14 November 2024
EMA/564703/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Gohibic

International non-proprietary name: vilobelimab

Procedure No. EMEA/H/C/006123/0000

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact Telephone +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

ADA	Anti-Drug Antibody
ADCC	Antibody Dependent Cellular Cytotoxicity
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event Of Special Interest
AEX	Anion Exchange Chromatography Membrane
ALT	Alanine Aminotransferase
AMC	Amsterdam Medical Centre
AMG	Arzneimittelgesetz (German Medicines Act)
ANCOVA	Analysis Of Covariance
aPTT	Activated Partial Thromboplastin Time
AR	Assessment Report
ARDS	Acute Respiratory Distress Syndrome
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical Code
AUC	Area Under The Curve
BARDA	Biomedical Advanced Research And Development Authority
BDRM	Blind Data Review Meeting
BMI	Body Mass Index
BSC	Best Supportive Care
BSIHS	Baseline IHS4 Score
BW	Body Weight
C5a	Complement Component 5a
C5aR	Complement Component 5a Receptor
CCI	Commercially Confidential Information
CCIT	Container Closure Integrity Testing
CCS	Container Closure System
CEX	Cation Exchange Chromatography
CFR	Us Code Of Federal Regulations
CHMP	Committee For Evaluation Of Human Medicinal Products
CHO	Chinese Hamster Overy Cell Line
CI	Confidence Interval
CIC	Circulating Immune Complex
CIF	Cumulative Incidence Function
CIOMS	Council For International Organizations Of Medical Sciences
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CI	Confidence Interval
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease

COVID-19	Corona Virus Disease 2019
CPA	Critical Performance Attributes
CPP	Critical Process Parameters
CPV	Continued Process Verification
CQA	Critical Quality Attribute
CRO	Contract Research Organisation
CRP	C-Reactive Protein
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria For Adverse Events
CV	Coefficient Of Variation
DILI	Drug-Induced Liver Injury
DMF	Drug Master File
DNA	Deoxyribonucleic Acid
DoE	Design Of Experiment
DP	Drug Product
DRF	Dose Range Finding Study
DS	Drug Substance
EC	European Commission
ECG	Electrocardiogram
ECMO	Extracorporeal Membrane Oxygenation
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicine Agency
EOPCB	End Of Production Cell Bank
EOS	End Of Study
EOT	End Of Treatment
EPAR	European Public Assessment Report
EQ-5D	Euroqol 5D (Quality Of Life Assessment Tool)
ERA	Environmental Risk Assessment
ETF	Ema's Emergency Task Force
EU	European Union
EURD	European Union Reference Date
EVA	Ethylene Vinyl Acetate
EVOH	Ethylene Vinyl Alcohol
FAS	Full Analysis Set
FDA	Us Food And Drug Administration
FFT	Flexible Freeze Thaw Bag
FITC	Fluorescein Isothiocyanate
FMEA	Failure Modes And Effects Analysis
FUV	Follow-Up Visit

G0F	Fucosylated Glycan G0f
G1F	Fucosylated Glycan G1f
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GLP	Good Laboratory Practice
GMO	Genetically Modified Organism
GMP	Good Manufacturing Practice
GOLD	Global Initiative For Chronic Obstructive Lung Disease
GPA	Granulomatosis With Polyangiitis
GPP	General Process Parameter
HC	Heavy Chain Constant Region
HCP	Host Cell Protein
HE	Haematoxylin And Eosin Staining
hIGHG4	Human Igg4 Heavy Chain Constant Region
hIGKC	Human Kappa Light Chain Constant Region
HL	Half Antibody Heavy And Light Chain
HMW	High Molecular Weight
HPLC	High-Performance Liquid Chromatography
HR	Hazard Ratio
HRP	Horseradish Peroxidase
HS	Hidradenitis Suppurativa
IB	Investigator's Brochure
IBD	International Birth Date
ICF	Informed Consent Form
ICH	International Council For Harmonization Of Technical Requirements For Pharmaceuticals For Human Use
ICU	Intensive Care Unit
IDMC	Independent (Clinical Trial) Data Monitoring Committee
IEC	Independent Ethic Committee
IFN	Interferon
IFX-1	Vilobelimab
IgG	Immunoglobulin G
IL	Interleukin
IMC	Intermediate Care
IMP	Investigational Medicinal Product
IMV	Invasive Mechanical Ventilation
IND	Investigational New Drug
INN	International Non-Proprietary Name
INR	International Normalised Ratio
IPC	In-Process Control
IRB	Institutional Review Board
IRR	Infusion-Related Reaction
IRT	Interactive Response Technology
ISI	Integrated Summary Of Immunogenicity

KD	Dissociation Constants
kDa	Kilodalton
KM	Kaplan-Meier
KPA	Key Performance Attributes
KPP	Key Process Parameters
L&P	Labelling And Secondary Packaging
LC	Light Chain Constant Region
LDH	Lactate Dehydrogenase
LH	Light Chain Variable Region
LIVCA	Limit Of In Vitro Cell Age
LLOQ	Lower Limit Of Quantification
LMW	Low Molecular Weight
LOCF	Last Observation Carried Forward
LPS	Lipopolysaccharide
LS	Least Square
MAA	Marketing Authorisation Application
MAC	Complement Membrane Attack Complex
MAC	Membrane Attack Complex
MCB	Master Cell Bank
MCP	Monocyte Chemoattractant Protein
MCV	Mean Corpuscular Volume
MO	Major Objection
MPA	Microscopic Polyangiitis
MRC-5	Human Diploid Cell Strain
MRI	Magnetic Resonance Imaging
MS	Mass Spectrometry
MVM	Minute Virus Of Mice
NA	Not Available Or Not Applicable
NAS	New Active Substance
NGHC	Non-Glycosylated Heavy Chain
NGNA	N-Glycolylneuraminic Acid
NIH	National Institutes Of Health
NOAEL	No Observed Adverse Effect Level
NOCB	Next Observation Carried Back
NONMEM	Nonlinear Mixed Effects Modelling
NOR	Normal Operating Range
NYHA	New York Heart Association Functional Classification
OC	Other Concern
OECD	Organisation Of Economic Co-Operation And Development
OFAT	One Factor At A Time
OL	Open-Label
OLE	Open-Label Extension
OOS	Out Of Specification

PAES	Post-Authorisation Efficacy Studies
PAR	Proven Acceptable Range
PASS	Post-Authorisation Safety Studies
PBS	Phosphate-Buffered Saline
PC	Process Characterisation
pcd	Pictogram/Cell/Day
PD	Pharmacodynamic
PDE	Permitted Daily Exposure
PDL	Population Doubling Level
PG	Pyoderma Gangrenosum
Ph. Eur.	European Pharmacopoeia
pI	Isoelectric Point
PI	Product Information
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic
PMN	Polymorphonuclear Neutrophils
PND	Postnatal DAY
PP	Process Parameter
PPD	Protected Personal Data
ePPND	Enhanced Pre-And Postnatal Development
PPQ	Process Performance Qualification
PPS	Per-Protocol Set
PRAC	Pharmacovigilance Risk Assessment Committee
PRV	Pseudorabies Virus
PSUR	Periodic Safety Update Report
PT	Preferred Term
PTM	Post-Translational Modification
PUPSIT	Post-Use Filter Integrity Testing
PVDF	Polyvinylidene Fluoride
QP	Qualified Person
qPCR	Quantitative Polymerase Chain Reaction
QRD	Quality Review Of Documents
QTPP	Quality Target Product Profile
RH	Relative Humidity
RI	Renal Impairment
RMP	Risk Management Plan
RR	Respiratory Rate
RRT	Renal Replacement Therapy
RS	Reference Standard
RTSM	Randomisation And Trial Supply Management
RVLP	Retrovirus-Like Particle
SA	Scientific Advice
SAD	Single Ascending Dose Study

SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SARS	Severe Acute Respiratory Syndrome
SD	Standard Deviation
SEM	Scanning Electron Microscopy
SMQ	Standardised MedDRA Query
SOC	Standard Of Care
SPR	Surface Plasmon Resonance
SUS	Single-Use System
TCR	Tissue-Cross Reactivity Study
TEAE	Treatment-Emergent Adverse Events
TIN	Tubulointerstitial Nephritis
TK	Toxicokinetic
TMDD	Target Mediated Disposition
TNF	Tumour Necrosis Factor
TOR	Time Out Of Refrigeration
TOST	Two One-Sided Test
TRAE	Treatment-RELATED Adverse Events
TSB	Tryptic Soy Broth
TSE	Transmissible Spongiform Encephalopathy
UF/DF	Ultrafiltration/Diafiltration
UPB	Unprocessed Bulk
US	United States Of America
USP	United States Pharmacopoeia
UTI	Urinary Tract Infection
VERO	African Green Monkey Kidney Epithetical Cell Line
VF	Viral Filtration
VH	Heavy Chain Variable Region
VHP	Vaporised Hydrogen Peroxide
VL	Light Chain Variable Region
VPC	Visual Predictive Check
VTE	Venous Thromboembolism
WCB	Working Cell Bank
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The applicant InflaRx GmbH submitted on 28 July 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Gohibic, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 May 2022.

The applicant applied for the following indication:

Gohibic is indicated for treatment of adult patients with SARS-CoV-2-induced septic acute respiratory distress syndrome (ARDS) receiving invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on the applicant's own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0118/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0118/2023 was not yet complete as some measures had been deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Applicant's request(s) for consideration

1.5.1. New active substance status

The applicant requested the active substance vilobelimab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant received scientific advice from the CHMP (EMA/SA/0000058706) on 23/04/2021. Brigitte Schwarzer-Daum and Jens Reinhardt were appointed as Rapporteurs.

The scientific advice pertained to the following quality, non-clinical and clinical aspects:

• Production scale and planned marketing authorisation application timelines for the applicant's CMC development programme including process characterisation and process validation

• Agreement with current production in China, with the option to transfer parts of the process to Europe at a later stage

• Shelf-life and the planned shelf-life extension strategy

• Non-clinical data package for MAA

• Integrated summary of immunogenicity as well as the planned timelines vis a vis MAA

• Dose selection and PK and ADA analysis in phase 3

• Study design of the phase III part of study PANAMO and statistical analysis plan

• Advise on the preliminary safety profile for vilobelimab

• Safety database for MAA

• Initiation of paediatric studies after positive B/R is shown in adults

• Rolling review.

Vilobelimab has also been discussed at EMA's Emergency Task Force (ETF).

1.7. Steps taken for the assessment of the product

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

Rapporteur: Filip Josephson Co-Rapporteur: Antonio Gomez-Outes

CHMP Peer reviewer(s): N/A

The appointed CHMP co-rapporteur had no such prominent role in scientific advice relevant for the indication subject to the present application.

The application was received by the EMA on	28 July 2023
The procedure started on	17 August 2023
The CHMP Rapporteur's first assessment report was circulated to all CHMP and PRAC members on	6 November 2023
The CHMP Co-Rapporteur's first assessment report was circulated to all CHMP and PRAC members on	21 November 2023
The PRAC Rapporteur's first assessment report was circulated to all PRAC and CHMP members on	21 November 2023
The CHMP agreed on the consolidated list of questions to be sent to the applicant during the meeting on	14 December 2023

The applicant submitted the responses to the CHMP consolidated list of questions on	25 April 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs joint assessment report on the responses to the list of questions to all CHMP and PRAC members on	03 June 2024
The PRAC agreed on the PRAC assessment overview and advice to CHMP during the meeting on	13 June 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs joint updated assessment report on the responses to the list of questions to all CHMP and PRAC members on	20 June 2024
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	27 June 2024
The applicant submitted the responses to the CHMP list of outstanding issues on	17 September 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs joint assessment report on the responses to the list of outstanding issues all CHMP and PRAC members on	02 October 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs joint updated assessment report on the responses to the list of outstanding issues to all CHMP and PRAC members on	10 October 2024
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	15 October 2024
The CHMP agreed on a 2nd list of outstanding issues in writing to be sent to the applicant on	17 October 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs joint preliminary assessment report on the responses to the 2nd list of outstanding issues to all CHMP and PRAC members on	30 October 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs joint updated assessment report on the responses to the 2nd list of outstanding issues to all CHMP and PRAC members on	07 November 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Gohibic on	14 November 2024
Furthermore, the CHMP adopted a report on new active substance (NAS) status of the active substance contained in the medicinal product	14 November 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The therapeutic indication claimed by the applicant is:

Gohibic is indicated for treatment of adult patients with SARS-CoV-2-induced septic acute respiratory distress syndrome (ARDS) receiving invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO).

2.1.2. Epidemiology

Coronavirus disease 2019 (COVID-19) is a highly contagious infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 has resulted in more than 6 million deaths worldwide.

Individuals of all ages are at risk of SARS-CoV-2 infection. However, the probability of severe COVID-19 is higher in people aged ≥65 years, those who are not vaccinated against COVID-19 or who have poor responses to COVID-19 vaccines. Data on comorbid health conditions among patients with COVID-19 indicate that patients with cardiovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, diabetes with complications, neurocognitive disorders, and obesity are at increased risk of severe COVID-19. Other conditions that may lead to a high risk of severe COVID-19 include cancer, cystic fibrosis, immunocompromising conditions, liver disease (especially in patients with cirrhosis), pregnancy, and sickle cell disease. Transplant recipients and people who are taking immunosuppressive medications are also at high risk of severe COVID-19 (CDC, 2023).

2.1.3. Biologic features

Autopsies of patients with severe COVID-19 has shown widespread complement activation in the lung and kidney (Gao et al. 2020). Elevated concentrations of the complement factors C5a and C5b-9 have been reported in patients with severe COVID-19 (Cugno et al. 2020). The anaphylatoxin C5a attracts neutrophils and monocytes to the infection site and strongly activates these cells, causing tissue damage by oxidative radical formation and enzyme release.

2.1.4. Clinical presentation and diagnosis

Two main processes are thought to drive the pathogenesis of COVID-19. Early in the clinical course, the disease is primarily driven by the replication of SARS-CoV-2. Later in the clinical course, the disease is driven by a dysregulated immune/inflammatory response to SARS-CoV-2 infection that may lead to further tissue damage and thrombosis. Based on this understanding, therapies that directly target SARS-CoV-2 are anticipated to have the greatest effect early in the course of the disease, whereas immunosuppressive, anti-inflammatory, and antithrombotic therapies are likely to be more beneficial after COVID-19 has progressed to stages characterised by hypoxaemia and endothelial dysfunction.

Clinical manifestations of COVID-19 vary, from asymptomatic or pauci-symptomatic forms to clinical illness characterised by acute respiratory failure requiring mechanical ventilation, septic shock, and

multiple organ failure. Severe COVID-19 is characterised by hepatic and renal dysfunction in the presence of leukopenia, lymphopenia, increase of D-dimers, strong inflammatory cytokine activation, and activation of the complement cascade (Guan et al. 2020, Huang et al. 2020, Liu et al. 2020, Garg et al. 2020, Wiersinga et al. 2020, Gao et al. 2020). Furthermore, severe disease is associated with increased blood neutrophil levels and neutrophil infiltration in the heart and liver (Wang et al. 2020).

The definition of *severe illness* according to the NIH COVID-19 Treatment Guidelines is having SpO2 less than 94% on room air, a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (PaO2/FiO2) of less than 300, marked tachypnoea with a respiratory frequency of greater than 30 breaths/min, or lung infiltrates that are greater than 50% of total lung volume. Patients with severe COVID-19 illness may become critically ill with the development of acute respiratory distress syndrome (ARDS).

2.1.5. Management

WHO recommends the use of systemic corticosteroids for severe or critical COVID-19 disease. Moreover, interleukin-6 (IL-6) receptor blockers such as tocilizumab, are recommended given in in combination with corticosteroids.

It is also recommended to use venous thromboembolism prophylaxis in hospitalised patients who require mechanical ventilation or ECMO (NIH COVID-19 Treatment Guidelines).

The mortality of patients with COVID-19 under MV/ECMO remains high and therapeutic options are inadequate. New therapeutic principles to prevent disease progression and reduce mortality in late-stage COVID-19 pneumonia could therefore be useful (European Respiratory Society).

2.2. About the product

Vilobelimab (IFX-1) is a chimeric human/mouse monoclonal immunoglobulin (Ig) G4 antibody which specifically binds to the soluble human complement split product C5a. Vilobelimab is composed of 1,328 amino acids and has an approximate molecular weight of 148 - 149 kDa.

C5a is a strong chemoattractant for neutrophils and with chemotactic activity for monocytes and macrophages. C5a is generated when the complement system is activated in settings of inflammation and other immunological and inflammatory disorders. Complement activation products such as high levels of C5a and C5b-9 have been reported in patients with severe COVID-19.

Vilobelimab has been shown to block C5a-induced biological effects such as CD11b up-regulation on granulocytes as well as lysozyme release from neutrophils.

The recommended dose is 800 mg administered by intravenous infusion after dilution for a maximum of 6 (six) doses over the treatment period. 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 hospitalised, (even if discharged from the intensive care unit (ICU)).

2.3. Quality aspects

2.3.1. Introduction

The finished product is presented as concentrate for solution for infusion containing 200 mg/vial (10 mg/mL) of vilobelimab as active substance.

Other ingredients are: sodium chloride, sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, polysorbate 80 and water for injection.

The product is available in a vial (type I clear glass) closed with a stopper (bromobutyl rubber) and sealed with a flip off cap (pack size of 4 vials).

2.3.2. Active substance

2.3.2.1. General information

Vilobelimab (INN) is a chimeric human/mouse anti-human C5a monoclonal IgG4 antibody. This IgG4 kappa antibody contains murine heavy and kappa light chain variable (VH and VL) regions, and human gamma 4 heavy chain and kappa light chain constant regions. The two light chains (LCs) and two heavy chains (HCs) are covalently linked by disulfide bonds. The main secondary structure compositions are β-sheet and random coil. Theoretical molecular mass of vilobelimab is 148.3-148.8 kDa (glycosylated intact mass).

The major identified post-translational modifications (PTMs) for vilobelimab are N-glycosylation and N-terminal Q cyclisation on the heavy chain and C-terminal K loss on the heavy chain. One glycosylation site is on heavy chain N296 and the main N-glycoforms are G0F and G1F. There is no O-glycosylation. Vilobelimab also has aspartic acid (D) isomerisation on the peptide A25-K38 of light chain and D101 of heavy chain, deamidation on light chain N141, heavy chain N314, N383, N388 and N433, oxidation on heavy chain M251, and N314 succinimide. The value of the formulated active substance solution isoelectric point (pI) is 5.7 – 7.3 and the pH is 6.7 – 7.3.

Vilobelimab binds to its target, human C5a, rapidly and is capable of an almost complete blockade of C5a-induced biological effects while not disturbing the cleavage of C5 and not affecting C5b and the formation of complement membrane attack complex (MAC) in vitro.

The applicant requested vilobelimab to be considered as a new active substance (NAS). During the assessment, a major objection (MO) was raised concerning the applicant's justification of vilomelimab NAS claim, requesting additional information about database searches performed by the applicant for structurally related substances in relation to the therapeutic moiety of the claimed NAS. The applicant has adequately addressed this issue and, therefore, vilobelimab is to be qualified as a new active substance as it was concluded that it is not a constituent of a medicinal product previously authorised within the European Union.

2.3.2.2. Manufacture, process controls and characterisation

The active substance is manufactured, tested and released, in accordance with good manufacturing practice (GMP), at a facility in China. The WCB and MCB were manufactured in the US and Germany. Future WCBs will be manufactured in China.

At the time of submission, no valid EU GMP certificates were available for the two active substance manufacturing and testing sites (China). For this reason, MOs were raised during the assessment and GMP inspections were triggered. The outcome of these inspections was that the sites are in compliance with the principles and guidelines of GMP. Copies of the GMP certificates were provided by the applicant by the time of CHMP opinion and the MOs were considered resolved.

Description of manufacturing process and process controls

The manufacturing process of vilobelimab active substance consists of two main stages, i.e. the cell culture and harvest (upstream) process and the purification (downstream) process. Detailed flowcharts of the upstream and downstream processes, including critical process parameters (CPP), key process parameters (KPP), critical performance attributes (CPA) and key performance attributes (KPA) are also provided.Vilobelimab active substance is manufactured in a suspension-adapted Chinese hamster ovary (CHO-S) cell line with a serum free medium. The upstream manufacturing process consists of eight different process steps. The manufacturing process is initiated by thawing a vial of the working cell bank (WCB) of the production cell line and inoculation in a shake flask. Thawing is followed by several cell expansion steps in shake flasks and bioreactors before final cultivation in the production scale bioreactor. The production bioreactor is harvested through centrifugation and depth filtration. The purpose of each step is sufficiently outlined and further details on operating conditions for each step are provided in this section of the dossier. Critical and key process parameters and attributes are listed for all steps, with corresponding normal operating ranges (NORs) and proven acceptable ranges (PARs).

The downstream manufacturing process of vilobelimab active substance is performed in seven steps. Vilobelimab is purified using a conventional monoclonal antibody downstream process consisting of antibody capture, viral inactivation, cation (CEX)/anion exchange, viral filtration, ultrafiltration and diafiltration (UF/DF) and final formulation of active substance. The purpose of each step is sufficiently outlined. Operational sequences are described for all individual steps. For chromatographic steps, column diameters, bed heights, chromatographic resin, conditions for sample load, wash and elution, sample collection and column equilibration are provided. For filtration steps the filter membrane types, the pressure and filter load capacity are stated. Where relevant, the hold times for respective pools are defined. Process parameters and performance attributes are listed and are classified based on criticality.

Reprocessing is allowed for the viral filtration and bulk fill steps when the post use filter integrity test fails or if there is mechanical failure of equipment or if the operation is not executed as intended and per validated procedures. This is considered acceptable.

One batch of vilobelimab active substance is defined as the material derived from one bioreactor and subsequently purified, concentrated and formulated in 10 mM phosphate, 150 mM NaCl, 0.05% (w/v) polysorbate 80, pH 7.0, to the final target protein concentration of 10 mg/mL. The batch numbering system is described. The typical final active substance batch size is stated.

Vilobelimab active substance is stored in a bag. The components of the bag are clearly stated. Specifications for the bag are stated and an example of the vendor certificate is provided. Also, a schematic drawing is included. The contact layer conforms with Ph. Eur. 3.1.7 (polyethylene-vinyl-acetate) and complies with US FDA 21 CFR 177.1350. This is found to be acceptable.

An extractable and leachable study on the active substance container is ongoing. The design of the extractable study is sufficiently described. A summary of the extractables assessment was provided. The applicant commits to continue the study and monitor leachable compounds during the active substance storage to further evaluate the safety of the container (Recommendation).

Overall, the active substance manufacturing process has been adequately described and is found acceptable.

Control of materials

Descriptions of raw materials used in master cell bank (MCB) and WCB preparation and active substance manufacturing are provided. Compendial and non-compendial raw materials are listed and specifications for all non-compendial raw materials are provided. All buffers and solutions used in the

process are listed with corresponding specifications. Resins, membranes and filters used are listed and the manufacturer of each consumable is stated. No human or animal derived materials are used in the active substance manufacturing process and acceptable documents have been provided for raw materials of biological origin used in the establishment of cell substrate. In conclusion, sufficient information on raw materials used in the active substance manufacturing process has been submitted.

Sufficient information has been provided regarding source, history and generation of the cell substrate. The vector maps of the plasmids encoding for the full length vilobelimab light chain and heavy chain were provided. Stable cell lines for vilobelimab production were made by performing multiple rounds of transduction of the CHO-S parental cell line with retrovector particles containing the plasmids for human IgG4 heavy chain and human kappa light chain. An enzyme-linked immunosorbent assay (ELISA) was used to screen clonal cell lines for protein titre. The top twenty clones were set up in shake flasks for fed batch overgrowth productivity testing. Selected clones were cryopreserved and passed QC testing for use as potential research cell bank. One clone was finally chosen for MCB generation. A WCB of the CHO-S parental production cell line was also produced. Overall, the generation of the cell banking system has been described in sufficient detail. The characterisation and virus testing of the parental cell line, MCB and WCB are in accordance with ICH Q5A and ICH Q5D. Additionally, detailed description of cultivation and establishment of future WCBs has been provided and is considered acceptable. Creation of a new MCB is not anticipated for the duration of the product.

Detailed descriptions have been presented for the establishing of the limit of in vitro cell age (LIVCA) and end of production cell bank (EOPCB) production. The impact of additional passages on product quality, process performance, cell substrate stability and safety at scale was evaluated and all the results meet the acceptance criteria. The results from testing of the EOPCB confirm CHO identity and the results from virus testing is as expected for CHO cells (some reverse transcriptase activity detected and presence of A-type and C-type retrovirus-like particles – RVLPs). The results are satisfactory.

In addition, acceptable information on monitoring of MCB and WCB stability has been provided. Also, the data presented from studies of genetic stability are deemed acceptable and confirm the genetic stability of the cell banks.

In conclusion, sufficient information is provided regarding testing of MCB and WCB and release of future WCBs. Genetic stability has been demonstrated for cells at and beyond the limit of cell age.

Control of critical steps and intermediates

The control strategy for the active substance manufacturing process includes CPPs, KPPs, CPAs and KPAs. Actions taken if limits are exceeded are specified. The classification of process parameters and their specified ranges/limits based on their impact on the critical quality attributes (CQAs) of the active substance and/or process performance is adequately justified and is supported. The relationships between the process parameters and quality attributes of the active substance were initially assessed by Failure Modes and Effects Analysis (FMEA), considering the possible impact of each attribute on safety and efficacy is applied. Overall, the approach is found acceptable.

There are no isolated intermediates during vilobelimab manufacturing process, but there are in-process pools that the applicant refers to as process intermediates. Hold times and storage conditions for process intermediates are presented. The methods used for CPAs and viral testing, including acceptance criteria, are described. For compendial methods, references are given to the corresponding Ph. Eur. chapter. A summary of the validation of the remaining methods is presented. The information provided is found sufficient to confirm the suitability of the in-process controls.

In conclusion, acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests.

Process validation

Vilobelimab active substance manufacturing process validation follows a three-stage approach involving process design, process performance qualification (PPQ) and continued process verification (CPV).

PPQ campaign

The PPQ campaign of the commercial process (Process 6) was performed at the commercial facility and scale. The PPQ was based on meeting predefined acceptance criteria for CPPs, CPAs, KPPs and KPAs. The acceptance criteria, action limits, expected ranges for performance attributes and criticality of process parameters were defined using existing process knowledge, development and manufacturing experience, risk ranking and filtering and an extensive process characterisation programme comprising of design of experiment (DoE) or one factor-at-a-time (OFAT) studies. Overall, the design of the process validation is found acceptable.

Three consecutive PPQ batches were included in the study. All CPPs, KPPs, CPAs and KPAs results met the acceptance criteria. The results from the PPQ campaign support consistent and adequate production of vilobelimab active substance.

CPV programme

CPV will be used to provide assurance that the process remains in a state of control during routine commercial manufacturing. The activities mainly include the establishment of CPV programme monitoring plan, periodic CPV monitoring data review, CPV change management and continued process verification. CPV requires frequent monitoring and statistical analysis of process parameters. The provided information is found acceptable and the CPV programme is endorsed.

Reprocessing

A reprocessing validation study was performed at small scale for the viral filtration and active substance bulk fill steps. The results are found acceptable. Reprocessing protocols for both steps at scale are provided. This is endorsed.

Impurity clearance

A process- and product-related impurity clearance study was performed concurrently at commercial scale to demonstrate the capacity of the downstream process to retain impurities. The study design and the results obtained are found acceptable, sufficiently demonstrating that the impurities can be removed to acceptably low levels.

Hold time validation

A microbial hold time study for all media, buffer solutions and process intermediates of the vilobelimab active substance manufacturing process was outlined to confirm the established hold time limits for the media, buffer solutions and in-process pools under specified conditions, including the storage vessel type and temperature. Tryptic soy broth was used to mimic the media, buffer solutions and in-process pools. The approach is found acceptable and the microbial hold times are found justified.

Resin lifetime studies

The lifetime of the resins and membranes used for affinity chromatography, CEX and AEX were validated at laboratory scale. The resin lifetime validation study at commercial scale is still in execution. To date, all results have met acceptance criteria and no trends have been reported. The resin lifetime studies are found acceptable.

Mixing validation

Mixing assessment of all media and buffers was performed via FMEA. All media were assessed to be low risk and therefore not further evaluated. However, mixing validation for three selected buffers and three in-process pools was performed. Test items and acceptance ranges for the individual buffers and in-process pools were defined. All results met the acceptance criteria. The mixing validation study is found acceptable.

Extractables and leachables

A risk assessment was performed for the purpose of evaluation of extractables and leachables for plastic materials used in the vilobelimab manufacturing process. Risk evaluation was performed considering the duration of contact, temperature of contact, solvent, material reactivity, additional mitigating factors were taken into account and final established risk level was either low, moderate or high. It is clarified by the applicant that for low risk level category, extraction profile from the vendors could be leveraged and no additional extraction study is needed and for moderate risk level, components need to meet regulatory USP VI requirements and extractable data are needed to demonstrate whether the risk is under control. Overall, the risk assessment is properly documented in dossier and conclusions are considered adequately justified.

Shipping validation

Vilobelimab active substance is manufactured at WuXi Biologics Co., Wuxi, China and will be transported to Germany, for finished product manufacturing. The conditions for shipping are adequately described and the strategy described for shipping validation is found acceptable. The shipping validation has been completed both for summer and winter shipping conditions. The results are summarised in the dossier and found acceptable.

In conclusion, the vilobelimab active substance manufacturing process has been validated adequately.

Manufacturing process development

The commercial active substance manufacturing process was developed in parallel with the clinical development programme. Six process versions and three different manufacturing sites have been used during development. The differences between processes are adequately summarised and comparative flow chart diagrams are provided. The major changes implemented during development are related to scale up and site changes. A WCB was introduced with Process 4. The current process is referred to as Process 6. This process is essentially the same as Process 5, but due to a manufacturing suite change, some adaptations were made to commercial scale GMP production. The description of process development history is found acceptable.

Comparability between the six different process versions were evaluated in three separate comparability exercises taking a stepwise approach. Extensive reports are provided for all three individual comparability exercises. The analytical comparability assessment comprised comparison of process performance, batch release data, stability data, extended characterisation (covering primary and higher order structure as well as molecular weight and biological activity) and forced degradation studies. The number of batches used in the comparability studies are considered acceptable. The attributes and parameters compared are found acceptable and in line with ICH Q5E. Slight differences were observed during the comparability studies, as expected, however these differences are not considered to preclude the comparability claim. Overall, the comparability approach is found acceptable and it can be concluded that a consistent quality of the active substance was maintained following the changes to the manufacturing process.

Characterisation

The vilobelimab active substance has been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure of a human

IgG4-type antibody. Characterisation of vilobelimab active was performed with regards to primary structure, PTMs, higher order structure, general characteristics and biological functions and activities. The batch used for characterisation was produced from the current manufacturing Process 6, which is endorsed.

Characterisation of biological activity for vilobelimab was investigated by employing orthogonal methods, addressing C5a binding and Fc binding. In general, the approach to determine the C5a and Fc binding of vilobelimab is agreed to and the characterisation is considered appropriate for this type of molecule.

Furthermore, heterogeneity of the active substance was adequately characterised. The product related impurities identified are typical for a biological product and include size variants, charge variants and fragments.

In conclusion, the characterisation is considered appropriate for this type of molecule and the analytical results obtained for vilobelimab are consistent with the proposed structure.

2.3.2.3. Specification

The proposed active substance specifications are provided. The proposed panel of release tests covers general tests (appearance, pH, protein concentration, osmolality, polysorbate 80), identity, purity, product-specific impurities, process-specific impurities, biological activity, glycosylation profile and microbiological content (bioburden, bacterial endotoxins).

The panel of tests is in line with ICH Q6B and is considered appropriate for routine control of the active substance manufacturing. The specification was established based on pharmacopeial guidance or literature, release data for the active substance and the finished product, results from stability studies, analytical variability and manufacturing experience. During the assessment, the applicant was requested to tighten the acceptance criteria for potency, glycosylation profile, process- and product-related impurities, in line with the limits found clinically justified and/or process capability.

The applicant has described a tentative plan to develop and implement an endotoxin assay based on recombinant Factor C (instead of animal lysate) within 3 years. This is encouraged. Further, the applicant commits to review the active substance specification limits following the generation of additional data (n=30) (Recommendation).

Overall, the proposed specifications and their associated justifications are considered acceptable.

Analytical methods

The analytical methods used have been adequately described. The tests for appearance, clarity, degree of coloration, pH, osmolality, bacterial endotoxin and bioburden are stated to comply with the corresponding Ph. Eur. chapters. Non-compendial methods were appropriately validated in accordance with ICH guidelines.

Batch analysis

Results from batch analyses of three process 5 batches and eight process 6 batches (including the PPQ batches) are presented. All results complied with the proposed specification limits in place at the time of testing. The provided release data from the commercial process confirm consistency of the active substance manufacturing process.

Reference materials

Five different reference standards have been used during the development of vilobelimab. The history of reference standards is adequately described in terms of batch number, manufacturer, date of fill, storage conditions and use of standard. For the commercial process, a two-tiered reference standard system is used. The primary (RS4) and working (RS5) reference standards are derived from the same finished product batch. The preparation of the current reference standards is found acceptably described. The qualification of the primary and working reference standard is also described. Since RS4 and RS5 are identical material, solely RS4 material was used for qualification. All acceptance criteria of the qualification methods were met. In conclusion, the qualification of the current reference standards is considered acceptable.

The primary reference standard is re-evaluated annually and information on RS5 obtained through routine testing is evaluated. A tentative expiry date of 5 years was assigned to RS4 and RS5. The expiry date will be updated based on the conclusion of the re-evaluation. This approach is found acceptable.

