma C_{max} and AUC values for vilobelimab increased in an approximate dose proportional manner. C_{max} and AUC values were comparable for male and female monkeys. Analysis of the pharmacodynamics of IFX-1 indicate that the antibody in monkey plasma is functional from 1 hour post-first administration through the end of the recovery period (58 days). The no observed adverse effect level (NOAEL) is considered the highest dose administered, 50 mg/kg associated with an $AUC_{24\text{-}144h}$ of 24,695 ug·hr/mL and C_{max} of 1472 ug/mL on Days 15/16.

Study Title: 26-Week Chronic Toxicity Study of IFX-1 by Repeated 30-Min Intravenous Infusion to Cynomolgus Monkeys. (Study #30041): In the 26-week IV toxicity and TK study in cynomolgus monkeys (42-52 months of age), male and female animals (n = 3/sex/group) were administered IFX-1 by 30 minute IV infusions (5 mL/kg) at doses of (0, 15, or 50 mg/kg) once per week for 26 weeks. The additional 6 week recovery group consisted of 2 animals/sex HD group and 1 animal/sex for the vehicle control group.

One female monkey receiving 50 mg/kg died on Day 71 one hour after receiving the infusion (11^{th} infusion overall). This animal had high levels of anti-drug antibodies (ADA) and microscopic findings (multifocal centrilobular perivasculitis and inflammatory cell infiltration in center veins of liver, congestion in kidneys and adrenals) were consistent with an ADA-reaction. The death is considered drug-related but may not be relevant for human safety determinations. There were no effects observed on body weight, food and water consumption, ECG, blood pressure, respiratory rate, hematology and lymphocyte typing, clinical chemistry, immunotoxicology parameters (immunoglobulins, and cytokines), urinalysis, ophthalmology exam, auditory exam, organ weights, gross pathology, bone marrow, histopathology, or local tolerance (infusion site). CH50 levels were reduced by up to 36% in animals receiving 15 or 50 mg/kg IFX-1. This reduction was observed at each sampling time point including after the first infusion of drug. No anti-drug-antibodies (ADA) were detected on Day 43 in surviving animals. ADA were not assessed at the end of the study. Plasma C_{max} and AUC values for vilobelimab increased in an approximate dose proportional manner. C_{max} and AUC values were comparable for male and female monkeys. Analysis of the pharmacodynamics of IFX-1 indicate that the antibody in monkey plasma was able to block rhC5a activity by at least

81%. The NOAEL is considered the highest dose administered, 50 mg/kg/wk associated with an $AUC_{0\text{-tlast}}$ of 47,066 ug·hr/mL and C_{max} of 2,554 ug/mL on Days 176/177.

11.3 Reproductive and Developmental Toxicity

Study Title: A 13-Week Toxicity Study of IFX-1 by Intravenous Infusion in Cynomolgus Monkeys With Evaluation of Effects on Male Fertility (Study #20233332): In the 13-week study, 3 males/group were intravenously administered 0, 15, 18, or 50.6 mg/kg IFX-1 once weekly. The age of the male monkeys was 4.6 to 7.9 and confirmed to be sexually mature. There were no test article-related effects on mortality, clinical signs, body weight, food consumption, ECG, testes volume, sperm motility or concentration, semen morphology, organ weight, or histopathology of the prostate gland, seminal vesicles, testes, and epididymides. One HD and one control animal were ADA positive on Day 1. All other animals were ADA negative through Day 92 of the study. The NOAEL is considered 50.6 mg/kg/wk associated with an $AUC_{0\text{-tlast}}$ of 37,200 ug·hr/mL and C_{max} of 2,410 ug/mL.

Study Title: Test item-related influence on female fertility from "26-Week Chronic Toxicity Study of IFX-1 by Repeated 30-Min Intravenous Infusion to Cynomolgus Monkeys (Study #30041)": There were no test article-related changes in the gross pathology or histopathology of female reproductive organs. All females administered 50 mg/kg/wk IFX-1 had 2-5 observable menstrual cycles during the course of the 26 week study. There were no discernible differences in menstrual cycles between control and IFX-1-treated females. The NOAEL is considered the highest dose administered, 50 mg/kg/wk associated with an $AUC_{0\text{-tlast}}$ of 45,470 ug·hr/mL and C_{max} of 2,560 ug/mL on Days 176/177.

Study title: An Enhanced Pre- and Postnatal Developmental Toxicity Study of IFX-1 Administered by Intravenous Injection (Infusion) in Pregnant Cynomolgus Monkeys with a 6 Month Postnatal Evaluation (Study #20177164): Pregnant cynomolgus monkeys were administered vilobelimab from GD20/22, at the beginning of organogenesis, and once every 7 days until the end of gestation at intravenous doses up to 50.6 mg/kg/wk. There were no vilobelimab-related adverse effects on maternal health, pregnancy outcome, embryo-fetal development, or neonatal growth and development up to 6 months of age. Vilobelimab crossed the placenta in cynomolgus monkeys and vilobelimab plasma concentrations were similar in infants relative to maternal animals on PND28 and were 8-12 times higher in infants relative to maternal animals on PND91. Vilobelimab concentrations decreased from PND28 to PND91 and was not detected in infant plasma on PND183. The NOAEL is considered 50.6 mg/kg/wk associated with an $AUC_{0\text{-tlast}}$ of 38,400 ug·hr/mL and C_{max} of 2060 ug/mL on GD140. AUC and C_{max} were not reported for surviving infants.

11.4 Other Toxicity Studies

In a tissue cross reactivity study (Study #PZN0001), human and monkey tissue samples representing 37 different organs/tissues in each species were incubated with vilobelimab. Staining was observed across most of the tissues assessed. There was

high intensity staining in blood, haemopoietic, circulatory, immune, and central/peripheral nervous system tissues. The Requester postulates this widespread staining pattern is due to post-mortem generation of C5a and coagulation related to tissue harvesting and may not reflect the clinical use.

In an in vitro assay, vilobelimab was incubated with human blood to assess binding to blood cells and stimulation of cytokine release. There was no specific binding of vilobelimab to human blood cells at concentrations up to 100 ug/mL. Vilobelimab did not induce cytokine release from human blood at concentrations up to 1000 nM vilobelimab.

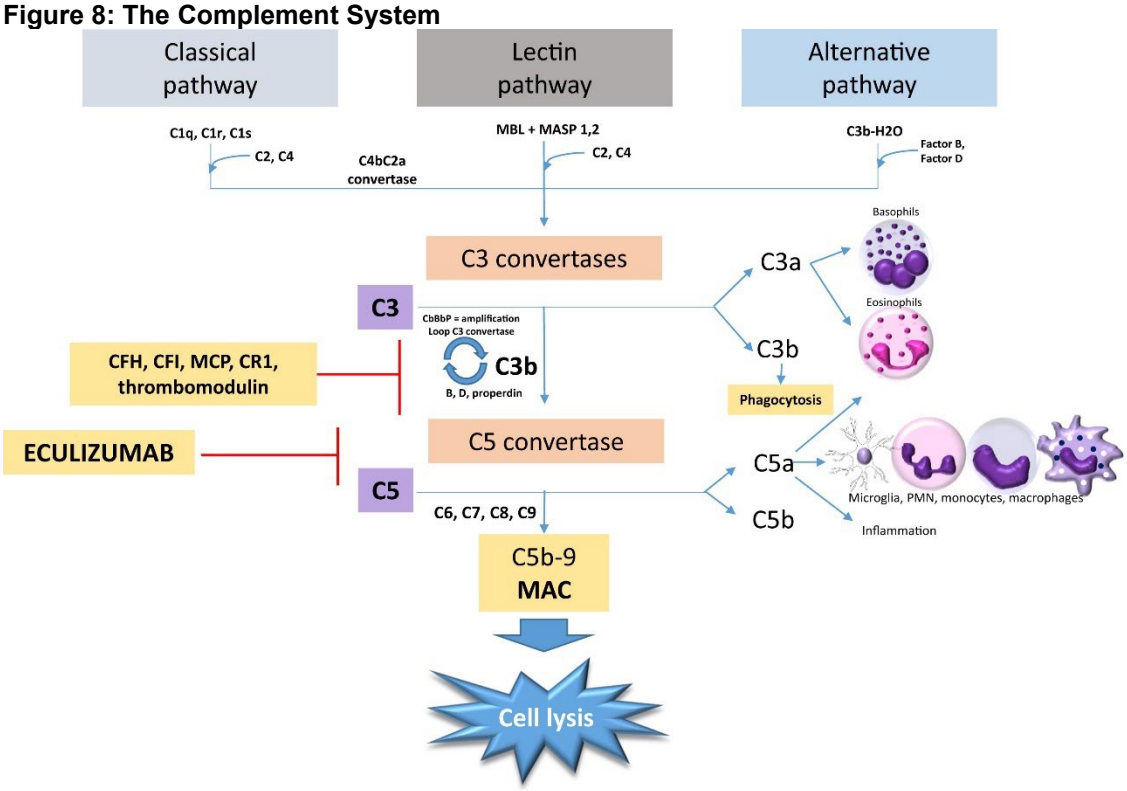
12 Nonclinical Data to Support Efficacy

12.1 Mechanism of Action

Vilobelimab has a novel mechanism of action compared to the existing therapies for hospitalized patients with COVID-19. Vilobelimab is an IgG4 monoclonal antibody that targets an inflammatory response by C5a by binding to the C5a split product of C5, a component in the complement cascade (Figure 8). Immune complexes induce C5a production and inflammatory cytokine release; C5a can attract neutrophils and monocytes that trigger further inflammation. Vilobelimab blocks the biological effects induced by C5a. C5a targets the inflammatory immune response of the patient to the SARS-CoV-2 infection, which drives disease progression in critically ill COVID-19 patients. The Requester reports that C5a has been shown to play a critical role in various viral ARDS settings, including avian flu, middle eastern respiratory syndrome (MERS), influenza, and others.

In this context, the complement system is thought to trigger pro-inflammatory cytokines and inflammatory markers that may contribute to the observed hyperinflammation in some patients with severe COVID-19 which is associated with worse outcomes. Thus, vilobelimab, a product that binds and inhibits the action of C5a, may inhibit the COVID-19-associated inflammatory response.

Figure 8: The Complement System



Source: Image from (Amari Chinchilla et al. 2020).

The Requester conducted a series of in vitro studies assessing vilobelimab inhibition of C5a. Vilobelimab was not studied in in vivo animal models of SARS-CoV-2 infection and/or COVID-19 disease. The Requester referenced a publication in which IFX-1 was studied in an African green monkey model of H7N9 viral infection.

12.2 In Vitro Studies

Study Title: General Properties of CaCP29-IgG4, an Anti-C5a Antibody: CaCp29-IgG4 Affinity

Analysis (Study #A001): CaCP29 is highly specific to human C5a with a K_D affinity of 0.51 nM.

Study Title: General Properties of CaCP29-IgG4, an Anti-C5a Antibody: Determination of the Relevant Species (Study #A002): In a CD11b functional assay, CaCP29-IgG4 blocked the effects from primate-derived C5a but did not interact with rat, rabbit, or dog C5a. Monkey was identified as the only pharmacologically relevant species.

Study Title: General Properties of CaCP29-IgG4, an Anti-C5a Antibody: Competitive Binding of C5a with Nature Receptors (Study #A004): CaCP29 is able to block the biological effects induced by recombinant human C5a or endogenous C5a (eC5a) by interrupting the binding to its natural receptors.

Study Title: General Properties of CaCP29-IgG4, an Anti-C5a Antibody: C5 Interference and Influence on CaCP29-IgG4 Stability (Study #A006): There is no interference between plasma protein C5 and CaCP29-IgG4. Blood C5 had no influence on CaCP29-IgG4's efficacy in blocking C5a effects in human whole blood. CaCP29 showed stability and functionality in human blood and plasma.

Study Title: CaCP29-IgG4 Efficacy Analysis: Blocking Activity of CaCP29-IgG4 to rhC5a and eC5a (Study B001): CaCP29-IgG4 was shown to be a bivalent antibody evidenced by a nearly complete blockade of the biological effects from two C5a molecules by one antibody.

Study Title: CaCP29-IgG4 Efficacy Analysis: Stability and Functionality of CaCP29-IgG4 in Primates (Study #B002): In 10-day and 58-day studies in monkeys, CACP29-IgG4 showed stability and functionality in primates as evidenced by the blockade of C5a-induced CD11b expression on granulocytes.

Study Title: IFX-1 Efficacy Analysis: Ex Vivo Efficacy Studies for C5a Blockade (Study #B004): In ex vivo human whole blood models, IFX-1 demonstrated the ability to suppress cytokine release in response to living bacteria and zymosan A (a fungal wall component).

Study Title: CaCP29-IgG4 Efficacy Analysis: Binding and Blocking Activity of CaCP29-IgG4 to rhC5a-desArg (Study #B006): C5a is rapidly desarginated by serum carboxypeptidase N to the C5a-desArg derivate. rHC5a-desArg exhibited comparable activity to rhC5a for up- and down-regulation of cell surface proteins, such as CD11b and CD88 but was found to be less potent in causing enzyme release (degranulation) and more potent in IL-8 production in the presence of LPS. CaCP29-IgG4 binds equally to C5a-desArg and C5a, and it is able to effectively block the biological effects induced by rhC5a-desArg.