Qualification of future primary and working reference standards are described. The acceptance criteria are acceptably defined to maintain appropriate control over the quality attributes of the reference standard. Overall, the strategy for qualification of future reference standards is endorsed.

2.3.2.4. Stability

The proposed shelf-life for vilobelimab active substance is 24 months when stored at 5 ± 3°C, in the container closure system (CCS) described in the dossier. The stability programme presented for the active substance involves long-term (5 ± 3°C), accelerated (25 ± 2°C/60 ± 5% relative humidity, RH) and stress (40 ± 2°C/75 ± 5% RH) stability studies. Also, a forced-degradation study (including

thermal stress, photo stability, oxidative agents, extreme pH, agitation and freeze-thaw cycles) was conducted, in order to define the major degradation pathways and stability-indicating capabilities of the test methods. All stability studies have been carried out in line with ICH guidelines. The parameters tested during stability and associated acceptance criteria are the same as for release, apart from identity, polysorbate 80, process-related impurities and glycosylation profile, which are only tested at release. In addition, slightly wider limits are applied to product-related impurities.

The primary stability study is based on eight batches manufactured at the commercial scale: two GMP batches manufactured by Process 5, three GMP batches manufactured by Process 6 and three PPQ batches. The stability samples were stored as 3 mL in 5 mL bags, which the applicant considered to be representative of the final container since it is constructed from the same multi-layer film. However, the films were of different thickness, and it was demonstrated that the final container had approximately 20% better water vapour barrier properties than the bags used for the stability studies. As a result, an increase in protein concentration and osmolality was observed in active substance samples during storage. This increase was demonstrated in a separate investigation not to occur during storage in the final container. Moreover, from the data provided it is anticipated that the use of 5 mL bags can be regarded as worst-case, as compared to the final container. Therefore, the stability study is found acceptable and the results are regarded as reliable, with an overestimation of protein concentration and osmolality over time.

Data from the accelerated and stressed conditions studies support the stability indicating profile of the active substance and the suitability of the analytical methods. This is further supported by results from forced degradation study, which have shown that vilobelimab is only sensitive to the thermal treatment among all the studied conditions.

Long-term stability data are available up to 36 months for one Process 5 GMP batch and up to 24 months for one Process 5 GMP batch and three Process 6 GMP batches. The stability studies for the PPQ batches are still ongoing and data are available for up to 12 months for all three batches. All results comply with the current shelf-life specifications. Clear trends in quality attributes have been observed, concerning decrease in purity with increase in impurities. However, the applicant discussed levels of impurities tested in patients that indicate no additional safety risks and therefore, it is concluded that the established acceptance criteria for active substance shelf-life specification is clinically justified.

In conclusion, based on the currently available data generated from the primary stability studies, the proposed shelf-life for vilobelimab active substance of 24 months when stored at 5 ± 3°C, in the CCS described in the dossier, is considered acceptable.

2.3.3. Finished medicinal product

2.3.3.1. Description of the product and Pharmaceutical development

The finished product is a concentrate for solution for infusion containing 200 mg of vilobelimab per vial (10 mg/mL) and it is a clear to slightly opalescent, colourless, aqueous, isotonic, buffered, preservative-free, sterile solution. An overfill is applied to allow extraction of the nominal content of 20.0 mL per vial. The product is supplied as a pack size of four vials to allow for administration of the dose of 800 mg after dilution with a sodium chloride solution (0.9%) by the intravenous (IV) route. The qualitative and quantitative composition of a unit vial of the vilobelimab concentrate for solution for infusion 200 mg/vial (10 mg/mL) is shown in Table 1.

Table 1: Composition of the finished product

Component	Reference	Function	Concentration	Amount[2] in 20.0 mL/vial	Amount per mL solution
Monoclonal antibody vilobelimab	In-house	Active ingredient	10.0 mg/mL	200.0 mg	10.0 mg
Sodium chloride	Ph. Eur., USP	Tonicity agent	8.8 g/L	176.0 mg	8.8 mg
Sodium dihydrogen phosphate dihydrate	Ph. Eur., USP	Buffer	0.5 g/L	10.2 mg	0.5 mg
Di-sodium hydrogen phosphate dihydrate	Ph. Eur., USP	Buffer	1.2 g/L	24.0 mg	1.2 mg
Polysorbate 80 (Tween 80)[1]	Ph. Eur., NF	Surfactant and stabilizer	0.5 g/L	10.0 mg	0.5 mg
Water for injection (WFI)	Ph. Eur., USP	Solvent	up to 1 L	19748 mg	987.4 mg

[1] Theoretical amount, 10% polysorbate solution is prepared in advance using diafiltration buffer

[2] The amount is calculated taking into consideration that the density of the solution is 1.0084 kg/L

The section on description and composition of the finished product is found acceptable. All excipients in the composition comply with Ph. Eur. grade and are commonly used excipients in parenteral formulations for biological products. There are no excipients of human or animal origin, or novel excipients used in the finished product. The formulation for the active substance and the finished product is the same. No additional excipients are added to the active substance to produce the finished product. The compatibility of the active substance with excipients is supported by stability data. There are no formula overages in the vilobelimab finished product. The formulation was not changed during development and will be further used in the commercial phase.

The formulation development section describes and justifies the chosen formulation and is sufficiently comprehensive. The quality target product profile (QTPP) presented in Table 2 summarises the quality characteristics used to guide the pharmaceutical development of vilobelimab finished product.

Table 2: Quality target product profile of vilobelimab finished product

QTPP Element	Target
Dosage form	Concentrate for solution for infusion
Route of administration	Intravenous infusion
Strength	200 mg/20 mL/vial
Clinical dose	800 mg administered by intravenous infusion after dilution given up to 6 (six) times over the treatment period
Container closure system	Type I borosilicate glass vial, FluroTec rubber stopper and aluminium seal
Storage	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.
Shelf life	24 months for DS and 48 months for DP
Drug product quality attributes	Identification Appearance Quantity Biological activity Physicochemical Purity Safety General

To evaluate the impact of variation of the critical formulation parameters on the quality and stability of vilobelimab active substance and finished product, a formulation robustness study was designed at the target composition and within a range of pH, sodium chloride concentration and polysorbate 80 concentration. The study results showed that the proposed formulation is robust within the formulation design space.

The container closure system consists of 20 mL clear glass vials with a 20 mm Flurotec coated bromobutyl elastomeric stopper and crimped with a 20 mm aluminium-plastic seal cap. All product-contacting materials comply with relevant pharmacopeial requirements. Sufficient information with respect to sterilisation of the glass vials and rubber stoppers has been provided, in-line with the requirements in the EMA guideline EMA/CHMP/CVMP/QWP/850374/2015 (Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container). Container closure integrity is being monitored by vacuum decay leak testing, both at release and as part of the long-term stability programme. This is acceptable. The applicant has presented both extractable and leachable studies for the finished product container closure system. The extractable results shows that the safety threshold of 30% of the permitted daily exposure (PDE) was not exceeded. For the ongoing leachables study, the results up to date were also within the safety limit, demonstrating that there is no concern for human health originating from the proposed commercial containers. applicant's commitment to finalise the leachables and to notify the agency in the event of any issues arising from this study has been provided and is endorsed. Overall, the development of the container closure system is considered adequately described and compatibility between the finished product and the proposed container closure system is demonstrated.

An in-use study was also conducted to assess the compatibility of the finished product with different commonly used consumables and to evaluate the stability of the diluted finished product. The data show that vilobelimab finished product is compatible with the evaluated syringes and needles combination during solution extraction and injection. The diluted finished product is shown to be compatible with the infusion bags and sets tested and can be stored for up to 4 hours when exposed to ambient temperature (up to 25 °C) and light or for up to 72 hours at 2-8 °C, protected from light. Overall, the data from the compatibility study support the instructions in the SmPC.

2.3.3.2. Manufacture of the product and process controls

The manufacture, control, packaging and release of the finished product is performed, in accordance with GMP.

The finished product manufacturing process is described. The process consists of the active substance pooling and mixing to produce final bulk, sterile filtration, followed by aseptic vial filling and stoppering with sterile container closure components. The finished product manufacturing process involves single-use systems made entirely or partly of polymer material. The sterile filtration system consists of two redundant 0.2 µm sterile filters in series. The sterile filters are subjected to both pre-use and post-use filter integrity testing (PUPSIT). The vials are capped, and 100% manually, visually inspected. The capped vials are stored at 2 - 8°C before further processing.

No reprocessing has been described in the dossier. A batch of vilobelimab finished product is generated by a single batch of active substance.

A summary of CPPs and corresponding NORs and PARs is also presented in the dossier. The CPPs as well as NOR and PARs have overall been acceptably justified by manufacturing process development. The process parameters were assessed using FMEA to identify parameters with higher or medium risk to have an impact on CQAs or KPAs. Parameters with a high or medium risk were further studied in process characterisation studies. A two-step approach was introduced to classify the category of process parameter and summarise the historical data to establish the proposed PARs and NORs. Also, the compatibility between the active substance and the materials of all components that the active substance is in contact with during finished product manufacturing is considered adequately demonstrated by characterisation studies.

The finished product manufacturing process development history from clinical development and onto commercial development has been presented.

A comparability assessment was performed between the process used to manufacture clinical batches and the intended commercial process. The results support the conclusion that a consistent quality of the finished product was maintained. In addition, it was shown that the active substance manufacturing process changes did not impact the quality of the finished product. Taken together, comparability of the finished product between clinical and commercial is considered demonstrated. Overall, the manufacturing process development for vilobelimab finished product has at large been sufficiently described and justifies the commercial manufacturing process.

The proposed commercial batch size range was validated. The acceptance criteria for specific process parameters (PP), CQAs and IPCs were predefined in the validation protocol. Prior to process validation, three GMP batches for clinical supply were conducted to assess process performance. Subsequently, three PPQ batches have been produced following the PPQ protocol and the batch record requirements. The process validation includes validation of manufacturing steps, product mixing studies, media fill and hold times validation, sterile filter validation and shipping qualification.

At the time of submission of the marketing authorisation application (MAA), the majority of the process validation results were still pending and for this reason an MO was raised, which was adequately resolved by the applicant upon provision of the requested information.

Overall, the process validation results for process parameters and in process testing for are considered satisfactory. The proposed process and hold times are supported by the PPQ runs. The media fill strategy is described and results are acceptable. Sterile filter validation is performed in accordance with EMA/CHMP/CVMP/QWP/850374/2015 (Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container). A detailed summary of the deviations occurred during validation, together with an impact assessment of each deviation, has been presented. The results of the investigations indicate that these deviations had no impact on the process itself and did not impact product quality. This conclusion is endorsed.

The applicant has provided preliminary results of three summer validation shipment runs from the finished product manufacturing site in Germany to a site in Ireland, where labelling and secondary packaging (L&P) is performed. The preliminary data set of the shipping validation studies demonstrated acceptable temperature control within the intended transportation conditions and that the shipment had no impact on product quality. L&P validation activities are also ongoing. Upon completion of shipping and L&P validation activities, the applicant commits to update the dossier. It is expected that the validation of shipping and L&P activities will be successful and a summary of validation conclusion should be provided prior to placing the medicine on the market (Recommendation).

In conclusion, the manufacturing process has been adequately validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

2.3.3.3. Product specification

The finished product release and shelf-life specification is provided in. The proposed panel of tests cover appearance and description (clarity, colour and degree of opalescence), general tests (pH, osmolality, extractable volume, particulate matter, polysorbate 80), identity, protein content, potency, purity/impurity, microbiological tests (endotoxin and sterility) and container closure integrity. The formulated finished product is identical to the vilobelimab active substance, therefore with the exception of a few tests only conducted at finished product release (visible and subvisible particles, extractable volume, container closure integrity, sterility) and some tests conducted only at the level of the active substance (glycosylation profile, process-related impurities, bioburden), all other tests at release are identical for both active substance and the finished product, largely with the same acceptance criteria (apart for the acceptance criteria for product-related impurities in the finished product specification where slightly wider limits are proposed). The acceptance criteria are found clinically justified throughout the shelf-life of the finished product.

During the assessment, the applicant was requested to tighten the acceptance criteria for potency and product-related impurities, in line with the active substance acceptance criteria and/or process capability.

The applicant has provided a summary of the elemental impurities risk assessment. The total contribution by all potential sources of elemental impurities was calculated by applying the component-based approach (ICH Q3D option 2b). The predicted elemental impurity contributions from all sources were determined to be below the control threshold. The applicant's conclusion that no additional controls need to be included in the overall control strategy is supported.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

No new impurities have been identified in the finished product compared to the ones already identified for the active substance.

In summary, the specifications proposed for the finished product are in line with the ICH Q6B and Ph. Eur. 2031 monograph and are considered appropriate for routine control of the finished product.

Analytical methods

Many tests used for release and stability testing of the finished product are also used for release and stability testing of the active substance. These methods and their validation results are presented, discussed and assessed in the corresponding active substance sections and their validations cover both the active substance and the finished product. The non-compendial analytical procedures were validated in accordance with ICH Q2 and the compendial methods have been verified according to the appropriate compendial chapters.

Batch analysis

Batch analyses data has been provided for sixteen small scale finished product batches (ten batches containing Process 5 active substance and six batches containing Process 6 active substance), which were used in clinical trials and stability testing. In addition, batch analyses data for seven commercial scale finished product batches are presented. The batch analysis data complies overall with the limits proposed in the finished product release specification in place at the time of manufacture and confirm process and product consistency.

Reference materials

The reference standards are the same as those used for testing of the active substance. Reference is made to the corresponding active substance section.

2.3.3.4. Stability of the product

The proposed shelf life for the finished product is 12 months when stored at the recommended storage condition of 2°C to 8°C, in the CCS described in the dossier.

Stability studies have been carried out in accordance with ICH Q5C using one GMP (supportive) and one clinical Process 3 batch, three clinical Process 4 batches and one PPQ batch, under long-term (5 ± 3°C), accelerated (25 ± 2°C/60 ± 5% RH) and stressed (40 ± 2°C/75 ± 5% RH) conditions. Photostability studies were carried out in accordance with ICH Q1B. A stability protocol has been provided and studies will be continued through 48 months. The stability studies have been performed in same container closure system intended to be used for commercial manufacture. The parameters tested during stability and associated acceptance criteria are the same as for release, apart from the wider limits for product-related impurities throughout shelf-life and apart from tests for identity and for endotoxin which are performed only at release. Sterility and extractable volume are tested only at the end of shelf-life and not tested during stability. Overall, the provided stability protocols are acceptable.

Real-time stability data are provided up to 24 months for the clinical Process 3 batch, up to 12 months for the three clinical Process 4 batches and up to 9 months for the PPQ batch. In addition, real-time stability data are provided up to 48 months for the supportive GMP Process 3 batch.

The results to date from all long-term stability studies demonstrate that all tested criteria are within specification with no significant trends, apart from a slightly increase in charge variants observed for the supportive GMP Process 3 batch.

Data from the accelerated and stressed conditions studies support the stability indicating profile and the suitability of the analytical methods. The results for the photostability study indicate that light exposure does not have an impact on the quality of the finished product. Nevertheless, as a precautionary measure, a recommendation to avoid direct exposure of the product to light is included in the SmPC. This is considered acceptable.

Overall, based on the currently available data, a shelf-life of 12 months can be granted for the finished product stored at the recommended condition of 2 - 8°C, in the CCSs described in the dossier. Compatibility of the finished product with the infusion medium (0.9% sodium chloride solution) and in-use stability studies for the diluted finished product have been discussed in the Pharmaceutical development section of this report and support the instructions in the SmPC (i.e. *Chemical and physical in-use stability has been demonstrated for 72 hours at 2 to 8 °C and for 4 hours at up to 25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and*

would normally not be longer than 24 hours at 2 to 8 °C, unless reconstitution/dilution (etc.) has taken place in controlled and validated aseptic conditions.

2.3.3.5. Adventitious agents

TSE statements have been provided for materials used in the production of the active substance and no materials of animal or human origin are used for the manufacture of vilobelimab active substance and finished product. Information has also been provided for media components used for establishing of MCB and WCB. Overall, acceptable information has been provided, confirming compliance with the Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal products (EMEA/410/01 Rev. 3).

Information on virus testing of cell banks is presented in the active substance section on Control of materials. The results are as expected for CHO-cells, with some RT-activity and presence of A- and C-type RVLPs and no evidence of adventitious microbial or viral contamination. Results from IPCs testing of the active substance unprocessed bulk (UPB) has also been provided and this includes several tests for adventitious virus such as an in vitro assay for adventitious virus and detection of minute virus of mice (MVM) DNA, demonstrating that no adventitious viral agents were detected in the batches manufactured to date. Summaries of the test methods and validation results have been provided. The information is acceptable.

A summary of the virus clearance studies has been provided to demonstrate the ability of the four purification steps (Protein A chromatography, low pH, CEX and viral filtration) to remove or inactivate exogenously added model viruses. Sufficient information has been presented on choice of validated steps and the four model viruses used (Murine Leukaemia Virus - X-MuLV, Pseudorabies Virus - PRV, Minute Virus of Mice - MVM and Reovirus Type 3 - Reo-3). The model viruses chosen are acceptable as they cover a range of viral characteristics that can be resistant to clearance. The worst-case conditions for virus reduction applied in the respective step have been described in sufficient detail and justifications for the chosen conditions have also been given. Furthermore, sufficient description has been provided of the small-scale process, which is considered qualified and representative of the commercial scale process. The virus spiked runs were performed in duplicates and for the two chromatography steps, both new and used resins were included in the experiments. Data from the runs also includes information on mass balance and recovery to demonstrate the mode of virus removal in the chromatography steps. In addition, sufficient information was provided with regards to the cleaning and sanitisation steps for the two columns used, demonstrating appropriate prevention of cross-contamination of virus between batches. For the low pH step, data demonstrating the kinetics of inactivation has also been presented and is considered adequate. Calculation of RVLPs per dose has also been performed demonstrating a sufficient safety margin when using new resins in chromatography steps and when using aged resins.

Overall, the data presented demonstrates that adequate and sufficient steps have been taken to assure a safe product free from adventitious agents.

2.3.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied quality-by-design (QbD) principles in the development of the active substance and/or finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product.

Four MOs were raised during the assessment for the insufficient substantiation of the NAS claim, for the lack of valid EU GMP certificates for the two active substance manufacturing and testing sites in China and for the lack of process validation data for the finished product manufacturing process. The requested documentation/information were provided by the applicant by the time of CHMP opinion.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, which pertain to: finalisation of the active substance container leachable study, review of the active substance specification limits once data from a sufficient number of batches will be available and finalisation of the validation of shipping and labelling and secondary packaging activities prior to commercialisation of the finished product. These points are put forward and agreed as recommendations for future quality development.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.3.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The applicant commits to provide the updated results for active substance container leachable assessment when the study is concluded at the end of proposed shelf-life.
2. The applicant commits to review the active substance specification limits following the generation of additional data (n=30).
3. The applicant commits to update the dossier following completion of the validation of shipping and labelling and secondary packaging activities prior to placing the medicine on the market.

2.4. Non-clinical aspects

2.4.1. Introduction

The non-clinical development programme of vilobelimab is presented in below sections.

2.4.2. Pharmacology

2.4.2.1. Primary pharmacodynamic studies

Mechanism of action

Vilobelimab is a chimeric monoclonal immunoglobulin G4 (IgG4) antibody which specifically binds to soluble human C5a. Complement activation has been shown in lung and kidneys by autopsies of deceased patients with severe Covid-19. In addition, elevated C5a levels in plasma from severely ill Covid-19 patients has been reported in the literature. C5a is a strong anaphylatoxin and proinflammatory mediator that can attract neutrophils and other leukocytes to an ongoing infection. The treatment rational also gains support from a suggested role of C5a inducing neutrophil-driven lung damage.

The complement split product C5a is generated in the complement activation cascade through at least three well-described pathways (the classical, the alternative, and the lectin pathway). All pathways merge at the level of C3, which activates C5 convertase, leading to cleavage of C5 into C5a and C5b. The latter binds with C6, C7, C8, and multiple C9 molecules, ultimately leading to the formation of the terminal membrane attack complex (MAC) on the surface of pathogenic bacteria, which forms transmembrane channels in the bacterial cell membrane that lead to cell lysis and death. In addition to the cleavage of C5 by the C5 convertases, C5a can also be generated directly in the “extrinsic pathway” by the cleaving activity of naturally occurring enzymes, including but not limited to proteins of the coagulation pathways such as thrombin and plasmin.

Inhibition of upstream complement cascade components such as C3 and C5 results in specific blocking of C5 cleavage to C5a and generation of C5b, and thereby, blocks MAC formation. Preventing MAC formation results in an increased risk of infection. By selective blockage of the anaphylatoxin C5a, the MAC formation is intended to be left intact and the neutrophil bactericidal function thereby to be preserved. This has been shown in the literature to occur in septic animals treated with anti-C5a antibody.

Primary pharmacodynamics in vitro

The binding affinity of vilobelimab for human C5a was tested by different surface plasmon resonance (Biacore) methods. Different batches of vilobelimab were tested with similar results. A K_D of 0.51 nM were reported for the affinity of vilobelimab in solution for free recombinant human C5a (rhC5a), and a K_D of 9.6 pM for surface-coated vilobelimab binding to purified native human C5a in solution, respectively.

In order to test the vilobelimab affinity for C5a from various non-human species, without recombinant or purified C5a being available from these species, detection of CD11b up-regulation on granulocytes in response to overproduced zymosan-induced endogenous C5a (eC5a) in plasma was used. If vilobelimab was able to bind to C5a from the tested animal species in a similar fashion as to human C5a, it would prevent the CD11b upregulation on granulocytes. This functional assay was used to determine that vilobelimab bound only to C5a in monkey and human plasma, but not to C5a from dog, rabbit and rat. Since recombinant murine C5a was commercially available, an ELISA was used to show that affinity of vilobelimab for murine C5a was approximately 15,000-fold lower than the vilobelimab affinity for human C5a. Based on these data and the low homology between mouse and human C5a (64%), mouse was also excluded as a relevant species for vilobelimab testing. Minipig was also excluded due to lack of assay reagent availability and low (68%) sequence homology to human C5a. In conclusion, Cynomolgus monkey was identified as the only currently available pharmacologically relevant experimental species for vilobelimab testing.

Two functional assays were used to demonstrate vilobelimab effect in human whole blood. C5a-induced CD11b expression on granulocytes, as analysed by flow cytometry; and C5a-induced lysozyme release by degranulation of blood cells, as detected by a lysozyme assay kit. A 7-fold increase of CD11b expression on peripheral blood granulocytes from healthy volunteers was observed upon rhC5a stimulation. The increased CD11b expression was suppressed by 95% and 94% in the presence of different batches of vilobelimab at a 1:1 antibody/antigen (Ab/Ag) ratio ($p<0.001$), and by 85% and

87% at ratio 0.5:1. A significant increase in lysozyme releases from human blood cells was also observed upon rhC5a stimulation, which was blocked by 99% by the addition of vilobelimab /C5a at molar ratios 1:1 and 96% at 0.5:1. The observed blocking was significant for all vilobelimab/rhC5a combinations in comparison to the stimulated but vilobelimab-free sample, $p<0.0001$. Vilobelimab alone and control IgG4 had no influence on lysozyme releases, and IgG4 control with various concentrations had no blocking effect on rhC5a-induced lysozyme releases in this assay. Vilobelimab also suppressed endogenous C5a (eC5a) induced CD11b up-regulation. The eC5a-induced CD11b upregulation was comparable to rhC5a-induced CD11b up-regulation. As a source of eC5a was used zymosan activated plasma (from 8 different donors).

By allowing vilobelimab to be present during the C5a-mediated CD11b upregulation on granulocytes, it was tested whether vilobelimab could compete with the natural ligands to C5a. In addition, no direct binding of fluorescence (FITC)-labelled vilobelimab to the surface of neutrophils, or bridged binding to neutrophils via receptor-bound C5a or any binding of pre-formed vilobelimab/C5a complex to neutrophils could be detected by flow cytometry.

The influence of C5 on the binding of rhC5a was also evaluated in an *in vitro* system. After pre-incubation of vilobelimab with whole blood or plasma, where C5 is expected to be present at high concentration, vilobelimab retains its ability to reduce rhC5a-induced CD11b levels, albeit with a lower activity compared to conditions without pre-incubation. The possible causes for this decrease in activity were discussed by the applicant: (1) degradation of the antibody by proteinases; (2) non-specific binding to Fc receptors on blood cells and/or (3) binding to plasma proteins such as C5. However, the estimated molar ratio of plasma C5 (final concentration: 267 nM) to vilobelimab for this assay is 16:1. Despite the high level of C5 in the whole blood, vilobelimab is still effective in blocking rhC5a-induced CD11b up-regulation. Therefore, the influence of plasma C5 on vilobelimab blocking activity on C5a in this assay can be considered to be minor and vilobelimab to be relatively stable in human whole blood. On this regard, the effect of vilobelimab on terminal MAC formation following complement activation was analysed in human and monkey plasma samples. No changes in haemolytic activity were observed following the addition of 50 µg/ml vilobelimab, but the maximum concentration tested is lower than the estimated C_{max} in COVID-19 patients and a decrease in CH50 has been described in the toxicity studies in monkeys and in clinical trials.

Elevated complement factors (C3a, C5a and C5b-9) were identified in Hidradenitis suppurativa (HS) patient plasma. The mean eC5a level of the patient group was 36 ng/mL, which is 1.63-fold higher than that of the control group (22 ng/mL). Vilobelimab, at 5, 20, 50 nM, was able to completely prevent CD11b upregulation induced also by this source of eC5a.

To assess the efficacy of vilobelimab in a setting closer to clinical septicaemia, an *ex vivo* whole blood infection model was employed, where whole blood is stimulated with live E.coli leading to complement activation and a subsequent high production of C5a, which in turn promotes inflammatory mediator release such as IL-8. Co-incubation with vilobelimab, at 200 and 400 but not 100 nM, was able to partly but significantly reduce the resulting IL-8 release ($p<0.01$). In a model with zymosan stimulation of whole blood, vilobelimab appeared to have a similar IL-8-reducing effect but experimental details were lacking, and no statistical analysis was provided.

C5a is rapidly dearginated by serum carboxypeptidase N to the C5a-desArg derivate. According to the applicant, it is considered that C5a-desArg is less potent and displays the first stage in deactivation of the anaphylatoxin activity. Nevertheless, no difference was observed between the binding properties of vilobelimab to rhC5a-desArg and rhC5a.

Neutrophil-specific immune complexes, consisting of rabbit anti-human polymorphonuclear neutrophils (PMN) polyclonal antibodies (pAB) + anti-rabbit IgG, were shown to dose-dependently stimulate C5a production (up to 7-fold of normal plasma level) followed by CD11b upregulation in whole blood. Anti-

PMN antibodies alone did not show this effect. Vilobelimab at 10 ug/ml sharply reduced the presence of free C5a and completely blocked the induction of IC-driven CD11b expression. This indicates that the upregulation of CD11b in the presence of ICs indeed was driven by the complement factor C5a. PMN non-specific ICs were also shown to induce C5a followed by CD11 upregulation but to a lesser extent than the PMN specific ICs did.

Immune complexes were shown to also drive IL-6 and IL-8 release in whole blood. Vilobelimab at 10 ug/ml reduced the detected IL-6 levels by 24% and 67% for non-PMN-specific and PMN -specific ICs, respectively (no statistical significance testing reported). Vilobelimab, at 40 µg/ml, reduced the non-PMN-specific IC-stimulated IL-8 level to lower limit of detection and significantly reduced the IL-8 level in the PMN-specific IC-treated cells (p=0.0007). In the presence of 80 µg/ml vilobelimab, both the non-PMN and PMN-specific IC stimulated IL-8 upregulation was suppressed to lower limit of detection.

In order to test the vilobelimab affinity for C5a from various non-human species, without recombinant or purified C5a being available from these species, detection of CD11b up-regulation on granulocytes in response to overproduced zymosan-induced endogenous C5a (eC5a) in plasma was used. If vilobelimab was able to bind to C5a from the tested animal species in a similar fashion as to human C5a, it would prevent the CD11b upregulation on granulocytes. This functional assay was used to determine that vilobelimab bound only to C5a in monkey and human plasma, but not to C5a from dog, rabbit and rat. Since recombinant murine C5a was commercially available, an ELISA was used to show that affinity of vilobelimab for murine C5a was approximately 15,000-fold lower than the vilobelimab affinity for human C5a.

Based on these data and the low homology between mouse and human C5a (64%), mouse was also excluded as a relevant species for vilobelimab testing. Minipig was also excluded due to lack of assay reagent availability and low (68%) sequence homology to human C5a. In conclusion, Cynomolgus monkey was identified as the only currently available pharmacologically relevant experimental species for vilobelimab testing, However, available information about the CD11b assays performed with human and monkey C5a did not allow to compare the potency of vilobelimab in different species (e.g. the concentration of vilobelimab is described in the monkey assay, while the viloberlimab:eC5a ratio is described in the human assay). Upon request the applicant has provided the antibody concentrations used in *in vitro* studies performed on human samples. These data allow a comparison of the potency of vilobelimab in similar experiments in human and monkey systems and demonstrated that the blocking activity of vilobelimab seems to be higher in human than in monkey systems, but the differences are not considered significant. Vilobelimab was found to be stable in cynomolgus monkey plasma as detected by a rhC5a based ELISA. Primate plasma obtained during the dose-range finding and the repeat-dose toxicity studies was able to block C5a-induced CD11b expression on human granulocytes. The results indicate that vilobelimab is functional in primate plasma samples for up to 10 days after single injection and for up to 6 weeks after repeated injection.

Primary pharmacodynamics in vivo

Given that vilobelimab cross-reacted only to monkey C5a and the nature of the proposed indication, no pharmacodynamic *in vivo* study was conducted.

Nevertheless, supportive data was provided from a monkey model of acute lung injury induced by the H7N9 virus. In this model, treatment with vilobelimab at 5 mg/kg significantly reduced viral titres in the lungs and lung damage measured by HE staining, in the treated monkeys on day 3 post-infection, compared to the control animals. In addition, the levels of IL-1B, IL-e, IP-10, IFN-γ, TNF-α and MCP-1 were significantly reduced after treatment, indicating that treatment with vilobelimab reduced the inflammatory response in infected monkeys. In addition, immunohistochemical analysis of macrophage and neutrophil infiltration in the lungs revealed that the treated animals had fewer infiltrating cells in the lungs. Elevated levels of the complement cleavage product C5a during SARS-CoV2 and H7N9

infection have been described in the literature, which provide support for using an H7N9 infection model in the context of immune inflammation mediated by SARS-CoV2 infection. Nevertheless, only a single dose of vilobelimab was tested in this study, with a C_{max} of about 40 µg/ml. This value is much lower that the estimated in COVID-19 patients.

2.4.2.2. Secondary pharmacodynamic studies

To assess whether free or surface-bound vilobelimab or vilobelimab in complex with rhC5a can induce cytokine release in human whole blood, whole blood was incubated with 100, 500 or 1000 nM of vilobelimab or vilobelimab that was coated to a 96-well plate at 62.5, 125, 250 or 500 µg/ml, or C5a/vilobelimab complex at 100, 500 or 1000 nM. After a 4-hour incubation at 37°C, cytokine levels of IL-6, IL-8 and tumour necrosis factor-alpha (TNF-a) in the supernatants were analysed using commercial ELISA kits. While LPS, as a positive control, induced a significant production of IL-6, IL-8 and TNF-α, soluble vilobelimab or surface bound vilobelimab had no effect on these cytokine releases at all tested concentrations. After stimulation of human whole blood with vilobelimab/rhC5a complex preparations, low levels of TNF-a were observed, as well as after stimulation with 1000 nM rhC5a or vilobelimab not in complex. In the light of that the stimulation with LPS caused up to 10 times higher TNF-a levels, the applicant suggests these results are negligible. It is also noted, that the vilobelimab/rhC5a IC stimulated TNF-a level was similar or lower than the levels after stimulation with rhC5a only. Moreover, since the isotype of vilobelimab, IgG4, is known to have no complement fixation property, and binding to Fc receptors are weak, no substantial inflammatory responses induced by vilobelimab in human whole blood were expected by the applicant. However, IgG4 immune complexes appear not completely inflammatory inert since deposits in tubular basement membranes associated with tubulointerstitial nephritis (TIN) have been reported in the literature. In addition, a potential IC associated, and anti-drug antibody (ADA) related fatal case in the current 26-week study is discussed in the toxicological section.

2.4.2.3. Safety pharmacology programme

Extended core battery safety pharmacology examinations/tests and histological analysis was incorporated into the cynomolgus monkey toxicity studies, i.e. in the 2- and 26-week repeat-dose toxicity studies. The endpoints included central nervous system (CNS) examination, electrocardiogram (ECG), blood pressure evaluations and respiratory rate examinations. In addition, a voltage clamp hERG assay with CHO hERG Duo cells and manual patch-clamp technique was conducted.

No vilobelimab-related safety concerns were detected in the performed studies for the (CNS), the cardiovascular system or the respiratory system. Based on these results, the applicant claim no adverse effects in humans would be expected. However, in the 2-week toxicity study where CNS and respiratory tests were carried out, there was no or very low marginal to the clinical exposure (AUC) at 800 mg (see toxicology section).

2.4.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies with vilobelimab were reported, which is accepted.

2.4.3. Pharmacokinetics

The non-clinical pharmacokinetics of vilobelimab after single and repeated administrations have been conducted in dose-range and repeat-dose toxicity studies and in an enhanced pre-and postnatal development (ePPND) in cynomolgus monkeys. The assays used for quantification of vilobelimab and

ADA detection in pivotal toxicology studies was appropriately conducted in line with GLP and fulfilled all acceptance criteria.

In the DRF study only 1 animal/sex were in each dose group, so the relevance of the pharmacokinetics (PK) data from this study is limited.

In monkeys, the exposure increased in a slight over proportional manner with no obvious differences between genders. Higher variability in dose proportionality was observed after repeated dosing. For example, the C_{max} and AUC increased more than dose-proportional between 1 and 15 mg/kg but not between 15 and 50 mg/kg in the 2-week toxicity study, while the AUC also increased more than dose proportional between 15 and 50 mg/kg after 26 weeks of treatment. Accumulation of vilobelimab was observed after multiple doses. Accumulation ratio increased with dose (from 1.2 at 15 mg/kg to 1.5-1.7 at 50 mg/kg in the 2-week toxicity study) and treatment duration (from 1.2-1.7 after 2 weeks of treatment to 2.6 after 13 weeks of treatment).

In the 2-weeks study the AUC exposure increased 3 to 4-fold after a recovery period of 58 days, as expected according to the half life ($T_{1/2}$)(4.1-7.7 days) calculated in the 26-week repeated dose toxicity study. No toxicokinetics (TK) evaluation was done in recovery animals of the 26-week study. The observed t_{max} at 50 mg/kg ranged from 41.6 to 163 hours. No ADAs were found in treated animals, however with the plausible exception for the early terminated female animal in the 26 weeks, while ADA-positive adult females and infants were found in the ePPND study.

Distribution, metabolism and excretion data have not been conducted as the metabolic pathways of monoclonal antibodies can be regarded as well characterised and understood.

2.4.4. Toxicology

A limited toxicology programme with vilobelimab has been evaluated in non-clinical studies in agreement with relevant guidelines (ICH M3, ICH S6).

The toxicity profile of vilobelimab has been characterised in cynomolgus monkey via an acute toxicity study, repeat-dose toxicity studies for up to 26 weeks with a 6-week recovery period and in an enhanced pre-and postnatal development (ePPND) toxicology study with a 3-month postnatal evaluation. Safety pharmacology, male and female fertility and local tolerance was investigated as part of repeated toxicology studies.

As vilobelimab has not demonstrated cross-reactivity in species other than humans or non-human primates, toxicological studies were only conducted in non-human primates (Cynomolgus monkey),

All pivotal toxicology studies were conducted in compliance with GLP regulations. The intravenous (IV) route of administration was utilised in all toxicology studies to match the intended clinical dose.

2.4.4.1. Single dose toxicity

In a DRF toxicology study vilobelimab was well tolerated at single doses up to 50 mg/kg. However, as there was only 1 animal/sex per dose group the relevance of the data from this study is limited.

2.4.4.2. Repeat dose toxicity

In support of chronic administration in humans, repeated dose studies have been conducted for up to 26 weeks, in which vilobelimab was administered once weekly by intravenous infusion. Chronic administration is not expected in COVID-19 patients; on the contrary a more intensive dosing regimen was chosen during the first week of treatment (days 1, 2, 4 and 8). From a non-clinical point of view,

the safety of this regimen would be supported by the 2-week subchronic toxicity study with repeated administration of vilobelimab on days 1, 2, 8 and 15. Toxicokinetic and ADA evaluation was included in all three studies. As part of the 2- and 26 weeks studies safety pharmacology, CH50 (total haemolytic complement activity, tested at 50% lysis of red blood cells) measurements indicating the capability to generate MAC through the classical complement pathway-mediated C5 activation, evaluation of immunoglobulins and cytokines, and PD analysis was included. In addition, analysis of complement factors (C4d and Bb) and circulating immune complex (CIC-C1q) in plasma was included in the 26-weeks study.

No treatment related changes on organ weight, food and drinking, water consumption, haematological and biochemical parameters, and no bone marrow and histopathological findings was observed. The measured immunoglobulins, cytokines, complement factors and circulating immune complex in plasma serum revealed no significant treatment-related changes. A reduction in body weight was noted in treated animals in all three studies. However, this reduction was slight and/or not statistically significant and is not considered treatment related.

Concerning mortality, in the 26-weeks study, one high dose female died on test day 71. Plasma samples were taken from this animal (from day 43) which revealed the presence of vilobelimab specific ADAs which further was not confirmed using another assay (C5a-based PK ELISA assay). Further, a histopathological examination was undertaken to investigate the presence of immune complex associated signs such as vasculitis and glomerulonephritis in the kidney and liver of the animal. The findings revealed a potential sign of an immune-mediated reaction. The available CH50 data (from day 43) revealed no decrease in CH50 and therefore no signs of C5 depletion / complement activation at this time point

CH50 was slightly reduced in male and female animals treated with 15 or 50 mg/kg vilobelimab compared to control animals. Similarly, in humans, CH50 tended to decrease slightly during treatment with vilobelimab, but generally remained above the lower normal range and returned to baseline values after dosing. Based on pharmacology studies, binding of vilobelimab to C5 cannot be ruled out and this non-specific binding could explain the CH50 reduction observed in monkeys and humans.

The PD analysis showed that vilobelimab was almost fully functional in animals dosed at 15 and 50mg/kg in both 2- and 26-weeks studies. Vilobelimab blocking of C5a ranged approximately from 91% to ≤100% at these doses.

2.4.4.3. Genotoxicity

Vilobelimab is a recombinant protein made up entirely of naturally occurring amino acids and contains no inorganic linkers, synthetic organic linkers or other non-protein portions. Therefore, vilobelimab would not react directly with DNA or other chromosomal material and no genotoxicity studies have been conducted.

2.4.4.4. Carcinogenicity

No carcinogenicity studies were conducted. This was justified by that the high molecular weight of monoclonal antibodies, such as vilobelimab, cause a low risk for a genetic damage to patients. Further, no signs of treatment related neoplastic proliferative lesions were observed in the repeated toxicology studies.

2.4.4.5. Reproductive and developmental toxicity

The applicant has not conducted a separate fertility and early embryonic studies as the male and female reproduction organs was evaluated sexually matured monkey in the 13- and 26-weeks repeated toxicology studies.

Male fertility was assessed in 3 animals/group dosed at 0, 15 and 50 mg/kg/week for 13-weeks aged 4.9-7.9 years and included testicular volume, semen evaluation, organ weights of reproductive organs, and histopathologic evaluation of reproductive tissues. No treatment related findings were observed. However, a significant increase in percent abnormal sperm (coiled or bent tails) was noted in animals in the low (+4.3%) and high (+1.8%) dose groups compared to the control group (+0.8%). This is explained by individual variation in as one low-dose male influenced this mean individually with 7.5% abnormal sperm and had a percentage of abnormal sperm greater than 5% compared to 1.5% and 2.5% for the other low-dose males, during the first pre-study collection.

Female fertility was assessed in 3 animals/group at 0, 15, and 50 mg/kg/week for 26-weeks aged 3.7-4.3 years and included examination of oestrus cycles, and organ weights, macroscopic examination and histopathological evaluation of reproductive organs. Sexual maturity was evaluated by monitoring their oestrus cycles throughout the study. It was concluded that almost all female animals on the study were sexually mature or gained sexual maturity during the study. No treatment related changes of organ weights or histopathological findings of the reproduction organs were observed.

An enhanced pre- and postnatal development study was conducted in cynomolgus monkeys dosed at 0, 15 and 50 mg/kg/week from GD20-22 until parturition (GD165 +/- 10). No treatment related maternal toxicity or teratogenic effects, concerning aborted fetuses, or died/euthanised early infants or surviving infants were observed. ADAs were detected during the gestation period in three low dose (15 mg/kg) and one high dose (50 mg/kg) adult females. The number of ADA-positive females increased at postpartum, where 10 low-dose (15 mg/kg) and 7 high-dose (50 mg/kg) adult females were ADA positive. ADA was also detected in 2/14 (15 mg/kg) and 1/14 (50 mg/kg) infants most likely due to the known transfer of maternal antibodies to the fetus during the late gestation period and/or colostrum. The plasma concentrations in ADA-positive animals were similar compared to ADA-negative animals (for both adult females and infants), indicating that ADA did not impact vilobelimab exposure. Of note, the predictivity of development of ADAs towards a human protein in nonclinical test species to the clinical situation is low. The NOAEL was set to 50 mg/kg/week.

2.4.4.6. Toxicokinetic data

Toxicokinetic analysis was performed in the repeat toxicology studies and the ePPND study. In the 2-weeks study, where animals were administrated the same regimen as in the clinic, there was no significant difference in exposure between genders and slight over-proportional AUC exposure and accumulation at 50 mg/kg were seen. However, in male and female recovery animals the $AUC_{0\text{-}inf}$ exposure increased with 3 to 4-fold, as expected according to the $T_{1/2}$ (4.1-7.7 days) calculated in the 26-week repeated dose toxicity study. No obvious gender difference and a slight over-proportional AUC exposure at 50 mg/kg was also seen in the 26-weeks study. The applicant provided no toxicokinetics from recovery animals in this study.

In dams in the e-PPND study the AUC and Cmax exposure was dose-proportional at gestation Day (GD) 20 and GD 140. However, the exposure appears to be low compared to females in the 26-week study. Exposure was observed in F_1 infants that was decreased with time from PND28 (postnatal day) to PND183 and no apparent gender differences were observed on all postnatal days.

The (No observed adverse effects level (NOAEL) in cynomolgus monkeys for systemic and developmental effects is 50 mg/kg. However, exposure level predictions based on the population PK model cannot be considered reliable for the estimation of safety margins.

2.4.4.7. Local tolerance

Local tolerance was evaluated as part of the general toxicity studies. In these studies, vilobelimab was formulated in PBS with 0.05% Tween 80, pH 7.0 and administrated by 30-minute or 1 hour iv infusion at doses of up to 50 mg/kg for a duration of up to 26-weeks (26 doses). No local irritation was observed in neither study.

2.4.4.8. Other toxicity studies

A tissue-cross reactivity study was performed with vilobelimab using a full panel normal tissues from 3 human donors and 2 cynomolgus monkey donors revealed a widespread staining pattern. This is expected since C5 is largely present and C5a is generated after death by unspecific complement activation in the circulation and within the tissues in the post-mortem subjects, and subsequently deposited on tissues and on cells. It is agreed that this is a positive artefactual staining. It can be concluded that this TCR study is inconclusive.

2.4.5. Ecotoxicity/environmental risk assessment

A justification for not submitting environmental risk assessment data have been submitted by the applicant. The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, vilobelimab is not expected to pose a risk to the environment.

2.4.6. Discussion on non-clinical aspects

The pharmacological characterisation of vilobelimab comprised studies in which the binding affinity to human C5a was investigated using (surface plasmon resonance) SPR. The results showed a K_D of 0.51nM for recombinant human C5a (rhC5a) and a K_D of 9.6 pM for purified native human C5a. The binding affinity to non-human primates was not investigated. Therefore, the choice of species was based on the results of a potency study investigating CD11b upregulation on granulocytes of different animal species in response to overproduced endogenous C5a (eC5a) in blood after addition of Zymosan A. The study concludes that vilobelimab is able to block the effects of primate-derived C5a, but not of other species, and provides a rationale for identifying the cynomolgus monkey as the only relevant species for toxicity assessment, which is agreed. However, a direct comparison with human-derived C5a was not performed in the study. Upon request the applicant has provided the antibody concentrations used in in-vitro studies performed on human samples. These data allow a comparison of the potency of vilobelimab in similar experiments in human and monkey systems and demonstrated that the blocking activity of vilobelimab seems to be higher in human than in monkey systems, but the differences are not considered significant.

Given that vilobelimab cross-reacted only to monkey C5a and the nature of the proposed indication, no pharmacodynamic in vivo study was conducted. This strategy was accepted in a CHMP scientific advice and is further supported.

Presence of vilobelimab at low nM concentration prevented CD11b upregulation, therefore it was concluded that vilobelimab successfully compete with the natural ligands in whole blood for both

recombinant and eC5a. The provided ex-vivo studies in whole blood is considered sufficient to show vilobelimab is efficacious in blocking the activity of C5a and no further preclinical studies are required.

No vilobelimab-related safety concerns were detected in the performed studies for the central nervous system (CNS), the cardiovascular system or the respiratory system, as integrated in the repeat-toxicological studies. Based on these results, the applicant claimed that no adverse effects in humans would be expected. However, in the 2-week toxicity study where CNS and respiratory tests were carried out, there was no or very low marginal to the clinical exposure (Cmax). Thus, the performed safety pharmacology evaluation of CNS and respiratory system at the actual exposure levels is of limited value.

The non-clinical pharmacokinetics of vilobelimab after single and repeated administrations has been conducted in dose-range and repeat-dose toxicity studies and in an ePPND in cynomolgus monkeys. The assays used for quantification of vilobelimab and ADA detection in pivotal toxicology studies was appropriately conducted in line with GLP and fulfilled all acceptance criteria.

The toxicity of vilobelimab has been tested in 2- 13- and 26-weeks repeat-dose studies and an ePPND study in cynomolgus monkey at doses up to 50 mg/kg. Overall, vilobelimab was well-tolerated and no treatment related adverse effects or findings was observed in most of the parameters evaluated that also included pharmacodynamic activity (C5 blockade), safety pharmacology, immunogenicity and immunotoxicity, autoimmunity, and effects on cytokines, complement factors and circulating immune complex.

CH50 was slightly reduced in male and female animals treated with 15 or 50 mg/kg vilobelimab compared to control animals. Similarly, in humans, CH50 tended to decrease slightly during treatment with vilobelimab, but generally remained above the lower normal range and returned to baseline values after dosing. Based on pharmacology studies, binding of vilobelimab to C5 cannot be ruled out and this non-specific binding could explain the CH50 reduction observed in monkeys and humans.

According to the applicant, the high levels of ADA and potential IC formation suggest an ADA-mediated immune reaction occurring after repeated-dosing of vilobelimab. The CHMP agreed that the cause of death in animal study is likely due to ADA-mediated immune reaction and thus, of low relevance to humans.

The assessment of male and female fertility was conducted as part of the 13- and 26- weeks studies, respectively. From a 3R (replacement, reduction and refinement) perspective, the relevance for conducting the 13-weeks study could be questioned as this study was conducted after the 26-weeks study which could include assessment of male fertility.

In conclusion, the NOAEL in cynomolgus monkeys for systemic and developmental effects is 50 mg/kg.

As the clinical concerns regarding to the population PK model have not been solved, predictions based on this model cannot be considered reliable for the estimation of safety margins. This limitation is adequately described in the section 5.3 of the SmPC.

No carcinogenesis nor mutagenesis studies have been conducted which is acceptable due to the nature of vilobelimab and its short-term duration of use.

2.4.7. Conclusion on non-clinical aspects

The SmPC adequately reflects non-clinical data. From a non-clinical point of view, the pharmacologic, pharmacokinetic and toxicological characterisation is considered appropriate and in support of the approval of Gohibic.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

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

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 3: Summary of clinical studies with vilobelimab

Study Number; Phase; Status	Study Design and Patient Population	Treatment (number of patients for vilobelimab)	Vilobelimab material	PK Data
IFX-1-P2.9 Phase II/III; Completed* PANAMO	Adaptive, randomised, multicentre study in adults with severe or critical COVID-19 pneumonia: Phase III part in critical COVID-19 requiring invasive ventilation	Phase II: Vilobelimab (n = 15) 800 mg i.v. infusion at days 1, 2, 4, 8, 11/12/13 if needed, 15, and 22, when still in hospital. Phase III: Vilobelimab (n=177) 800 mg i.v. infusion or matching placebo (n = 191) at days 1, 2, 4, 8, 15, and 22 as long as in hospital	DS process 5, DP process 3	Sparse PK, Phase III: D8 & day of hospital discharge
IFX-1-P1.1 Phase I Completed	Dose escalation, placebo-controlled, double-blind in healthy volunteers	Single dose vilobelimab (n = 15; 0.02, 0.1, 0.5, 2, 4 mg/kg) or placebo	IFX-v-1*	Rich PK
IFX-1-P2.1 Phase II Completed SCIENS	Randomised, placebo-controlled, double-blind study in patients with early septic organ dysfunction	Vilobelimab: n=48 (16 per cohort) Cohort 1: 2 doses of 2 mg/kg vilobelimab or placebo over 12h Cohort 2: 2 doses of 4 mg/kg vilobelimab or placebo over 24h Cohort 3: 3 doses of 4 mg/kg vilobelimab or placebo over 72h For subjects >100 kg the dose was based on 100 kg BW	IFX-v-2*	Rich PK until D4
IFX-1-P2.2 Phase II Completed	Randomised, placebo-controlled, double-blind study in patients undergoing complex cardiac surgery	Single dose Cohort 1: 1 mg/kg vilobelimab (n=23)/ placebo Cohort 2: 2 mg/kg vilobelimab (n=18)/ placebo Cohort 3: 4 mg/kg vilobelimab (n=21)/ placebo Cohort 4: 8 mg/kg vilobelimab (n=20)/ placebo	IFX-2016-01*	Rich PK after the surgery
IFX-1-P2.3 Phase II Completed	Open-label study in patients with HS	9 doses of 800 mg (days 1, 4, 8, 15, 22, 29, 36, 43, 50) n=12	IFX-2016-03, IFX-2016-04*	Included in popPK
IFX-1-P2.4 Phase II Completed	Randomised, placebo-controlled, double-blind study (with OLE) in patients with moderate to severe HS	Main Period Induction Phase (2 wk): Cohort 1: placebo, Cohort 2: vilobelimab 400 mg Day 1,4; (n=34), Cohort 3: vilobelimab 800 mg Day 1,4,8; (n=35), Cohort 4: vilobelimab 800 mg Day 1,4,8,15; (n=36), Cohort 5: vilobelimab 800 mg Day 1,4,8, 1200 mg D15; (n=36) Maintenance Phase (from day 29 for 14 wks):	Numerous batches, all DS process 3 and DP process 3	Sparse PK, subgroup with rich PK Included in popPK

		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: Wk 16 HiSCR responders (n=72): OL vilobelimab 800 mg Q4W (from day 141 for 20 wks) Wk 16 HiSCR non-responders (n=84): 1-3 x vilobelimab 800 mg DB induction in 2 wk, OL Vilobelimab 800 mg Q2W (from day 141 for 20 wk)		
IFX-1-P2.5 Phase II Completed	Randomised, double-blind, double-dummy, active-controlled, 2-part in adult patients with GPA or MPA	16-week treatment period. Group A: vilobelimab 800 mg + reduced dose GC Group B: Placebo-vilobelimab + standard dose GC Group C: vilobelimab 800 mg + Placebo – GC Vilobelimab: intravenous, 800 mg at days 1, 4, 8, 15, 29, 43, 57, 71, 85, 99,113	Numerous batches, all DS process 3, DP process 2	Sparse PK
IFX-1-P2.6 Phase II Completed	Randomised, double-blind, parallel group, placebo-controlled, in adult patients with GPA or MPA	16-week treatment period days 1, 4, 8, 15, 29, 43, 57, 71, 85, 99, 113 Group A: vilobelimab 400 mg + SoC (n=7) Group B: vilobelimab 800 mg + SoC (n=6) Group C: Placebo + SoC (n=6)	Numerous batches, all DS process 3, DP process 2	Sparse PK
IFX-1-P2.7 Phase IIa Completed	Open-label, exploratory study in adults with an ulcerative form of PG	800 mg vilobelimab on: Days 1, 4, 8, followed by Q2W dosing starting on Day 15 with either 800mg, 1,600mg or 2,400mg up to Day 179 intravenously	Numerous of unclear DP and DS process*	Sparse PK
IFX-1-P2.8 Phase II Ongoing	Open-label, 2-arm, parallel group Phase II study of vilobelimab alone or vilobelimab + pembrolizumab in patients with anti-PD-1- or anti-PDL1-treatment resistant/refractory locally advanced or metastatic cSCC	Arm A: Vilobelimab 800 mg on days 1, 4, 8, 15 followed by 1600 mg q2w from day 22. Arm B: Safety run in part: 3 escalating vilobelimab doses in combination with fix dose pembrolizumab (400 mg q6w): Vilobelimab 400 mg, 600 mg, or 800 mg on days 1, 4, 8, 15 followed by 800 mg,	N/A	N/A

		1200 mg, or 1600 mg q2w from day 22. Phase 2 part: vilobelimab MTD + pembrolizumab 400 mg q6w.		
IFX-1-P3.4 Phase III Ongoing	A randomised, double-blind, placebo-controlled, multicentre, adaptive phase III trial to investigate efficacy and safety of vilobelimab in the treatment of ulcerative pyoderma gangrenosum	Arm 1: Patients will be treated with vilobelimab 2400 mg IV, Q2W for 26 weeks (with last administration scheduled at Week 24). Arm 2: Patients will receive placebo IV in the same schedule as patients in Arm 1.	N/A	N/A

BSC = best supportive care, cSCC = Cutaneous squamous cell carcinoma, GPA = granulomatosis with polyangiitis, HiSCR = Hidradenitis Suppurativa Clinical Response, HS = hidradenitis suppurativa, i.v. = intravenous, MPA = Microscopic polyangiitis, OL = open-label, PD-1/PD-L1 = Programmed death receptor 1 / Programmed death-ligand 1, PG = pyoderma gangrenosum, GC= glucocorticoids, qw = every week , Q2W = every 2 weeks, Q3W = every 3 weeks, Q4W = every 4 weeks, Q6W = every 6 weeks, SoC = standard of care, wk = week(s).
*The DS and DP process number could not be identified by the assessor based on the provided documentation.

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

Vilobelimab (IFX-1, CaCP29) is a first-in-class chimeric immunoglobulin (Ig) G4 monoclonal antibody which binds to the soluble human complement cleavage product C5a after cleavage from C5 while leaving C5b generation and the associated membrane attack complex (MAC) formation intact.

Vilobelimab is intended for treatment of adult patients with SARS-CoV-2 induced septic acute respiratory distress syndrome (ARDS) receiving invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation. The intended posology is 800 mg vilobelimab given as a 30 to 60 minutes iv infusion within 48h of intubation. A maximum of 6 doses are to be administered, on day 1, 2, 4, 8, 15 and 22.

PK is available from studies listed in

Table 3, with exception of the studies that are still ongoing (2.8 and 3.4). Most studies are in other indications than the currently applied for indication, with widely different posologies. There are 6 versions of drug substance and 4 drug product processes, where DP 4 is the intended commercial product. The use of different processes in clinical studies are summarised in

Table 3 where it could be identified.

CHMP scientific advice was received regarding the integrated summary of immunogenicity, dose selection and PK and ADA analysis.

Methods

Quantification of vilobelimab

Concentrations of free vilobelimab in human plasma were determined using two validated ELISAs. Desarginated human C5a was used for capture of vilobelimab, and an anti-human IgG4 conjugated to HRP and TMD were used for detection, where the colorimetric signal was proportional to the vilobelimab concentration.

Immunogenicity

A standard multi-tiered approach consisting of screening, confirmation, and titre was developed to evaluate anti-drug antibodies (ADA). The neutralisation potential of ADAs was not assessed as the applicant considered vilobelimab to have a low immunogenic potential.

Three ADA methods (at Nuvisan, InflaRx and Eurofins) are available. All three ADA methods are bridging assays with similar principles. The bridging is either between ADA, a vilobelimab coated plate and biotinylated vilobelimab, or between ADA, biotinylated and ruthenylated vilobelimab. The confirmation assay consisted of signal depletion upon addition of free vilobelimab.

PK analysis

Standard non-compartmental analysis was performed in the early studies where rich sampling was applied, and population PK (popPK) was used for studies 2.3 and 2.4 in HS patients.

Population PK analysis

A popPK model was developed using data from HS patients and not covid-19 patients. The main application of the HS model are comparisons with Ctrough day 8 in covid 19 patients.

Traditional model selection using Nonlinear Mixed Effects Modeling (NONMEM, Version 7.3) with a covariate analysis using forward addition/backward elimination.

The final population PK model described the PK as two-compartment with parallel linear and Michaelis-Menten clearance (Table 4).

Table 4: Final popPK model in HS patients (top: fixed parameters; bottom: omega, standard deviation and correlation)

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

RSE is relative standard error = parameter estimate/standard error of the estimate

Parameter (units)	ETA(1) Vmax (mg/mL)	ETA(2) Central Volume of distribution (L)	ETA(3) Km (ng/mL)	ETA(4) Linear Clearance (L/hr)	ETA(5) IOV on Vmax
ETA(1) Vmax (mg/hr)	0.215 (0.304)	-	-	-	-
ETA(2) Central Volume of distribution (L)	0.257 (0.349)	0.298 (0.0731)	-	-	-
ETA(3) Km (ng/mL)	-0.305 (0.347)	-0.446 (0.17)	0.586 (0.149)	-	-
ETA(4) Linear Clearance (L/hr)	0.468 (0.172)	0.834 (0.0838)	-0.324 (0.276)	0.395 (0.0975)	-
ETA(5) Inter-occasion variability (IOV) on Vmax	-	-	-	-	0.0912 (0.158)

RSE is relative standard error = parameter estimate/standard error of the estimate

The population PK model developed in HS patients was used to simulate the time course of vilobelimab concentrations in virtual HS and COVID-19 patients. To construct virtual HS and virtual COVID-19 populations of 1000 subjects, individual covariates were randomly sampled from the distribution of observed covariate values in the respective populations. Hence, the potential correlations between the covariates were preserved. Furthermore, the following five covariates were retained in the model: age, body weight, BSC5A, EGFR and baseline IHS4 score (BSIHS). Of note, IHS4 is a scoring system designed to assess HS severity. IHS4 scores were assumed to be 0 for all the simulated COVID-19 subjects. Simulated and observed IFX-1 PK profiles in COVID-19 subjects are depicted in Figure 1. The data showed that the majority of the observed Ctrough at day 8 were included within the 95% PI of simulated data supporting the ability of the population PK model to adequately predict vilobelimab Ctrough in COVID-19 subjects. The simulated and observed distribution of IFX-1 Ctrough at day 8 in COVID-19 subjects are presented in Table 5.

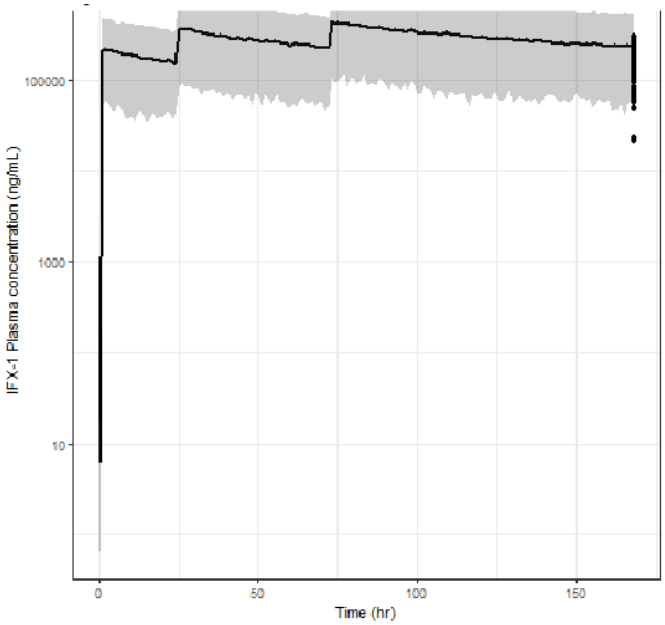


Figure 1: Simulated and observed vilobelimab c/t profiles in COVID subjects. The black line and the grey area represent the median and the 95% prediction interval (PI) simulated with the model. The black dots represent observed IFX-1 Ctrough at day 8 in COVID-19 patients.

Table 5: Observed and simulated Day 8 Ctrough in 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

Absorption

No in vitro dissolution, bioavailability, comparative bioavailability, or bioequivalence studies have been carried out with vilobelimab as it is administered as an intravenous infusion. No effect of food is anticipated.

Distribution

In the single ascending dose (SAD)study 1.1, Vz across doses 0.02-4 mg/kg was 0.0572-0.157 L/kg, with 0.0833 at the 4 mg/kg dose.

Elimination

No specific studies have been performed to characterise the elimination of vilobelimab. Vilobelimab is expected to be degraded into peptides and its constituent amino acids through proteolysis.

In the SAD study 1.1 (0.02-4 mg/kg, Table 6*)*, CL decreased with increasing doses with 0.01-0.06 mL/min/kg L/kg. T1/2 increased from 11h at the lowest dose to reach a plateau of 95-101h at the two highest doses.

Dose proportionality, time dependencies and immunogenicity

Dose proportionality was assessed in the SAD study IFX-1-P1.1 for all parameters at single doses 0.02-4 mg/kg. PK profiles and parameters are shown in Figure 2 and Table 6. While Cmax was nearly dose proportional, AUC_{0-t} and AUC_{0-inf} increased slightly more than dose-proportionally. For $t_{1/2}$ and CL, a dose-independence could not be concluded. For V_z, no dose-dependency was observed.

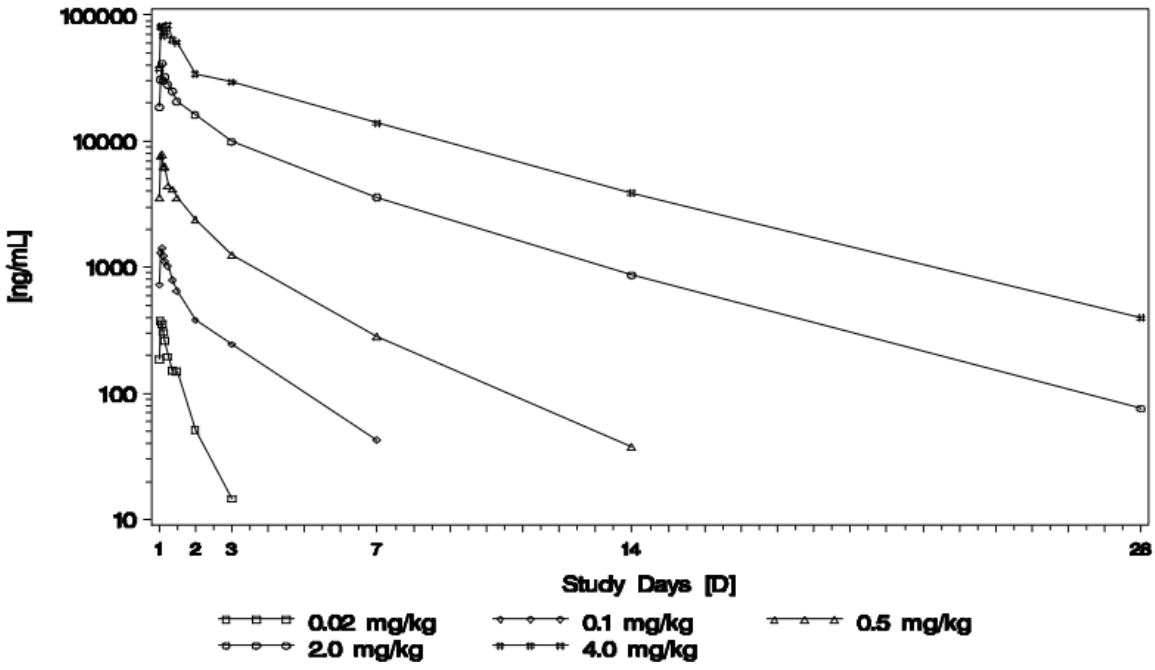


Figure 2: Vilobelimab concentration/time profiles in healthy subjects, Study IFX-1-P1.1

Table 6: Summary of vilobelimab PK parameters, study IFX-1-P1.1

		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)

[a] median and range, other parameters are mean (standard deviation); * N=2;

The applicant has not presented data on time dependency.

The risk assessment for vilobelimab immunogenicity is presented in Table 7. In the vilobelimab group of phase III study (2.9, PANAMO), 2.1% (2/95) were ADA positive at baseline. At the time of hospital discharge, one patient (1/32, 3%) had treatment emergent ADAs, with no reportable titre. For the remaining completed studies, excluding study IFX-1-P2.4, treatment emergent ADAs were detected in 3% of patients treated with vilobelimab (7/211 patients). In study IFX-1-P2.4 (HS), post-baseline ADAs were detected in 12% of patients treated with vilobelimab. Highest frequency of ADA positive patients was observed in the 400 mg Q4W and in the 800 mg Q4W groups.

Within all studies, only one of the ADA positive patients showed any clinical signs of hypersensitivity to vilobelimab.

Table 7: Immunogenicity risk assessment for vilobelimab

Immunogenicity risk factors		Low risk	Moderate risk		Higher risk
Product related factors	**Similarity to unique endogenous counterparts**	No similarity	Partial similarity		Complete similarity
	Degree of foreignness/Primary sequence	Fully human	Human with mutations	Partially human	Non-human
	Glycosylation pattern	Fully human	Partially human		Non-human
	Mode of action	Immunosuppressive	Not applicable		Immunostimulatory
Process related risks (CMC)	**Expression system**	Mammalian			Yeast/Bacterial
	Aggregates	Relatively low level	To be determined		Relatively high level
	Impurities	Relatively low	To be determined		Relatively high level
Posology related risks	**Route of administration**	IV	IM	IP	SC/Inhaled
	Dosing regimens	Single dose	Multiple dosing	Chronic dosing	Intermittent dosing
	Clearance in humans	Fast			Slow
	Dose	High	To be determined		Relatively low
Patient related risks	**Immune status of patient**	Immune compromised	Normal immune system		Activated immune system
	Concomitant medication	Immunosuppressive co-medication	Not applicable		Immunostimulatory co-medication
	Concentration of endogenous counterpart	Relatively high	Not applicable		Relatively low/absent

The parameters in orange are indicative of vilobelimab characteristics considering clinical implication for COVID-19 clinical study (IFX-1-P2.9)
IM: intramuscular; IP: intraperitoneal; IV: intravenous; SC: subcutaneous.

Pharmacokinetics in target population

PK in the target population is available from the phase I/II study IFX-1-P2.9 (PANAMO). Immunogenicity data was only collected in the phase III part.