Study Title: IFX-1 Efficacy Analysis: Immune Complex Mediated Complement Activation (Study #B017): IFX-1 blocked C5a generated by the stimulation of immune complexes specific to human polymorphonuclear leukocytes (PMNs) as well as unspecific immune complexes.

Study Title: IFX-1 Efficacy Analysis: IFX-1 Blocked the Immune Complex-Induced Complement Activation and Cytokine Production (Study #B020): IFX-1 decreased C5a levels and reduced CD11b signals in immune complex-stimulated blood samples below the basal level. IFX-1 also inhibited the production of IL-6 produced by PMN-specific immune complexes and inhibited the production of IL-8 produced by non-specific immune complexes.

Study Title: Biacore Analysis of Human C5a Binding to Anti-Human C5a antibodies (Study #IFX06): All 3 anti-human C5a antibodies tested bound to all 4 C5a proteins from different sources.

Study Title: General Properties of CaCP29-IgG4, an Anti-C5a Antibody: CaCP29 Influence on C5 Cleavage (Study #A005): C5a is derived by cleavage from C5. The cleavage via the classical and the alternative pathway is not disturbed by CaCP29-IgG4 as indicated by the presence of C5b-9 and the functionality of the MAC.

12.3 In Vivo Studies

African green monkeys were inoculated with influenza A virus strain A/Anhui/1/2013 (H7N9) on Day 1. (Sun et al. 2015) Thirty minutes after virus inoculation, monkeys were intravenously administered saline (n=6) or 5 mg/kg IFX-1 (n=4). Monkeys were euthanized on Day 4 and Day 8. Saline control animals developed mild or multifocal bronchointerstitial pneumonia by Day 3 which progressed on Day 7 to more severe degeneration of bronchiolar epithelial cells and pneumocytes and interstitial edema. IFX-1-treated animals had less interstitial edema and less inflammatory infiltrates with mild expansion of the parenchymal wall on Day 3 and Day 7. Serum cytokine levels (IL-1β, IL-6, IP-10, IFNγ, TNF-α, and MCP-1) were reduced in IFX-1 treated monkeys compared to saline control. Semi-quantitative histopathology indicated less macrophage and neutrophil infiltration in the lungs of IFX-1 treated animals. This study suggests that inhibition of C5a by IFX-1 may be beneficial in treating respiratory virus-associated pneumonia. One of the limitations of this model is that IFX-1 was administered immediately after viral inoculation whereas in the COVID clinical setting viral exposure would have occurred several days to weeks prior to vilobelimab administration. The authorized vilobelimab clinical dose of 800mg (~13 mg/kg, assuming a body weight of 60kg) is approximately 3-fold higher than the dose used in the monkey influenza A study and will be administered repeatedly compared to a single dose in the monkey study.

13 Supply Information

- Vilobelimab is available in single dose vials dispensed in a 4-vial carton configuration (NDC: 83000-110-04). Each vial contains 200 mg/20 mL of vilobelimab, with each dose requiring four vials. The current supply projections for vilobelimab are summarized in the table below.

Table 30. Dose Vial Supply

Approximate Vials (Doses)[1]	Supply availability
	(b) (4)

14 Chemistry, Manufacturing, and Controls Information

- Vilobelimab is a recombinant chimeric human/mouse monoclonal IgG4 antibody that specifically binds to the soluble human complement split product C5a after cleavage from C5. Vilobelimab is produced in Chinese Hamster Ovary (CHO)

cells and consists of murine heavy and kappa light chain variable (VH and VL) regions, and human gamma 4 heavy chain and kappa light chain constant regions. Vilobelimab is composed of 1328 amino acids with an approximate molecular weight of 148.5-148.6 kDa. The mechanism of action (MOA) of vilobelimab is to bind and inhibit the complement factor C5a-mediated inflammatory response as a result of C5a-induced tissue damage and organ failure in viral sepsis and acute respiratory distress syndrome.

- Vilobelimab is formulated as a 10 mg/mL sterile solution in (b) (4) sodium phosphate, (b) (6) sodium chloride, and (b) (4) % polysorbate 80 at pH (b) (6)

- The chemistry, manufacturing, and controls (CMC) data supporting EUA 118 are provided in Module 3 of the EUA, with the exception of CMC information for the placebo used in the supporting clinical studies, which is cross-referenced to IND 136470. The data submitted in the EUA and where applicable in IND 136470 support the conclusion that the manufacture of vilobelimab is sufficiently controlled and leads to a product that is suitable for use under EUA.

- Several changes were made in the drug substance and drug product manufacturing processes during product development including changes in manufacturing facilities, scales, processes, and container closure systems. The analytical comparability data support that the material proposed for use under the EUA is comparable to the material used in the supporting clinical studies.

- The requested expiration dating period of 24 months at 2-8°C for drug product is supported based on the totality of the provided drug product stability data, including 36 months of real time stability data from two drug product Process (b) (4) lots and 40 months of real time stability data from one drug product Process (b) (4) lot. The requested expiration dating period of (b) (4) for drug substance is supported by up to (b) (4) real time long-term stability data.

- The in-use compatibility and stability data support the proposed procedures for preparation, handling, storage, and administration of vilobelimab.

15 Manufacturing Site Inspections

Table 31. 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]	(b) (4)		IND-151995	InflaRx GmbH	N/A	Compliant
			IND-151995	InflaRx GmbH	N/A	Compliant
			IND-151995	InflaRx GmbH	N/A	Compliant
			IND-151995	InflaRx GmbH	N/A	Compliant

Source: Compliance Management System

Based on FDA's evaluation of the manufacturing process and control strategy, and the listed facilities, FDA considers the following conditions to the authorization as necessary to protect the public health:[3]

The Requester will manufacture vilobelimab to meet all quality standards and per the manufacturing process and control strategy as detailed in the Requester's EUA request. The Requester 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 I.

[3] See the evaluation documented in OMQ's Authorization Recommendation Memo for Emergency Use Authorization in CMS Case #654513, as well as OPQ's Chemistry, Manufacturing, and Controls EUA Assessment Memo, dated March 9, 2023, associated with EUA 118

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

The Requester will submit information to the Agency within three working days of receipt concerning significant quality problems with distributed drug product of vilobelimab 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 must be submitted for all potentially impacted lots.

  The Requester will include in its notification to the Agency whether the batch, or batches, in question will be recalled. If FDA requests that these, or any other batches, at any time, be recalled, the Requester must recall them.

  If not included in its initial notification, the Requester must submit information confirming that the Requester 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. The Requester must submit this information as soon as possible but no later than 45 calendar days from the initial notification.

- The Requester will list vilobelimab with a unique product NDC under the marketing category of Emergency Use Authorization. Further, the listing will include each establishment where manufacturing is performed for the drug and the type of operation performed at each such establishment.

16 Clinical Trial Site Inspections

Given the small number of subjects enrolled at each clinical study site and absence of concerns regarding data integrity or reliability of study results, no site inspections were performed or deemed necessary for the PANAMO trial supporting this request.

17 Animal Study Site Inspections (Efficacy and PK/PD)

No site inspections were performed or deemed necessary.

18 Recommendations From Treatment Guidelines and Other Sources

At the time of this review, the NIH COVID-19 Treatment Guidelines Panel recommends using the following therapies for hospitalized COVID-19 patients who require mechanical ventilation or ECMO:

Table 32. NIH COVID-19 Treatment Guidelines for Hospitalized Patients Requiring Mechanical Ventilation or ECMO

Patient Disposition	Clinical Scenario	Recommendation for Antiviral or Immunomodulator	Recommendation for Anticoagulant Therapy
Hospitalized and requires MV or ECMO	Most patients	Promptly start 1 of the following, if not already initiated: • Dexamethasone plus PO baricitinib (BIIa) • Dexamethasone plus IV tocilizumab (BIIa) If baricitinib, tofacitinib, tocilizumab[1,2], or sarilumab cannot be obtained: • Dexamethasone (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).

Source: https://www.covid19treatmentguidelines.nih.gov/tables/therapeutic-management-of-hospitalized-adults/ (NIH 2022)
[1] If PO baricitinib and IV tocilizumab are not available or not feasible to use, PO tofacitinib can be used instead of PO baricitinib, and IV sarilumab can be used instead of IV tocilizumab
[2] If a Janus kinase (JAK) inhibitor or an anti-IL-6 receptor mAb 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.
Rating of recommendations: A=Strong; B=Moderate; C=Weak
Rating of evidence: I=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; ICU = intensive care unit; IV = intravenous; MV = mechanical ventilation; PO, by mouth

19 Risk-Benefit Assessment and Recommendations for Emergency Use

The effectiveness and safety of vilobelimab in hospitalized adult patients when initiated within 48 hours of requiring invasive mechanical ventilation or ECMO due to COVID-19 infection were primarily evaluated in the Phase 3 portion of the PANAMO trial. This was a multicenter, prospective, randomized, double-blind, placebo-controlled, clinical trial comparing vilobelimab dosed with background standard of care (SOC, i.e., dexamethasone) to placebo with background SOC. Patients in the PANAMO trial were selected based on recent need for invasive mechanical ventilation. As such, the study population was clearly defined, and there are no concerns about the ability to identify a similar patient population in clinical practice.

Patients in the vilobelimab + SOC group were less likely to die before Day 28 compared to patients in the placebo + SOC group. The primary endpoint of all-cause mortality at Day 28 demonstrated mortality rates of 31.7% in the vilobelimab group and 41.6% in the

placebo group with a statistically significant estimated hazard ratio of 0.67 (95% CI =0.476, 0.955; p=0.0266). The mortality risk by Day 60 was similar to the results at Day 28 and remained lower in the vilobelimab group compared to placebo.

The incidence of treatment emergent adverse events (TEAEs) in the trial was high given the severity of disease in this patient population; however, the overall incidence was the same (91%) in both treatment groups. More nonfatal serious adverse events related to infection occurred in the vilobelimab + SOC group than placebo + SOC, and this difference was primarily driven by an increased risk of pneumonia and sepsis. However, serious adverse events leading to death were lower in the vilobelimab + SOC group and TEAEs leading to treatment discontinuation were infrequent and similar between treatment groups.

Based on the totality of scientific evidence available, it is reasonable to believe that vilobelimab may be effective the treatment of COVID-19 in hospitalized adults when initiated within 48 hours of receiving invasive mechanical ventilation or ECMO, and that the known and potential benefits of vilobelimab outweigh its known and potential risks for this population of critically ill patients who continue to experience high mortality rates despite availability of alternative therapies. Therefore, the review Division recommends issuance of an EUA for vilobelimab for the treatment of COVID-19 in hospitalized adults when initiated within 48 hours of receiving invasive mechanical ventilation or ECMO as detailed in the Fact Sheets.

20 Considerations for Adverse Event Monitoring

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

If used in clinical trials conducted 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 healthcare 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 vilobelimab occurring during vilobelimab treatment within 7 calendar days from the onset of the event. The reports should include unique identifiers and the words "Vilobelimab Treatment under Emergency Use Authorization EUA."

21 Mandatory and Discretionary Requirements for Use of the Product Under the EUA

See Letter of Authorization.

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

InflaRx will make available the authorized Fact Sheet for Health Care Providers (See Appendix 26.3) and the authorized Fact Sheet for Patients and Caregivers (See Appendix 26.4) through a dedicated website for the EUA covering vilobelimab at www.Gohibic.com. The carton and container labeling will include the URL and a QR code (carton only) to refer providers to the Fact Sheets.

23 Outstanding Issues/Data Gaps

Not applicable.

24 References

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Web Pages

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NIH, 2023, Coronavirus Disease 2019 (COVID-19) Treatment Guidelines, National Institutes of Health, accessed, 2023, https://www.covid19treatmentguidelines.nih.gov.