Phase II part

30 patients receiving oxygen supplementation or being intubated were treated with either best supportive care (BSC) alone or BSC plus up to 7 IV doses of vilobelimab 800 mg over a period of 29 days. The first 5 vilobelimab treatments at Days 1, 2, 4, 8, and 15 were to be administered to all patients in Arm A. Treatment at Day 22 was only administered in the event that a patient had not previously been extubated and discharged from the intensive care unit (ICU). When a patient's clinical situation worsened after Day 8, although an initial clinical benefit was observed, 1 additional administration of 800 mg vilobelimab between Days 11 and 13 could have been given at the investigator's discretion.

All 15 patients allocated to the vilobelimab group received at least 1 dose of vilobelimab 800 mg treatment; 3 patients received 7 infusions, 3 patients received 6 infusions, 4 patients received 5 infusions, 4 patients received 4 infusions and one patient received 3 infusions. Thirteen patients recovered and completed the study, while 2 patients died (having received 3 and 4 vilobelimab infusions, respectively). All patients received concomitant medications during the study. Patients in the vilobelimab group had a mean body weight of 83.2 kg, with a range of 48 to 125 kg.

Vilobelimab pre-dose drug concentrations ranged from 84846 to 248592 ng/mL (571 to 1674 nM) with a geometric mean of 151702 ng/mL (1022 nM) on Day 2 (24 hours after dosing on Day 1) and from 80060 to 200746 ng/mL (539 to 1352 nM) with a geometric mean of 139503 ng/mL (939 nM) on Day 8 (96 hours after dosing on Day 4 [Figure 3]). Beyond Day 8, PK and PD data are too sparse to be representative (Table 8).

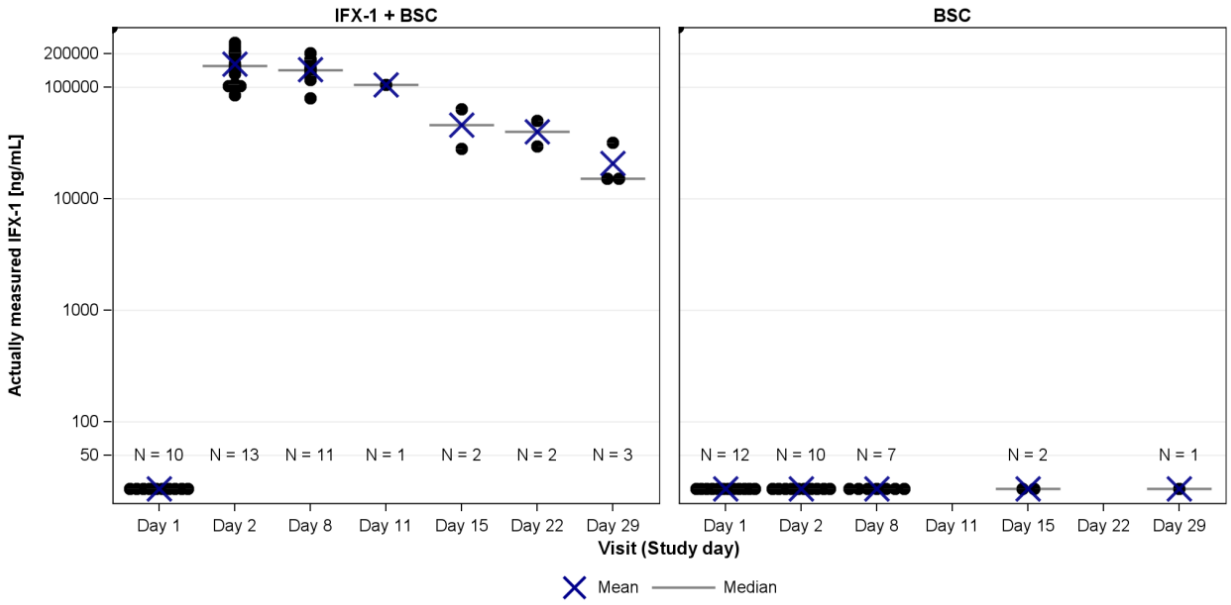


Figure 3: Measured vilobelimab concentrations [ng/mL] in study IFX-1-P2.9 phase II part. BSC = best supportive care; Values reported as being below the lower limit of quantification (LLOQ) are set to half of LLOQ. Source: IFX-1-P2.9 CSR (Phase II) – Figure 14.4.1.3.

Table 8: Plasma concentrations of vilobelimab (ng/mL) in study IFX-1-P2.9 phase II part

	Vilobelimab [ng/mL] Concentrations		
Statistics	Day 2 (pre-dose)	Day 8 (pre-dose)	Day 29
n (%)	13 (86.7%)	11 (73.3%)	3 (20%)
Geom. Mean	151,701.94	139,502.83	19,422.50
Geom. CV %	36.15	25.09	44.51
Min – Max	84,846.2 – 248,592.1	80,060.0 – 200,745.8	15,182.7 – 31,731.2

BSC = best supportive care, CV = coefficient of variation, Max = maximum, Min = minimum, SD = standard deviation. Source: IFX-1-P2.9 CSR (Phase II) – Table 14.4.1.1.

Phase III part

Patients were treated with a maximum of 6 IV doses of vilobelimab 800 mg + SOC (Arm A, n = 175) or Placebo + SOC (Arm B, n = 189) at Days 1, 2, 4, 8, 15, and 22, as long as the patient was still hospitalised (even if discharged from the ICU).

Patients in the vilobelimab group had a mean body weight of 94.5 kg, with a range of 60 to 149 kg (n = 175, patients who received at least one dose). 26.9% (47) in the vilobelimab group had eGFR below 60 mL/min/1.73m2 (all others above). Patients with chronic liver impairment Child Pugh B and C were excluded from this study.

PK samples were to be collected up to 3 times: pre dose at screening and on Day 8, as well as on the day of hospital/ICU discharge. PK samples were collected only in sites in the Netherlands, France, Belgium, and Germany (vilobelimab, n=93).

ADA sampling was performed at baseline and hospital discharge. One patient in each treatment group had treatment-induced ADAs. In the vilobelimab group, this patient had received 6 infusions and was baseline ADA negative and confirmed positive at hospital discharge (Day 40); a titre value was not reportable. This patient received 6 infusions of vilobelimab up to Day 22.

On Day 8, mean vilobelimab trough concentrations in plasma, ranged from 21,799.3 to 302,972.1 ng/mL with a geometric mean of 137,881.3 ng/mL in the vilobelimab group. Beyond Day 8, sampling for PK was too sparse to be representative. Additionally, the blood samples were taken on the day of hospital discharge, which was highly variable both in terms of absolute time and time relative to last dose. An attempt was made to group together patients with similar discharge days to demonstrate the mean reduction in exposure to vilobelimab over time (Figure 4 and Figure 5).

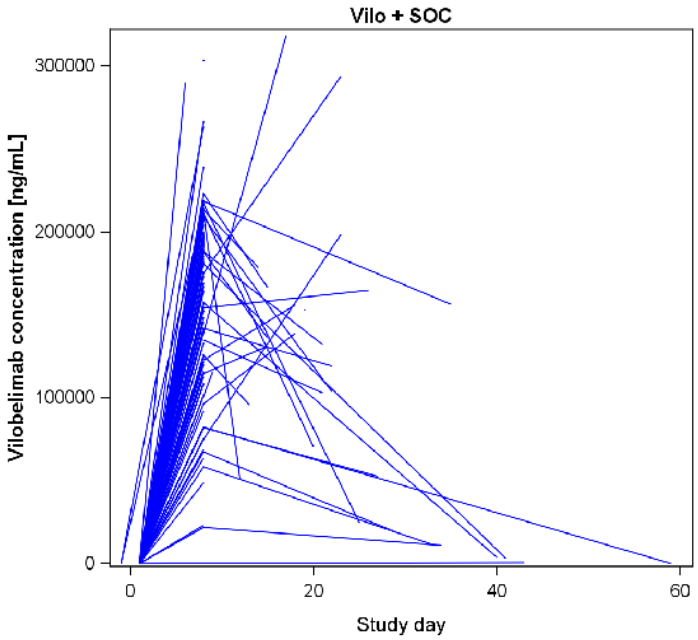


Figure 4: Spaghetti plot of vilobelimab concentration – study IFX-1-P.2.9 vilobelimab group

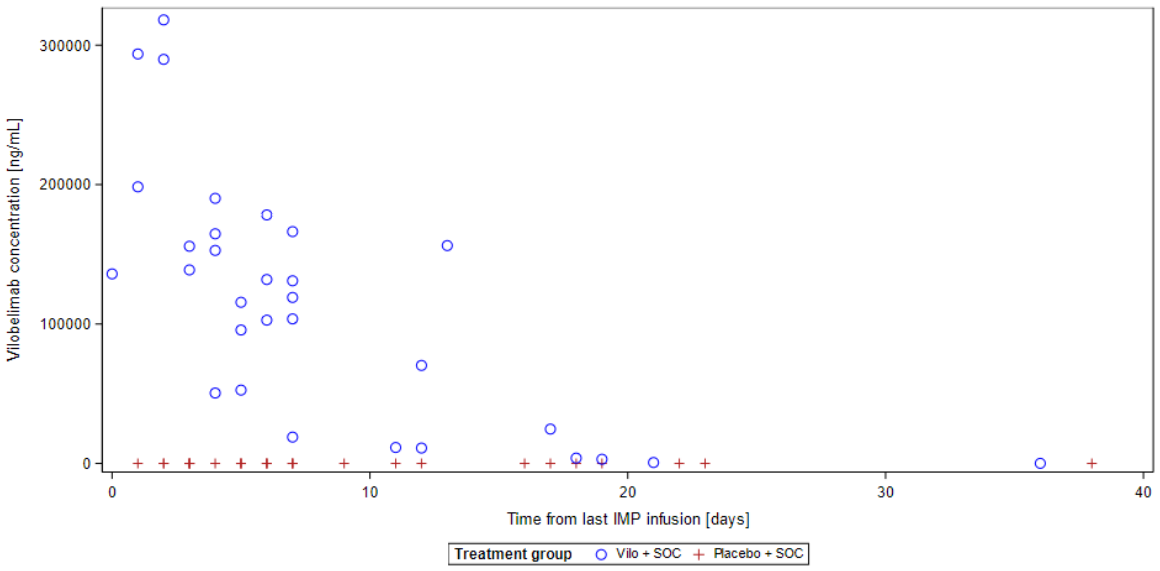


Figure 5: Vilobelimab concentration at hospital discharge by time from last infusion

Special populations

The impact of hepatic insufficiency, gender, race or age on the PK of vilobelimab has not been studied.

Estimated glomerular filtration rate (eGFR) was included in the final population PK model as a covariate effect on Clearance and Vmax. The 95th (142 ml/min/1.73m2) and 5th (69.2 ml/min/1.73m2) percentile values of eGFR were compared to the median value (101 ml/min/1.73m2).

The availability of PK data in elderly is listed in Table 9.

Table 9: Number of elderly subjects with PK data for vilobelimab

Study	Age 65-74 (Older subjects number / total number vilobelimab treated subjects)	Age 75-84 (Older subjects number / total number vilobelimab treated subjects)	Age 85+ (Older subjects number / total number vilobelimab treated subjects)
IFX-1-P1.1	0 / 15	0 / 15	0/ 15
IFX-1-P2.1	9 / 48	17 / 48	4 / 48
IFX-1-P2.2	23 / 82	36 / 82	1 / 82
IFX-1-P2.3	1 / 12	0 / 12	0 / 12
IFX-1-P2.4	3 / 175	1 / 175	0 / 175
IFX-1-P2.5	10 / 33	3 / 33	0 / 33
IFX-1-P2.6	3 / 13	2 / 13	0 /13
IFX-1-P2.7	7 / 19	0 / 19	0 / 19
IFX-1-P2.9 Ph2	2 / 15	0 / 15	0 / 15
IFX-1-P2.9 Ph3	39 / 175	8 / 175	0 / 175
Total	97 / 587	67 / 587	5 / 587

Exposure of vilobelimab stratified by bodyweight is presented in Figure 6.

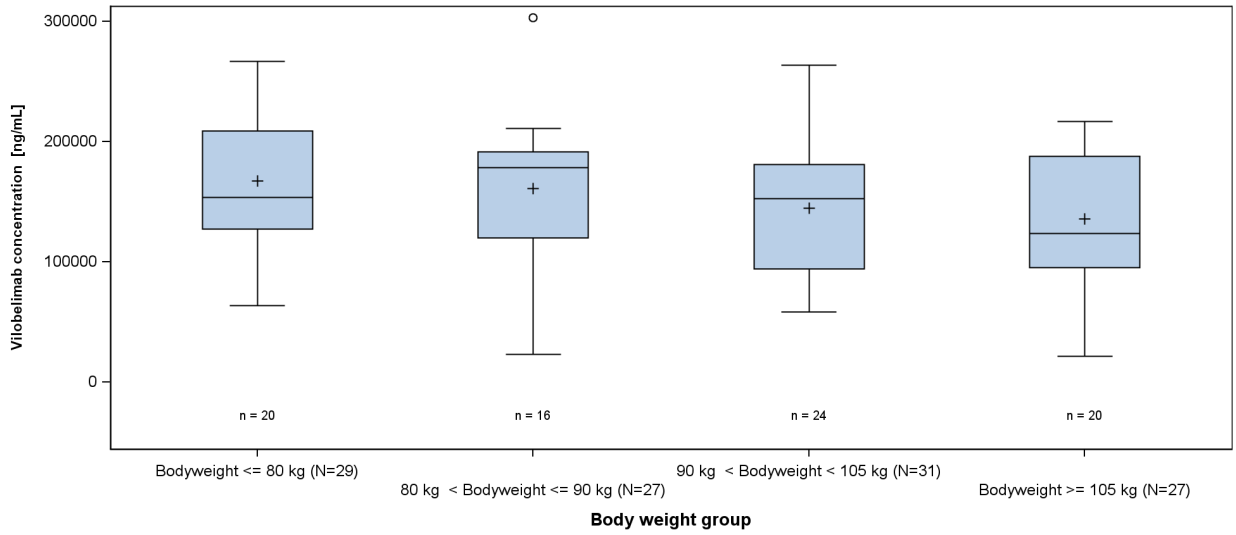


Figure 6: Box plot for vilobelimab concentration [ng/mL] at day 8 by bodyweight group in PANAMO

*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 lower/upper line of box + 1.5 * (3rd quartile – 1st quartile), circle = values below/above whiskers.*

Pharmacokinetic interaction studies

The applicant did not conduct interaction studies with vilobelimab.

In study IFX-1-P1.1, vilobelimab did not induce any clinically relevant time-or dose-related changes in mean inflammatory parameters in healthy subjects. No clinically relevant differences between the Placebo and the active treated groups were observed IL-6, IL-10, IFN-ɣ, IL-8 and TNF-α.

Exposure relevant for safety evaluation

No exposure is available in the target population using the intended posology. As a conservative scenario, the geomean exposure simulated from the popPK (comparability analysis using only PK data in HS patients) can be used: AUCtau: 52828046 ng h/mL and Cmax 836727 ng/mL.

2.5.2.2. Pharmacodynamics

Mechanism of action

Vilobelimab (IFX-1) is a chimeric monoclonal immunoglobulin (Ig) G4 antibody which specifically binds to the soluble human complement split product C5a. Vilobelimab is composed of 1,328 amino acids and has an approximate molecular weight of 148 - 149 kDa.

C5a is a chemoattractant for neutrophils and also has chemotactic activity for monocytes and macrophages. C5a is generated when the complement system is activated in settings of inflammation and other immunological and inflammatory disorders. Complement activation products such as high levels of C5a and C5b-9 have been reported in patients with severe COVID-19.

Vilobelimab has been shown to block C5a-induced biological effects such as CD11b up-regulation on granulocytes as well as lysozyme release from neutrophils.

Primary and secondary pharmacology

The pharmacological characterisation of vilobelimab comprised of primary pharmacology studies which assessed binding affinity, species specificity as well as pharmacodynamic assays in whole blood or plasma. Vilobelimab binding is highly specific to human and non-human primate C5a. It was shown that vilobelimab is similarly effective on C5a and desarginated C5a (C5a-desArg) an active human metabolite of C5a. Vilobelimab was shown to block C5a-driven inflammatory responses in human whole blood models and reduce the neutrophil and macrophage infiltration in a model of virus (H7N9)-induced lung injury in monkeys.

Secondary pharmacology studies data indicate that vilobelimab/C5a complex does not induce cytokine production in human whole blood. Vilobelimab does not affect cleavage of C5 and the formation of the terminal membrane attack complex (MAC) in vitro, which is a crucial defence mechanism leading to bacterial lysis.

Relationship between plasma concentration and effect

A PK/PD analysis was conducted for HS patients but not covid-19 patients. Post hoc estimates of measure of vilobelimab exposure were plotted against % change in plasma C5a (Figure 7). The relationship described is linear, as an Emax relationship was unsuccessful. However, visual inspection of this plot suggests that near complete suppression of C5a may be possible. Based on the linear

relationship, the concentration that results in 50% reduction in C5a may be approximately 120,000 ng/ml. Based on this estimate, a target threshold of 360,000 ng/ml was established, and it was estimated to be well on the upper part of the exposure-response relationship. This value (360,000 ng/ml) was used in simulations and is the target concentration for essentially full suppression of C5a in the vast majority of patients. This degree of suppression may not be required for clinical efficacy.

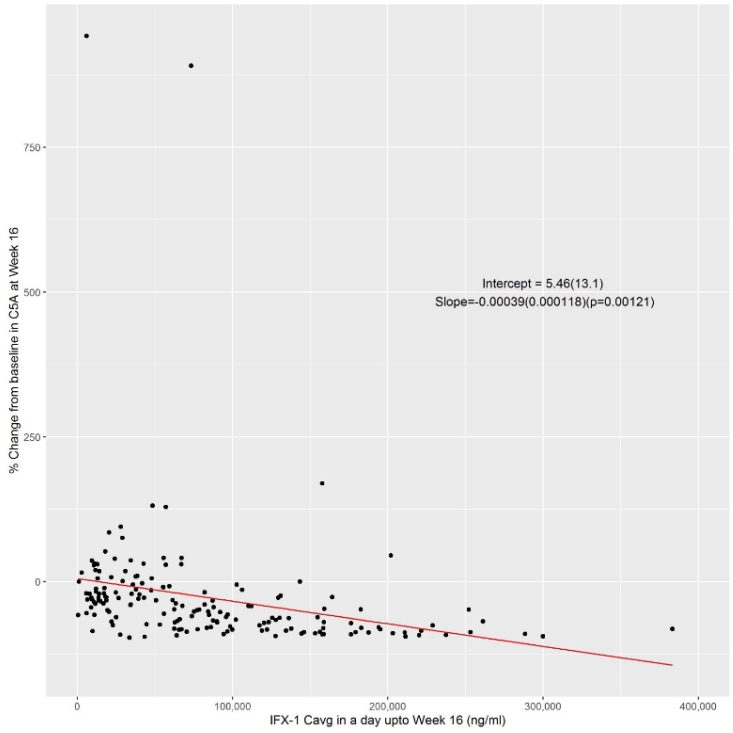


Figure 7: Study IFX-1-P2.4 Cavg of vilobelimab vs C5a

PANAMO Phase II clinical data on C5a and C3a plasma concentrations

C5a plasma concentrations

Baseline (Day 1) blood samples for C5a measurement (pretreatment) were available for 10 patients in the vilobelimab group and 12 patients in the BSC group.

Baseline concentrations of C5a were highly elevated in all patients (normal range in healthy subjects, 33.7 ng/mL - 53.6 ng/mL and were comparable between both treatment groups.

Table 10: Summary of plasma concentrations of C5a (ng/mL) (full analysis set)

	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).

C3a plasma concentrations

Baseline (Day 1) blood samples for C3a measurement (pretreatment) were available for 8 patients in the IFX-1 group and for 13 patients in the BSC group.

Table 11: Summary of plasma concentrations of C3a (ng/mL) (full analysis set)

	C3a [ng/mL] Concentrations			
Statistics	**Day 1**	**Day 2**	**Day 8**	**Day 29**
IFX-1 group (N=15)				
n (%)	8 (53.3%)	12 (80%)	12 (80%)	2 (13.3%)
Mean (SD)	393.01 (144.74)	403.62 (161.29)	498.01 (280.98)	140.52 (25.39)
Min – Max	177.2 – 584.0	225.3 – 727.6	171.3 – 1150.1	122.6 – 158.5
Median (Q1 – Q3)	387.45 (290.99 – 513.00)	330.13 (295.46 – 536.56)	502.71 (271.78 – 621.18)	140.52 (122.57 – 158.48)
CV %	36.83	39.96	56.42	18.07
Geom. Mean	366.88	376.71	431.35	139.37
Geom. CV %	43.20	39.80	61.44	18.32
BSC group (N=15)				
n (%)	13 (86.7%)	13 (86.7%)	7 (46.7%)	1 (6.7%)
Mean (SD)	478.33 (187.97)	501.05 (223.91)	467.78 (222.60)	230.98 (-)
Min – Max	248.1 – 818.9	189.7 – 960.2	180.8 – 825.9	231.0 – 231.0
Median (Q1 – Q3)	397.75 (323.77 – 611.98)	451.98 (373.30 – 643.33)	480.75 (270.21 – 651.43)	230.98 (230.98 – 230.98)
CV %	39.30	44.69	47.59	-
Geom. Mean	446.08	456.04	419.71	-
Geom. CV %	40.25	48.54	55.98	-

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).

PANAMO Phase III clinical data on C5a plasma concentrations

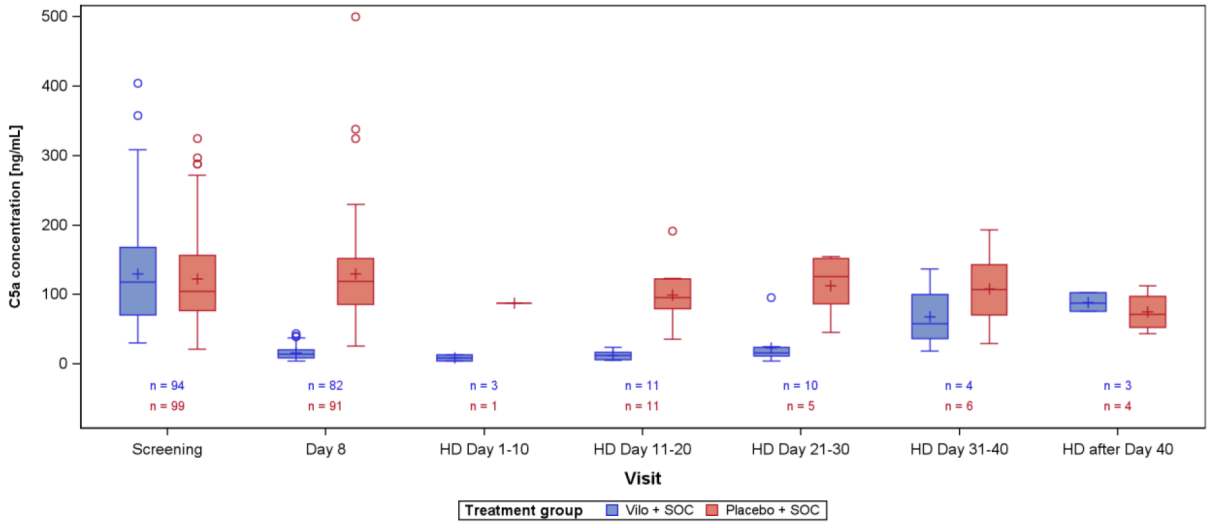
Screening blood samples for C5a measurement were available for 94 patients in the VILO group and for 99 patients in the placebo group. Eighteen patients (7 vilobelimab /11 placebo) had plasma C5a concentrations within the range reported for healthy subjects (healthy donor range 43.6+6.3). At Day 28, 14 patients were still alive (78%), and 4 patients died (1 vilobelimab/3 placebo).

Table 12: Summary of plasma C5a concentrations (ng/mL) by visit (safety analysis set)

	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.

Figure 8: Box plot of plasma C5a concentrations (ng/mL) by visit (safety analysis set)



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.

2.5.3. Discussion on clinical pharmacology

Only a minimum of PK data is available for the target population. Phase II/III study 2.9 (PANAMO) is the only one with the intended posology. Sparse PK is available from the 15 subjects in the phase II part of the study, while only two samples were collected in the phase III part, at day 8 Ctrough and upon hospital discharge. Additionally, popPK analyses were limited to HS patients from studies 2.3 and 2.4 who had a different posology, without a dose on day 2 and further doses after day 22.

The PK of vilobelimab seems to be target-mediated, thus PK in other indications where the target levels may differ is only poorly informative, in particular in case of sparse sampling. Studies 2.3 and 2.4, which are studies in HS patients are included in the popPK analysis, where the data in HS patients is compared to the target population. The PK in healthy subjects (study 1.1) is the main source to describe the PK of vilobelimab, with the limitation of being single dose and at much lower doses than intended (up to 4 mg/kg in study 1.1 compared to 800 mg intended dose for the target population). Rich PK sampling is also available from studies 2.1 and 2.2, however there are limitations as the studies were performed in other indications and with another posology.

An additional issue is the use of drug substance from 6 different processes, where PK with the final drug substance 6 (in drug product 4) has not been described.

In consequence, it can be concluded that the available PK data is very limited and that several uncertainties limit its use. The PK data has thus only a descriptive role in this application. In order to be approvable, the dossier will need to rely on efficacy and safety, without any possible bridging based on PK.

Information on the limitations of PK data in the target population has been included in the SmPC section 5.2.

Methods

Quantification of vilobelimab

The method for quantification of vilobelimab in human citrated plasma is in general adequately validated and showed sufficient selectivity and specificity. The missing bioanalytical reports were provided and confirmed the adequacy of the bioanalysis. The applicant also confirmed that potentially haemolytic samples were diluted so that an impact on PK is unlikely. Additional long term stability data was provided covering all sample analyses.

Immunogenicity

The ADA strategy follows current guidelines and white papers, including validation and cutpoint determination and is generally adequate. There are however issues with the drug tolerance (see below). Given the short administration period of vilobelimab in the intended indication, the lack of data on the neutralisation potential of ADAs is acceptable.

The first assay has probably insufficient drug tolerance for use at D28, at least for the 2 and 4 mg/kg doses. At D70, the vilobelimab concentration may be low enough to have interpretable immunogenicity results. At that timepoint, all ADA samples were tested negative, which is reassuring.

The second assay was only transferred from the first assay and not fully revalidated, thus the concerns regarding drug tolerance from the first assay are the same. Additionally, the screening cutpoint from the first assay validation was applied without assessment of its adequacy, while the confirmatory screening cutpoint was reassessed based on 6 sources of plasma, which is much lower than the recommended 50 individual samples. In studies 2.1, 2.2 and 2.3, samples for ADA analysis were taken at timepoints where the vilobelimab concentration still exceeded the drug tolerance levels, thus underestimating the ADA levels. Consequently, any ADA negative samples should be considered inconclusive.

The ECL ADA assay has strong interference by both C5a (false positive) and vilobelimab (false negative). Drug tolerance was 10 µg/mL vilobelimab for 100 ng/ml ADA, which is lower than the vilobelimab concentration in the majority of ADA samples. Since the presence of drug strongly

decreases the signal, these should thus be considered inconclusive rather than negative, and when positive, titres are likely underestimated.

Overall, the reliability of the immunogenicity results is questioned, and immunogenicity is likely underestimated in all clinical studies. In the case of a chronic indication in the future, the applicant is strongly encouraged to develop a new ADA assay, following the recommendation given in the CHMP scientific advice.

Population PK analysis

The current population PK analysis was based on a pooled dataset from 2 phase II clinical studies, which includes data from patients with Hidradenitis Suppurativa (HS) (study IFX-1-P2.3 and study IFX-1-P2.4). The strategy for population PK model development was initiated including 12 patients from Study IFX-1-P2.3 and 162 patients from Study IFX-2-P2.4 with a total of 1833 PK observations. Different dosing regimens (800 mg single dose, 400 mg q4w, 800 mg q4w, 800 q2w and 1200 mg q2w) were administered in patients with Hidradenitis Suppurativa (HS) and no COVID-19 patients were included in the model development.

It could have been useful to pool covid-19 and HS PK data and investigate disease as a covariate. The level of evidence in Covid-19 patients is very limited, which undermines the impact of the population PK model and model-based PK/PD predictions.

Standard methods have been used. Only 15 patients were included in the PK sub study and had rich PK data. Updated diagnostic plots and clarification on the popPK have been provided as requested. Overall, the population PK model seems not suitable to describe data from study IFX-1-P2.3. This highlights that differences in the PK properties may occur between HS patients, which represents a relevant limitation in the attempt to extrapolate the PK properties of vilobelimab in Covid-19 patients. The empirical nature of the popPK model together with the deviations identified in model performance highlights the poor predictive capacity of the popPK model as a tool that allows justifying non-tested regimens or justify the PK properties in special sub-groups of populations.

The clinical relevance of the selected covariates was further investigated. Bodyweight had a clear effect on exposure. Over a body weight range of 124-65 kg (95th- 5th percentile) the magnitude of bodyweight effect is 0.8 – 1.16 times the reference exposure (AUC) for 90.3 kg (median value). Regarding the clinical relevance of this effect, see the discussion on special populations below.

The applicant used the popPK model developed on data from HS patients and simulated out exposure in covid-19 patients. The covariate ISH4 was set to 0 and covariates from covid-19 populations were used. The exposure was simulated to be very similar between covid-19 and HS patients. This is expected as the models used are the same and only slight difference in covariates were implemented.

From Figure 1 and Table 5, observed covid-19 ctrough at day 8 are lower than the simulated day 8 ctrough. Median exposure in HS patients is around 50% higher. Therefore, the applicant's conclusion that the PK is comparable is not agreed with. The CHMP considered that no comparison between observed data in HS and covid 19 is possible (different dosing regimens). Nevertheless, the predicted exposure could be used as a conservative scenario to calculate safety margins in non-clinical studies.

The SmPC information regarding PK is limited describing the observed data, with the observed C_{trough} in COVID-19 patients.

Absorption

No PK data comparing the different process materials has been presented. Provided analytical comparability between all 6 drug substance processes is demonstrated, the lack of data is acceptable.

Distribution

Vilobelimab has limited extravascular distribution, in line with other IgGs. This is adequately described in the SmPC section 5.2.

Elimination

Proteolytic degradation is expected and the lack of studies characterizing the elimination is acceptable.

The CL decrease and t1/2 increase with increasing doses are consistent with target mediated disposition. This is described in the elimination section of SmPC 5.2 for CL and t1/2 from study 1.1.

Dose proportionality, time dependencies, immunogenicity

Target mediated disposition (TMDD) is apparent from the concentration-time profiles at different doses, with more than dose proportional increases in AUC. PK is expected to depend on the vilobelimab dose and the amount of available target. TMDD may evolve over time as target levels normalise. An impact of immunogenicity on the last doses cannot be excluded, see below.

The impact of time-dependency on the exposure of vilobelimab has not been characterised, which could be highly relevant for monoclonal antibodies. However, due to the scarce experimental evidence collected and the limited impact of the pharmacokinetics in the decision-making process in COVID-19 patients, this issue is not further pursued.

In study 1.1, at D70 PK samples were below LLOQ for all groups, thus the negative immunogenicity from D70 data can be relied on for this timepoint.

Immunogenicity appears to be relatively low across indications. However, due to the poor drug tolerance of the assays, immunogenicity is likely to be underestimated. Based on the risk assessment provided by the applicant (Table 7), the immunogenicity risk is expected to be moderate and not low as claimed by the applicant.

Any analysis of the influence of ADA on PK, efficacy or safety is likely biased by the poor drug tolerance. Given the extent of drug interference, nearly all samples are expected to be classed as inconclusive, thus an updated analysis of the impact on PK, efficacy or safety is not expected to lead to informative conclusions and is therefore not requested.

Overall, due to the poor drug tolerance of the ADA assays, no conclusion can be drawn on the immunogenicity of vilobelimab, nor on its impact on PK, efficacy or safety. Given the posology in the intended indication, the lack of robust data is unfortunate but acceptable. ADAs are not expected to arise before the second week of treatment, thus the impact on the intended posology is minor.

Pharmacokinetics in target population

The observed data from both the phase II and phase III parts are used to describe the PK in the target population in the SmPC, which is adequate.

Special populations

As requested, the applicant presented available PK data from the PANAMO study stratified by bodyweight. There is a trend for lower mean concentration with increasing bodyweight, however the range is overlapping across bodyweight groups, in particular quartiles 2-4. The applicant further supports the lack of clinical relevance of the lower mean exposure with C5a levels, which also overlap

across bodyweight groups, without detectable trend. Overall, this indicated that the proposed flat dose regimen is adequate across the studied bodyweight range and there is no need for an adapted dose.

It is agreed that the effect of mild renal impairment is not clinically relevant. The SmPC section 5.2 adequately reflects the lack of expected effect.

Data on other special populations has not been presented. The PK of an antibody is not expected to be affected in special populations. The SmPC section 5.2. proposed text is considered adequate.

Pharmacokinetic interaction studies

Data from study IFX-1-P1-1 does not suggest an immunomodulation potential. Given the nature of the test item, no interactions are expected, therefore the lack of interaction studies is acceptable.

Information on the (low) interaction potential is adequately described in the SmPC section 4.5.

Relationship between plasma concentration and effect

The PK/PD graphical analysis conducted is for HS and not COVID-19 patients. Therefore, the regulatory impact for this application is low. The applicant draws conclusions from the analysis and have added a target threshold of 360,000 ng/ml. This threshold is not considered relevant for covid-19 patients. Several concerns have been raised questioning the adequacy of the population PK model at the structural level to fully capture the complex PK processes in HS patients. In this regard, it is highly uncertain whether similar exposure levels would be achieved in COVID-19 patients due to the impact of disease conditions and pathophysiological processes involved across both indications.