25 Appendices

25.1 Additional Efficacy Analyses

Table 33: WHO Ordinal Scale Score by Visit (Full Analysis Set, LOCF)

	Baseline		Day 8		Day 15		Day 22		Day 28	
WHO	VILO	Placebo	VILO	Placebo	VILO	Placebo	VILO	Placebo	VILO	Placebo
0	0	0	0	1 (0.5%)	2 (1.1%)	4 (2.1%)	2 (1.1%)	5 (2.6%)	8 (4.5%)	15 (7.9%)
1	0	0	0	1 (0.5%)	2 (1.1%)	3 (1.6%)	5 (2.8%)	4 (2.1%)	11 (6.2%)	7 (3.7%)
2	0	0	1 (0.6%)	0	3 (1.7%)	7 (3.7%)	12 (6.8%)	12 (6.3%)	20 (11.3%)	25 (13.1%)
3	0	0	4 (2.3%)	4 (2.1%)	13 (7.3%)	21 (11.0%)	24 (13.6%)	29 (15.2%)	18 (10.2%)	15 (7.9%)
4	0	0	26 (14.7%)	31 (16.2%)	37 (20.9%)	26 (13.6%)	30 (16.9%)	25 (13.1%)	24 (13.6%)	17 (8.9%)
5	0	0	12 (6.8%)	14 (7.3%)	12 (6.8%)	5 (2.6%)	6 (3.4%)	2 (1.0%)	3 (1.7%)	3 (1.6%)
6	72 (40.7%)	59 (30.9%)	68 (38.4%)	55 (28.8%)	38 (21.5%)	31 (16.2%)	32 (18.1%)	18 (9.4%)	20 (11.3%)	11 (5.8%)
7	105 (59.3%)	132 (69.1%)	53 (29.9%)	62 (32.5%)	35 (19.8%)	41 (21.5%)	19 (10.7%)	27 (14.1%)	19 (10.7%)	21 (11.0%)
8	0	0	13 (7.3%)	23 (12.0%)	35 (19.8%)	53 (27.7%)	47 (26.6%)	69 (36.1%)	54 (30.5%)	77 (40.3%)

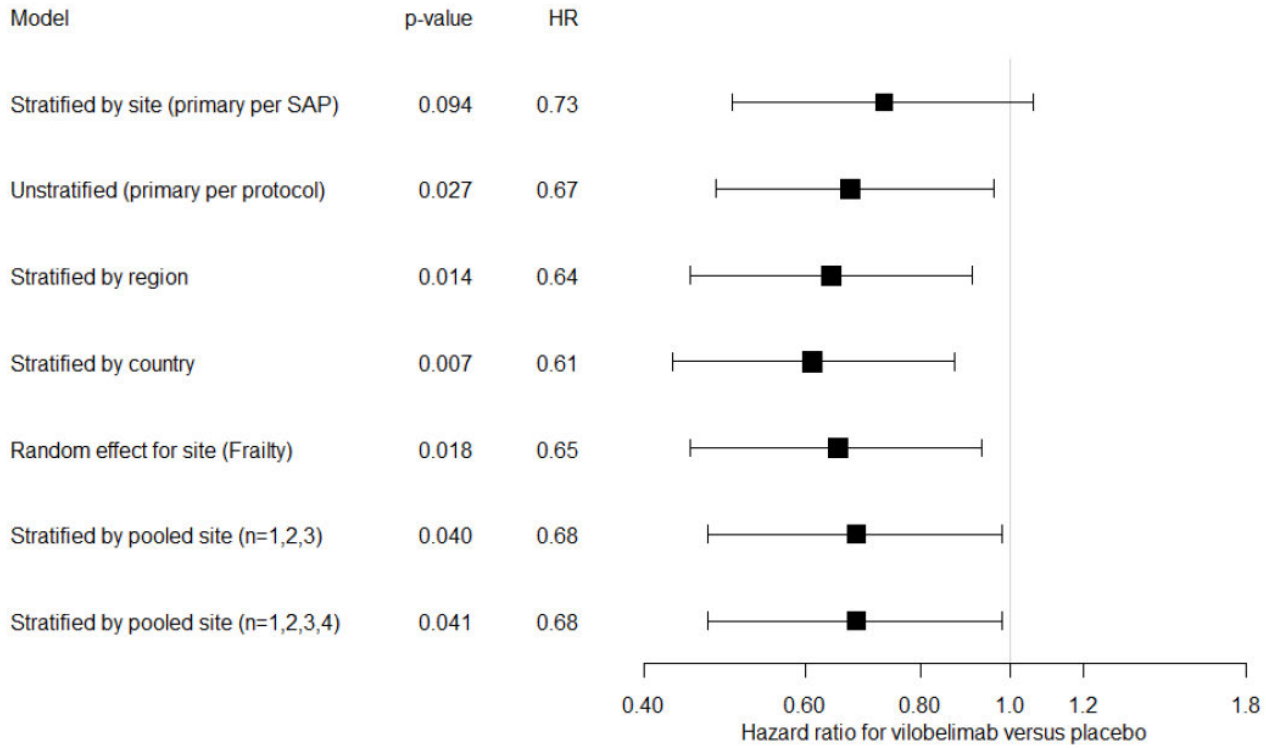
Source: Reviewer's analysis generated using adsl.xpt and adqs.xpt
Abbreviations: LOCF = least observation carried forward; SOC = standard of care, WHO = World Health Organization; VILO = vilobelimab

Table 34: Age Distribution in Subjects From Brazil (Full Analysis Set)

Subject Age	**VILO + SOC (N = 34)**	**Placebo + SOC (N = 40)**	**Total (N = 74)**
Age			
Mean (SD)	52.5 (12.67)	45.8 (13.74)	48.9 (13.59)
Median	53.5	44.5	48.5
IQR	41.0, 59.0	35.5, 55.0	40.0, 56.0
Min, max	30.0, 78.0	22.0, 74.0	22.0, 78.0
Age group, n (%)			
≥ 18 years and < 40 years	6 (17.6)	12 (30.0)	18 (24.3)
≥ 40 years and < 50 years	7 (20.6)	14 (35.0)	21 (28.4)
≥ 50 years and < 60 years	14 (41.2)	8 (20.0)	22 (29.7)
≥ 60 years and < 70 years	2 (5.9)	3 (7.5)	5 (6.8)
≥ 70 years and < 80 years	5 (14.7)	3 (7.5)	8 (10.8)

Source: Adapted from clinical Study Report Table 14.1.6.1 (page 389); results reproduced by the reviewer using adsl.xpt
Abbreviations: IQR = Interquartile Range, Max = maximum, Min = minimum, SD = standard deviation, SOC = standard of care, VILO = vilobelimab

Figure 9: Forest Plot of Different Cox Regression Analysis Approaches for 28-Day All-Cause Mortality (Full Analysis Set)



The bottom two Cox regression approaches used site-stratification but with small sites (n < 4, n < 5) within country pooled to one new hypothetical larger site within country.

Source: Clinical study report Figure 10-5.

Table 35: Overview of Infusion Related Reactions From All Trials in Subjects Who Received Vilobelimab

USUBJID	Time and Day of Onset From Start of the Infusion	Dose	Symptoms/Severity/ Grade	Intervention	Further Infusions, Premedication
Phase 3 PANAMO					
(b) (6)	2 hr 25 min Day 1 (dose #1)	800 mg	Trunk rash; Mild/grade 1	None	4 subsequent infusions, no premedication
(b) (6)	18 hr 47 min Day 8 (dose #4)	800 mg	Rash, feeling warm; mild/grade 1	None	No further infusions (subject discharged day of IRR, reaction resolving)
(b) (6)	Unknown Day 4 (dose #3)	800 mg	Rash; mild/grade 1	Promethazine (route unknown) x 4 days	1 subsequent infusion, no premedication
Phase 2 PANAMO					
(b) (6)	10 min Day 1 (dose #1)	800 mg	Burning and redness bilateral eyes; mild/grade 1	None Dose interrupted and resumed (time unknown)	Prophylaxis prior to Day 2 (clemastine IV, hydrocortisone IV) and Day 8 dose (clemastine IV only)

USUBJID	Time and Day of Onset From Start of the Infusion	Dose	Symptoms/Severity/ Grade	Intervention	Further Infusions, Premedication
Pyoderma gangrenosum					
(b) (6)	2 days Day 29 (dose #2)	1600 mg Q2W	Rash; Serious; severe/Grade 3	Prednisone PO	Discontinued
Hidradenitis suppurativa					
(b) (6)	IRR1: 45 min Day 30 (dose #2) IRR2 45 min Day 58 (dose #3)	400 mg Q4W	IRR1: Hypersensitivity (no symptom details) IRR2: Hypersensitivity (no symptom details)	IRR1: dimetidine IV, hydrocortisone IV IRR2: levocetirizine PO, hydrocortisone IV	Both doses interrupted IRR1: no premedication prior to subsequent infusions; IRR2: dexchlorpheniramine prior to subsequent 4 infusions
(b) (6)	IRR1: 10 min Day 16 (dose #2) IRR2 15 min Day 85 (dose #6)	800 mg Q2W	IRR1: Chills, dizziness, nausea; all moderate/grade 2 IRR2: Chills, feeling hot, intestinal pain, diarrhea, vomiting; all severe/grade 3	IRR1: Paracetamol PO, dexchlorpheniramine IV, metoclopramide IV IRR2: loperamide PO, paracetamol PO, dexchlorpheniramine IV	Both doses interrupted IRR1: no premedication prior to subsequent infusions; IRR2: dexchlorpheniramine prior to subsequent 4 infusions

Source: IR response from the Requester regarding IRR.
Abbreviations: IRR = infusion related reaction; IV = intravenous; PO = by mouth; Q2W = every 2 weeks; Q4W = every 4 weeks; USUBJID = unique subject ID.

25.2 Pharmacometrics Review

25.2.1 Population PK Analysis

Review Summary

In order to support the Emergency Use Authorization (EUA) request for the emergency use of vilobelimab (IFX-1) for the treatment of coronavirus disease 2019 (COVID-19) in hospitalized adults when initiated within 48 hours of receiving mechanical ventilation, or extracorporeal membrane oxygenation (ECMO), the Requester utilized the previously developed population pharmacokinetic (PK) / pharmacodynamic (PD) model using data collected from two Phase 2 studies conducted in patient with hidradenitis suppurativa (HS) (Study #IFX-1-P2.3 and study IFX-3-1-P2.4) and conducted comparability analysis of IFX PK profiles in HS and severe COVID-19 patients. The reviewer did not identify significant discordance in the Requester's analysis.

In the Requester's original EUA submission dated September 29, 2022, the Requester only submitted the population pharmacokinetic (popPK) report for vilobelimab which is based on HS patient population. In addition, the Requester did not simulate vilobelimab

PK profiles following proposed COVID dosing regimen (i.e., 800 mg on Day 1, 2, 4, 8, 15 and 22 as long as the patient is hospitalized). Information requests were sent to the Requester on November 10, 2022 and December 13, 2022 to ask for additional analysis to compare the PK profiles between the HS and COVID patients,[4] more specifically, to simulate VILO PK profile following proposed dosing regimen and compare it with observed VILO in PANAMO COVID-19 study.[5] The Requester submitted their IR response and were deemed acceptable.

Introduction

The objective of this analysis was to compare the IFX-1 exposure between HS and COVID-19 patients at the proposed dosing regimen for COVID-19 indication (1 hour IV infusion of 800 mg on Days 1, 2, 4, 8, 15 and 22) with specific emphasis on concentration level at the end of the dosing interval (C_{trough}) at Day 8 after the first dose administration.

Model Development

Data

The PopPK analysis was performed based on data collected from 12 patients from Study #IFX-1-P2.3 and 162 patients from Study #IFX-2-P2.4. A total of 1833 PK observations (175 from IFX-2-P2.3 and 1658 from Study IFX-1-P2.4) were included in the analysis. Brief descriptions of the studies included are presented in Table 36.

NONMEM (Version 7.3) and either the first-order conditional estimation with interaction (FOCE-I) method or the importance sampling with mean a posteriori (IMPMAP) method were used for PopPK modeling. All graphical analyses were performed using R, Version 3.6,1. Goodness of fit plots were performed using Xpose 4.0 Version 1.0. Visual Predictive Check (VPC) plots were generated using Perl-speaks-NONMEM program version 4.9.0. Table 36 provides summary statistics of the baseline demographic covariates in the analysis dataset.

[4] DARRTS, EUA118, Larose, Ji Hyun, 11/10/2022, COR-EUA-11 (Pre-EUA advice/Information Request)

[5] DARRTS, EUA118, Larose, Ji Hyun, 12/13/2022, COR-EUA-11 (Pre-EUA advice/Information Request)

Table 36. Summary of Studies With PK Sampling Included in Population PK Analysis

Study # & Study Design	Dosage Regimen & Study Description	Number of Subjects in PopPK Analysis, Subject Type and Food Status	Dose(s)
IFX-1-P2.3 Phase 2	An open-label, single-center, Phase II study consisting of 3 study periods, with a total duration of 22 weeks.	N=12 Patients with moderate or severe HS	1600 mg QW
IFX-1-P2.4 Phase 2	A randomized, two-period, placebo-controlled double-blind (Main Period) and open-label (Maintenance Phase of Extension Period) multicenter study.	N=162 Patients with moderate or severe HS	Main periods start at week 0 consists of 2 weeks induction phase and 14 week maintenance phase. 5 cohorts: placebo, IFX-1 400 mg every 4 weeks (q4w), 800 mg q4w, 800 mg every 2 weeks (q2w), and 1200 mg q2w. Subjects from all cohorts who were HS Clinical Response (HiSCR) responders at Week 16 received IFX-1 at a dose of 800 mg q4w, starting at Week 20 through Week 40. Subjects who lost response during the Extension Period had an optional visit 2 weeks later.

Source: Table summarized from Abbreviated Population Pharmacokinetic/Pharmacodynamic modeling Report for IFX-1 Date Apr. 6, 2020
Abbreviations: HS = hidradenitis suppurativa; popPK = population pharmacokinetics; Q2W = every 2 weeks; Q4W = every 4 weeks; QW = every week.

Base Model

The base model for IFX-1 was two-compartment with parallel linear and Michaelis-Menten elimination. (Chiba et al. 1980) Between-occasion variability was included on maximum volume (Vmax) with the occasion interval set to 1000 hours between time = 0 and time = 4000, resulting in 5 intervals. A full OMEGA matrix was included with between subject variability (BSV) on Vmax, Volume, Km, and linear clearance.

Covariate Analysis

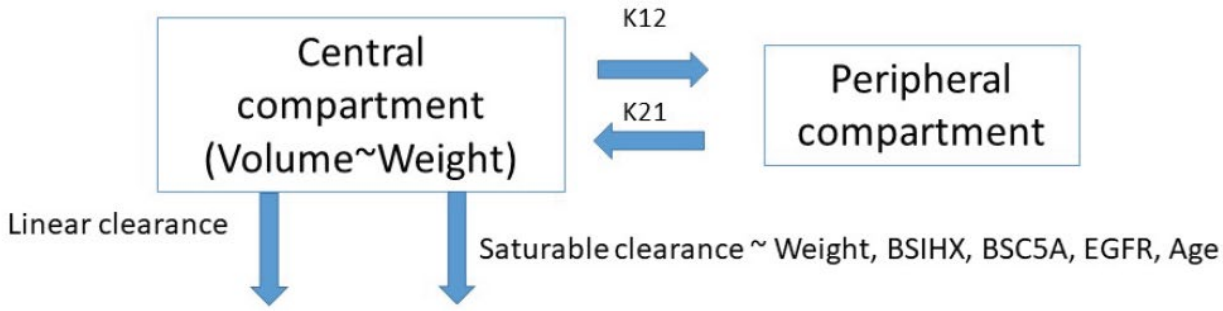
Pre specified covariates hypotheses included the effect of body weight or body mass index (BMI) on clearance/Vmax of IFX-1, ADA on clearance/Vmax, age on clearance/Vmax of IFX-1, estimated glomerular filtration rate (eGFR) on clearance/Vmax of IFX-1, baseline total AN count on clearance/Vmax of IFX-1, baseline number of draining fistulas on clearance/Vmax of IFX-1, antibiotic use on clearance/Vmax of IFX-1, iHS4 on clearance /Vmax of IFX-1, and baseline Ca on clearance/Vmax. These covariates were added individually in six rounds, and the model after prespecified hypotheses were used to make exploratory plots for additional covariate relationships. Based on exploratory parameter-covariate plots, the following exploratory hypotheses were tested in forward selection: body surface area (BSA) on

clearance, baseline number of abscesses and nodules (BSAN) on volume, and antibiotics on Km. Then the model covariates went through the backward elimination.

Final Model

The final model diagram is listed in Figure 10. Doses are administered intravenously to the central compartment. A peripheral compartment is supported by the data with mass transfer rate constants of 0.0109/hr into the peripheral and 0.0120/hr from the peripheral back to the central compartment. Two routes of elimination were supported by the data: a linear route and a saturable (Michaelis-Menten) route. The central volume of distribution was dependent on body weight, and the saturable elimination was dependent on the weight, the baseline IHS score (BSIHX), the baseline C5a (BSC5s), eGFR and Age. Final parameter estimates are given in Table 37. Goodness of fit (GOF) plots are listed in Figure 11. Visual predictive check (VPC) plots are listed in Figure 12. Overall, the final PopPK model provides reasonable estimation of IFX-1 in patients with HS.

Figure 10. Diagram of the Final Model



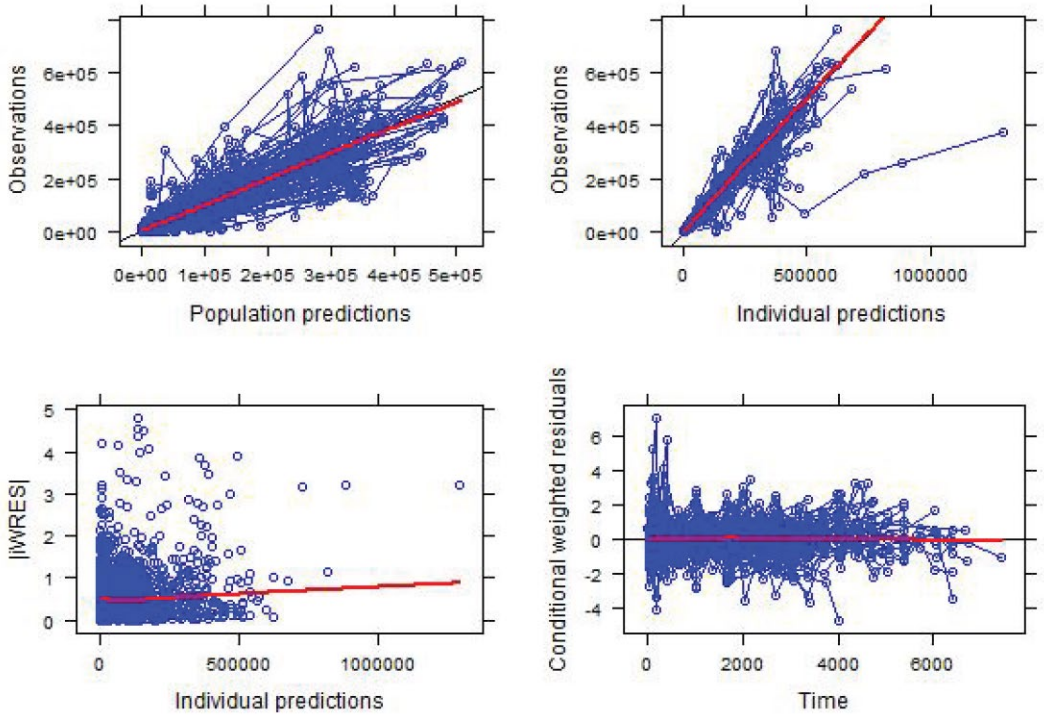
Source: Figure 9, Abbreviated Population Pharmacokinetic/Pharmacodynamic modeling Report for IFX-1 Date Apr. 6, 2020

Table 37. Population Parameter Estimate for the Final PopPK Model

Parameter, description (units)	Estimate excluding outliers (RSE)	Estimate including outliers, Model 82
THETA(1) Vmax (mg/hr)	1.80 (0.0792)	1.87
THETA(2) Central volume of distribution (L)	3.72 (0.0313)	3.78
THETA(3) Additive error	88.9 (0.257)	46.29
THETA(4) Proportional error	0.221 (0.0227)	0.258
THETA(5) Km (ng/mL)	13600 (0.0698)	17490
THETA(6) Linear clearance (L/hr)	0. 0138 (0.0650)	0.0125
THETA(7) K12	0.0109 (0.0712)	0.001
THETA(8) K21	0.0120 (0.0700)	0.0109
THETA(10) Body weight on Vmax	0.864 (0.135)	0.599
THETA(11) Baseline IHS on Vmax	0.313 (0.0639)	0.274
THETA(12) Baseline C5A on Vmax	0.127 (0.218)	0.1
THETA(13) eGFR on Vmax	0.167 (0.374)	0.187
THETA(14) Age on Vmax	0.236 (0.319)	0.28
THETA(16) Weight on central volume of distribution	0.231 (0.430)	0.225

Source: Table 4, Abbreviated Population Pharmacokinetic/Pharmacodynamic modeling Report for IFX-1 Date Apr. 6, 2020
RSE is relative standard error = parameter estimate/standard error of the estimate.
Abbreviations: eGFR = estimated glomerular filtration; PopPK = population pharmacokinetics; Vmax, maximum volume.

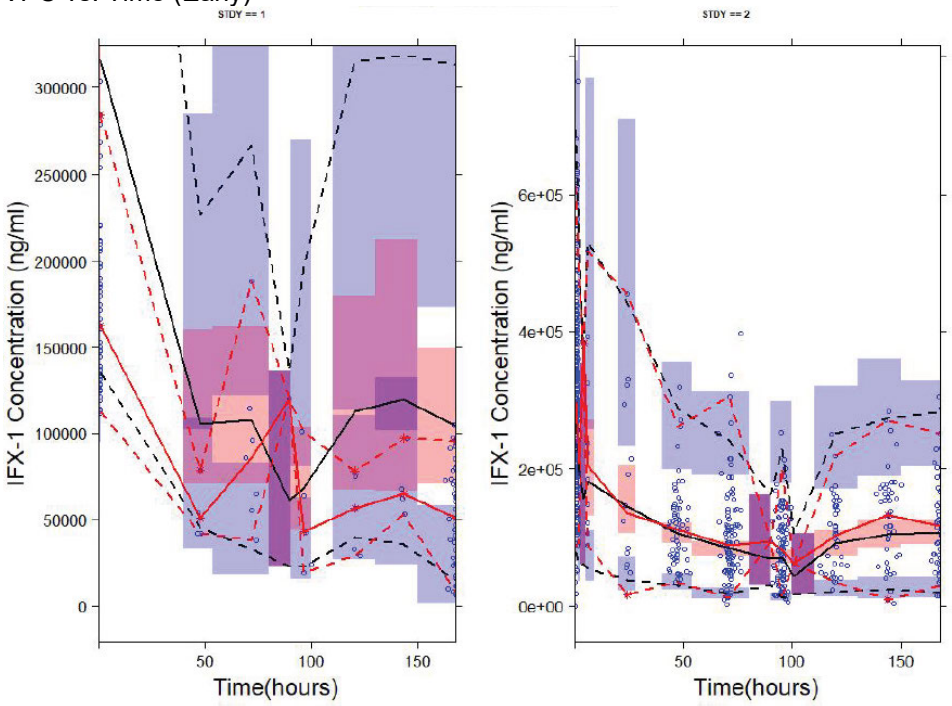
Figure 11. Goodness-of-Fit Plots for Final PopPK Model



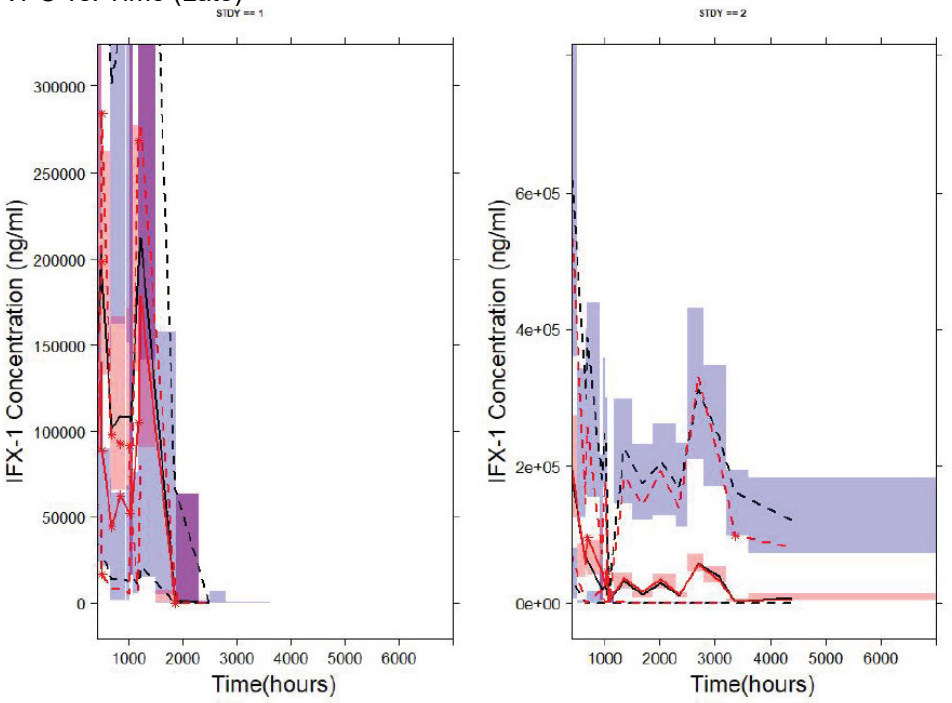
Source: Figure 10, Abbreviated Population Pharmacokinetic/Pharmacodynamic modeling Report for IFX-1 Date Apr. 6, 2020
Upper left plot is population prediction (ETA = 0) vs observed, upper right is individual prediction (ETA not equal to 0) vs observed, lower left is individual prediction vs absolute value of individual weighted residual, lower right is Time (hours) vs conditional weighted residual. Red line is (loess) smooth. Black line is line of unity (intercept = 0, slope = 1). The lines connect data from the same subject.

Figure 12. VPC Plots of the Final PopPK Model

VPC vs. Time (Early)



VPC vs. Time (Late)



Source: Figure 11 and 12, Abbreviated Population Pharmacokinetic/Pharmacodynamic modeling Report for IFX-1 Date Apr. 6, 2020
Note: The solid red line is the median of the observed data, the solid black line is the median of the simulated data. The dashed lines are the upper and lower 95% interval for observed (red) and predicted (black). The red blocks are the 95% CI of the predicted median, the blue blocks are the upper and lower limits of the 95% CI of the 95% interval of the simulated data. STDY==1 is IFX-1-P2.3, STDY==2 is IFX-1-P2.4.