The adequacy of the population PK model developed in HS patients to serve as a predictive tool for generating predicted exposure outcomes is questionable based on the differences between observed and predicted C_{trough} at Day 8. This clearly impacts the confidence of the PK predictions that are used for efficacy evaluation.

A linear pharmacodynamic model was proposed to relate the post-hoc C_{min} estimates in HS patients vs the reduction in plasma C5a. Several variants of the model were tested. However the model was unable to fully capture the different behaviours observed and should not be used for further model-informed predictions of C5a levels.

No exposure-safety analysis was conducted to understand the impact of different PK endpoints in the prediction of safety events.

Plasma concentration of C5a in clinical samples from the PANAMO study

Phase II

Baseline mean and median concentrations of C5a were elevated and comparable between both treatment groups. It is noted that the min-value in the BSC group on Day 1 and Day 2 overlap with the range in healthy individual. In the vilobelimab group it seems that all baseline (Day 1) values were elevated.

The results indicate that vilobelimab can inhibit C5a to a certain degree in plasma from patients with severe pneumonia due to COVID-19. However, the clinical benefit of C5a inhibition in this study is still uncertain as differences between treatment groups with regard to clinical endpoints were small (see Clinical efficacy section 2.6.5).

Vilobelimab seem to specifically bind to C5a and did not have any effect on C3a concentrations (a proinflammatory mediator upstream of C5a in the complement pathway).

Phase III

At screening the mean and median plasma concentrations of C5a were elevated in both treatment groups. However, the min-values in both groups shows that there were patients with C5a concentration within the range reported for healthy subjects. Unfortunately, relatively few C5a plasma samples were available at screening. Of the patients with available samples 19% (18/94) were within the range reported for healthy individuals. The numbers are very small and therefore no firm conclusion on the connection between screening C5a concentrations and clinical effect of vilobelimab can be drawn. It is anticipated that post-authorisation studies would further elucidate the relation between C5a concentrations and vilobelimab efficacy, in case of an approval.

By Day 8 mean and median C5a levels were reduced in the vilobelimab group while C5a levels were still elevated in the placebo group. Upon hospital discharge too few samples were available to give any reliable results.

2.5.4. Conclusions on clinical pharmacology

The presented dossier has numerous limitations. For this reason the PK data can only be considered descriptive, which is adequately reflected in the SmPC section 5.2.

2.5.5. Clinical efficacy

Information on the efficacy and safety of vilobelimab in treatment of adult patients with SARS-CoV-2 induced septic acute respiratory distress syndrome (ARDS) is derived primarily from the pivotal “PANAMO” phase III study. The Phase II PANAMO was hypothesis-generating and supported the design of the phase III study.

Table 13: Overview of the clinical phase II and III studies of vilobelimab in COVID-19 patients

Study Number; Phase; Status	Study locations	Study Design and Patient Population	Study Objectives	Number of Patients	Dosing Schedule	Primary Endpoints
PANAMO Phase II Completed	3 sites in the Netherlands	Randomised, open-label, controlled study in COVID-19 patients highly oxygen dependent, which included those on non-invasive ventilation as well as IMV	E, S, PK, PD	Total 30 (vilobelimab: 15, BSC: 15)	Vilobelimab 800 mg IV infusion at Days 1, 2, 4, 8, 11/12/13 if needed, 15, and 22, as long as the patient was still in hospital.	The relative change (%) from baseline (Day 1 before study drug administration within 1 h before or after randomisation) in Oxygenation Index (PaO2 / FiO2) in supine position at Day 5.
PANAMO Phase III Completed	46 sites in 9 countries: Netherlands, France, Germany, and Belgium, Brazil, Mexico, and Peru, Russia and South Africa	Randomised, double-blind, placebo-controlled multicentre study in critically ill COVID-19 patients receiving IMV including ECMO	E, S, PK, PD, I	Total 369 (vilobelimab + SoC: 178, placebo + SoC: 191)	Vilobelimab 800 mg IV infusion or matching placebo at Days 1, 2, 4, 8, 15, and 22 as long as the patient was still in hospital.	28-day all-cause mortality using site-stratified cox regression analysis adjusting for age (Full Analysis Set)

2.5.5.1. Dose-response studies

No dose response studies have been performed in targeted patient population with severe COVID-19.

2.5.5.2. Main study(ies)

"PANAMO" Phase II Study

Title: A Pragmatic Adaptive Open-label Randomized Phase II/III Multicenter Study of IFX-1 in Patients With Severe COVID- 19 Pneumonia Methods

The PANAMO study consisted of two parts: Phase II and Phase III. The Phase II study was an open-label, randomised, 2-arm phase evaluating BSC + vilobelimab (IFX-1; Arm A) and BSC alone (Arm B) to explore the choice of endpoints and study population specifications for the Phase III study. Patients were randomised 1:1 with 15 patients in each arm. The study was conducted in patients with severe COVID-19 pneumonia. The exploratory randomised open-label study design was deemed appropriate for the Phase II part based on pragmatic considerations and clinical reasoning in a new and urgent pandemic setting under ICU conditions with very limited knowledge about the course and implications of SARS-CoV-2-induced disease.

Methods

Study Participants

Inclusion Criteria

Patients eligible for inclusion into the study had to meet all of the following inclusion criteria:

1. At least 18 years of age or older

2. Clinically evident or otherwise confirmed severe pneumonia as evidenced by at least one of the following criteria:

- Chest X-ray or computed tomography (CT)-scan or magnetic resonance imaging (MRI) with pulmonary infiltrates consistent with pneumonia
- Clinical history in past 14 days of newly developed severe shortness of breath (> 29 breaths / minute) in the absence of oxygen supply or spontaneous peripheral oxygenation ≤ 92 with need for oxygen supply, or need for non-invasive or invasive ventilation (in conjunction with a positive test for SARS-CoV-2 infection)

3. Oxygenation Index at time of enrolment (PaO2 / FiO2) ≤ 250 and ≥ 100 in supine position

4. SARS-CoV-2 infection confirmation (tested positive in last 14 days or test results to be obtained within 24h after enrolment, both with locally available test system)

5. No use OR stop of any corticosteroid treatment at time point of enrolment (topical treatment and systemic dose of ≤ 10mg prednisone / day equivalent allowed)

Exclusion Criteria

Patients eligible for inclusion into the study must not have met any of the following exclusion criteria:

1. Oxygenation Index at time of enrolment (PaO2 / FiO2) < 100 or > 250 in supine position

2. Intubated > 48h at time point of enrolment

3. Patients who demonstrated an improvement in past 24h prior to enrolment in oxygenation and ventilation / support parameters which indicated an expected resolution of lung dysfunction in the next 24h without additional intervention according to judgment of the Investigator with one or more of the following parameters present:

- Improvement in oxygenation index of > 30% relative to previous measure (last 24h in supine position)
- Extubation if intubated before

4. Known history of COPD (GOLD category C or D)

5. Known history of chronic dialysis OR received renal replacement therapy in past 14 days

6. Received new other biologic treatment attempt for COVID-19 in the past 14 days

7. Received treatment with a viral replication inhibitor in past 3 days

8. Received cytokine adsorption therapy in past 3 days

9. Known hypersensitivity to IFX-1 or any other ingredient of the study medication

10. Known pregnancy

11. Received organ or bone marrow transplantation in past 3 months

12. Known mechanically resuscitation in past 14 days

13. Patient moribund or expected to die in next 12h according to the judgment of the Investigator

14. Patients otherwise considered restricted from receiving full supportive care (including ICU support)

15. Existing diagnosis of progressed cancer or other life-limiting disease with life expectancy < 6 months

16. Known to have received anti-cancer therapy for oncological disease in past 4 weeks

17. Known severe congestive heart failure (NYHA-Class III - IV)

The inclusion criteria reflect a patient population with severe pneumonia induced by COVID-19 receiving high oxygen support at the time of first dose IMP. Study criteria specified no treatment with systemic corticosteroids at relevant doses (see below)

Reporting period

This is the first clinical study report (CSR) for this study, which summarised the final data analysis on the exploratory Phase II part of the study. The Phase III part of the study was ongoing at the time of Phase II CSR writing. Database lock date: 19-Jan-2021

Treatments

The investigational treatment IFX-1 was administered as an add-on to BSC. IFX-1 800 mg IV was administered to all patients randomised to the IFX-1 group. Patients received a maximum of 7 doses over a period of 29 days + BSC or until hospital discharge; those in the control group received BSC only. Five doses of IFX-1 were to be administered at Days 1, 2, 4, 8, and 15. A dose at Day 22 was to be administered to patients who were still intubated and not discharged from ICU on Day 22. One additional dose of IFX-1 could have been given between Days 11 and 13 at the discretion of the Investigator if signs of worsening after Day 8 of any previous clinical improvement were detected.

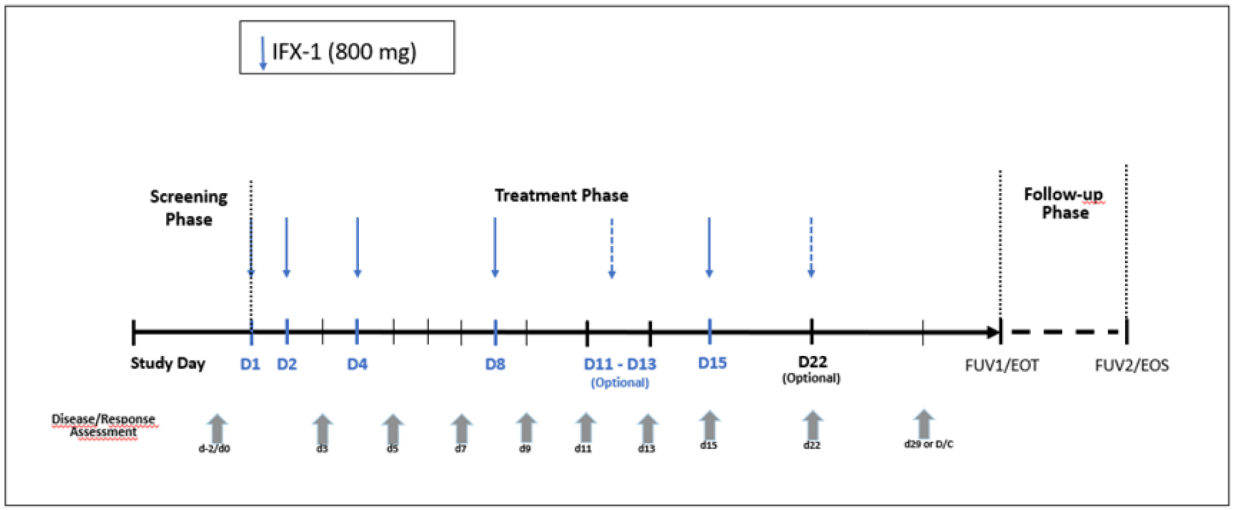
Treatment with IFX-1 was discontinued if patients were discharged from hospital. IFX-1 was administered as a 30-minute IV infusion. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes was permitted (i.e., infusion time was 30 minutes (-5 min/+10 min). Administrations were given as shown in Figure below.

The first dose of IFX-1 was administered on Day 1.

BSC in the participating centres consisted of intensive care therapy according to current guidelines, evidence, and best practice, including but not limited to lung protective ventilation, thrombosis prophylaxis, renal replacement therapy, when indicated, and access to advanced therapies including extracorporeal membrane oxygenation.

Use of antimalarials (e.g., chloroquine) was allowed during the study; however, active concomitant treatment with other immunomodulatory drugs was not allowed.

Figure 9: Vilobelimab (IFX-1) administration



D = Day; D/C = discharge; EOS = end of study; EOT = end of treatment; FUV = follow-up visit

It is noted that in the Phase II corticosteroids were not to be used, although topical treatment and systemic dose of ≤ 10mg prednisone/day equivalent were allowed. It is noted that 4 vs. 3 patients used systemic corticosteroids in the IFX-1+BSC and BSC only groups respectively. This contrasts with the Phase III where the majority of the patients (95.7%) were co-treated with systemic corticosteroids with no dose restrictions.

Objectives

Primary Objective(s)

The primary objective of Phase II of this study was to explore the effect of IFX-1 on COVID-19 related severe pneumonia (hypothesis generating).

Secondary Objectives

The secondary objectives of the study were:

- To assess and define other parameters of efficacy
- To assess the safety of IFX-1

Outcomes/endpoints

Primary Endpoint

The primary endpoint of Phase II of the study was the relative change (%) from baseline (Day 1 prior to study drug administration at ± 1h of randomisation) in Oxygenation Index (PaO2 / FiO2) in supine position at Day 5.

Secondary Endpoints

- All cause 28-day mortality (%)
- Number of patients (%) achieving an Early Response as defined as meeting ALL of the following criteria at Day 7 after enrolment:

    - Patient alive and extubated OR oxygenation index ≥ 300 OR improvement of ≥ 30% from baseline
    - Temperature < 38°C in absence of fever decreasing medication of at least 4h
    - White blood cell count within normal limit of local laboratory quantifications
- Number of patients (%) reaching a Late Response as defined by either being discharged alive from hospital until Day 28 OR meeting ALL of the following criteria at Day 28 of the trial:
    - Patient alive and extubated
    - Patient discharged from intensive care unit (ICU)
    - Patient free of shortness of breath (respiratory rate [RR] < 20) in absence of oxygen supply
    - Patient free of fever (< 37.6°C)
- Relative change (%) from baseline (Day 1 prior to study drug administration at ± 1h of randomisation) in Oxygenation Index (PaO2 / FiO2) in supine position at Day 3, 7, 9, and 11

Other Endpoints

- Change from baseline in alanine aminotransferase (ALT) and aspartate aminotransferase (AST)
- Change from baseline in troponin I adjusted to glomerular filtration rate (GFR)
- Change from baseline in creatinine
- Change from baseline in lymphocyte counts
- Change from baseline in neutrophil counts
- Change from baseline in D-dimers
- Change from baseline in Glasgow Outcome Scale
- Time to reach ICU discharge criteria as defined by ALL of the three criteria below:
    - Alive and extubated
    - No need for continued (>3h per day) non-invasive ventilation
    - Free of vasopressor and inotropic therapy

Pharmacokinetic/Pharmacodynamic Endpoints

Assessment of complement activation parameters and plasma concentrations of IFX-1

Safety Endpoints

Frequency, severity, and relatedness to study drug of treatment-emergent adverse events (TEAEs) and serious TEAEs (SAEs)

The primary objective of the phase II study was to explore the effects of vilobelimab on COVID-19 related severe pneumonia and for this purpose the change in oxygenation index from baseline was assessed as the primary endpoint. Mortality was assessed as a secondary endpoint.

Sample size

No formal sample size calculation was performed for this Phase II part of the trial. A total of 30 patients were deemed sufficient to learn enough about the uncertainties around the design parameters relevant for the Phase III part. The phase II PANAMO trial was not powered to show statistically significant differences in clinical endpoints.

Randomisation and blinding (masking)

Patients were randomised to two treatment arms in a ratio of 1:1:

- Arm A: IFX-1 (up to 7 doses of 800 mg) plus BSC (IFX-1 group)
- Arm B: BSC alone (control group)

Patients were centrally assigned to a treatment arm by the Investigator via the randomisation module of the eCRF. The IMP was assigned to each patient by the Investigator at the investigation site. Sites were each given a randomisation block and instructed to assign the first patient to Arm A, the second patient to Arm B, etc.

The randomisation list was only available to the CRO (Metronomia) staff involved in the production of the randomisation list and set-up of the online randomisation tool.

This was an open-label, randomised study.

Statistical methods

Analysis Sets

All randomised patients were included in the Full Analysis Set (FAS). If not otherwise stated, all analyses were based on the FAS. There was no separate Safety Analysis Set. There was no Per-Protocol Analysis Set.

General statistical specifications

For continuous data, the basic statistics sample size, arithmetic mean, standard deviation (SD), minimum, median, first quartile (Q1) and third quartile (Q3), and maximum were calculated. All hypothesis testing was reported using two-sided tests with 95% CI.

Categorical data was displayed in frequency tables showing sample size, absolute, and relative frequency. For each protocol-defined study day of interest, the longitudinal behaviour of continuous data was evaluated using basic statistics. If applicable, absolute and relative changes from baseline were calculated. Differences in relative changes from baseline between treatment groups by study day were tested by means of the Mann-Whitney-U test (standard normal approximation).

Oxygenation Index (Primary Endpoint)

The primary endpoint (percentage change from baseline (Day 1 before study drug administration within 1h before or after randomisation) in PaO2 / FiO2) in supine position at Day 5) was analysed with a linear repeated measures model with post-baseline time points (at Days 3, 5, 7, 9, 11, and 15) as outcome variables and the baseline value as explanatory variable.

Deceased patients were included in the model with an outcome of 0 after death. Patients discharged from the ICU whose Oxygenation Index was no longer assessed were analysed by LOCF.

Treatment arm, time point, the interaction between treatment arm and time point, the interaction between baseline value and time point, age, sex, and intubation status (yes/no) at baseline were included as further explanatory variables. The model used an unstructured covariance matrix and made use of the Kenward-Roger degrees of freedom approximation. Least square (LS) mean differences between treatment arms and their 95% CIs were calculated and displayed for each time point separately (Days 3, 5, 9 and 15), with the evaluation at Day 5 reflecting the primary endpoint.

The operational situation at the sites demanded flexibility in the daily Oxygenation Index measurement time points. Using the actual measurement time points for analysis could induce a time-dependent bias in the data. This was handled using linear interpolation between measurement time points to analyse the data.

Descriptive statistics for the absolute values of the derived Oxygenation Index as well as absolute and relative changes from baseline were displayed by days since randomisation (baseline, 3, 5, 7, 9, 11, 15) including the p-value for each time point from the Mann-Whitney- U-test to test for differences in the relative changes from baseline between treatment arms.

Missing data

If no pre-randomisation measurement of the Oxygenation Index was available, the baseline value was set to the first non-missing post-randomisation value (i.e. NOCB). The first non-missing measurement could be the zero imputed value for deceased patients (i.e. baseline was also zero). If no measurement existed at all, the baseline value was set to missing.

Supportive Analyses

The primary efficacy analysis was restricted to all Oxygenation Index values measured in “supine position for ≥2 hours” only. A sensitivity analysis repeated the primary efficacy analysis (including baseline value assessment) using all recorded Oxygenation Index values.

All-cause Mortality and 28-day Mortality

All-cause mortality was analysed as a censored time-to-event variable with Kaplan-Meier methods. The proportion of patients still alive at 28 Days was derived based on the product limits estimator in each treatment arm. Adjustment for relevant baseline covariates (age, sex, PaO2/FiO2) was realised by the Cox proportional hazard model. 28-day mortality was derived from the “One minus Kaplan-Meier estimator” evaluated at Day 28 (672h post randomisation) and was tabulated separately along its linear 95% CIs. Cox proportional hazards regression modelling was performed in order to regress the survival hazard on relevant baseline covariates (age, sex, and Oxygenation Index).

Multiple Comparison/Multiplicity

No confirmatory hypothesis testing and no adjustment for multiple testing was performed in the Phase II part of this trial.

Interim analysis

An interim analysis was performed after the first 30 patients treated in Phase II had reached at least Day 15 of the study schedule (or deceased before Day 15) to assess the clinical benefit of the treatment.

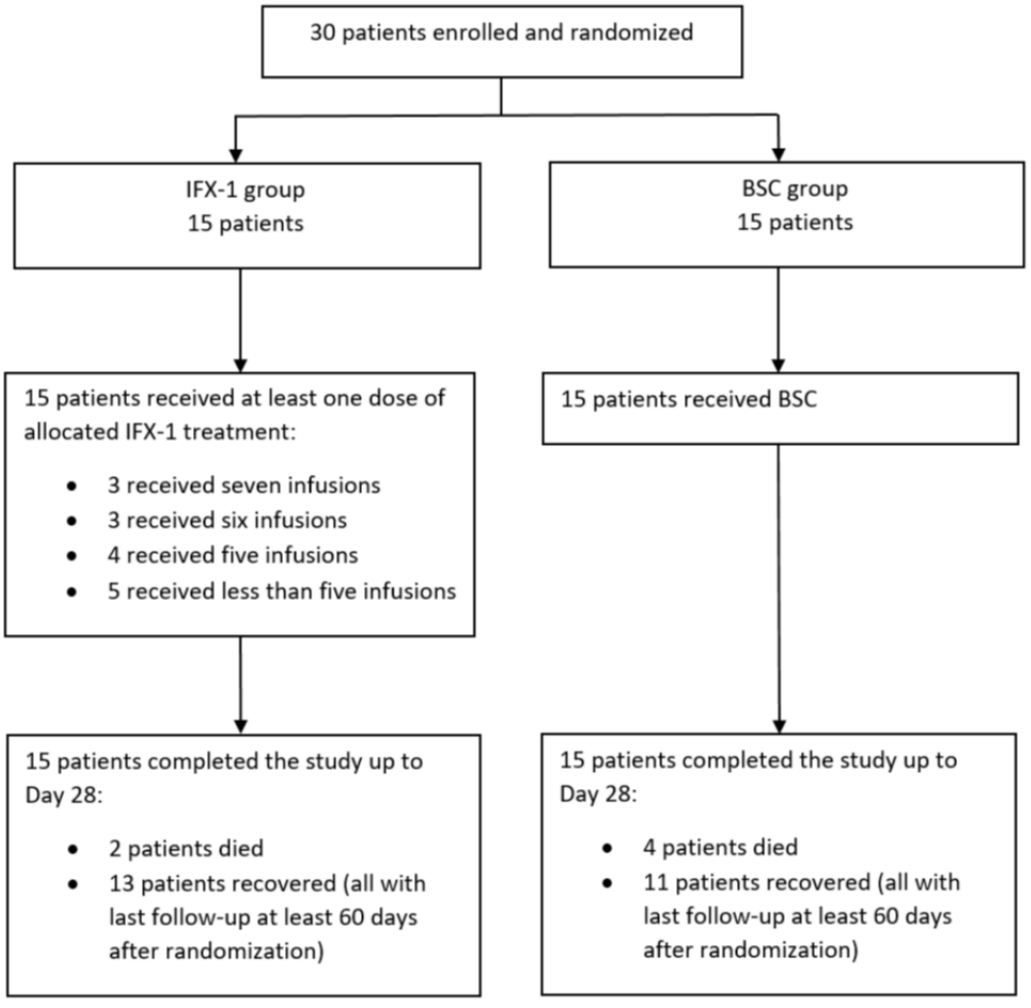
Safety Analyses

The occurrence of AEs will be compared between treatment arms. Treatment-emergent AEs (TEAEs) will be analysed according to the number and percentage of subjects who had a TEAE, as well as the number of TEAEs with the respective Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term. Additionally, the number and percentage of subjects with TEAEs will be further grouped by severity and causal relationship. The number and percentage of subjects with SAEs and the number of SAEs will be analysed. Where AEs are grouped by severity or relationship, the maximum severity/relationship per Subject and class of AE will be considered.

The Phase II study was hypothesis generating and not powered to show statistically significant differences in clinical endpoints. The interim analysis supported changes made in the protocol for the Phase III study regarding efficacy endpoints and safety measures.

Results

Participant flow



Note: Patients randomized to IFX-1 group received IFX-1 + BSC and patients randomized to BSC group received BSC only.
BSC = Best Supportive Care

Recruitment

Study location

The Phase II part of the study was conducted at 3 sites in the Netherlands.

Study period

First patient, first visit: 31-Mar-2020 for Phase II

Last patient, last visit: 08-Jul-2020 for Phase II

Conduct of the study

Protocol Amendments

Phase II part of the study was conducted in the Netherlands according to two protocol versions (V1.2 and V1.4).

Table 14 presents the protocol document history and summarises the key changes to each previous protocol version. The original protocol was amended four times. Patients were enrolled under Protocol V1.2 (dated 28-Mar-2020) and V1.4 (dated 09-Apr-2020).

Table 14: Protocol development history

Protocol version	Date submitted	Date approved	Summary of changes to previous version	Patients enrolled under this version (Yes/No)
1.0	24-Mar-2020	Not approved	Original protocol	No
1.1	27-Mar-2020	Not approved	Incorporated electronic randomization, added in protocol. Added day of primary endpoint (D5)	No
1.2 (First patient enrollment)	28-Mar-2020	29-Mar-2020	Added details of consent procedure in section 6.4 Updated safety section 9.2 (not all SAEs to be documented immediately). Added independent DSMB, paragraph 5.3 Added paragraph about privacy and handling of personal data and material, appendix 2, section IV Added clarification about handling of biospecimen and to ensure that this topic is consistently documented throughout the protocol, General Review and Registration form (Dutch: Algemeen Beoordelings- en Registratieformulier = ABR) and ICF.	Yes
1.3	01-Apr-2020	Not approved	Procedure for deferred consent has been adjusted: to strive for legal representative consent by telephone before 2nd IMP administration, of which is also confirmation per email or if no email available, to have 2nd investigator present during phone call. Exclusion criteria related to COPD is updated: Class C or D according to GOLD-classification added Table 1 updated: timing of consent adjusted Figure 1 updated: to make more clear that extra IMP dose between D11 and D13 can occur.	No
1.4 (Amended)	10-Apr-2020	11-Apr-2020	Updated section to reflect the most current version of the "Procedure telefonisch consent en email". Textual adjustments in protocol as ICF was targeting patients on ICU who were intubated, however also non-intubated and severe COVID-19 patients could comply to in- and exclusion criteria.	Yes

Changes in the Planned Analysis

The analyses of early and late response as planned in the protocol were not performed due to limited data available to confirm whether patients were to be counted as responders. For example, for the evaluation of early response, there were patients for whom documentation of white blood cell count was insufficient to clearly state whether and when a patient became a responder or not.

The intubation status as baseline covariate for time to ICU discharge was dropped, since all patients starting on ICU were also intubated at baseline. eGFR and eGFR in categories was added as an additional endpoint not mentioned in the protocol.

Baseline data

Table 15: Demographics and other baseline characteristics (full analysis set)

	Total (N=30) n (%)	IFX-1 + BSC (N=15) n (%)	BSC (N=15) n (%)
Sex [n (%)]			
Female	8 (26.7%)	4 (26.7%)	4 (26.7%)
Male	22 (73.3%)	11 (73.3%)	11 (73.3%)
Age at screening [years]			
n	30	15	15
Mean (SD)	60.2 (8.7)	57.5 (8.6)	62.8 (8.1)
Min – Max	41 – 75	41 – 73	49 – 75
Median (Q1-Q3)	60.5 (55.0 – 66.0)	59.0 (51.0 – 62.0)	62.0 (56.0 – 70.0)
Age categories [n (%)]			
≥ 18 and < 65 years	22 (73.3%)	13 (86.7%)	9 (60.0%)
≥ 65 and < 85 years	8 (26.7%)	2 (13.3%)	6 (40.0%)
≥ 85 years	0 (0.0%)	0 (0.0%)	0 (0.0%)
≥ 18 and < 40 years	0 (0.0%)	0 (0.0%)	0 (0.0%)
≥ 40 and < 50 years	3 (10.0%)	2 (13.3%)	1 (6.7%)
≥ 50 and < 60 years	11 (36.7%)	6 (40.0%)	5 (33.3%)
≥ 60 and < 70 years	10 (33.3%)	5 (33.3%)	5 (33.3%)
≥ 70 and < 80 years	6 (20.0%)	2 (13.3%)	4 (26.7%)
≥ 80 years	0 (0.0%)	0 (0.0%)	0 (0.0%)
Race [n (%)]			
White	19 (63.3%)	8 (53.3%)	11 (73.3%)
Asian	7 (23.3%)	5 (33.3%)	2 (13.3%)
Black or African American	4 (13.3%)	2 (13.3%)	2 (13.3%)
BMI [kg/m^2]			
n	21	10	11
Mean (SD)	27.7 (3.6)	27.3 (4.4)	28.0 (3.0)
Min – Max	20 – 33	20 – 33	23 – 32
Median (Q1 – Q3)	28.9 (25.4 – 30.0)	27.3 (23.3 – 31.1)	29.1 (25.4 – 30.0)

BMI = body mass index, BSC = best supportive care, Max = Maximum, Min = Minimum, N = total number of patients in the corresponding treatment group, n = number of patients with available values, Q1 = first quartile, Q3 = third quartile, SD = standard deviation
Percentages are based on the number of patients in the respective cohort

Table 16: Disease characteristics (full analysis set)

	Total (N=30) n (%)	IFX-1 + BSC (N=15) n (%)	BSC (N=15) n (%)
Days since onset of first COVID-19 symptom			
n	30	15	15
Mean (SD)	11.33 (5.57)	9.80 (3.76)	12.87 (6.72)
Median	4.0 – 33.0	4.0 – 18.0	5.0 – 33.0
Minimum-Maximum	11.00 (8.00 – 13.00)	11.00 (7.00 – 12.00)	13.00 (9.00 – 14.00)
Days since COVID-19 diagnosis			
n	30	15	15
Mean (SD)	2.60 (2.04)	2.60 (2.10)	2.60 (2.06)
Median	0.0 – 6.0	0.0 – 6.0	0.0 – 6.0
Minimum-Maximum	2.00 (1.00 – 4.00)	2.00 (0.00 – 4.00)	2.00 (1.00 – 4.00)
Intubated at randomization [n (%)]			
No	12 (40.0%)	7 (46.7%)	5 (33.3%)
Yes	18 (60.0%)	8 (53.3%)	10 (66.7%)
Oxygenation support at randomization [n (%)]			
Invasive ventilation	18 (60.0%)	8 (53.3%)	10 (66.7%)
Oxygen mask	8 (26.7%)	6 (40.0%)	2 (13.3%)
Nasal cannula	4 (13.3%)	1 (6.7%)	3 (20.0%)
Status at randomization [n (%)]			
On ICU at randomization	18 (60.0%)	8 (53.3%)	10 (66.7%)
On IMC at randomization	7 (23.3%)	5 (33.3%)	2 (13.3%)
On normal ward at randomization	5 (16.7%)	2 (13.3%)	3 (20.0%)
Number of relevant comorbidities [n (%)] [a]			
No relevant comorbidities	10 (33.3%)	4 (26.7%)	6 (40.0%)
1 relevant comorbidity	15 (50.0%)	7 (46.7%)	8 (53.3%)
2 relevant comorbidities	4 (13.3%)	3 (20.0%)	1 (6.7%)
3 relevant comorbidities	1 (3.3%)	1 (6.7%)	0 (0.0%)

BSC = best supportive care, ICU = intensive care unit, IMC = intermediate care, N = total number of patients in the corresponding treatment group, n = number of patients with available values, SD = standard deviation
Percentages are based on the number of patients in the respective cohort
[a] The following comorbidities were considered as relevant prognostic factors: hypertension, diabetes, chronic lung disease (COPD / asthma), severe cardiovascular disease (coronary artery disease), severe liver disease (liver fibrosis), cancer or being immunocompromised (HIV, transplant patients, pancytopenia, others).

All patients tested positive for SARS-CoV-2 infection within 14 days prior to or within 24h after enrolment, per protocol inclusion criteria.

Table 17: COVID-19 symptoms reported for at least 2 patients by MedDRA PT (full analysis set)

MedDRA Preferred Term	Total (N=30) n	(%)	IFX-1 + BSC (N=15) n	(%)	BSC (N=15) n	(%)
Any symptom	**30**	**(100.0)**	**15**	**(100.0**	**15**	**(100.0)**
Dyspnoea	28	(93.3)	14	(93.3)	14	(93.3)
Cough	21	(70.0)	10	(66.7)	11	(73.3)
Pyrexia	11	(36.7)	5	(33.3)	6	(40.0)
Fatigue	4	(13.3)	1	(6.7)	3	(20.0)
Malaise	4	(13.3)	3	(20.0)	1	(6.7)
Decreased appetite	3	(10.0)	1	(6.7)	2	(13.3)
Headache	3	(10.0)	1	(6.7)	2	(13.3)
Nausea	3	(10.0)	1	(6.7)	2	(13.3)
Ageusia	2	(6.7)	1	(6.7)	1	(6.7)
Chest pain	2	(6.7)	1	(6.7)	1	(6.7)
Diarrhoea	2	(6.7)	1	(6.7)	1	(6.7)
Hypoxia	2	(6.7)	2	(13.3)	0	(0.0)

BSC = best supportive care, Medical Dictionary for Regulatory Activities, N = total number of patients in the corresponding treatment group, n = number of patients with a COVID-19 history with the corresponding preferred term and cohort; PT = Preferred Term
Percentages are based on the number of patients in the respective cohort
Coding based on the MedDRA version 23.0 (including COVID-19 related terms)
SARS-CoV-2 infection confirmation (tested positive in last 14 days or test results to be obtained within 24h after enrollment

Table 18: Concomitant diseases reported for at least 3 patients by MedDRA SOC and PT (full analysis set)

MedDRA System Organ Class Preferred Term	Total (N=30)		IFX-1 + BSC (N=15)		BSC (N=15)	
	n	(%)	n	(%)	n	(%)
Any	**29**	**(96.7%)**	**14**	**(93.3%)**	**15**	**(100.0%)**
Metabolism and nutrition disorders	**21**	**(70.0%)**	**10**	**(66.7%)**	**11**	**(73.3%)**
Type 2 diabetes mellitus[a]	7	(23.3%)	3	(20.0%)	4	(26.7%)
Obesity	6	(20.0%)	2	(13.3%)	4	(26.7%)
Hypokalaemia	5	(16.7%)	3	(20.0%)	2	(13.3%)
Hypercholesterolaemia	3	(10.0%)	3	(20.0%)	0	(0.0%)
Vascular disorders	**12**	**(40.0%)**	**6**	**(40.0%)**	**6**	**(40.0%)**
Hypertension	9	(30.0%)	6	(40.0%)	3	(20.0%)
Respiratory, thoracic and mediastinal disorders	**9**	**(30.0%)**	**4**	**(26.7%)**	**5**	**(33.3%)**
Sleep apnoea syndrome	3	(10.0%)	2	(13.3%)	1	(6.7%)
Infections and infestations	**7**	**(23.3%)**	**3**	**(20.0%)**	**4**	**(26.7%)**
Cardiac disorders	**6**	**(20.0%)**	**3**	**(20.0%)**	**3**	**(20.0%)**
Atrial fibrillation	3	(10.0%)	2	(13.3%)	1	(6.7%)
Coronary artery disease	3	(10.0%)	1	(6.7%)	2	(13.3%)
Musculoskeletal and connective tissue disorders	**6**	**(20.0%)**	**4**	**(26.7%)**	**2**	**(13.3%)**
Gastrointestinal disorders	**5**	**(16.7%)**	**3**	**(20.0%)**	**2**	**(13.3%)**
Nervous system disorders	**5**	**(16.7%)**	**2**	**(13.3%)**	**3**	**(20.0%)**
Hepatobiliary disorders	**4**	**(13.3%)**	**3**	**(20.0%)**	**1**	**(6.7%)**
Psychiatric disorders	**4**	**(13.3%)**	**1**	**(6.7%)**	**3**	**(20.0%)**
Endocrine disorders	**3**	**(10.0%)**	**1**	**(6.7%)**	**2**	**(13.3%)**
Surgical and medical procedures	**3**	**(10.0%)**	**0**	**(0.0%)**	**3**	**(20.0%)**

Overall, the baseline characteristics are comparable between treatment groups in this relatively small study.