In original submission of EUA dated September 29, 2022, the Requester conducted simulation for the following proposed dosing regimens: 1) 800 mg loading dose, 800 mg

every 2 weeks (Q2W); 2) 800 mg loading dose, 1200 mg Q2W; 3) 800 mg loading dose, 1600 mg Q2W; 4) 800 mg loading dose, 2400 mg Q2W; 5) 2400 mg Q2W at steady state. The Requester deems 1600 mg Q2W is the regimen with the dose that ensures at the median greater than 90% of the day with IFX-1 concentration greater than 50,000 ng/ml (C_{trough}), which is a threshold determined to be correlated with clinical response in HS patients. However, the Requester did not simulate IFX-1 PK profiles following proposed COVID dosing regimen (i.e., 800 mg on Day 1, 2, 4, 8, 15 and 22 as long as the patient is hospitalized). Information requests were sent to Requester on November 10, 2022 and December 13, 2022 to ask for additional analysis to compare the PK profiles between the HS and COVID patients,[6] more specifically, to simulate VILO PK profile following proposed dosing regimen and compare it with observed VILO in PANAMO COVID-19 study.[7]

The Requester submitted their IR response in December 20, 2022. To compare the IFX-1 exposure between HS and COVID-19 patients, the Requester used the following multi-step simulation approach:

1. Simulate IFX-1 PK profile in virtual HS patients (n = 1000) following 1 hour IV infusion of 800 mg doses on Days 1, 2,4, 8, 15 and 22.
2. Simulate IFX-1 PK profile in virtual COVID-19 patients (n = 1000) following 1 hour IV infusion of 800 mg doses on Days 1, 2,4 ,8 ,15 and 22.
3. Compare the median and 5^{th}-95^{th} percentiles for C_{trough} at day 8 between HS and COVID-19 simulated patients.
4. Compare the median and 5^{th}-95^{th} percentiles for C_{trough} at Day 8 between COVID-19 simulated patients and actual observations from study IFX-1-P2.9.

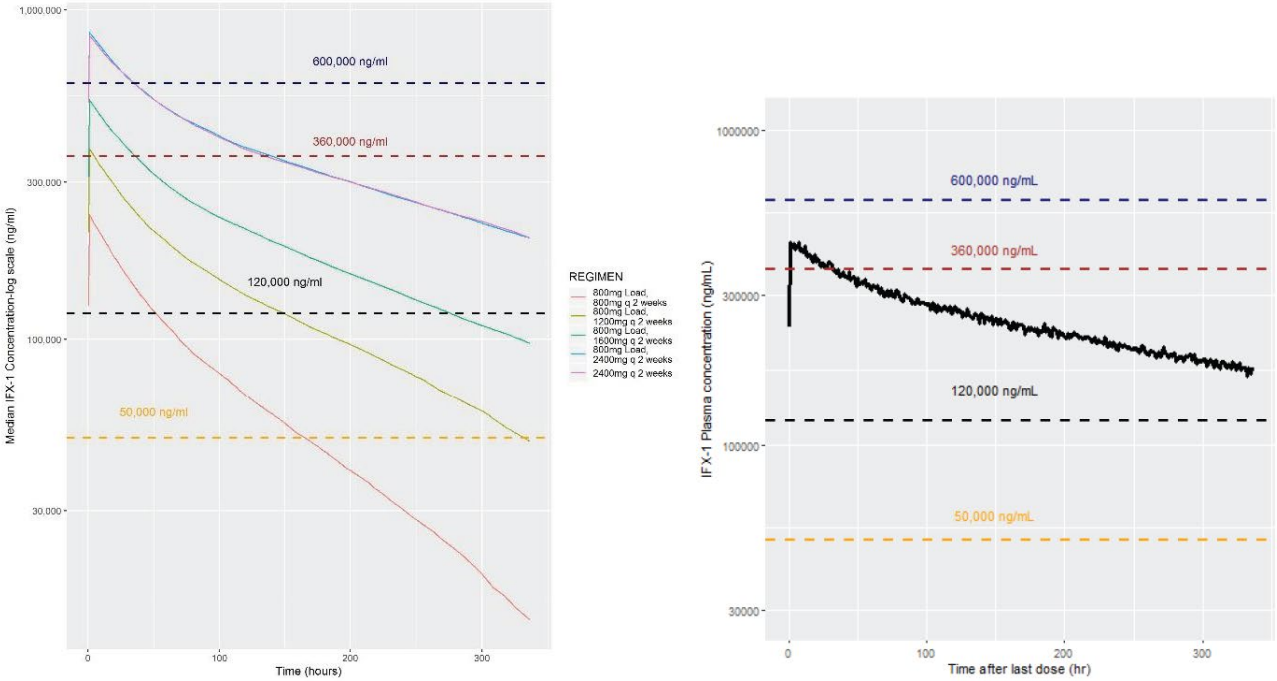
Individual subject concentrations were simulated in R version 4.1.3 using the rxode2 package version 2.0.10. Statistical analysis and plotting of the simulation results were performed in R version 4.1.3.

The summary of simulated average concentration (C_{avg}), area under the curve over the dosing interval (AUC_{tau}), maximum observed concentration (C_{max}) and concentration at the end of the dosing interval (C_{trough}) in HS virtual subjects using the proposed dosing regimen for COVID-19 indication is listed in Table 38 and presented in Figure 13. Previously, 120,000 ng/ml of IFX-1 C_{avg} approximately corresponds to a 50% reduction of baseline C5a levels based on visual inspection of plots of the relationship between C_{avg} and C5a response in HS patients. The value of 360,000 ng/ml was postulated as the target concentration which is three-fold of the EC_{50} and would be near the top of the concentration-response relationship, based on an estimate of EC_{50} of 120,000 ng/ml. These proposed thresholds are reflected in the plots below.

[6] DARRTS, EUA118, Larose, Ji Hyun, 11/10/2022, COR-EUA-11 (Pre-EUA advice/Information Request)

[7] DARRTS, EUA118, Larose, Ji Hyun, 12/13/2022, COR-EUA-11 (Pre-EUA advice/Information Request)

Figure 13. Plots of Median IFX-1 Concentration by Simulated Dosing Regimens.



Source: Figure 1, Comparability Analysis of IFX-1 Pharmacokinetic Profiles in Hidradenitis Suppurativa and Severe COVID-19 Pneumonia Patients, Dec 20, 2022
Note: Previously simulated dosing regimens (left) and COVID-19 dosing regimen (right).

Table 38. Summary of C_{avg}, C_{trough}, C_{max}, and AUC_{tau} at Steady-State Based on Simulation

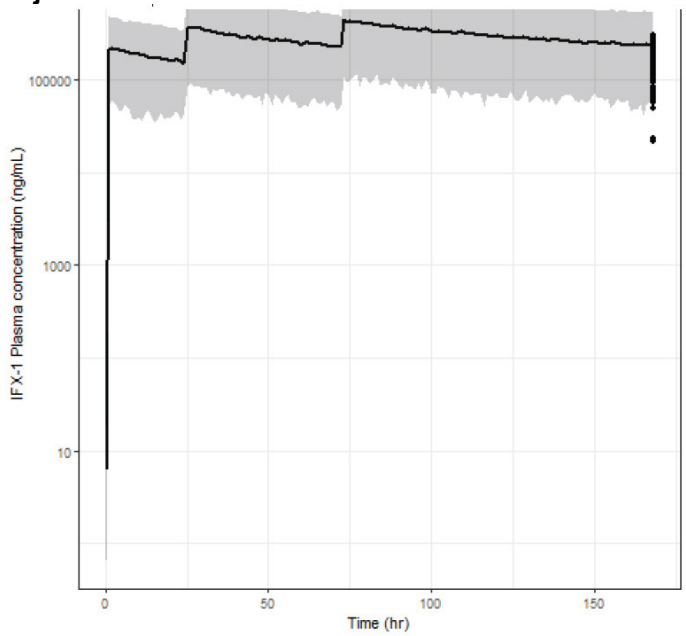
Parameter	800 mg LD on Days 1, 4, and 8 followed by 800 mg MD q2w	800 mg LD on Days 1, 4, and 8 followed by 1200 mg MD q2w	800 mg LD on Days 1, 4, and 8 followed by 1600 mg MD q2w	800 mg LD on Days 1, 4, and 8 followed by 2400 mg MD q2w	2400 mg MD	COVID-19 regimen: 800 mg MD on Days 1, 2, 4, 8, 15 and 22
C_{avg}-Geometric Mean (ng/mL)	68300	133000	209000	374000	369000	314480
C_{avg}-Geometric CV (%)	58.7	57.2	53.9	49.1	45.8	36.7
C_{avg}-Median (ng/mL)	67000	133000	210000	372000	369000	318207
AUC_{tau}-Geometric Mean (ng*hr/mL)	23000000	44600000	70100000	126000000	124000000	52828046
AUC_{tau}-Geometric CV (%)	58.7	57.2	53.9	49.1	45.8	36.7
AUC_{tau}-Median (ng*hr/mL)	22500000	44600000	70500000	125000000	124000000	53458770
C_{max}-Geometric Mean (ng*hr/mL)	237000	381000	536000	860000	848000	836727
C_{max}-Geometric CV (%)	34	35.5	35.7	35.4	34.8	36.4
C_{max}-Median (ng*hr/mL)	240000	379000	535000	856000	836000	841468
C_{trough}-Geometric Mean (ng/mL)	11600	38400	81700	190000	188000	205659
C_{trough}-Geometric CV (%)	274	196	138	87	76.2	100
C_{trough}-Median (ng/mL)	14000	48900	97400	203000	204000	230644

Source: Table 2, Comparability Analysis of IFX-1 Pharmacokinetic Profiles in Hidradenitis Suppurativa and Severe COVID-19 Pneumonia Patients, Dec 20, 2022

The data showed that COVID-19 dosing regimen has similar PK profile as 800 mg loading dose, 1600 mg Q2W dosing scheme based on simulation, which meet the proposed threshold concentration. In addition, simulated (based on the model developed in HS patients) and observed IFX-1 PK profiles in COVID-19 subjects are depicted in Figure 14. The majority of the observed C_{trough} at day 8 were included within the 95% prediction interval (PI) of simulated data, which is similar to the VPC vs Time (late) results depicted in HS patients Figure 12. This suggests the PopPK model can reasonably predict IFX-1 C_{trough} in COVID-19 subjects. The simulated and observed distribution of IFX-1 C_{trough} at day 8 in COVID-19 subjects are presented in Figure 15 and Table 39. The data showed that observed IFX-1 C_{trough} are within the predicted range. However, the predicted median C_{trough} is ~50% higher than the observed C_{trough} in COVID-19 subjects, which is also consistent with the slight overprediction at elimination

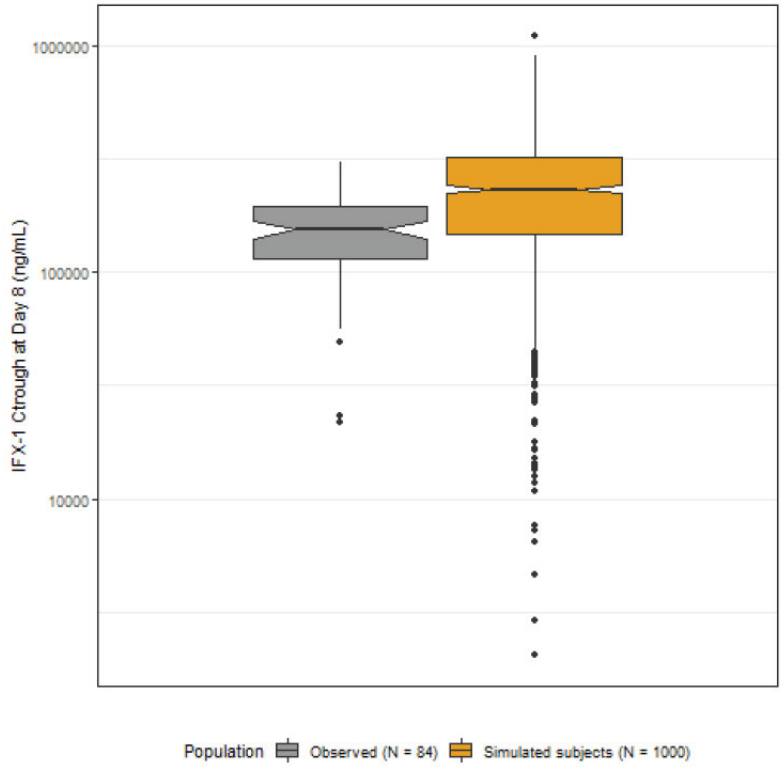
phase for the popPK model in HS patients as depicted in Figure 12 (VPC vs. Time (late)). However, due to the small sample size and sparse PK sampling in the COVID program, the potential effect of disease and other demographic covariates on IFX-1 PK cannot be fully excluded to explain the 50% difference between the model predicted and the observed median C_{trough} value at current stag. Nevertheless, the observed median IFX-1 C_{trough} value on Day 8 (154,2000 ng/mL) in patients with COVID-19 following the studied dosing regimen is still higher than the IC_{50} concentration (i.e., 120,000 ng/ml) needed for reduction C5a levels from the baseline as projected from patients with HS.

Figure 14. Simulated and Observed IFX-1 Time-Concentration PK Profiles Up to Day 8 in COVID-19 Subjects



Source: Figure 2, Comparability Analysis of IFX-1 Pharmacokinetic Profiles in Hidradenitis Suppurativa and Severe COVID-19 Pneumonia Patients, Dec 20, 2022
Note: The black line and the grey area represent the median and the 95% prediction interval (PI) simulated with the model. The black dots represent observed IFX-1 C_{trough} at day 8 in COVID-19 patients.