Numbers analysed

A total of 30 patients were enrolled and randomised in the study and were included in the FAS. All of the 15 patients randomised in the IFX-1 group received at least 1 dose of study drug. All efficacy, safety, and PK/PD analyses were based on the FAS.

Outcomes and estimation

Primary endpoint

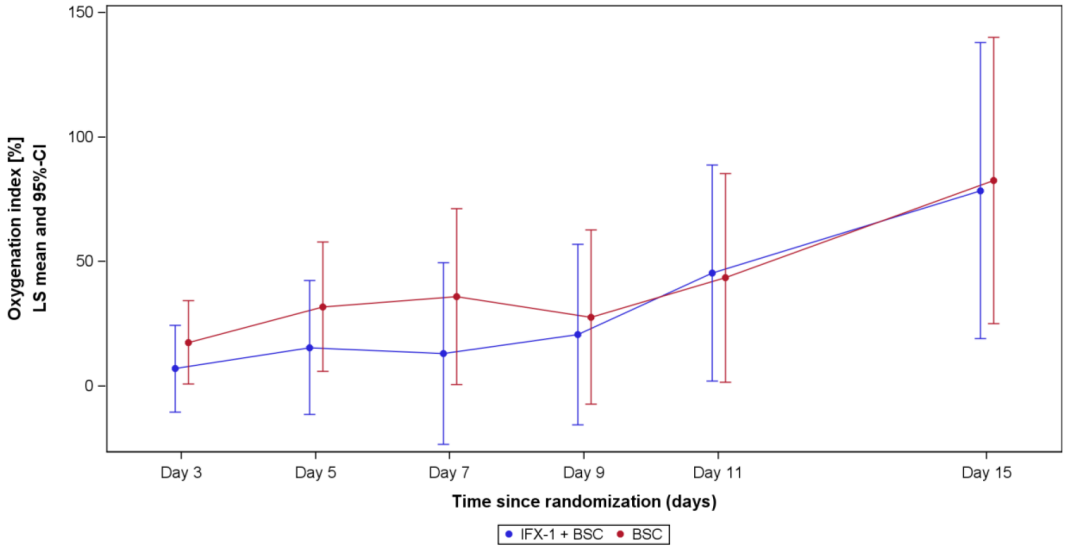
Analysis of derived PaO2/FiO2 measured in the supine position according to the protocol at Day 5 (primary outcome) demonstrated that mean (SD) values were 148.2 (77.8) mmHg (range 0–263 mmHg) in the IFX-1 group and 181.6 (93.5) mmHg (range 61–329 mmHg) in the BSC group. Linear repeated measures modelling for the primary endpoint of relative change in PaO2/FiO2 was performed with adjustment for the covariates of baseline PaO2/FiO2, time point, sex, age, and intubation status. The relative LS-mean change in PaO2/FiO2 at Day 5 showed a 15.5% increase in the IFX-1 group versus a 31.9% increase in the BSC group, with no statistically significant between-group difference observed (–16.4% [95% CI –53.2; 20.3]; p=0.3677).

Table 19: Primary analysis: LS means for relative change in oxygenation index (supine position ≥ 2 hours) (full analysis set)

	Arithmetic mean	LS mean	SE LS means	95% CI*	p-value
Day 3					
IFX-1 + BSC	-0.2	7.1	8.44	[-10.3 ; 24.4]	
BSC	11.3	17.6	8.15	[0.8 ; 34.4]	
Difference	-11.4	-10.5	11.19	[-33.6 ; 12.5]	0.3567
Day 5					
IFX-1 + BSC	8.2	15.5	13.13	[-11.4 ; 42.4]	
BSC	25.7	31.9	12.68	[6.0 ; 57.9]	
Difference	-17.5	-16.4	17.91	[-53.2 ; 20.3]	0.3677
Day 7					
IFX-1 + BSC	6.0	13.1	17.78	[-23.4 ; 49.6]	
BSC	29.6	36.0	17.17	[0.8 ; 71.2]	
Difference	-23.6	-22.9	24.47	[-73.2 ; 27.3]	0.3575
Day 9					
IFX-1 + BSC	13.8	20.7	17.65	[-15.5 ; 56.9]	
BSC	21.1	27.8	17.05	[-7.2 ; 62.8]	
Difference	-7.2	-7.1	24.29	[-57.0 ; 42.8]	0.7730
Day 11					
IFX-1 + BSC	38.0	45.5	21.12	[2.1 ; 88.9]	
BSC	37.4	43.5	20.40	[1.7 ; 85.4]	
Difference	0.7	1.9	29.16	[-58.0 ; 61.9]	0.9473
Day 15					
IFX-1 + BSC	70.6	78.5	28.92	[19.1 ; 138.0]	
BSC	76.9	82.6	27.94	[25.2 ; 140.0]	
Difference	-6.3	-4.1	40.08	[-86.5 ; 78.3]	0.9192

BSC = best supportive care, CI = confidence interval, LS = least squares, SE = standard error
*Wald-type 95 % CIs

Figure 10: Primary analysis: LS means plot of relative change in oxygenation index (supine position ≥ 2 hours) by day since randomisation (full analysis set)



BSC = best supportive care, CI = confidence interval, LS = least squares
Solid lines interpolate between the LS-means (dots) at the study days of interest; 95% CIs included (vertical lines).

The Phase II was not powered to show statistically significant differences in clinical endpoints and the primary endpoint LS mean relative change in PaO2/FiO2 at Day 5 was not met. The PaO2/FiO2 ratio showed overall large variability.

Sensitivity Analysis

During the course of the study, several patients had to be placed in the prone position due to severe hypoxaemia and could therefore not be assessed regularly in the supine position as required by the study protocol. Thus, the primary endpoint of Oxygenation Index (in supine position) contained a high number of missing values, which were imputed using linear interpolation and last observation carried forward methods, limiting the validity of the endpoint. Thus, a sensitivity analysis of the primary endpoint using all recorded Oxygenation Index values (irrespective of position) was performed. Sensitivity analysis of derived PaO2/FiO2 (using all Oxygenation Index values, including baseline value independent of positioning of patients) at Day 5 after randomisation showed that mean (SD) PaO2/FiO2 was 158.1 (62.6) mmHg (range, 84–265 mmHg) in the IFX-1 group and 189.0 (88.8) mmHg (range, 71–329 mmHg) in the BSC group. The relative LS-mean change at Day 5 showed a 17.0% increase in the IFX-1 group versus a 41.4% increase in the BSC group, with no statistically significant difference between-group difference observed (–24.4% [95% CI –58.0; 9.3]; p=0.1495). LS-mean changes in Oxygenation Index at the other time points were also not significantly different between the two groups.

Secondary Efficacy Endpoints

Overall Survival and 28-day Mortality

Table 20: All-cause mortality at day 28 and Cox model for all-cause mortality (full analysis set)

Treatment group	Number of deaths (n, %)	28-day mortality [%]*	95% CI*
IFX-1 + BSC (N=15)	2 (13.3%)	13.33%	[0.00% ; 30.54%]
BSC (N=15)	4 (26.7%)	26.67%	[4.29% ; 49.05%]

Parameter	HR	95% CI*	p-value
Treatment (IFX-1 + BSC)	0.651	[0.103 ; 4.135]	0.6494
Sex (male)	0.259	[0.034 ; 1.972]	0.1920
Age (1 year increment)	1.168	[1.011 ; 1.348]	0.0349
Baseline Oxygenation Index (1 mmHg increment)	0.969	[0.935 ; 1.003]	0.0765

BSC = best supportive care, CI = confidence intervals, HR = hazard ratio
A patient was right-censored at his/her time of last available measurement, if the patient had no documented discharge/death/safety follow-up.
*Derived from the 'one minus Kaplan-Meier estimator' for overall survival and its linear (Wald-type) confidence intervals evaluated 672h (day 28) post randomization.

Overall, 2 patients in the IFX-1 group and 4 patients in the BSC group died. Kaplan-Meier estimates of mortality by 28 days were 13.33% (95% CI 0.00, 30.54) for IFX-1 and 26.67% (95% CI 4.26; 49.05) for BSC. The adjusted hazard ratio (HR) for death was 0.651 (95% CI 0.103; 4.135).

In the vilobelimab group, 1 patient died after a tube failure with resulting severe hypoxia, and 1 patient with a history of severe COPD died due to respiratory failure. In the BSC group, all 4 patients died of COVID-19-induced multiorgan failure.

Other endpoints

Kidney function: 3% change (improvement) from baseline at Day 15 in mean eGFR in the vilobelimab + BSC group versus –14% change (worsening) in the control group [difference 17% (95% CI –8 43)]).

Lymphocytopenia: Normalised by Day 15 in 13 patients [87%] in the vilobelimab + BSC group and in 7 patients [47%] in the control group).

Induced marker of fibrinolysis (D-dimers): Within the first 2 days relative increase of 170% in the vilobelimab + BSC group vs 23% in the control group was observed. At 4 days increases of 268% vs 54% in the vilobelimab + BSC group and the control group, respectively, was observed.

Ancillary analyses

Not applicable

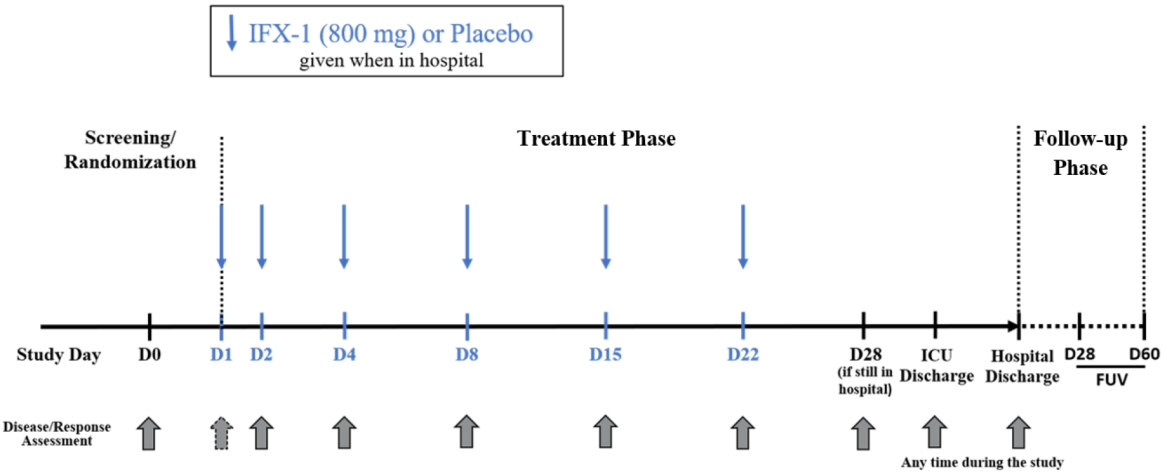
"PANAMO" Phase III Study

Title: A Pragmatic Adaptive Open-label Randomized Phase II/III Multicenter Study of IFX-1 in Patients With Severe COVID- 19 Pneumonia Methods

The Phase III part was a 1:1 randomised, double-blind, placebo-controlled multicentre study evaluating vilobelimab for the treatment of invasively mechanically ventilated critically ill COVID-19 patients. In both treatment arms standard of care (SOC) was also allowed.

The design of Phase III was based on an evaluation of the Phase II part.

Table 21: Phase III design



D = day; FUV = follow-up visit; ICU = intensive care unit; IMP = investigational medicinal product

Methods

Study Participants

Inclusion Criteria

Patients had to meet all of the following criteria at randomisation to be enrolled into Phase III of the study:

1. At least 18 years of age or older
2. Patient on invasive mechanical ventilation (but not more than 48 hours post intubation at time point of first IMP administration)
3. Patients with a PaO2 / FiO2 ratio of < 200 and > 60 at randomisation (one representative measurement within 6 hours before randomisation)
4. SARS-CoV-2 infection confirmation (tested positive in last 14 days before randomisation with locally available test system)

Exclusion Criteria

Patients who fulfilled any of the following criteria at randomisation were not eligible to participate in Phase III of the study:

1. Intubated > 48 hours at time point of first IMP administration
2. Expected stop of invasive ventilation or expected extubation in the next 24 hours without additional intervention according to judgment of the Investigator
3. Known history of chronic dialysis OR received renal replacement therapy in past 14 days OR anticipated to receive renal replacement therapy within 24 hours after randomisation
4. Known history of progressed COPD as evidenced by use of daily maintenance treatment with long-acting bronchodilators or inhaled/oral corticosteroids for more than two months
5. Treatment of COVID-19 with investigational antibody treatment(s) which were not approved or not included in locally adopted treatment guidelines (e.g., WHO guidance, National Institutes of Health [NIH] COVID-19 treatment guidelines) for this indication in the past seven days (Note: Antibody treatment[s] given within past seven days for pre-existing diseases, other than COVID-19, were allowed.)
6. At time point of randomisation, treatment of COVID-19 with investigational treatments which were not approved or not included in locally adopted treatment guidelines for this indication (e.g., WHO guidance, NIH COVID-19 treatment guidelines), including SARS-CoV-2 multiplication inhibitor(s) or immunomodulator(s). (Note: If a locally adopted treatment guideline recommended drugs such as remdesivir, dexamethasone, or anticoagulation, this would be allowed. Adopted guidelines and updates had to be documented at study initiation and throughout the conduct of the study.)
7. Received cytokine adsorption therapy in past three days
8. Known hypersensitivity to IFX-1 or any other ingredient of the study medication
9. Serum or urine pregnancy test positive before randomisation (required for women of childbearing potential)
10. Received organ or bone marrow transplantation in past three months
11. Known cardio-pulmonary mechanical resuscitation in past 14 days
12. Patient moribund or expected to die in next 24 hours according to the judgment of the investigator
13. Known to have received anti-cancer therapy for haemato-oncological disease in past four weeks OR known to have active malignant disease at time point of randomisation
14. Known severe congestive heart failure (corresponding to e.g. NYHA Class III-IV, left ventricular ejection fraction < 40%)
15. Known history of chronic liver disease (Child-Pugh B or C)
16. Participating in or has participated in other investigational interventional studies (drug or device) within the last seven days before randomisation

The inclusion criteria and exclusion criteria are adequate and reflect a patient population with acute respiratory distress syndrome due to COVID-19, requiring mechanical ventilation.

Treatments

Patients were assigned to one of the following treatment groups in a ratio of 1:1:

Patients were treated with a maximum of 6 intravenous (IV) doses of vilobelimab 800 mg + SOC (Arm A) or Placebo + SOC (Arm B) at Days 1, 2, 4, 8, 15, and 22, as long as the patient was still hospitalised (even if discharged from the intensive care unit [ICU]).

In addition to the IMP, all patients received SOC for the treatment of COVID-19, which included venous thromboembolism prophylaxis with anticoagulants at a minimum. Other international or country-specific recommended treatments for COVID-19 per the locally adopted treatment recommendations (including but not limited to corticosteroids, COVID-19 therapies [tocilizumab, baricitinib and remdesivir], and other locally adopted SOC) were allowed as concomitant medications. SOC treatment was given at the Investigator's discretion and could start and stop at any time.

Since the SoC was expected to evolve rapidly during the conduct of the Phase III (Oct 2020 to Nov 2021), the protocol permitted SoC according to established local and national guidelines.

Corticosteroids for systemic use were used by a total of 171/177 (96.6%) patients in the vilobelimab group and 181/191 (94.8%) patients in the placebo group. Thus, there is no efficacy demonstration in the absence of systemic corticosteroids which is reflected in the indication statement.

Objectives

Primary Objective

The primary objective of Phase III was to demonstrate the efficacy of vilobelimab to improve survival outcomes of invasively mechanically ventilated COVID-19 pneumonia patients (confirmative).

Secondary Objectives

The secondary objectives of Phase II and Phase III were:

• To assess and define other parameters of efficacy

• To assess the safety of vilobelimab

Outcomes/endpoints

Primary Endpoint

Based on the preliminary interim analysis of efficacy data from Phase II, the primary endpoint chosen for Phase III was 28-day all-cause mortality.

Secondary Endpoints

The secondary efficacy endpoints in Phase III were:

- 60-day all-cause mortality (proportion of patients deceased until Day 60)
- Proportion of patients with an improvement in the 8-point ordinal scale (Day 15, Day 28)
- Proportion of patients developing acute kidney failure (eGFR < 15 mL/min/1.73m², assessed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation requiring race information) during ICU stay and at Day 28
- Proportion of patients free of any renal replacement therapy (RRT) within 28 days upon randomisation.

Other Endpoints

The other endpoints in Phase III were:

- Time to first extubation (time to first end of invasive lung support)
- Proportion of patients achieving 8-point ordinal scale score 3 or below (patients alive and free of respiratory failure) at Day 15 and Day 28
- Glasgow Outcome Scale score assessed at Day 60
- Quality of life assessed by EuroQol 5D (EQ-5D) at Day 60.

Safety Endpoints

The safety endpoints in Phase III were:

- Frequency, severity, and relatedness to study drug of treatment-emergent adverse events (TEAEs) and serious TEAEs (SAEs).

Sample size

The planned sample size was 360 patients (180 per arm), which was estimated to yield 90% power to show efficacy in the primary analysis. This calculation assumed a 28-day mortality of 30% in the placebo arm and 15% in the treatment arm (that is, a 50% reduction) and a one-sided significance level of 2.5%.

In a protocol amendment, the applicant decided to increase the sample size to account for screening failures (patients who were randomised despite being ineligible for the trial) and patients who withdrew consent within 48 hours after randomisation. The protocol amendment did not specify how much the sample size would be increased, but the statistical analysis plan later clarified that it would be increased by approximately 10%, resulting in a total of approximately 400 patients.

The applicant performed one interim analysis when half of the patients had been randomised. Initially, the applicant had planned to stop both for futility and efficacy, but the plan to stop for efficacy was removed in a protocol amendment.

Randomisation and blinding (masking)

Patients were assigned to treatments through an Interactive Web Response System. Patients were assigned to one of the following treatment groups in a ratio of 1:1:

- Arm A: 800 mg VILO + SOC (henceforth referred to as the VILO group)
- Arm B: Placebo + SOC (henceforth referred to as the Placebo group)

Randomisation was stratified by site. Variable block sizes of 2 or 4 were used. Small sites were allowed to use only a block size of 4 and large sites were allowed to use block sizes of only 2.

The block size was described in the document RTSM Specification and Randomization Unblinding Addendum. Only unblinded personnel had access to this document. The block size was not disclosed in the study protocol.

Patients, Investigators and clinical site staff, persons performing the assessments, and data analysts remained blinded to the identity of the treatment during the entire course of the study until database lock, using the following methods: (1) randomisation data were kept strictly confidential until the time of unblinding, and were not accessible by anyone else involved in the study, except for the IDMC

Statistician; (2) the identity of the treatments was concealed by the use of study drugs that were identical in packaging, labelling, schedule of administration, and appearance.

Unblinding was only permitted in the case of patient emergencies and for the IDMC including the Phase III interim analysis following Stage 1.

Procedures for emergency unblinding were in place for when knowledge of the IMP received was necessary, e.g., to be able to provide appropriate emergency medical treatment. One patient was unblinded, and this was due to breastfeeding of a mother who gave birth three days before randomisation.(see later under conduct of the study).,

Statistical methods

Analysis sets

The primary and secondary endpoints were evaluated on the full analysis set (FAS). This set was defined as all randomised patients, except for those who were randomised in error (patients who were randomised despite being ineligible for the trial) AND who did not receive IMP.

The primary and secondary endpoints were also evaluated on the per-protocol set (PPS). This set was defined as all patients who were in the FAS and did not have any major protocol deviations, as specified in the Blind Data Review Meeting (BDRM) plan.

Adverse events were evaluated on the safety analysis set (SAF). This set was defined as all patients who received at least one infusion of IMP. Patients were analysed as belonging to the treatment group if they received any VILO infusion at any timepoint; if not, they were analysed as belonging to the placebo group.

Estimands

All intercurrent events were handled using a treatment policy strategy.

Analysis methods for efficacy

A one-sided significance level of 2.5% was used in the efficacy analyses.

Cox regression, adjusted for age and site, was used to analyse mortality by Day 28 (or Day 60, for the secondary endpoint). Patients were counted as having died if a date of death or fatal adverse event had been documented, and this date occurred before Day 28 (or Day 60). Other patients were censored at Day 28 (or Day 60) or the date of last contact, whichever occurred first. The date of last contact was defined as the latest of the following dates: any documented regular or unscheduled study visit, discharge alive, (deferred) informed consent by the patient (not by relatives / investigator), or transfer to another hospital. For protocol version 2.0, unscheduled visit telephone calls at or after Day 28 were taken into account for survival status if available.

Logistic regression was used to analyse the endpoints of improvement in 8-point ordinal scale, the development of acute kidney failure, and of being alive and free of respiratory failure. These models were adjusted for age.

Ordinal logistic regression, adjusted for age, was used to analyse the Glasgow Outcome Scale.

Competing risks survival analysis was used to analyse time to first renal replacement therapy (RRT) and time to first extubation, while accounting for deaths. Cumulative incidence was calculated using a Aalen-Johansen-type estimator. The cumulative incidence curves were compared using Gray's test. The Fine and Gray subdistribution hazards regression model was also used, with adjustment for age. This

analysis provided subdistribution hazard ratios (sHRs). For instance, a sHR of 1.18 would imply an 18% increase in the (subdistribution hazard) event rate. The median time to event and its (non-parametric) 95% CI were calculated based on all patients having the event and who were alive. In order to evaluate the aetiology of the underlying processes, two cause-specific Cox regression models were also performed, with adjustment for age.

Analysis of covariance (ANCOVA) was used to analyse quality of life (EQ-5D visual analogue scale and index). These models were adjusted for age and sex.

Missing data

For the endpoint of improvement in 8-point ordinal scale, data that were missing data due to hospital discharge were imputed using multiple imputation. This imputation was based on logistic regression for a monotone missing pattern, unless the patient was discharged from the hospital (improvement assumed) or died (no improvement assumed). In this model, the explanatory variables were treatment group, age, treatment discontinuation, and last available 8-point ordinal scale score.

Missing eGFR values were also imputed using a multiple imputation based on logistic regression for a monotone missing pattern. The explanatory variables were treatment group, age, treatment discontinuation, hospital discharge (not included if the patient was in an ICU), and last available eGFR value.

Missing data for the endpoint of being alive and free of respiratory failure was imputed using the same type of multiple imputation as described above. The model included the following explanatory variables: treatment group, age, treatment discontinuation, hospital discharge, and last available 8-point ordinal scale score.

A complete-case analysis was performed for the Glasgow outcome scale and the EQ-5D endpoints.

Sensitivity analyses and supportive analyses

For patients whose survival status was unknown at Day 28, the analysis was repeated under four different scenarios: (1) all patients in both treatment groups survived, (2) all patients in both treatment groups died, (3) all patients from the placebo were assumed to have survived and all patients from the treatment group were assumed to have died (a worst case scenario), and (4) multiple imputation.

Subgroup analyses

Many subgroup analyses were pre-specified in the SAP for the primary efficacy analysis (28-day mortality):

- Site
- Country
- Region (Western Europe, South America, South Africa/Russian Federation)
- Sex
- Age group (≥18 and <40 years; ≥40 and <50 years; ≥50 and <60 years; ≥60 and <70 years; ≥70 and <80 years; ≥80 years)
- Comorbidities (Hypertension, Diabetes, Coronary Heart Disease, Chronic Obstructive Lung Disease, Carcinoma, Chronic Kidney Disease)
- Standard of care (corticosteroids for systemic use, antithrombotic agents, remdesivir, or anti-IL-6 treatment [sarilumab, tocilizumab, levilimab, siltuximab, olokizumab, or clazakizumab])

- Ordinal scale score at baseline
- BMI (<18.5, ≥18.5 and <25, ≥25 and <30, ≥30 and <35, ≥35)
- Use of antithrombotic agents (none, only prophylactic use, only therapeutic use, both prophylactic and therapeutic use)
- eGFR at baseline (<60 versus ≥60 mL/min/1.73m²)
- Bacterial infection status at baseline
- Delta variant status
- ARDS severity at baseline (mild, moderate, severe)

Time from hospitalisation to randomisation (between 0 and <3 days, between 3 and 7 days, and >7 days)Multiplicity

The secondary endpoints were ordered as follows:

1. 60-day all-cause mortality
2. Improvement in the 8-point ordinal scale at Day 15
3. Improvement in the 8-point ordinal scale at Day 28
4. Acute kidney failure during at Day 28
5. No renal replacement therapy at Day 28.

The first secondary endpoint was only tested statistically if the primary endpoint was significant. If the first secondary endpoint was also significant, the full significance level of 2.5% was passed on to the remaining secondary endpoints.

Multiplicity in the 4 remaining endpoints was addressed using the fallback method. This means that endpoints were tested sequentially, and that the significance level was divided in the following way: 2%, 0.2%, 0.2%, and 0.1%. If a test was not significant, then the next test was performed at the level specified in the list. If a test was significant, then the next test was tested at the level specified in the list plus the level used for the previous test. For example, if secondary endpoints 1-4 were all significant, the fifth secondary endpoint was tested at the 2.5% level; if endpoint 4 was not significant, then the fifth endpoint was tested at an alpha of 0.1%.

For acute kidney failure, the analysis was part of the multiple testing process up to Day 28, but the analysis of acute kidney failure during ICU stay was not (it was an exploratory analysis only)

Interim analyses

One interim analysis was conducted when half of the target sample size (180 patients) had been reached. At this time, the trial would have been stopped for futility if the z-statistic, which was obtained from the Cox model, had been 0 or less. No correction for multiplicity was done because stopping for futility does not increase the type-1 error.

Before unblinding, the applicant changed the primary analysis model from an unstratified Cox model to a site-stratified Cox model. This change was made in the statistical analysis plan but not in the final protocol. Although both analyses would be acceptable, the stratified analysis should be regarded as the primary analysis, as it was the last analysis to be specified before unblinding. The applicant also conducted post-hoc analyses, exploring different ways of pooling sites and running a random effect (frailty) model.

Multiplicity was controlled for the primary endpoint and the first 5 secondary endpoints using a combination of sequential testing and a fallback method.

Two versions of the SAP were performed : Version 01 was dated 09-Sep-2021, which means that it was finalised under the final study protocol (version 4.0, 12-May-2021) and close to the end of the trial (last patient's last visit: 01-Dec-2021). The main difference between version 01 and version 02 is that version 02 states that the primary analysis should be stratified by site.

Results

Participant flow

Figure 11: Flowchart of patient disposition (all randomised patients)

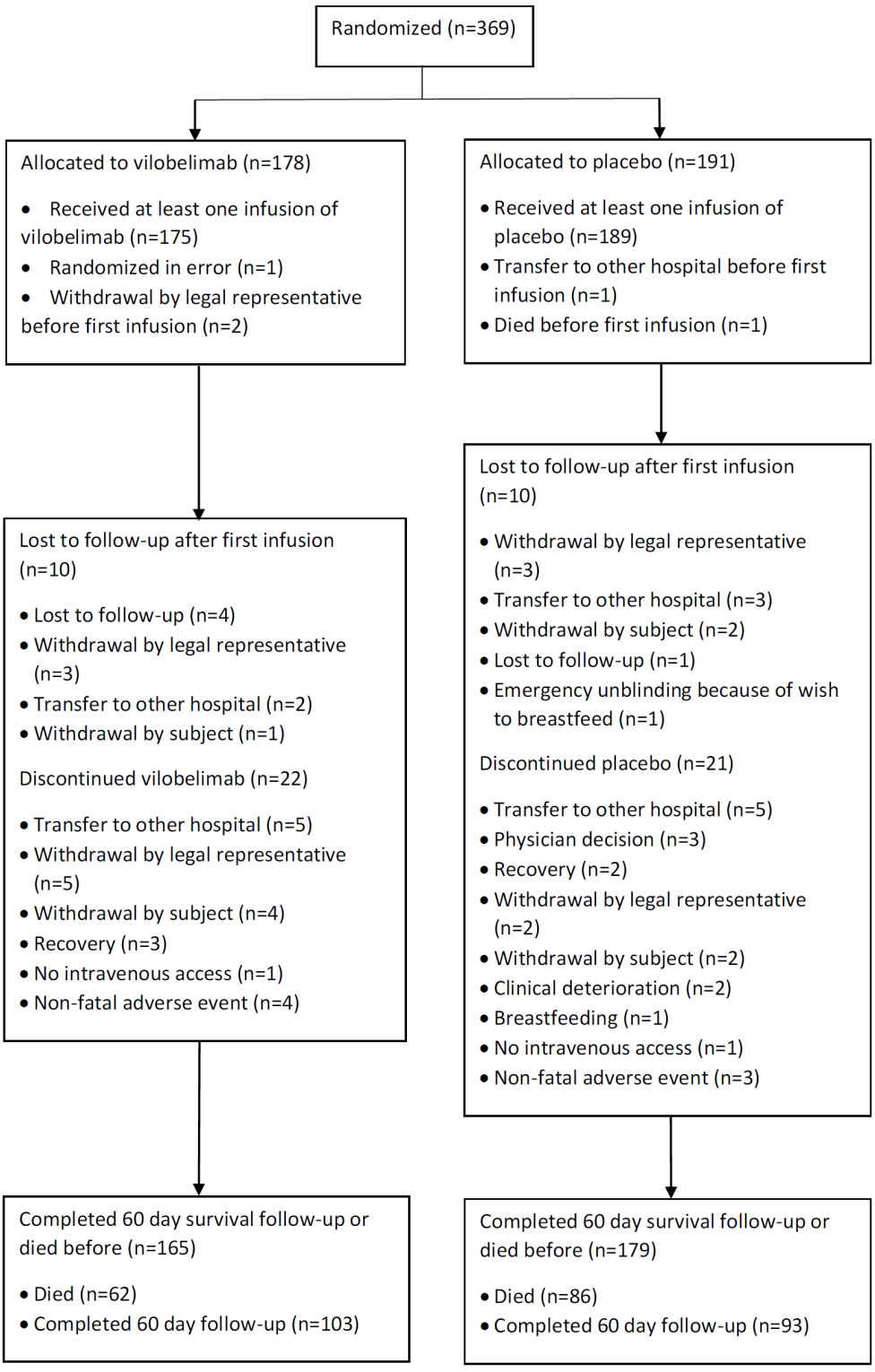


Table 22: Patient disposition (all randomised population)

	VILO+SOC (N = 178) n	(%)	Placebo+SOC (N = 191) n	(%)	Total (N = 369) n	(%)
Patients randomized	178	(100.0%)	191	(100.0%)	369	(100.0%)
Netherlands	69	(38.8%)	70	(36.6%)	139	(37.7%)
Germany	10	(5.6%)	11	(5.8%)	21	(5.7%)
Mexico	18	(10.1%)	19	(9.9%)	37	(10.0%)
Peru	6	(3.4%)	9	(4.7%)	15	(4.1%)
Brazil	34	(19.1%)	40	(20.9%)	74	(20.1%)
Russian Federation	11	(6.2%)	12	(6.3%)	23	(6.2%)
France	17	(9.6%)	18	(9.4%)	35	(9.5%)
Belgium	8	(4.5%)	7	(3.7%)	15	(4.1%)
South Africa	5	(2.8%)	5	(2.6%)	10	(2.7%)
Western Europe	104	(58.4)	106	(55.5%)	210	(56.9%)
South America	58	(32.6%)	68	(35.6%)	126	(34.1%)
South Africa/Russian Federation	16	(9.0%)	17	(8.9%)	33	(8.9%)
Patients randomized in error	1	(0.6%)	0	(0.0%)	1	(0.3%)
Patients with early withdrawal within 48 hours after randomization	5	(2.8%)	0	(0.0%)	5	(1.4%)
Patients treated with at least one IMP dose	175	(98.3%)	189	(99.0%)	364	(98.6%)
Completed alive[a]	103	(57.9%)	93	(48.7%)	196	(53.1%)
Deceased after randomization before Day 28	54	(30.3%)	77	(40.3%)	131	(35.5%)
Deceased between Day 28 and Day 44	7	(3.9%)	8	(4.2%)	15	(4.1%)
Deceased between Day 45 and Day 60	1	(0.6%)	2	(1.0%)	3	(0.8%)
Premature study termination for reasons other than death	13	(7.3%)	11	(5.8%)	24	(6.5%)
Premature termination of treatment without termination of study	9	(5.1%)	6	(3.1%)	15	(4.1%)
Reasons for premature study termination	75	(42.1%)	98	(51.3%)	173	(46.9%)
Death	62	(34.8%)	87	(45.5%)	149	(40.4%)
Withdrawal by legal representative	5	(2.8%)	3	(1.6%)	8	(2.2%)
Other[b]	2	(1.1%)	5	(2.6%)	7	(1.9%)
Lost to follow-up	4	(2.2%)	1	(0.5%)	5	(1.4%)
Withdrawal by patient	1	(0.6%)	2	(1.0%)	3	(0.8%)
Randomized in error	1	(0.6%)	0	(0.0%)	1	(0.3%)
Reasons for premature treatment termination	71	(39.9%)	87	(45.5%)	158	(42.8%)
Adverse event[c]	50	(28.1%)	68	(35.6%)	118	(32.0%)

	VILO+SOC (N = 178) n	(%)	Placebo+SOC (N = 191) n	(%)	Total (N = 369) n	(%)
Other[b]	8	(4.5%)	9	(4.7%)	17	(4.6%)
Withdrawal by legal representative	7	(3.9%)	2	(1.0%)	9	(2.4%)
Withdrawal by patient	3	(1.7%)	1	(0.5%)	4	(1.1%)
Recovery[d]	2	(1.1%)	2	(1.0%)	4	(1.1%)
Physician decision	0	(0.0%)	3	(1.6%)	3	(0.8%)
Clinical deterioration	0	(0.0%)	2	(1.0%)	2	(0.5%)
Randomized in error	1	(0.6%)	0	(0.0%)	1	(0.3%)
Protocol version						
2.0	66	(37.1%)	69	(36.1%)	135	(36.6%)
3.0 or later	112	(62.9%)	122	(63.9%)	234	(63.4%)

IMP = investigational medicinal product, SOC = standard of care, VILO = vilobelimab

a Patients completing the study alive were defined as patients who completed the follow-up visit Day 60 alive.

b A majority of these patients were transferred to another hospital (Listing 16.2.1.3).

c A total of 111 patients (30.1%) had fatal AEs (VILO, 46 patients [25.8%]; Placebo, 65 patients [34.0%]).

d 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 randomized patients in the respective treatment group.

A total of 18 patients discontinued the study due to a transfer to another hospital, 12 of whom performed the Day 60 follow-up (counted as study completers), and 6 of whom did not (counted as premature study terminations).

The majority of patients were enrolled in Western Europe (56.9%) and South America (34.1%) and 98.6% were treated with at least one IMP dose. Overall, the disposition of patients was comparable between the vilobelimab and placebo groups.

Recruitment

Study period

First patient, first visit: 01-Oct-2020 for Phase III

Last patient, last visit: 01-Dec-2021 for Phase III

Study sites

46 sites in nine countries: France (10 sites), Brazil (seven sites), Germany (seven sites), Mexico (six sites), Netherlands (five sites), Belgium (four sites), Peru (three sites), Russian Federation (three sites), and South Africa (one site)

Conduct of the study

The clinical study protocol (CSP) was amended three times.

Amended Protocol Version 2.0, Dated 30-Jul-2020:

Amendment 1 was issued after completion of the explorative Phase II part of this adaptive study (30 patients). Based on interim analysis results and discussion with the Expert Committee, the Phase III design was established. The changes in this amendment primarily included the addition of information on the updated study design, endpoints, conduct, treatment administration, and statistical methods.

Amended Protocol Version 3.0, Dated 17-Dec-2020:

The changes introduced in this amendment primarily included the accounting for drop-outs/replacement patients and corresponding adaptations of the overall patient number and statistical analysis sets, specific timing of intubation in relation to the first IMP administration (inclusion and exclusion criteria), specifications regarding the diverse consenting options in an ICU setting, modifications of the Schedule of Assessments including timing of assessments and the follow-up visit, emergency unblinding procedure added, and clarifications on AE reporting.

Amended Protocol Version 4.0, Dated 12-May-2021:

Amendment 3 was issued following scientific advice recommendations of the USA FDA and the European Medical Agency; the following changes were introduced:

- Removed the statistical 'stop for efficacy' criterion for the interim analysis, adapted the power calculation, clarified the randomisation of additional patients, upgraded the '60-day mortality' endpoint to the first secondary endpoint, adapted the order of the secondary endpoints, and added an exploratory endpoint. These adaptations were performed to eliminate statistical concerns of regulatory authorities about the early stop for efficacy at the interim analysis and to clarify the final analysis.
- Increased the number of sites from 45 to 60 sites to improve the ability to enrol the study in a timely manner.

In the second amendment Version 3.0 an additional 24 h was added for IMP treatment after randomisation to give more leeway for preparation and provision. This change led to a specification of the inclusion criterion no 2.; Patient on invasive mechanical ventilation (but not more than 48h post intubation at time point of first IMP administration) to ensure the correct target population was included.

To ensure collection of 28-day data (primary efficacy endpoint) in case patient may be discharged from the hospital before, the day 28 follow-up visit with respective assessments was added to the time schedule (and remained as a treatment period visit when the patient is still in the hospital).

Changes in the Planned Analysis

The following changes or deviations from analyses planned in the study protocol were made in the SAP before unblinding.

The planned analysis that was pre-specified in the study protocol for the primary endpoint of 28-day all-cause mortality was Cox regression analysis adjusting for age, without considering the randomisation stratification. The protocol-specified approach was later changed to site-stratified Cox regression analysis adjusting for age, upon recommendation by the US FDA to consider an analysis approach accounting for the randomisation stratification. The analysis of the secondary endpoint of 60-day all-cause mortality was also changed in the SAP to a site-stratified Cox regression analysis. Additionally, rather than analysing the simple proportion of patients with or without RRT (as specified in the protocol), the time to initiation of RRT was analysed using time-to-event methods for competing risks to estimate the proportion of patients who required RRT. This was done to take into account the competing risk of death.

Emergency Unblinding of Treatment Assignment

Unintended emergency unblinding of one patient occurred during the study on 26-Jan-2021 due to breastfeeding of a mother who gave birth three days before randomisation (24-Jan-2021) into the study. Breastfeeding would not have been possible shortly after treatment termination according to the Core study protocol (CS) and Individual Case Form (ICF) stipulations for male patients, which was

transferred to breastfeeding female patients (i.e., "… male patient with a pregnant or breastfeeding partner, you must also remain abstinent … throughout the study and until 3 months after the last dose of the study drug."), if the applied study drug was vilobelimab. To obtain this necessary information, the patient was unblinded. No changes were made to the protocol or SAP due to the unplanned unblinding and all staff involved in preparation and finalisation of the SAP were not aware of the treatment allocation of any patient. The study proceeded as originally planned. This single case of unblinding is understood and unlikely impacted the overall outcome.

Before unblinding, the applicant changed the primary analysis model from an unstratified Cox model to a site-stratified Cox model. This change was made in the statistical analysis plan (SAP) but not in the protocol. The change was made because it was anticipated that even within a country or region, variability in background mortality could be high across sites. Although both an unstratified and a site-stratified analysis would be acceptable, the stratified analysis should be regarded as primary, as it was the last to be specified before unblinding. Since the change in the SAP was introduced before unblinding, it is considered acceptable.

Changes Following Study Unblinding and Post-hoc Analyses

After study unblinding, it was considered to pool sites which only contributed small patient numbers. Pooling sites by medically meaningful factors was taken into consideration but was difficult due to these factors being either partially unknown or variable over the course of the trial. Based on these considerations, the following analysis approaches were chosen for the primary and secondary endpoints (all-cause mortality at Days 28 and 60) as post-hoc analyses:

- Age-adjusted Cox regression without site-stratification (as specified in the protocol).
- Logistic regression with mortality as a binary endpoint and multiple imputation for missing data (pre-specified supplementary analysis).
- Stratified Cox regression with various ways of pooling site information:
    - pooling by region [Western Europe, South America, and South Africa/Russian Federation]
    - pooling by country [Belgium, France, Germany, Netherlands, Brazil, Mexico, Peru, South Africa, and Russian Federation])
    - pooling sites with n<4 into one larger site by country
    - pooling sites with n<5 into one larger site by country
- Age-adjusted Cox regression with random effect for site ("frailty" model) (post-hoc analysis).
- Simple log-rank test (post-hoc analysis).

Additional post-hoc analyses included the following:

- Additional descriptive summaries and group comparisons for age by country
- Subgroup analyses for 28-day and 60-day all-cause mortality by age categories (≤ 30, 31-40, 41-50, 51-60, and > 60 years of age)
- Frequency table of survival status for 60-day all-cause mortality (to match the table for 28-day all-cause mortality)
- Analysis of 60-day all-cause mortality based on logistic regression using a multiple imputation method for missing values (to match the analysis for 28-day all-cause mortality)
- Adverse events grouped by MedDRA system organ class and high-level group term

- Adverse events grouped by MedDRA system organ class and high-level group term per 100 patient days in hospital
- Embolic and thrombotic adverse events by MedDRA high level group term per 100 patient days in hospital

Baseline data

Table 23: Demographics and other baseline characteristics (full analysis set)

	VILO+SOC (N = 177)	Placebo+SOC (N = 191)	Total (N = 368)
Race (n [%])			
White	115 (65.0%)	119 (62.3%)	234 (63.6%)
American Indian or Alaskan Native	22 (12.4%)	24 (12.6%)	46 (12.5%)
Other	16 (9.0%)	19 (9.9%)	35 (9.5%)
Not reported	14 (7.9%)	16 (8.4%)	30 (8.2%)
Black or African American	5 (2.8%)	8 (4.2%)	13 (3.5%)
Asian	4 (2.3%)	5 (2.6%)	9 (2.4%)
Multiple	1 (0.6%)	0 (0.0%)	1 (0.3%)
	VILO+SOC (N = 177)	**Placebo+SOC (N = 191)**	**Total (N = 368)**
Ethnicity (n [%])			
Not Hispanic or Latino	70 (39.5%)	73 (38.2%)	143 (38.9%)
Hispanic or Latino	60 (33.9%)	68 (35.6%)	128 (34.8%)
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 [%])			
Male	125 (70.6%)	127 (66.5%)	252 (68.5%)
Female	52 (29.4%)	64 (33.5%)	116 (31.5%)
Age (years)			
n	177	191	368
Mean (SD)	56.7 (13.2)	55.9 (14.5)	56.3 (13.9)
Min – Max	23 – 81	22 – 81	22 – 81
Median (Q1 – Q3)	58.0 (47.0 – 67.0)	57.0 (46.0 – 68.0)	58.0 (47.0 – 68.0)
Age categories (n [%])			
≥ 18 and ≤ 65 years	124 (70.1%)	133 (69.6%)	257 (69.8%)
> 65 and ≤ 85 years	53 (29.9%)	58 (30.4%)	111 (30.2%)
> 85 years	0 (0.0%)	0 (0.0%)	0 (0.0%)
≥ 18 and < 40 years	22 (12.4%)	30 (15.7%)	52 (14.1%)
≥ 40 and < 50 years	32 (18.1%)	31 (16.2%)	63 (17.1%)
≥ 50 and < 60 years	43 (24.3%)	39 (20.4%)	82 (22.3%)
≥ 60 and < 70 years	47 (26.6%)	55 (28.8%)	102 (27.7%)
≥ 70 and < 80 years	31 (17.5%)	35 (18.3%)	66 (17.9%)
≥ 80 years	2 (1.1%)	1 (0.5%)	3 (0.8%)
BMI (kg/m^2)			
n	177	191	368
Mean (SD)	31.9 (6.1)	31.9 (7.1)	31.9 (6.6)
Min – Max	22 – 54	18 – 55	18 – 55
Median (Q1 – Q3)	31.1 (27.8 – 34.5)	30.8 (26.9 – 36.5)	30.9 (27.4 – 35.5)
eGFR categories (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 (0.6%)	0 (0.0%)	1 (0.3%)
Neutrophil count (10^9/L)			
n	169	186	355
Mean (SD)	10.6 (4.6)	12.1 (11.3)	11.4 (8.8)
Min – Max	0 – 30	1 – 93	0 – 93
Median (Q1 – Q3)	10.1 (7.4 – 13.4)	9.6 (6.8 – 14.0)	9.9 (7.2 – 13.6)

	VILO+SOC (N = 177)	Placebo+SOC (N = 191)	Total (N = 368)
Lymphocyte count (10^9/L)			
n	170	185	355
Mean (SD)	0.82 (0.55)	0.79 (0.53)	0.80 (0.54)
Min – Max	0.1 – 4.0	0.1 – 4.8	0.1 – 4.8
Median (Q1 – Q3)	0.71 (0.46 – 0.93)	0.68 (0.44 – 1.01)	0.70 (0.45 – 1.00)
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 – pressors, RRT, ECMO	105 (59.3%)	132 (69.1%)	237 (64.4%)
Oxygenation index (PaO_2/FiO_2) (mmHg)			
n	177	191	368
Mean (SD)	131.9 (39.2)	130.6 (44.8)	131.2 (42.2)
Min – Max	61 – 305	61 – 417	61 – 417
Median (Q1 – Q3)	136.0 (102.0 – 162.0)	128.0 (93.0 – 163.0)	132.0 (97.0 – 162.5)
ARDS (n [%])			
Mild (< 200 mmHg < PaO_2/FiO_2 ≤ 300 mmHg)[a]	1 (0.6%)	1 (0.5%)	2 (0.5%)
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%)
Oxygenation support (n [%])			
Any organ support	177 (100.0%)	191 (100.0%)	368 (100.0%)
Mechanical ventilation	177 (100.0%)	191 (100.0%)	368 (100.0%)
Vasopressors	115 (65.0%)	136 (71.2%)	251 (68.2%)
ECMO	3 (1.7%)	3 (1.6%)	6 (1.6%)
RRT	1 (0.6%)	2 (1.0%)	3 (0.8%)
Time between onset of first COVID-19 symptoms and randomization (days)			
n	164	182	346
Mean (SD)	11.0 (5.1)	10.8 (5.5)	10.9 (5.3)
Min – Max	0 – 34	0 – 29	0 – 34
Median (Q1 – Q3)	11.0 (8.0 – 14.0)	11.0 (8.0 – 14.0)	11.0 (8.0 – 14.0)
Time between COVID-19 diagnosis and randomization (days)			
n	177	191	368
Mean (SD)	7.2 (4.8)	7.1 (4.8)	7.2 (4.8)
Min – Max	0 – 24	0 – 30	0 – 30
Median (Q1 – Q3)	7.0 (3.0 – 11.0)	7.0 (3.0 – 10.0)	7.0 (3.0 – 11.0)
Time between intubation onset and randomization (hours)			
n	167	182	349
Mean (SD)	24.0 (15.1)	22.6 (13.4)	23.2 (14.2)
Min – Max	0 – 48	1 – 48	0 – 48
Median (Q1 – Q3)	22.6 (10.1 – 39.2)	23.0 (10.1 – 32.5)	22.9 (10.1 – 35.7)
Time between intubation onset and first IMP administration (hours)			
n	165	180	345
Mean (SD)	25.9 (15.3)	24.4 (13.6)	25.2 (14.4)
Min – Max	0 – 52	3 – 51	0 – 52
Median (Q1 – Q3)	23.9 (12.0 – 41.2)	24.2 (11.5 – 35.3)	24.1 (11.6 – 38.4)

	VILO+SOC (N = 177)	Placebo+SOC (N = 191)	Total (N = 368)
Time between hospital admission and randomization (days)			
n	177	191	368
Mean (SD)	3.9 (2.9)	4.2 (4.1)	4.1 (3.6)
Min – Max	0 – 19	0 – 27	0 – 27
Median (Q1 – Q3)	3.0 (2.0 – 5.0)	3.0 (2.0 – 5.0)	3.0 (2.0 – 5.0)
Time between ICU admission and randomization (days)			
n	163	171	334
Mean (SD)	2.1 (2.1)	2.6 (3.5)	2.4 (2.9)
Min – Max	-2 – 11	0 – 22	-2 – 22
Median (Q1 – Q3)	2.0 (1.0 – 2.0)	1.0 (1.0 – 3.0)	2.0 (1.0 – 3.0)

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, Max = maximum, Min = minimum, PaO_2/FiO_2 = ratio of arterial oxygen partial pressure to fractional inspired oxygen, Q1 = first quartile, Q3 = third quartile, RRT = renal replacement therapy, SD = standard deviation, SOC = standard of care, VILO = vilobelimab

a Two patients with values greater than 300 were included in the mild ARDS severity category.

Percentages were based on the number of patients in the Full Analysis Set.

It is noted that a higher proportion of patients in the placebo group (132 patients [69.1%]) than in the VILO group (105 patients [59.3%]) had an ordinal score of seven. Thus, more patient in the placebo group needed additional organ support other than ventilation, including vasopressors. Also more patients were classified as having severe ARDS.

Since there appear to be imbalances in some baseline characteristics that could favour the vilobelimab group, the applicant was asked to provide two additional analyses for the primary endpoint: (1) a site-stratified Cox model adjusted for age, baseline ordinal scale, baseline diabetes status (yes/no), and baseline chronic kidney disease status (yes/no) and (2) an unstratified Cox model adjusted for these variables. These additional analyses showed smaller effect estimates and larger p-values than the original analyses did:

- Adjusted and site-stratified Cox model: Hazard ratio 0.775, p = 0.1903
- Adjusted and unstratified Cox model: hazard ratio 0.699, p = 0.0459

The smaller effect estimates, and larger p-values indicate that the original analysis is affected by a small degree of confounding in favour of the vilobelimab group due to beneficial baseline characteristics. However, the differences do not change the overall interpretation of the data.

An even number of patients were on ECMO at baseline with 3 patients in each arm.

The inclusion criteria states: that patients with a PaO2 / FiO2 ratio of < 200 and > 60 at randomisation could be included in the study. From the table above it is noted that two patients were classified as having mild ARDS at baseline, i.e. 200 mmHg < PaO2 / FiO2 ≤300 mmHg although the footnote says these patients had values greater than 300. The inclusion of the two patients were considered as minor deviations from the protocol by the applicant. The patients presented with COVID symptoms at randomisation and were intubated. Although the inclusion of the two patients clearly deviated from the specified criteria the impact on the overall study outcome is considered as minor.

Both inclusion and exclusion criteria specifically state that patients should not have been intubated more than 48 hours before IMP administration. There were 3 patients identified by the applicant with potential intubation deviation. For two patients the IMP was give on the same day as intubation, thus, only 24 h or less must have passed between intubation and IMP administration and no deviation from inclusion/exclusion criteria is identified. Another patient was administered placebo at 49h53 min, which is not regarded as a major issue.

Table 24: COVID-19 symptoms reported for at least 5% of all patients by MedDRA preferred term (full analysis set)

MedDRA Preferred Term	VILO+SOC (N = 177) n	(%)	Placebo+SOC (N = 191) n	(%)	Total (N = 368) n	(%)
Any symptom	170	(96.0%)	187	(97.9%)	357	(97.0%)
Dyspnoea	155	(87.6%)	168	(88.0%)	323	(87.8%)
Pyrexia	119	(67.2%)	121	(63.4%)	240	(65.2%)
Cough	96	(54.2%)	118	(61.8%)	214	(58.2%)
Fatigue	79	(44.6%)	89	(46.6%)	168	(45.7%)
Diarrhoea	27	(15.3%)	20	(10.5%)	47	(12.8%)
Nausea	13	(7.3%)	9	(4.7%)	22	(6.0%)
Myalgia	14	(7.9%)	17	(8.9%)	31	(8.4%)
Headache	12	(6.8%)	15	(7.9%)	27	(7.3%)
COVID-19 pneumonia	12	(6.8%)	12	(6.3%)	24	(6.5%)

COVID-19 = coronavirus disease 2019, MedDRA = Medical Dictionary for Regulatory Activities, SOC = standard of care, VILO = vilobelimab

Coding was based on the MedDRA version 24.1.

Percentages were based on the number of patients with at least one medical history entry of the specified MedDRA preferred term/total number of patients in the treatment group.

Table 25: Concomitant diseases reported for at least 5% of all patients by MedDRA system organ class and preferred term (full analysis set)

MedDRA System Organ Class Preferred Term	VILO+SOC (N = 177) n	(%)	Placebo+SOC (N = 191) n	(%)	Total (N = 368) n	(%)
Any	**163**	**(92.1%)**	**178**	**(93.2%)**	**341**	**(92.7%)**
Metabolism and nutrition disorders	**128**	**(72.3%)**	**144**	**(75.4%)**	**272**	**(73.9%)**
Obesity	68	(38.4%)	81	(42.4%)	149	(40.5%)
Diabetic complication	28	(15.8%)	46	(24.1%)	74	(20.1%)
Hyperglycaemia	17	(9.6%)	17	(8.9%)	34	(9.2%)
Overweight	13	(7.3%)	10	(5.2%)	23	(6.3%)
Hypercholesterolaemia	7	(4.0%)	13	(6.8%)	20	(5.4%)
Vascular disorders	**86**	**(48.6%)**	**97**	**(50.8%)**	**183**	**(49.7%)**
Hypertension	78	(44.1%)	87	(45.5%)	165	(44.8%)
Respiratory, thoracic and mediastinal disorders	**39**	**(22.0%)**	**44**	**(23.0%)**	**83**	**(22.6%)**
Renal and urinary disorders	**26**	**(14.7%)**	**44**	**(23.0%)**	**70**	**(19.0%)**
Acute kidney injury	17	(9.6%)	25	(13.1%)	42	(11.4%)
Chronic kidney disease	8	(4.5%)	14	(7.3%)	22	(6.0%)
Cardiac disorders	**29**	**(16.4%)**	**36**	**(18.8%)**	**65**	**(17.7%)**
Atrial fibrillation	13	(7.3%)	15	(7.9%)	28	(7.6%)
Psychiatric disorders	**30**	**(16.9%)**	**27**	**(14.1%)**	**57**	**(15.5%)**
Anxiety disorder	12	(6.8%)	13	(6.8%)	25	(6.8%)
Investigations	**26**	**(14.7%)**	**29**	**(15.2%)**	**55**	**(14.9%)**
Infections and infestations	**25**	**(14.1%)**	**25**	**(13.1%)**	**50**	**(13.6%)**
Blood and lymphatic system disorders	**11**	**(6.2%)**	**22**	**(11.5%)**	**33**	**(9.0%)**
Gastrointestinal disorders	**12**	**(6.8%)**	**20**	**(10.5%)**	**32**	**(8.7%)**
Endocrine disorders	**10**	**(5.6%)**	**16**	**(8.4%)**	**26**	**(7.1%)**
Hypothyroidism	8	(4.5%)	13	(6.8%)	21	(5.7%)
Musculoskeletal and connective tissue disorders	**9**	**(5.1%)**	**16**	**(8.4%)**	**25**	**(6.8%)**
Nervous system disorders	**9**	**(5.1%)**	**15**	**(7.9%)**	**24**	**(6.5%)**
Surgical and medical procedures	**16**	**(9.0%)**	**7**	**(3.7%)**	**23**	**(6.3%)**

MedDRA = Medical Dictionary for Regulatory Activities, SOC = standard of care, VILO = vilobelimab
Coding was based on the MedDRA version 24.1.
Percentages were based on the number of patients with at least 1 medical history entry of the specified MedDRA preferred term/total number of patients in the treatment group.

Table 26: Relevant comorbidities

	VILO+SOC (N = 177) n	(%)	Placebo+SOC (N = 191) n	(%)	Total (N = 368) n	(%)
Relevant Comorbidities (n [%])						
Hypertension						
No	96	(54.2%)	100	(52.4%)	196	(53.3%)
Yes	80	(45.2%)	90	(47.1%)	170	(46.2%)
Unknown	1	(0.6%)	1	(0.5%)	2	(0.5%)
Diabetes						
No	132	(74.6%)	126	(66.0%)	258	(70.1%)
Yes	45	(25.4%)	64	(33.5%)	109	(29.6%)
Unknown	0	(0.0%)	1	(0.5%)	1	(0.3%)
Coronary heart disease [n (%)]						
No	164	(92.7%)	174	(91.1%)	338	(91.8%)
Yes	12	(6.8%)	14	(7.3%)	26	(7.1%)
Unknown	1	(0.6%)	3	(1.6%)	4	(1.1%)
Chronic obstructive lung disease [n (%)]						
No	172	(97.2%)	188	(98.4%)	360	(97.8%)
Yes	5	(2.8%)	2	(1.0%)	7	(1.9%)
Unknown	0	(0.0%)	1	(0.5%)	1	(0.3%)
Carcinoma [n (%)]						
No	176	(99.4%)	187	(97.9%)	363	(98.6%)
Yes	1	(0.6%)	3	(1.6%)	4	(1.1%)
Unknown	0	(0.0%)	1	(0.5%)	1	(0.3%)
Chronic kidney disease [n (%)]						
No	168	(94.9%)	175	(91.6%)	343	(93.2%)
Yes	8	(4.5%)	15	(7.9%)	23	(6.3%)
Unknown	1	(0.6%)	1	(0.5%)	2	(0.5%)
Obesity[a] [n (%)]						
No	108	(61.0%)	110	(57.6%)	218	(59.2%)
Yes	69	(39.0%)	81	(42.4%)	150	(40.8%)

MedDRA = Medical Dictionary for Regulatory Activities, SOC = standard of care, VILO = vilobelimab

a Obesity was defined by documented medical history ongoing at baseline with MedDRA Preferred Term 'Obesity' or 'Central Obesity.'

Coding was based on the MedDRA version 24.1.

Percentages were based on the total number of patients in the Full Analysis Set.

In general, the comorbidities were comparable between the treatment groups. There are, however, notable differences in patients with diabetes and/or chronic kidney disease with higher proportions in the placebo groups.

Prior Medications

Prior medications were used by the majority of patients in the study (299 of 368 patients [81.3%]), with the most frequently used classes of prior medications (in ≥ 20% of all patients) being antithrombotic agents (136 patients [37.0%]), antibacterials for systemic use (132 patients [35.9%]), analgesics (113 patients [30.7%]), corticosteroids for systemic use (112 patients [30.4%]), psycholeptics (94 patients [25.5%]), and anaesthetics (81 patients [22.0%])

Prior medications for COVID-19 were used by 198 of 368 patients (53.8%). The most frequently used classes of prior medications given for COVID-19 (in ≥ 10% of all patients) were corticosteroids for systemic use (109 patients [29.6%]; most frequently dexamethasone in 82 patients [22.3%]), antithrombotic agents (108 patients [29.3%], most frequently enoxaparin in 52 patients [14.1%]),

and immunosuppressants (53 patients [14.4%], most frequently tocilizumab in 52 patients [14.1%]). Antivirals for systemic use (including remdesivir, casirivimab+imdevimab, favipiravir, and umifenovir) were used by 15 of 368 patients (4.1%).

Numbers analysed

Data Sets Analysed

One patient in the VILO group was excluded immediately after randomisation as "randomized by mistake" and was excluded from the primary analysis based on the FAS. A total of 364 patients (175 in the VILO group and 189 in the Placebo group) received at least one dose of study drug and were included in the SAF. The PPS included 360 patients who were in the FAS and did not have any major protocol deviations. All efficacy and PK/PD analyses were based on the FAS, and all safety analyses were based on the SAF. Additional efficacy analyses were conducted on the PPS.

	Total (N=369)		Vilo + SOC (N=178)		Placebo + SOC (N=191)	
	Pat.n	Pat.%	Pat.n	Pat.%	Pat.n	Pat.%
Patients enrolled	391					
Patients randomized	369	100.0	178	100.0	191	100.0
Full analysis set	368	99.7	177	99.4	191	100.0
Safety analysis set	364	98.6	175	98.3	189	99.0
Per protocol set	360	97.6	170	95.5	190	99.5

Outcomes and estimation

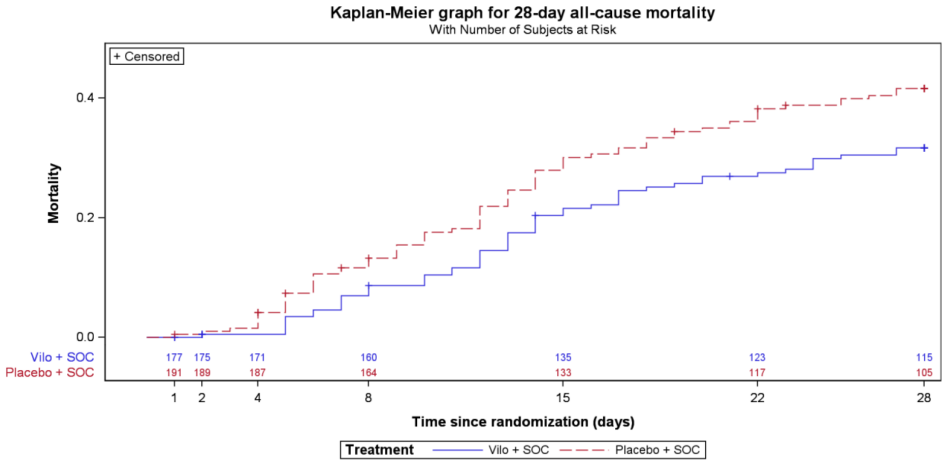
Primary Efficacy Analysis

Table 27: 28-day all-cause mortality, using site-stratified Cox regression analysis adjusting for age (full analysis set)

	VILO+SOC (N = 177)	Placebo+SOC (N = 191)
Proportion of patients with 28-day all-cause mortality from Kaplan-Meier estimate, %	31.65%	41.59%
Hazard ratio for VILO versus Placebo	0.728	
95% CI for hazard ratio[a]	(0.502, 1.056)	
p-value for hazard ratio	0.0941	

CI = confidence interval, SOC = standard of care, VILO = vilobelimab
Cox proportional hazards regression model with outcome 28-day all-cause mortality as a censored time-to-event variable and explanatory variables treatment arm and age, including a stratification by site.
A patient was right-censored at the date of their last contact (phone call, last available measurement, etc.).
a Wald-type confidence interval

Figure 12: Kaplan-Meier graph for 28-day all-cause mortality (full analysis set)



SOC = standard of care, VILO = vilobelimab
A patient was right-censored at the date of their last contact (phone call, last available measurement, etc.).

The pre-specified primary analysis of 28-day all-cause mortality, using site-stratified Cox regression analysis and adjusting for age, did not reach statistical significance (p-value =0.0941). Thus, this pivotal study did not meet the primary endpoint and is formally negative. Additional analyses of the primary endpoint were performed post hoc, see data and comments under Ancillary analyses below.

Secondary endpoints

The secondary efficacy endpoints in Phase III were: 60-day all-cause mortality, proportion of patients with an improvement in the 8-point ordinal scale at Days 15 and 28, proportion of patients developing acute kidney failure during ICU stay and at Day 28, and proportion of patients free of any RRT until Day 28.

Table 28: 60-day all-cause mortality, using site-stratified Cox regression analysis adjusting for age (full analysis set)

	VILO+SOC (N = 177)	Placebo+SOC (N = 191)
Proportion of patients with 60-day all-cause mortality from Kaplan-Meier estimate, %	36.51%	47.20%
Hazard ratio for VILO versus Placebo	0.735	
95% CI for hazard ratio[a]	(0.519, 1.039)	
p-value for hazard ratio	0.0815	

CI = confidence interval, SOC = standard of care, VILO = vilobelimab
Cox proportional hazards regression model with outcome 60-day all-cause mortality as a censored time-to-event variable and explanatory variables treatment arm and age, including a stratification by site.
A patient was right-censored at the date of their last contact (phone call, last available measurement, etc.).
a Wald-type confidence intervals

For the secondary endpoint 60-day all-cause mortality a similar hazard ratio was observed as for the primary endpoint.

Table 29: Proportion of patients with at least one point improvement in ordinal scale score at days 15 and 28 (full analysis set)

Parameter	VILO+SOC (N = 177) n (%)	Placebo+SOC (N = 191) n (%)
Ordinal Scale Score at Day 15		
Improved	82 (46.3%)	77 (40.3%)
Not improved[a]	86 (48.6%)	104 (54.5%)
Not evaluable[b]	9 (5.1%)	10 (5.2%)
Ordinal Scale Score at Day 28		
Improved	90 (50.8%)	85 (44.5%)
Not improved[a]	78 (44.1%)	96 (50.3%)
Not evaluable[b]	9 (5.1%)	10 (5.2%)

SOC = standard of care, VILO = vilobelimab

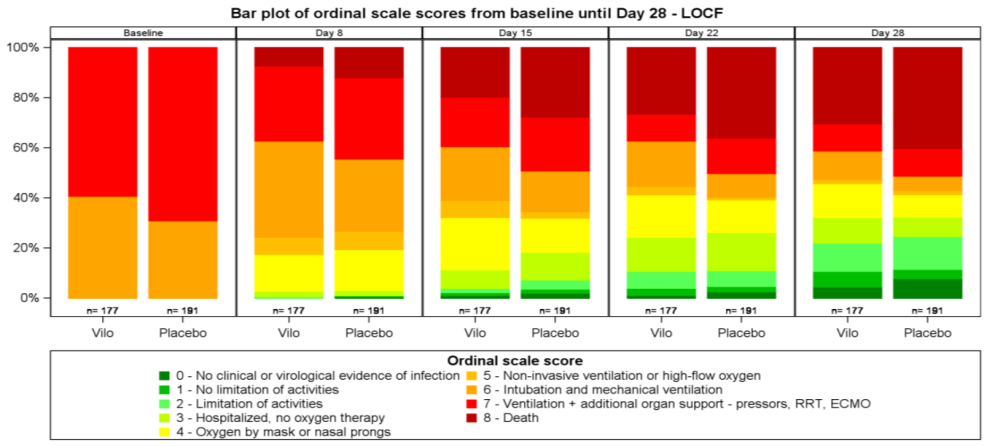
Ordinal scale: 0 = No clinical or virological evidence of infection, 1 = No limitation of activities, 2 = Limitation of activities, 3 = Hospitalized, no oxygen therapy, 4 = Hospitalized, oxygen by mask or nasal prongs, 5 = Hospitalized, non-invasive ventilation or high-flow oxygen, 6 = Hospitalized, intubation and mechanical ventilation, 7 = Hospitalized, ventilation + additional organ support - pressors, renal replacement therapy, extracorporeal membrane oxygenation (ECMO), 8 = Death

a Includes patients who died.

b Patients with no assessment at Day 28 or with withdrawal of consent before Day 28.