Figure 15. Distribution of Simulated and Observed IFX-1 C_{trough} at Day 8 in COVID-19 Subjects



Source: Figure 3, Comparability Analysis of IFX-1 Pharmacokinetic Profiles in Hidradenitis Suppurativa and Severe COVID-19 Pneumonia Patients, Dec 20, 2022

Table 39. Summary Statistics of IFX-1 C_{trough} at Day 8 in Observed and Simulated COVID-19 Subjects

COVID-19 Population	Size	Median (µg/mL)	5th percentile (µg/mL)	95th percentile (µg/mL)
Observed	84	154.2	59.1	236.6
Simulated	1000	231.3	50.0	534.1

Source: Table 3, Comparability Analysis of IFX-1 Pharmacokinetic Profiles in Hidradenitis Suppurativa and Severe COVID-19 Pneumonia Patients, Dec 20, 2022
Abbreviations: COVID-19 = coronavirus disease 2019; C_{trough} = trough plasma concentration

Summary of the Bioanalytical Assay for PK Assessment

Vilobelimab concentrations in human plasma were analyzed using a validated enzyme-linked immunosorbent assay (ELISA). The ELISA assay (PK ELISA ([(b) (4)])) has been originally developed and validated at [(b) (4)] and the validation summary is as shown in Table 40. This assay was then transferred from [(b) (4)] to menal GmbH, Germany, without changing the methodology of the assay. Cross

validation has been adequately performed at menal GmbH (Table 41, Table 42). Human plasma samples from Study IFX-1-2.9 have been stored at -70 °C to -85 °C and analyzed within the demonstrated stability duration.

Table 40. Summary of the Bioanalytical Assay Validation (PK ELISA ((b) (4)))

Calibration Range	7.81 -225 ng/mL
ULOQ	900 ng/mL in undiluted sample (ULQC = 225 ng/mL)
LLOQ	31.3 ng/mL in undiluted sample (LLQC = 7.81 ng/mL)
MRD	1:4
Intra-assay Accuracy and Precision	Between -7.42% and 16.2% (Bias) Between 0.915% and 13.0% (%CV)
Inter-assay Accuracy and Precision	Between -1.74% and 11.9% (Bias) Between 5.84% and 7.64% (%CV)
Stability	• 24 h at RT • 24 h at 5 °C ± 3 °C • Up to 7 months at -75 °C ± 15 °C • Up to 3 freeze/thaw cycles
Dilution linearity	Dilution linearity was demonstrated for the following dilution factors: 4, 10, 20, 50 and 100

Source: page 13 of 65, Bioanalytical Validation Report IFX-1-menal1
Abbreviations: %CV = geometric mean; ELISA = enzyme-linked immunosorbent assay; LLOQ = lower limit of quantification; LLQC = lower limit of quality control; MRD = minimal residual disease; PK, pharmacokinetics; ULOQ = upper limit of quantification; ULQC = upper limit of quality control.

Table 41. Intra-Assay Accuracy and Precision of the Bioanalytical Assay (PK ELISA (Menal))

QC [ng/mL]	Mean Accuracy* (Day 1 and Day 3)	%CV* (Day 1 and Day 3)	Total Error* (Day 1 and Day 3)
ULQC [225]	88.0-94.4%	3.7%-5.5%	11.1%-15.7%
HQC [167]	93.6-97.9%	2.7%-5.9%	4.8%-12.2%
MQC [93.8]	90.5-95.7%	2.7%-10.2%	7.0%-19.7%
LQC [46.9]	88.6-98.7%	2.2%-14.1%	3.5%-25.5%
LLQC1 [15.6]	98.5-113.6%	8.9%-12.9%	14.4%-22.4%
LLQC2 [12.5]	103.1-113.7%	6.9%-11.8%	14.9%-20.6%

* Acceptance criteria:
Mean accuracy, 80-120% of the nominal concentration; exception LLQC1, LLQC2 and ULQC (75-125%).
Mean precision (%CV), ≤20%; exception LLQC1, LLQC2 and ULQC (≤25%).
Total error for each QC level, ≤30%; exception LLQC1, LLQC2 and ULQC (≤40%).
%CV = percentage coefficient of variation, HQC = high quality control, LLQC = lower limit quality control, LQC = low quality control, MQC = medium quality control, PK = pharmacokinetic, QC = quality control, ULQC = upper limit quality control

Source: Table 5 of Summary of biopharmaceutic studies and associated analytical methods
(Additional assessment indicated that human plasma samples remained stable for up to three months when stored at -20 °C ± 10 °C. The incurred sample reproducibility (ISR) was tested to be 92.7% and the dilution factor is updated to be 64,000.)

Table 42. Inter-Assay Accuracy and Precision of the Bioanalytical Assay (PK ELISA (Menal))

QC [ng/mL]	Accuracy*	%CV*	Total Error*
ULQC [225]	89.5%-92.9%	22.8%	31.6%
HQC [167]	94.2%-97.3%	15.0%	19.2%
MQC [93.8]	90.8%-95.4%	9.1%	16.0%
LQC [46.9]	90.4%-96.9%	15.0%	21.3%
LLQC1 [15.6]	101.7%-110.4%	20.8%	26.8%
LLQC2 [12.5]	104.8%-112.1%	22.6%	31.1%

* Acceptance criteria:
Mean accuracy, 80-120% of the nominal concentration; exception LLQC1, LLQC2 and ULQC (75-125%).
Mean precision (%CV), ≤20%; exception LLQC1, LLQC2 and ULQC (≤25%).
Total error for each QC level, ≤30%; exception LLQC1, LLQC2 and ULQC (≤40%).
%CV = percentage coefficient of variation, HQC = high quality control, LLQC = lower limit quality control, LQC = low quality control, MQC = medium quality control, PK = pharmacokinetic, QC = quality control, ULQC = upper limit quality control

Source: Table 6 of Summary of biopharmaceutic studies and associated analytical methods
(Additional assessment indicated that human plasma samples remained stable for up to three months when stored at -20 °C ± 10 °C. The incurred sample reproducibility (ISR) was tested to be 92.7% and the dilution factor is updated to be 64,000.)

25.3 Fact Sheet for Health Care Providers

See attached.

25.4 Fact Sheet for Patients and Caregivers

See attached.

FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR GOHIBIC

HIGHLIGHTS OF EMERGENCY USE AUTHORIZATION (EUA)
These highlights of the EUA do not include all the information needed to use GOHIBIC under the EUA. See FULL FACT SHEET FOR HEALTHCARE PROVDERS for GOHIBIC.

GOHIBIC (vilobelimab) injection, for intravenous use
Original EUA Authorized Date: 04/2023

--------EMERGENCY USE AUTHORIZATION FOR GOHIBIC-------
The U.S. Food and Drug Administration has issued an EUA for the emergency use of GOHIBIC for the treatment of coronavirus disease 19 (COVID-19) in hospitalized adults when initiated within 48 hours of receiving invasive mechanical ventilation (IMV), or extracorporeal membrane oxygenation (ECMO). However, GOHIBIC is not FDA-approved for this use. (1)

See Full Fact Sheet for Healthcare Providers for the justification for emergency use of drugs during the COVID-19 pandemic, information on available alternatives, and additional information on COVID-19.

----------DOSAGE AND ADMINISTRATION----------
- Recommended dosage of GOHIBIC is 800 mg administered by intravenous infusion after dilution, for a maximum of 6 (six) doses over the treatment period as described below. (2.1)
- Start treatment within 48 hours of intubation (Day 1), followed by administration of GOHIBIC on Days 2, 4, 8, 15 and 22 as long as the patient is still hospitalized (even if discharged from ICU). (2.1)

Preparation and Administration
- Dilute 80 mL of GOHIBIC in 170 mL of 0.9% Sodium Chloride at room temperature using aseptic technique. (2.2)
- Administer diluted GOHIBIC via intravenous infusion over 30 – 60 minutes. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 200 mg/20 mL (10 mg/mL) in single-dose vials for further dilution. (3)

----------CONTRAINDICATIONS----------
No contraindications have been identified based on limited available data on emergency use of GOHIBIC authorized under this EUA. (4)

----------WARNINGS AND PRECAUTIONS----------
- GOHIBIC has been associated with an increase of serious infections. (5.1)
- Hypersensitivity reactions have been reported. (5.2)

----------ADVERSE REACTIONS----------
The most common adverse reactions (incidence ≥3%) are pneumonia, sepsis, delirium, pulmonary embolism, hypertension, pneumothorax, deep vein thrombosis, herpes simplex, enterococcal infection, bronchopulmonary aspergillosis, hepatic enzyme increased, urinary tract infection, hypoxia, thrombocytopenia, pneumomediastinum, respiratory tract infection, supraventricular tachycardia, constipation, and rash. (6.1)

You or your designee must report all SERIOUS ADVERSE EVENTS or MEDICATION ERRORS potentially related to GOHIBIC by (1) submitting FDA Form 3500 online, (2) by downloading this form and then submitting by mail or fax, or (3) contacting the FDA at 1-800-FDA-1088 to request this form. Please also provide a copy of this form to InflaRx GmbH at pvusa@inflarx.de (6.3)

----------USE IN SPECIFIC POPULATIONS----------
- Lactation: Discontinue drug or nursing taking into consideration importance of drug to mother. (8.2)

See PATIENT AND CAREGIVER FACT SHEET.

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the EUA are not listed.

FULL FACT SHEET FOR HEALTHCARE PROVIDERS

1 EMERGENCY USE AUTHORIZATION

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of GOHIBIC for the treatment of coronavirus disease 2019 (COVID-19) in hospitalized adults when initiated within 48 hours of receiving invasive mechanical ventilation (IMV), or extracorporeal membrane oxygenation (ECMO). However, GOHIBIC is not FDA-approved for this use.

Justification for Emergency Use of Drugs During the COVID-19 Pandemic
There is currently an outbreak of Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2, a novel coronavirus. The Secretary of HHS has:

- Determined that there is a public health emergency, or significant potential for a public health emergency, related to COVID-19[1].
- Declared that circumstances exist justifying the authorization of emergency use of drugs and biological products for the prevention or treatment of COVID-19[2].

An EUA is a FDA authorization for the emergency use of an unapproved product or unapproved use of an approved product (*i.e.*, drug, biological product, or device) in the United States under certain circumstances, including, but not limited to, when the Secretary of HHS declares that there is a public health emergency, or significant potential for a public health emergency that affects the national security or the health and security of United States citizens living abroad, and that involves biological agent(s) or a disease or condition that may be attributable to such agent(s). Criteria for issuing an EUA include:

- The biological agent(s) can cause a serious or life-threatening disease or condition;
- Based on the totality of the available scientific evidence (including data from adequate and well-controlled clinical trials, if available), it is reasonable to believe that:
    - The product may be effective in diagnosing, treating, or preventing the serious or life-threatening disease or condition; and
    - The known and potential benefits of the product – when used to diagnose, prevent or treat such disease or condition – outweigh the known and potential risks of the product, taking into consideration the material threat posed by the biological agent(s)

[1] *See* U.S. Department of Health and Human Services, Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3. February 4, 2020; https://www.federalregister.gov/documents/2020/02/07/2020-02496/determination-of-public-health-emergency. *See also* U.S. Department of Health and Human Services, Amended Determination of a Public Health Emergency or Significant Potential for a Public Health Emergency Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3(b). March 15, 2023 ("Amended Determination"); https://www.federalregister.gov/documents/2023/03/20/2023-05609/covid-19-emergency-use-authorization-declaration.

[2] *See* U.S. Department of Health and Human Services, Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3, 85 FR 18250 (April 1, 2020); https://www.federalregister.gov/documents/2020/04/01/2020-06905/emergency-use-authorization-declaration. *See also* Amended Determination ("The declarations issued pursuant to section 564(b)(1) of the FD&C Act that circumstances exist justifying the authorization of emergency use of certain in vitro diagnostics, personal respiratory protective devices, other medical devices and drugs and biological products, as set forth in those declarations, and that are based on the February 4, 2020 determination, remain in effect until those declarations are terminated in accordance with section 564 of the FD&C Act.").

- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the serious or life-threatening disease or condition.

Information Regarding Available Alternatives for the EUA Authorized Use

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 when initiated within 48 hours of receiving IMV, or ECMO. Veklury has demonstrated antiviral activity against SARS-CoV-2; whereas GOHIBIC acts by binding to C5a to block its interaction with the C5a receptor, both of which are components of the complement system 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 when initiated within 48 hours of requiring IMV, or ECMO. As noted, GOHIBIC offers a different mechanism of action. In addition, GOHIBIC has an intravenous route of administration; whereas, Olumiant is available as tablets, offering an alternative route of administration to adult patients who are mechanically ventilated or on ECMO.

Actemra, an interleukin-6 (IL-6) receptor antagonist, is also an FDA-approved alternative for the treatment of COVID-19 in hospitalized adults when initiated within 48 hours of receiving IMV, or ECMO. As noted, GOHIBIC offers a different mechanism of action.

Other therapeutics are currently authorized for the same use as GOHIBIC. For additional information on all products authorized for the treatment of COVID-19, please see https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization.

For information on clinical studies of GOHIBIC and other therapies for the treatment of COVID-19, see www.clinicaltrials.gov.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of GOHIBIC for the treatment of adults with COVID-19 is 800 mg administered by intravenous infusion after dilution *[see Dosage and Administration (2.2)]* for a maximum of 6 (six) doses over the treatment period as described below.

Treatment should be started within 48 hours of intubation (Day 1) followed by administration on Days 2, 4, 8, 15 and 22 as long as the patient is hospitalized (even if discharged from ICU).

2.2 Preparation and Administration

Preparation

Using aseptic technique, dilute and prepare GOHIBIC for intravenous infusion before administration.

- For the recommended dose of 800 mg GOHIBIC, dilute 80 mL of GOHIBIC in 170 mL of 0.9% Sodium Chloride at room temperature.
- Use a 250 mL infusion bag of 0.9% Sodium Chloride solution USP and the follow steps below:

- Withdraw 80 mL of 0.9% Sodium Chloride solution USP from the infusion bag and discard.
- Withdraw the 80 mL of GOHIBIC from the vials and add slowly to the 0.9% Sodium Chloride solution USP infusion bag to a final concentration of 3.2 mg/mL.
- To mix the solution, gently invert the bag to avoid foaming.

Storage of Diluted GOHIBIC

- Diluted GOHIBIC must be used within 4 hours when stored at room temperature 20°C to 25°C (68°F to 77°F).
- Diluted GOHIBIC stored under refrigeration at 2°C to 8°C (36°F to 46°F) must be used within 24 hours.
- After removal of diluted GOHIBIC from the refrigerator stored at 2°C to 8°C (36°F to 46°F), it must be left to acclimatize to room temperature prior to administration.

Administration

- Visually inspect for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if discoloration or visible particles are present.
- Administer diluted GOHIBIC via intravenous infusion over 30 - 60 minutes.
- Avoid concomitant administration of GOHIBIC with other drugs in the same intravenous line.

3 DOSAGE FORMS AND STRENGTHS

Injection: 200 mg/20 mL (10 mg/mL) clear to slightly opalescent, colorless solution in a single-dose vial.

4 CONTRAINDICATIONS

No contraindications have been identified based on the limited available data for the emergency use of GOHIBIC under this EUA.

5 WARNINGS AND PRECAUTIONS

There are limited clinical data available for GOHIBIC. Serious and unexpected adverse events (AEs) may occur that have not been previously reported with GOHIBIC use.

5.1 Serious Infections

Serious infections due to bacterial, fungal, and viral pathogens have been reported in patients with COVID-19 receiving GOHIBIC. In patients with COVID-19, monitor for signs and symptoms of new infections during and after treatment with GOHIBIC. There is limited information regarding the use of GOHIBIC in patients with COVID-19 and concomitant active serious infections. The risks and benefits of treatment with GOHIBIC in COVID-19 patients with other concurrent infections should be considered *[see Adverse Reactions (6)]*.

5.2 Hypersensitivity Reactions

Hypersensitivity reactions have been observed with GOHIBIC. If a severe hypersensitivity reaction occurs, administration of GOHIBIC should be discontinued and appropriate therapy initiated.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

The following adverse reactions have been observed in the clinical studies of GOHIBIC that supported the EUA. The adverse reaction rates observed in these clinical studies cannot be directly compared to rates in the clinical studies of other products and may not reflect the rates observed in clinical practice.

The safety of GOHIBIC is based on PANAMO, a Phase 3 randomized, placebo-controlled trial in COVID-19 patients requiring IMV or ECMO *[see Clinical Studies (14)]*. The analysis of adverse reactions included a total of 364 adult patients who received at least one dose of either GOHIBIC (n=175) or placebo (n=189) plus standard of care. Patients received GOHIBIC 800 mg administered by intravenous infusion on Days 1, 2, 4, 8, 15 and 22 or placebo.

During the study, there were 62 deaths in the GOHIBIC arm and 85 deaths in the placebo arm *[see Clinical Studies (14)]*. Fatal infections occurred in more placebo patients. Nonfatal serious infections occurred in 58 patients (33.1%) in the GOHIBIC arm and in 55 patients (29.1%) in the placebo arm. The most commonly reported nonfatal serious infections with GOHIBIC were pneumonia (18.9% vs 13.8% in placebo), sepsis (14.9% versus 7.4% in placebo), and septic shock (9.1% versus 7.4% in placebo).

Discontinuation of study treatment due to an adverse reaction occurred in 2.9% of the GOHIBIC group and 1.6% of the placebo group. Adverse reactions leading to discontinuation of GOHIBIC included eczema, bronchopulmonary aspergillosis, rash, hemodynamic instability, thrombocytopenia, and multi-organ failure.

The most common adverse reactions occurring in at least 3% of GOHIBIC-treated patients and at least 1% more frequently than observed in the placebo arm are summarized in Table 1.

Table 1. Adverse Reactions that Occurred in ≥3% of Patients Treated with GOHIBIC and at least 1% More Frequently than Observed in the Placebo Arm through Day 60

Adverse Reactions	**GOHIBIC + SoC (N=175)**		**Placebo + SoC (N=189)**	
	n	**(%)**	**n**	**(%)**
Pneumonia[1]	55	(31.4%)	44	(23.3%)
Sepsis[2]	38	(21.7%)	30	(15.9%)
Delirium[3]	22	(12.6%)	20	10.6%)
Pulmonary embolism	19	(10.9%)	17	(9.0%)
Hypertension	16	(9.1%)	13	(6.9%)
Pneumothorax	14	(8.0%)	11	(5.8%)
Deep vein thrombosis	11	(6.3%)	9	(4.8%)
Herpes simplex	11	(6.3%)	5	(2.6%)
Enterococcal infection	10	(5.7%)	8	(4.2%)
Bronchopulmonary aspergillosis	10	(5.7%)	7	(3.7%)
Hepatic enzyme increased	9	(5.1%)	7	(3.7%)
Urinary tract infection	9	(5.1%)	6	(3.2%)
Hypoxia	8	(4.6%)	6	(3.2%)

Adverse Reactions	GOHIBIC + SoC (N=175)		Placebo + SoC (N=189)	
	n	(%)	n	(%)
Thrombocytopenia	8	(4.6%)	2	(1.1%)
Pneumomediastinum	8	(4.6%)	0	(0.0%)
Respiratory tract infection	7	(4.0%)	5	(2.6%)
Supraventricular tachycardia	7	(4.0%)	1	(0.5%)
Constipation	6	(3.4%)	3	(1.6%)
Rash	6	(3.4%)	0	(0.0%)

SoC = standard of care.
[1] "Pneumonia" includes preferred terms containing the term "pneumonia"; does not include "COVID-19 pneumonia"
[2] "Sepsis" includes preferred terms containing the term "sepsis".
[3] "Delirium includes the following preferred terms: Delirium, Intensive care unit delirium
A patient is only listed once (regardless of event numbers) but one patient can be listed in different categories with one or additional reactions

6.3 Required Reporting for Serious Adverse Events and Medication Errors

The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all serious adverse events (SAEs)* and medication errors potentially related to GOHIBIC within 7 calendar days from the healthcare provider's awareness of the event, using FDA Form 3500 (for information on how to access this form, see below). The FDA requires that such reports, using FDA Form 3500, include the following:

- Patient demographics and baseline characteristics (e.g., patient identifier, age or date of birth, gender, weight, ethnicity, and race)
- A statement "GOHIBIC use for COVID-19 under Emergency Use Authorization (EUA)" under the "**Describe Event, Problem, or Product Use/Medication Error**" heading
- Information about the SAE or medication error (*e.g.*, signs and symptoms, test/laboratory data, complications, timing of drug initiation in relation to the occurrence of the event, duration of the event, treatments required to mitigate the event, evidence of event improvement/disappearance after stopping or reducing the dosage, evidence of event reappearance after reintroduction, clinical outcomes).
- Patient's preexisting medical conditions and use of concomitant products
- Information about the product (*e.g.*, dosage, route of administration, NDC #).

Submit AE and medication error reports, using Form 3500, to FDA MedWatch using one of the following methods:

- Complete and submit the report online: www.fda.gov/medwatch/report.htm
- Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:
  - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
  - Fax to 1-800-FDA-0178, or
- Call 1-800-FDA-1088 to request a reporting form

In addition, please provide a copy of all FDA MedWatch forms to:

InflaRx GmbH
Fax: **1-866-728-2630**
E-mail: **pvusa@inflarx.de**
Or call InflaRx GmbH at 1-888-254-0602 to report AEs.

The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory responses to requests from FDA for information about AEs and medication errors following receipt of GOHIBIC.

*SAEs are defined as:

- Death;
- A life-threatening AE;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect;
- Other important medical event, which may require a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly

7 DRUG INTERACTIONS

No drug interaction studies have been conducted with GOHIBIC.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on GOHIBIC use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. Placental transfer of monoclonal antibodies such as GOHIBIC is greater during the third trimester of pregnancy; therefore, potential effects on a fetus are likely to be greater during the third trimester of pregnancy. In an enhanced pre- and post-natal (ePPND) study conducted in cynomolgus monkeys, placental transport of GOHIBIC was observed but there was no evidence of fetal harm following intravenous administration of GOHIBIC throughout pregnancy at doses 2.5 times the maximum recommended human dose (MRHD) of 800 mg on a mg/kg basis *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk for major birth defects and miscarriage in clinical recognized pregnancies is 2% - 4% and 15% - 20%, respectively.

Data

Animal Data

In the ePPND study, pregnant cynomolgus monkeys received GOHIBIC from GD20 to GD22 (dependent on pregnancy determination), at the beginning of organogenesis, and once every 7 days until the end of gestation at intravenous doses up to 50.6 mg/kg/wk (2.5 times the MRHD on a mg/kg basis). There were no GOHIBIC-related adverse effects on maternal health, pregnancy outcome, embryo-fetal development, or neonatal growth and development up to 6 months of age (PND183). GOHIBIC crossed the placenta in cynomolgus monkeys and GOHIBIC plasma concentrations were similar in infants relative to maternal animals on PND28 and were 8-12 times higher in infants relative to maternal animals on PND91. GOHIBIC was not detected in infant plasma on PND183.

8.2 Lactation

Risk Summary

There are no available data on the presence of GOHIBIC in either human or animal milk, the effects on the breastfed infant, or the effects on milk production.

Maternal IgG is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to GOHIBIC are unknown.

The lack of clinical data during lactation precludes clear determination of the risk of GOHIBIC to an infant during lactation. Therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for GOHIBIC and any potential adverse effects on the breastfed child from GOHIBIC or from the underlying maternal condition.

8.3 Pediatric Use
GOHIBIC is not authorized or approved for the emergency use in pediatric patients for the treatment of coronavirus disease 2019 (COVID-19) in hospitalized patients when initiated within 48 hours of receiving invasive mechanical ventilation (IMV), or extracorporeal membrane oxygenation (ECMO).

8.4 Geriatric Use
Of the total number of GOHIBIC-treated patients in clinical studies for COVID-19 receiving invasive mechanical ventilation (IMV), or extracorporeal membrane oxygenation (ECMO), 53 (30%) were >65 years. No overall differences in effectiveness or safety of GOHIBIC have been observed between patients 65 years of age and older and younger adult patients.

11 DESCRIPTION

Vilobelimab is a chimeric human/mouse immunoglobulin G4 (IgG4) antibody consisting of mouse anti-human complement factor 5a (C5a) monoclonal binding sites (variable regions of heavy and light chain regions), and human gamma 4 heavy chain and kappa light chain constant regions. GOHIBIC is composed of 1,328 amino acids, and the glycosylated intact protein has an approximate molecular weight of 149 kDa produced in Chinese Hamster Ovary (CHO) cell line genetically engineered using ribonucleic acid transfer through a retro-vector system.

GOHIBIC (vilobelimab) injection is a clear to slightly opalescent, colorless solution for intravenous infusion after further dilution. GOHIBIC is provided in single-dose vials at a concentration of 200 mg/20 mL (10 mg/mL). Each mL also contains dibasic sodium phosphate (0.97 mg), monobasic sodium phosphate (0.4 mg), polysorbate 80 (0.5 mg), sodium chloride (8.8 mg), and Water for Injection. The pH is 6.6 – 7.3.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
GOHIBIC is a chimeric monoclonal IgG4-kappa antibody that binds to C5a with a dissociation constant of 9.6pM and blocks its interaction with the C5a receptor. C5a is part of the complement system and is activated as part of the innate immune response initiating an inflammatory cascade that includes increased vascular permeability, coagulation, proinflammatory cytokine release, and recruitment and activation of neutrophils and other myeloid cells.

12.2 Pharmacodynamics
The reduction of C5a plasma concentration was evaluated in PANAMO. The median plasma concentrations of C5a at baseline in patients with severe COVID-19 pneumonia requiring IMV or ECMO were elevated and the values were comparable between the GOHIBIC group (118.29 ng/mL) and the placebo group (104.62 ng/mL). In the GOHIBIC group, the median concentrations of C5a decreased to 14.53 ng/mL by Day 8 and remained at approximately this level up to Day 30 after the initiation of treatment. In the placebo group, the median concentrations of C5a remained approximately at the baseline level during the study up to Day 30 after the initiation of the treatment. However, the direct clinical relevance of C5a plasma concentration reduction is unclear.

12.3 Pharmacokinetics
In healthy subjects, following a single intravenous infusion of GOHIBIC ranging from 2 mg/kg to 4 mg/kg, GOHIBIC C_{max} showed dose proportionality while the AUC showed greater than dose proportionality. The elimination half-life of GOHIBIC following a 4 mg/kg single intravenous dose in healthy subjects was 95 hours.

Pre-dose plasma samples were collected in patients with severe COVID-19 pneumonia requiring IMV or ECMO. Following intravenous infusion of GOHIBIC 800 mg on Days 1, 2, and 4, the pre-dose geometric mean (geometric CV%) plasma concentration of GOHIBIC on Day 8 was 137.9 µg/mL (51%).

Drug Interaction Studies
No drug interaction studies have been conducted with GOHIBIC.

12.6 Immunogenicity
The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the study described below with incidence of anti-drug antibodies in other studies, including those of GOHIBIC or of other vilobelimab products.

In the Phase 3 clinical study, 2 patients developed treatment-induced anti-drug antibodies; one patient in the GOHIBIC group and one patient in the placebo group. The clinical relevance of the presence of anti-drug antibodies is unclear.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Animal studies have not been conducted to evaluate the carcinogenic potential of GOHIBIC. The malignancy risk in humans from an antibody that binds C5a, such as GOHIBIC, is currently unknown.

Male and female fertility parameters were evaluated as part of the 13-week and 26-week repeat-dose toxicity studies, respectively. There were no treatment-related changes to sperm morphology, count, or motility in male monkeys administered GOHIBIC for 13-weeks at intravenous doses up to 50.6 mg/kg/week (approximately 2.5 times the MRHD on a mg/kg basis). Following 26-weeks intravenous administration of GOHIBIC, there were no effects on female fertility including menstrual cyclicity identified at doses up to 50 mg/kg/week (approximately 2.5 time the MRHD on a mg/kg basis).

14 CLINICAL STUDIES

Clinical data supporting this EUA are based on PANAMO (NCT04333420), a Phase 3, double-blind, randomized, placebo-controlled multicenter trial evaluating GOHIBIC for the treatment of COVID-19 in adult (≥ 18 years) patients requiring IMV or ECMO. The multinational trial was conducted in Europe, Latin America, Russia, and South Africa. Efficacy analyses were based on 368 patients, 177 in the GOHIBIC group and 191 in the placebo group. The mean age of participation was 56 years [range: 22 to 81 years] and 68.5% were male. Common co-existing medical conditions included hypertension (46.2%), obesity (40.8%) and diabetes (29.6%) in the overall study population. All patients were mechanically ventilated and three patients in each arm were on ECMO. Additional demographics and baseline characteristics of patients in PANAMO are provided in Table 2.

Table 2. Demographics and Baseline Characteristics of Patients in PANAMO

	GOHIBIC + SoC[1] (N=177)	**Placebo + SoC (N=191)**
Age Group, n (%)		
18 – 39 years	22 (12.4%)	30 (15.7%)
40 – 65 years	102 (57.6%)	103 (53.9%)
> 65 years	53 (29.9%)	58 (30.4%)
WHO 8-point ordinal scale score[2]		
6 – Intubation and mechanical ventilation	72 (40.7%)	59 (30.9%)
7 – Ventilation + additional organ support (vasopressors, renal replacement therapy, ECMO)	105 (59.3%)	132 (69.1%)
Prior and concomitant medications		
Dexamethasone or systemic corticosteroid	176 (99.4%)	188 (98.4%)
Baricitinib	6 (3.4%)	6 (3.1%)
Tocilizumab	30 (16.9%)	31 (16.2%)
Remdesivir	10 (5.6%)	11 (5.8%)

[1] A total of 369 patients were randomized in the trial (178 to GOHIBIC and 191 to placebo), but one patient in the GOHIBIC group was randomized in error and not included in the efficacy analyses.
[2] World Health Organization 8-point ordinal scale

The primary endpoint in the study was time to death through Day 28. The Kaplan-Meier estimated 28-Day mortality rate in the GOHIBIC group was 31.7% and the estimated rate in the placebo group was 41.6%, resulting in a hazard ratio of 0.67 (95% CI [0.48, 0.96], p<0.05, Table 3). Results were similar at Day 60 (Table 3). Mortality through day 28 and 60 in PANAMO are provided in Table 3. The percentage of patients alive and either discharged from the hospital or no longer requiring supplemental oxygen at Day 28 were comparable in the GOHIBIC (35.0%) and placebo (36.1%) groups.

Table 3. Mortality through Day 28 and Day 60 in PANAMO

	GOHIBIC + SoC (N=177)	**Placebo + SoC (N= 191)**
Day 28 Mortality		
Number of Deaths	54	77
Percentage with Death[1]	31.7%	41.6%
Hazard Ratio[2] (95% CI)	0.67 (0.48, 0.96)	
Risk Difference[3] (95% CI)	-11.2% (-21.0%, -1.4%)	
Day 60 Mortality		
Number of Deaths	62	87
Percentage with Death[1]	36.5%	47.2%
Hazard Ratio[2] (95% CI)	0.67 (0.48, 0.93)	
Risk Difference[3] (95% CI)	-12.2% (-22.0%, -2.4%)	

Abbreviations: CI = confidence interval
[1] Results from Kaplan-Meier estimates. Percentages will not be proportional to the number of deaths divided by the total number of patients due to missing values (8 patients missing mortality status in GOHIBIC + SoC and 9 in placebo + SOC).
[2] Results from Cox proportional hazards regression with treatment and age as covariates. P-values < 0.05.
[3] Results based on a logistic regression model with treatment and age as covariates, and missing values handled by multiple imputation.

16 HOW SUPPLIED/STORAGE AND HANDLING

How supplied

GOHIBIC (vilobelimab) 200 mg/20 mL (10 mg/mL) injection is a clear to slightly opalescent, colorless solution in a single-dose vial (NDC 83000-110-04).

Storage and Handling

Store unopened vials refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze. Do not shake.

17 PATIENT COUNSELING INFORMATION

As a healthcare practitioner, you must communicate to the patient and/or caregiver information consistent with the “FACT SHEET FOR PATIENTS AND CAREGIVERS” and provide them with a copy of this Fact Sheet prior to administration of GOHIBIC. However, if providing this information will delay administration of GOHIBIC to a degree that would endanger the life of a patient, then information must be provided to the caregiver as soon as feasible after GOHIBIC administration.

18 MANUFACTURER INFORMATION

Manufactured by InflaRx GmbH, Winzerlaer Street 2, 07745 Jena, Germany.

Fact Sheet for Patients and Caregivers Emergency Use Authorization (EUA) of GOHIBIC for Coronavirus Disease 2019 (COVID-19)

You are being given this Fact Sheet because your healthcare provider believes it is necessary to provide you with GOHIBIC (vilobelimab) for the treatment of coronavirus disease 2019 (COVID-19). Taking GOHIBIC may benefit adults in the hospital with COVID-19 who require a machine that helps with breathing (invasive mechanical ventilation) or a machine that adds oxygen to the blood outside the body (extracorporeal membrane oxygenation or ECMO). This Fact Sheet contains information to help you understand the potential risks and potential benefits of receiving GOHIBIC.

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to make GOHIBIC available for use as a treatment for certain adults with COVID-19 (for more details about EUA please see "**What is an Emergency Use Authorization**?" at the end of this document). GOHIBIC is not FDA-approved for this use. Read this Fact Sheet for information about GOHIBIC. Talk to your healthcare provider about your options or if you have any questions. It is your choice for you to take GOHIBIC or stop it at any time.

What is COVID-19?
COVID-19 is caused by a virus called a coronavirus. You can get COVID-19 through contact with another person who has the virus.

COVID-19 illnesses have ranged from very mild (including some with no reported symptoms) to severe, including illness resulting in death. While information so far suggests that most COVID-19 illness is mild, serious illness can happen and may cause some of your other medical conditions to become worse. People of all ages with severe, long-lasting (chronic) medical conditions like heart disease, lung disease, and diabetes, for example, seem to be at higher risk of being hospitalized for COVID-19.

What are the symptoms of COVID-19?
The symptoms of COVID-19 may include fever, cough, and shortness of breath, which can appear 2 to 14 days after exposure. Serious illness, including breathing problems, can occur and may cause your other medical conditions to become worse.

What is GOHIBIC?
GOHIBIC is an investigational medicine used for the treatment of COVID-19 in hospitalized adults when initiated within 48 hours of receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO). GOHIBIC is investigational because it is still being studied. GOHIBIC is not FDA-approved to treat COVID-19.

There is limited information known about the safety or effectiveness of using GOHIBIC to treat people in the hospital with COVID-19. Available results from clinical trials in adults indicate that treatment with GOHIBIC may decrease the risk of dying in hospitalized adults with COVID-19 when initiated within 48 hours of receiving invasive mechanical ventilation or ECMO. The safety and effectiveness of GOHIBIC have not been studied in children hospitalized with COVID-19.

The FDA has authorized the emergency use of GOHIBIC for the treatment of COVID-19 in hospitalized adults when initiated within 48 hours of receiving invasive mechanical ventilation or ECMO under an EUA. For more information on EUA, see the "**What is an Emergency Use Authorization (EUA)**?" section at the end of this Fact Sheet.

What should I tell my healthcare provider before I receive GOHIBIC?
Tell your healthcare provider about all of your medical conditions including if you:

- Have allergies.
- Have an infection other than COVID-19.
- Are pregnant or plan to become pregnant.
- Are breast-feeding or plan to breastfeed.
- Have any serious illnesses.

Tell your healthcare provider about all the medicines you take, including prescription and, over-the-counter medicines, vitamins, and herbal supplements.

How will I receive GOHIBIC?

GOHIBIC is given to you through a vein (intravenous or IV) as an infusion. GOHIBIC will be given up to six doses. The first dose will be given within 48 hours of a tube being inserted (intubation) and a machine to help you breathe (ventilator), this is Day 1. The following administration of GOHIBIC will be given on Days 2, 4, 8, 15, and 22 as long as you are hospitalized [even discharged from the Intensive Care Unit (ICU)].

What are the important possible side effects of GOHIBIC?
GOHIBIC may cause serious side effects, including:

- **Serious infections: GOHIBIC** is a medicine that affects your immune system. **GOHIBIC** can lower the ability of your immune system to fight infections other than COVID-19.
- **Allergic Reactions:** Serious allergic reactions can happen during or after treatment with **GOHIBIC**. These reactions may be severe or life-threatening.

  Signs and symptoms of a serious allergic reaction with GOHIBIC may include:

  - trouble breathing
  - rash
  - swelling of your face, eyes, lips mouth, tongue and throat.

The most common side effects of GOHIBIC may include: Lung infection, sepsis, sudden confusion, sudden lung artery blockage, high blood pressure, collapsed lung, venous blood clotting (usually in the leg), herpes infection, certain infections caused by enterococci, urinary tract infection, low blood oxygenation, low platelets, the presence of air in the space in the chest between the two lungs, infection of the respiratory tract, heart arrythmia, constipation, and rash.

What other treatment choices are there?

Olumiant (baricitinib), Actemra (tocilizumab), and Veklury (remdesivir) are FDA-approved medicines for the treatment of COVID-19 in hospitalized patients who require invasive mechanical ventilation or ECMO. Talk with your healthcare provider to see if those therapies are appropriate for you. Like GOHIBIC, FDA may allow for the emergency use of other medicines to treat people in the hospital with COVID-19. Go to https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization for information on emergency use of other medicines that are not approved by FDA to treat people in the hospital with

COVID-19. Please consult with your healthcare provider on which medicine or combination of medicines might be right for you. Your healthcare provider may talk with you about clinical trials you may be eligible for.

It is your choice to be treated or not to be treated with GOHIBIC. Should you decide not to receive it, it will not change your standard medical care.

What if I am pregnant or breastfeeding?
There is no experience giving GOHIBIC to pregnant women or breastfeeding mothers. GOHIBIC may harm your unborn baby. It is unknown if GOHIBIC passes into your breast milk. If you are pregnant or breastfeeding, discuss your options and specific situation with your healthcare provider.

How do I report side effects or adverse events with GOHIBIC?
Contact your healthcare provider if you have any side effects that bother you or do not go away. Report side effects to FDA MedWatch at www.fda.gov/medwatch or call 1-800-FDA-1088. You may also report side effects to InflaRx GmbH by calling 1-888-254-0602.

How can I learn more about COVID-19?

- Ask your healthcare provider
- Visit https://www.cdc.gov/COVID19
- Contact your local or state public health department

What is an Emergency Use Authorization (EUA)?
The United States FDA has made GOHIBIC available under an emergency access mechanism called an EUA. The EUA is supported by a Secretary of Health and Human Service (HHS) declaration that circumstances exist to justify the emergency use of drugs and biological products during the COVID-19 pandemic.

GOHIBIC, as a treatment for COVID-19 has not undergone the same type of review as an FDA-approved product for this indication. The FDA may issue an EUA when certain criteria are met, which includes that there are no adequate, approved, and available alternatives. In addition, the FDA decision is based on the totality of scientific evidence available showing that it is reasonable to believe that the product meets certain criteria for safety, performance, and labeling and may be effective in treatment of patients during the COVID-19 pandemic.

All of these criteria must be met to allow for the product to be used in the treatment of patients during the COVID-19 pandemic.

The EUA for GOHIBIC as a treatment for certain people with COVID-19 is in effect for the duration of the COVID-19 declaration justifying emergency use of this product, unless terminated or revoked (after which the products may no longer be used under the EUA).

This Fact Sheet may be updated as new data become available. The most recent version of this Fact Sheet is available at www.gohibic.com.

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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