The proportion of patients with at least a one-point improvement in the 8-point ordinal scale score was similar between the VILO and Placebo groups at Days 15 and 28.

Figure 13: Bar plots for proportion of patients with at least one point improvement in ordinal scale score until day 28 (full analysis set)



LOCF = last observation carried forward, SOC = standard of care, VILO = vilobelimab

Percentages are based on the number of patients in the respective treatment group and visit.

Table 30: Proportion of patients developing acute kidney failure (based on eGFR) until days 28 and 60 and during ICU stay (full analysis set)

Parameter	VILO+SOC (N = 177) n (%)	Placebo+SOC (N = 191) n (%)
Acute kidney failure until Day 28		
Acute kidney failure	8 (4.5%)	12 (6.3%)
No acute kidney failure	158 (89.3%)	168 (88.0%)
Not evaluable[a]	11 (6.2%)	11 (5.8%)
Acute kidney failure until Day 60		
Acute kidney failure	8 (4.5%)	12 (6.3%)
No acute kidney failure	153 (86.4%)	165 (86.4%)
Not evaluable[a]	16 (9.0%)	14 (7.3%)
Acute kidney failure during ICU stay		
Acute kidney failure	5 (2.8%)	8 (4.2%)
No acute kidney failure	148 (83.6%)	153 (80.1%)
Not evaluable[a]	24 (13.6%)	30 (15.7%)

eGFR = estimated glomerular filtration rate, ICU = intensive care unit, SOC = standard of care, VILO = vilobelimab

A patient was defined as newly developing acute kidney failure if eGFR was < 15 mL/min/1.73m² at any time point after randomization until the respective timepoint of interest, with the baseline eGFR value not being below 15.

a Patients with withdrawal of consent before Day 28, Day 60, or ICU discharge (as applicable), or patients with no creatinine assessment after randomization until Day 28, Day 60, or during ICU stay (as applicable).

Proportion of Patients Free of Any Renal Replacement Therapy/Time to Initiation of Renal Replacement Therapy (Until Day 28)

The proportion of patients with initiation of RRT until Day 28 was 17 of 177 patients (9.6%) in the VILO group and 30 of 191 patients (15.7%) in the Placebo group. Treatment with VILO demonstrated a greater reduction in first RRT until Day 28 compared with Placebo (HR, 0.539 [95% CI: 0.297, 0.978], using cause-specific Cox proportional hazards model).

Ancillary analyses

Post-hoc analyses

Table 31: Primary and supplementary analyses of 28-day all-cause mortality (full analysis set)

Analysis Method	P-value	Hazard ratio (95% CI) or Risk Difference for Logistic Regression	No. of Patients Factually Contributing	Plan for Analysis
Cox regression including stratification by site	0.0941	0.728 (0.502; 1.056)	307	Pre-specified primary endpoint analysis method
Cox regression including no stratification	0.0266	0.674 (0.476; 0.955)	368	Original protocol-defined analysis method
Cox regression including stratification by region	0.0137	0.644 (0.454; 0.914)	368	Post-hoc analysis
Cox regression including stratification by country	0.0067	0.613 (0.430; 0.873)	368	Post-hoc analysis
Cox regression using "frailty" model (random effect for site)	0.0181	0.648 (0.453; 0.929)	368	Post-hoc analysis
Cox regression including stratification by site with sites with n<4 being pooled within country	0.0404	0.681 (0.472; 0.983)	368	Post-hoc analysis
Cox regression including stratification by site with sites with n<5 being pooled within country	0.0409	0.682 (0.473; 0.984)	368	Post-hoc analysis
Logistic regression (multiple imputation of missing values)	0.0293	-11.0% (-20.8%; -1.2%)	369[a]	Pre-specified sensitivity analysis
Simple log-rank test	0.0407	–	368	Post-hoc analysis

CI = confidence interval

Note: All Cox regression analyses were age-adjusted.

a One patient was randomized in error and was included in this sensitivity analysis.

The analysis of the primary endpoint without site-stratification was performed post-hoc with a nominal p-value of 0.0266.

Table 32: Primary and supplementary analyses of 60-day all-cause mortality (full analysis set)

Analysis Method	p-value	Hazard ratio (95% CI) or Risk Difference for Logistic Regression	No. of Patients Factually Contributing	Plan for Analysis
Cox regression including stratification by site	0.0815	0.735 (0.519; 1.039)	325	Pre-specified primary endpoint analysis method
Cox regression including no stratification by site	0.0163	0.670 (0.484; 0.929)	368	Original protocol-defined analysis method
Cox regression including stratification by region	0.0085	0.644 (0.465; 0.894)	368	Post-hoc analysis
Cox regression including stratification by country	0.0042	0.616 (0.442; 0.858)	368	Post-hoc analysis
Cox regression using "frailty" model (random effect for site)	0.0104	0.644 (0.460; 0.901)	368	Post-hoc analysis
Cox regression including stratification by site with sites with n<4 being pooled within country	0.0346	0.691 (0.490; 0.974)	368	Post-hoc analysis
Cox regression including stratification by site with sites with n<5 being pooled within country	0.0353	0.692 (0.491; 0.975)	368	Post-hoc analysis
Logistic regression (multiple imputation of missing values)	0.0162	-12.2% (-22.0%; -2.4%)	369[a]	Post-hoc analysis
Simple log-rank test	0.0315		368	Post-hoc analysis

CI = confidence interval
Note: All Cox regression analyses were age-adjusted.
a One patient was randomized in error and was included in this sensitivity analysis.

The post-hoc analyses of 60-day mortality showed similar trends as the 28-day mortality analyses.

Sensitivity analysis

Table 33: Logistic regression analysis for 28-day all-cause mortality (all randomised population)

Imputation Method for Patients with Unknown Survival Status at Day 28	P-value	Risk Difference (95% CI)[c]
Worst case imputation (in favor of Placebo)[a]	0.2772	-5.4% (-15.1%, 4.3%)
All alive imputation	0.0340	-10.4% (-19.9%, -0.9%)
All deceased imputation	0.0446	-10.1% (-19.9%, -0.3%)
Multiple imputation[b]	0.0293	-11.0% (-20.8%, -1.2%)

CI = confidence interval, SOC = standard of care, VILO = vilobelimab

a For patients with unknown survival status at Day 28, a worst case imputation approach for the logistic regression was used, i.e., all patients from the Placebo + SOC group were assumed to be alive and all patients from the VILO + SOC group were assumed to be deceased at Day 28.

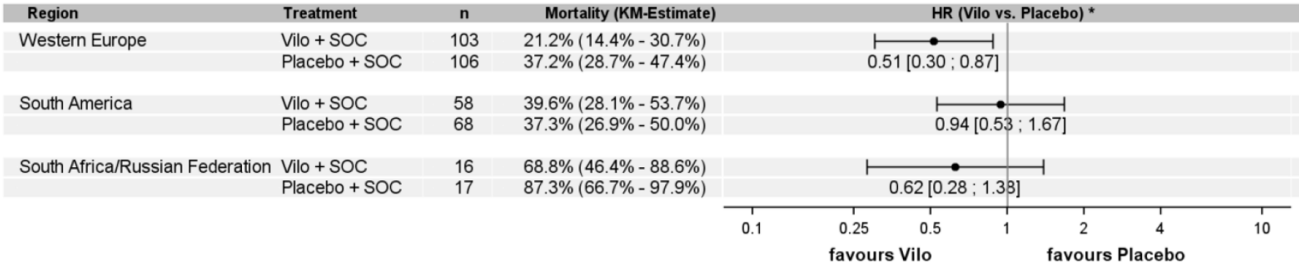
b Results are based on combining results from multiple imputation.

c Risk difference (VILO -Placebo) and CI estimated based on logistic regression (as described in Section 7.8.2.3 of the SAP).

The applicant examined whether the results were robust to changes in the way that patients with an unknown survival status at the end of the trial were handled. Although these sensitivity analyses are sufficient, it should be noted they are not directly comparable to the primary analysis because the statistical models and analysis sets are different (see Statistical methods). Furthermore, they are difficult to interpret because the primary analysis was not statistically significant.

Subgroup analyses

Table 34: Forest plot for 28-day all-cause mortality by region (full analysis set)

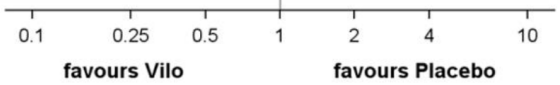


HR = hazard ratio, KM = Kaplan-Meier, n = number of patients in the analysis in the respective treatment group, SOC = standard of care, VILO = vilobelimab

*Hazard ratio from the Cox proportional hazards regression model with outcome 28-day all-cause mortality as a censored time-to-event variable and explanatory variables treatment arm and age. Hazard ratios are only displayed for subgroups with at least 10 patients and for which at least one event per treatment group has been observed.

Table 35: Forest plot for 28-day all-cause mortality by country (full analysis set)

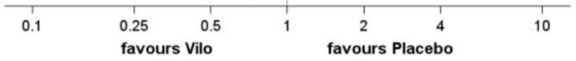
Country	Treatment	n	Mortality (KM-Estimate)	HR (Vilo vs. Placebo) *
Belgium	Vilo + SOC	8	12.5% (1.9% - 61.3%)	0.18 [0.01 ; 2.96]
	Placebo + SOC	7	28.6% (8.0% - 74.2%)	
Brazil	Vilo + SOC	34	38.2% (24.3% - 56.6%)	1.27 [0.55 ; 2.93]
	Placebo + SOC	40	25.0% (14.3% - 41.5%)	
Germany	Vilo + SOC	10	30.0% (10.8% - 67.1%)	0.64 [0.15 ; 2.73]
	Placebo + SOC	11	45.5% (22.0% - 77.1%)	
France	Vilo + SOC	17	0.0% (0.0% - 0.0%)	
	Placebo + SOC	18	27.8% (12.6% - 54.4%)	
Mexico	Vilo + SOC	18	42.2% (22.7% - 68.9%)	0.39 [0.15 ; 0.99]
	Placebo + SOC	19	71.1% (49.8% - 89.3%)	
Netherlands	Vilo + SOC	68	26.6% (17.4% - 39.2%)	0.57 [0.31 ; 1.04]
	Placebo + SOC	70	39.4% (28.8% - 52.2%)	
Peru	Vilo + SOC	6	40.0% (11.8% - 87.4%)	1.67 [0.23 ; 12.16]
	Placebo + SOC	9	22.2% (6.1% - 63.5%)	
Russian Federation	Vilo + SOC	11	72.7% (46.1% - 93.5%)	0.37 [0.14 ; 0.97]
	Placebo + SOC	12	100.0% (100.0% - 100.0%)	
South Africa	Vilo + SOC	5	60.0% (24.7% - 94.8%)	0.94 [0.16 ; 5.43]
	Placebo + SOC	5	60.0% (24.7% - 94.8%)	



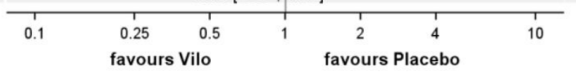
HR = hazard ratio, KM = Kaplan-Meier, n = number of patients in the analysis in the respective treatment group, SOC = standard of care, VILO = vilobelimab
*Hazard ratio from the Cox proportional hazards regression model with outcome 28-day all-cause mortality as a censored time-to-event variable and explanatory variables treatment arm and age. Hazard ratios are only displayed for subgroups with at least 10 patients and for which at least one event per treatment group has been observed.

Table 36: Forest plots for 28-day all-cause mortality by baseline ordinal scale score, eGFR category, and ARDS severity (full analysis set)

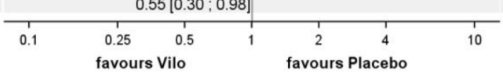
Ordinal scale score at baseline	Treatment	n	Mortality (KM-Estimate)	HR (Vilo vs. Placebo) *
6	Vilo + SOC	72	30.8% (21.3% - 43.3%)	0.80 [0.44 ; 1.46]
	Placebo + SOC	59	36.8% (25.8% - 50.7%)	
7	Vilo + SOC	105	32.1% (24.0% - 42.1%)	0.62 [0.40 ; 0.95]
	Placebo + SOC	132	43.7% (35.6% - 52.7%)	



EGFR categories at baseline	Treatment	n	Mortality (KM-Estimate)	HR (Vilo vs. Placebo) *
Missing	Vilo + SOC	1		
	Placebo + SOC	0		
< 60 mL/min/1.73m²	Vilo + SOC	47	41.5% (28.8% - 57.1%)	0.55 [0.31 ; 0.96]
	Placebo + SOC	61	59.4% (47.0% - 72.1%)	
>= 60 mL/min/1.73m²	Vilo + SOC	129	28.2% (21.2% - 37.1%)	0.79 [0.50 ; 1.23]
	Placebo + SOC	130	33.6% (26.2% - 42.5%)	



ARDS severity at baseline	Treatment	n	Mortality (KM-Estimate)	HR (Vilo vs. Placebo) *
Mild (200 mmHg < PaO2/FiO2 <= 300 mmHg)**	Vilo + SOC	1	0.0% (0.0% - 0.0%)	
	Placebo + SOC	1	0.0% (0.0% - 0.0%)	
Moderate (100 mmHg < PaO2/FiO2 <= 200 mmHg)	Vilo + SOC	133	29.1% (22.0% - 37.9%)	0.75 [0.48 ; 1.16]
	Placebo + SOC	135	34.6% (27.1% - 43.4%)	
Severe (PaO2/FiO2 <= 100 mmHg)	Vilo + SOC	43	40.0% (27.1% - 56.2%)	0.55 [0.30 ; 0.98]
	Placebo + SOC	55	59.5% (46.8% - 72.6%)	



ARDS = Acute respiratory distress syndrome, eGFR = Estimated glomerular filtration rate, HR = hazard ratio, KM = Kaplan-Meier, PaO2/FiO2 = Arterial oxygen partial pressure / fractional inspired oxygen (oxygenation index), n = number of patients in the analysis in the respective treatment group, SOC = standard of care, VILO = vilobelimab
*Hazard ratio from the Cox proportional hazards regression model with outcome 28-day all-cause mortality as a censored time-to-event variable and explanatory variables treatment arm and age. Hazard ratios are only displayed for subgroups with at least 10 patients and for which at least one event per treatment group has been observed.
** 2 Patients with values greater than 300 are included in the mild ARDS severity category.

The results from the subgroup analyses should be interpreted with caution. These results are only descriptive.

Summary of main efficacy results

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

Table 37: Summary of efficacy for trial "A Pragmatic Adaptive Randomized Controlled Phase II/III Multicenter Study of IFX-1 in Patients with Severe COVID-19 Pneumonia – "PANAMO" (Phase III)"

Title: *A Pragmatic Adaptive Randomized Controlled Phase II/III Multicenter Study of IFX-1 in Patients with Severe COVID-19 Pneumonia – "PANAMO" (Phase III)*			
Study identifier	Study Number: IFX-1-P2.9 EudraCT Number: 2020-001335-28 IND Number: 151995 ClinicalTrials.gov Identifier: NCT04333420		
Design	international, multicentre, adaptive, double-blind, placebo-controlled, randomised phase III		
	Duration of main phase: Duration of Run-in phase:	Up to 22 days Up to 24h approximately 38-day follow-up	
Hypothesis	Superiority		
Treatments groups	Arm A	Six doses of vilobelimab/IFX-1 800 mg on Days 1, 2, 4, 8, 15, and 22 as a 30-60-minute IV infusion	
	Arm B	Six doses of placebo on Days 1, 2, 4, 8, 15, and 22 as a 30-60-minute IV infusion	
Endpoints and definitions	Primary endpoint	28-day all-cause mortality	28-day all-cause mortality, i.e., the proportion of patients deceased until Day 28
	Secondary endpoint	60-day all-cause mortality	60-day all-cause mortality (proportion of patients deceased until Day 60)
Database lock	21-Mar-2022		
Results and Analysis			
Analysis description	Primary Analysis		

Analysis population and time point description	Full analysis set (FAS): The primary statistical analyses were performed based on all randomised patients according to the intention-to-treat principle, except for patients who were randomised in error (reason for early termination documented as “Randomised by mistake” in the eCRF) AND did not receive IMP. Safety analysis set (SAF): Safety analyses were based on all patients who received at least one infusion of IMP; patients were analysed according to the treatment they actually received. The actual treatment group of each patient was VILO if they received any VILO infusion at any timepoint, and Placebo if they received only Placebo infusions at all timepoints. Per protocol analysis set (PPS): The PPS consists of all patients who are in the FAS and did not have any major protocol deviations. Definitions of major protocol deviations and further details on assignment of patients to analysis sets were specified in the BDRM plan.			
Descriptive statistics and estimate variability	Treatment group	Arm A Vilo + SOC	Arm B Placebo + SOC	Total
	Number of subjects	177	191	368
	Primary endpoint: 28-day all-cause mortality, FAS, site stratified Cox regression, adjusting for age	31.65%	41.59%	
	95% CI:	25.25%, 39.22%	34.86%, 49.05%	
	Secondary endpoint: 60-day all-cause mortality, FAS, site stratified Cox regression adjusting for age	36.51%	47.20%	
	95% CI:	29.76%, 44.25%	40.27%, 54.67%	
Effect estimate per comparison	Primary endpoint: 28-day All-cause Mortality, Using Site-stratified Cox Regression Analysis Adjusting for Age (Full Analysis Set) Pre-specified primary endpoint analysis method	Comparison groups	Arm A: VILO+SOC Arm B: Placebo+SOC	
		Hazard ratio for VILO versus Placebo	0.728	
		95% CI for hazard ratio	(0.502, 1.056)	
		P-value	0.0941	
	Secondary endpoint: 60-day All-cause Mortality, Using Site-stratified Cox Regression	Comparison groups	Arm A: VILO+SOC Arm B: Placebo+SOC	
		Hazard ratio for VILO versus Placebo	0.735	
		95% CI for hazard ratio	(0.519, 1.039)	

	Analysis Adjusting for Age (Full Analysis Set) Pre-specified secondary endpoint analysis method	P-value (nominal)	0.0815

2.5.5.3. Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Controlled Trials	100/556	69/556	5/556
Non Controlled trials	14/56	7/56	6/56

Controlled trials contains subjects from study P1.1, P2.1, P2.2, P2.4, P2.5, P2.6, P2.9 and P3.4. Non-controlled trials contains subjects from study P2.3, P2.7 and P2.8.Patients from study P3.4 are not considered in this analysis as the study is an ongoing blinded study.

2.5.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

2.5.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

2.5.5.6. Supportive study(ies)

Not applicable.

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical studies

PANAMO Phase II

This study was a randomised, open-label study of vilobelimab with the objective to explore the effect (hypothesis generating) in patients with COVID-19 related severe pneumonia.

The study was randomised 1:1 with 15 patients in Arm A: BSC + vilobelimab and 15 patients in Arm B: BSC alone. Patients in Arm A were to be treated with a maximum of 7 intravenous (IV) doses of vilobelimab 800 mg over a period of 29 days.

This study guided the design of the pivotal trial PANAMO Phase III

PANAMO Phase III

PANAMO Phase III was a 1:1 randomised, double-blind, placebo-controlled multicentre study evaluating vilobelimab in adult patients with Sars-Cov-2 who were mechanically ventilated, and had been so for less than 48 hours at the time of randomisation. Moreover, patients had a PaO2 / FiO2 ratio of < 200 and > 60 at randomisation.

There were 178 patients in the vilobelimab group and 191 in the placebo group. Patients were treated with a maximum of 6 intravenous (IV) doses of VILO 800 mg + SOC (Arm A) or Placebo + SOC (Arm B) at Days 1, 2, 4, 8, 15, and 22, as long as the patient was still hospitalised.

In both treatment arms standard of care was allowed which included venous thromboembolism (VTE) prophylaxis at a minimum, and other international and country-specific recommended treatments for COVID-19 per the locally adopted treatment recommendations.

Eligible patients were at least 18 years of age with SARS-CoV-2 infection confirmation in the last 14 days before randomisation.

The phase III study was conducted at 46 sites in 9 countries. Most patients were randomised in the Western Europe region (210 of 369 patients, 56.9%). Overall, most patient were randomised in the Netherlands (139 of 369 patients, 37.7%) followed by Brazil (74 of 369, 20,1%), Mexico (37 of 369, 10.0%) and France (35 of 360, 9.5%).

The primary endpoint was 28-day all-cause mortality.

Secondary endpoints included 60-day all-cause mortality and other parameters to assess improvement or worsening in condition. The design and planned analyses of the phase III were based on evaluation of the phase II.

A one-sided significance level of 2.5% was used in the efficacy analyses. This is equivalent to 5% two-sided and hence acceptable. The applicant planned to exclude patients from analysis who were randomised despite being ineligible for the trial. This is not agreed by CHMP. However, only one patient was excluded from the primary analysis, so the risk of bias should be negligible.

Cox regression, adjusted for age and site, was used to analyse mortality by Day 28 (and Day 60, for the secondary endpoint). Patients were counted as having died if a date of death or fatal adverse event had been documented and if this date occurred before Day 28 (or Day 60). Other patients were censored at Day 28 (or Day 60) or the date of last contact, whichever occurred first.

Before unblinding, the applicant changed the primary analysis model from an unstratified Cox model to a site-stratified Cox model. Although both analyses would be acceptable, the stratified analysis should be regarded as the primary, as it was the last to be specified before unblinding.

The applicant examined whether the results were robust to changes in the way that patients with an unknown survival status at the end of the trial were handled. Although these sensitivity analyses are sufficient, they are not directly comparable to the primary analysis. While the primary analysis was based on a Cox regression model, adjusted for age and stratified by site, the sensitivity analysis was based on a logistic regression model, adjusted for age but not stratified by site. Another difference is that one randomised patient was excluded from the primary model, whereas all randomised patients were included in the sensitivity analysis.

Multiplicity was controlled for the primary endpoint and the first 5 secondary endpoints using a combination of sequential testing and a fallback method. This procedure is acceptable.

The initial plan by the applicant was to analyse the primary endpoint using Cox regression adjusting for age, without considering the randomisation stratification. The change of the primary analysis in the SAP was introduced based on recommendation received from United States Food and Drug Administration (US FDA). The stratification by site was chosen because it was anticipated that even within region and country, variability in background mortality by site could be high. When Cox regression with site-stratification was applied, 61 patients from smaller sites which either had no occurring events (no deaths for 55 patients in 17 sites) or enrolled only one patient irrespective of event (6 additional placebo patients who died from 6 additional sites) did not make a "factual contribution" to the analysis; that is, these patients did not contribute to the calculation of the Cox model (a mathematical property of the model), which in practice reduces the sample size and statistical power of the model.

It is acknowledged that the planned interim analysis for efficacy was removed after the applicant received EMA scientific advice, in which EMA discouraged stopping for efficacy when there is only a single pivotal trial (EMA/SA/0000058706). The decision rule for stopping for futility was if the z-statistic was 0 or less, which is acceptable.

Efficacy data and additional analyses

PANAMO Phase III

Regarding baseline characteristics, it is noticed that a higher proportion of patients in the placebo group had diabetes and/or chronic kidney disease at baseline. Also, more patients were classified as having severe ARDS and a higher proportion of patients in the placebo group (132 patients [69.1%]) than in the VILO group (105 patients [59.3%]) had an ordinal score of seven. Thus, more patients in the placebo group needed additional organ support other than ventilation.

Since there appear to be imbalances in some baseline characteristics that could favour the vilobelimab group, the applicant was asked to provide two additional analyses for the primary endpoint: (1) a site-stratified Cox model adjusted for age, baseline ordinal scale, baseline diabetes status (yes/no), and baseline chronic kidney disease status (yes/no) and (2) an unstratified Cox model adjusted for these variables. These additional analyses showed smaller effect estimates and larger p-values than the original analyses did, which indicates that the original analysis is affected by a small degree of confounding in favour of the vilobelimab group due to beneficial baseline characteristics. However, the differences do not change the overall interpretation of the data.

Systemic corticosteroids were used by a total of 171/177 (96.6%) patients in the vilobelimab group and 181/191 (94.8%) patients in the placebo group. Thus, efficacy has de facto been established as an add-on to corticosteroids, which is now reflected in the indication amended during the procedure.

The inclusion criteria states: that patients with a PaO2 / FiO2 ratio of < 200 and > 60 at randomisation could be included in the study. It is noted that two patients were classified as having mild ARDS at baseline (i.e. 200 mmHg < PaO2 / FiO2 ≤300 mmHg) and the footnote in the baseline characteristics table says these patients had values greater than 300. The inclusion of the two patients were considered as minor deviations from the protocol by the applicant. The patients presented with COVID symptoms at randomisation and were intubated. Although the inclusion of the two patients clearly deviated from the specified criteria the impact on the overall study outcome is considered as minor.

Moreover, according to inclusion and exclusion criteria, patients should not have been intubated more than 48 hours before first IMP administration. There were 3 patients identified by the applicant with potential intubation deviation. For two patients the IMP was give on the same day as intubation, thus, only 24 h or less must have passed between intubation and IMP administration and no deviation from

inclusion/exclusion criteria is identified. Another patient was administered placebo at 49h53 min, which is not regarded as a major issue.

One patient was emergency unblinded a couple of days after being randomised due to patient's wish to breastfeed after being extubated. This single case of unblinding unlikely impacted the overall outcome.

The protocol stipulated that those male patients treated with vilobelimab who had a pregnant or breastfeeding partner, would need to remain abstinent from intercourse or use condom until 3 months after last study dose. This seems reasonable. For women who were breastfeeding and then randomised into the study there was no specific instruction for unblinding and it seems questionable that maintaining breastfeeding or providing breastmilk would be possible during participation in the study.

Primary outcome measure

Importantly, the pre-specified primary analysis of 28-day all-cause mortality, which was a site-stratified Cox regression model and adjusted for age, did not reach statistical significance. The proportion of patients with 28-day mortality was 31.65% vs. 41.59% in the vilobelimab and placebo groups, respectively (HR 0.728 [95% CI: 0.502, 1.056], p-value =0.0941). Thus, this pivotal study did not meet the primary endpoint and is formally not a positive study.

The applicant's initial analysis using a Cox regression model adjusted for age, without considering the site-stratified randomisation procedure resulted in a HR of 0.674 (95% CI:0.476, 0.955) with a nominal two-sided p-value=0.0266.

It should be noted that the prespecified primary analysis had limited power to detect an effect of vilobelimab because it effectively excluded a large number of patients belonging to small study sites. The reason for this is that the trial had many small sites, and a site-stratified Cox model ignores sites with only one participant or no deaths.

Being aware of this limitation, the applicant conducted several post-hoc analyses. Most of these explored different ways to pool sites. One way was to pool all sites within a country or region, but this approach is limited by ignoring variability in mortality rates within countries or regions. Another approach was to pool small sites with less than 4 or 5 participants within each country. This approach may seem preferable because it is more granular than pooling all sites within a country. The applicant also tried changing to a frailty model, where study site was modelled as a random effect instead of a stratification factor. This analysis is acceptable.

The post-hoc analyses all had nominal p-values < 0.05 and the treatment effect appeared stronger than in the primary analysis. For the secondary endpoint 60-day all-cause mortality, a similar hazard ratio was observed as for the primary endpoint.

Although these analyses may be informative, the fact that they were performed post-hoc means that they are not type-I-error controlled. Therefore, the statistical strength of evidence is considered low.

The applicant was invited to an oral explanation (OE) to discuss the lack of efficacy observed in the PANAMO study. The CHMP considered the arguments put forward by the applicant related to the issue linked with the site stratification analysis.

It is acknowledged that the site-stratified analysis had limited power to detect an effect of vilobelimab because it effectively excluded a large number of patients. The reason for this is that the trial had many small sites, and a site-stratified Cox model ignores sites with only one participant or no deaths.

The applicant post-hoc analyses above described exploring different ways to pool sites where further discussed. It was acknowledged that there is no optimal way to pool sites because the definition of a small site is arbitrary and small sites do not necessarily have similar mortality rates.

The applicant also proposed to provide further evidence from the Just Breathe Platform study funded by BARDA, (US government) where a cohort of patients will be treated with vilobelimab. This study, supported by BARDA, aims at justifying grounds for approval under exceptional circumstances (see benefit risk section). Relevant information from this study presented by the applicant in the OE is provided below:

The Just Breathe platform study is a double-blind, placebo controlled, study enrolling moderate to severe ARDS patients according to the Berlin definition. It will enrol a broader patient population, i.e. patients with ARDS caused by COVID-19 and other viral and bacterial pulmonary infections across 60 sites in the US. The vilobelimab cohort will enrol severe ARDS patients and data from the sub population of COVID-19 ARDS patients will be generated. The study protocol has been finalised.

Patients will be stratified by level of ARDS severity. The identified or suspected inciting cause (e.g., viral, bacterial, aspiration.) of ARDS at randomisation will be captured allowing for subgroup analyses.

The primary endpoint of the study is all-cause mortality at Day 28. The vilobelimab cohort is expected to enrol 200 patients who will be randomised 1:1 to vilobelimab or placebo.

A master Statistical Analysis Plan will present the planned common analyses for all cohorts and describe any pooled analyses of cohort data regarding subgroups, biomarkers, and endpoints in ARDS.

At present, the first site is to be initiated in Q1 2025, study enrolment is anticipated to last for approximately 36 months and end of enrolment anticipated by the end of 2028.

Considering the explanations put forward by the applicant during the oral explanation, the CHMP by majority, considered that overall, the results of the pivotal trial support a reasonable possibility that vilobelimab would provide benefit to patients with ARDS due to Sars-Cov-2 infection.

The SmPC section 5.1 describes the pre-specified primary analysis of 28-day all-cause mortality using site-stratified Cox regression analysis. The presentation of the 28-day all-cause mortality analyses without site-stratification, in section 5.1 is however not considered acceptable by the CHMP.

The CHMP acknowledged the fact that the application is based on a single pivotal study and discussed that a further study to characterise the indication of efficacy against covid-related ARDS seen in the PANAMO was considered desirable. However, given the epidemiology and clinical features of Sars-Cov-2 omicron strains, this is not deemed feasible at present, where the pandemic situation has ended.

Therefore, a marketing authorisation under exceptional circumstances with the Just Breathe study as a specific obligation is considered justified. The second specific obligation will be to provide yearly updates on any new information concerning the efficacy and safety of Gohibic in adult patients with SARS-CoV2-induced acute respiratory distress syndrome (ARDS) who are receiving systemic corticosteroids.

2.5.7. Conclusions on clinical efficacy

The PANAMO study is formally not a statistically positive study. Thus, the statistical strength of evidence is lower than what is normally anticipated. Still, the results of the pivotal trial support that vilobelimab would provide benefit to patients with ARDS due to Sars-Cov-2 infection.

A study to further characterise the indication of efficacy against covid-related ARDS seen in the PANAMO would be desirable. However, given the epidemiology and clinical features of Sars-Cov-2 omicron strains, this is not deemed feasible.

Therefore, the CHMP considers the following measures necessary to address the missing efficacy data in the context of a MA under exceptional circumstances:

Conducting the Just breathe study is considered adequate to address aspects related to the requirements of a marketing authorisation under exceptional circumstances (see Benefit-Risk Balance section).

Providing yearly updates on any new information concerning the efficacy and safety of Gohibic in adult patients with SARS-CoV2-induced acute respiratory distress syndrome (ARDS) who are receiving systemic corticosteroids.

2.5.8. Clinical safety

Vilobelimab has been used in 9 completed clinical studies with different indications and dosing regimens. In total 587 patients received at least one dose of vilobelimab. Due to that vilobelimab treatment in the current application focuses on patients who are mechanically ventilated and therefore in a very poor general condition, only safety data from subjects in the PANAMO study were considered. The safety evaluation therefore focused on the phase III study using the phase II study for supportive data.

The Phase III of PANAMO was a randomised controlled trial conducted in critically ill COVID-19 patients receiving invasive ventilation. A total of 175 patients in the vilobelimab + SoC group were treated with at least one dose of study drug and 103 (57.9%) completed the study. In comparison, a total of 189 patients were treated with at least one dose of placebo and 93 (48.7%) completed the study. A total of 175 patients received at least one dose of 800 mg vilobelimab, 23% (40 patients) received 5 study drug infusions and about 40% (70) received all 6 planned infusions of 800 mg of vilobelimab (4800 mg). 50 patients (28.1%) in the vilobelimab + SoC group and 68 patients (35.6%) in the placebo + SoC group prematurely discontinued treatment due to an AE. The median duration of treatment was higher for patients in the vilobelimab + SoC group (15 days) as compared to patients in the placebo + SoC group (8 days).

The Phase II of the PANAMO study was a hypothesis-generating open-label Phase II in severe to critical COVID-19 to inform the randomised controlled Phase III design. The study included safety data from 30 enrolled patients who were treated for up to 29 days: 15 received vilobelimab 800 mg (maximum of 7 doses) + BSC and 15 received BSC alone. All 15 patients allocated to the vilobelimab + BSC group received at least one dose of vilobelimab 800 mg treatment; 3 patients received 7 infusions (5,600 mg), 3 patients received 6 infusions (4,800 mg), 4 patients received 5 infusions (4,000 mg), and 5 patients received <5 infusions. In the vilobelimab + BSC group, 13 patients recovered and completed the study, while 2 patients died. None of the vilobelimab + BSC group patients discontinued treatment because of an AE or SAE other than death. In the BSC group, 11 of the 15 patients recovered and completed the study, while 4 patients died.

2.5.8.1. Adverse events

Table 38: Overview of AEs (PANAMO study, phase III, safety analysis set)

Category	Vilobelimab + SoC (N = 175)		Placebo + SoC (N = 189)		Total (N = 364)	
Worst Severity	n	(%)	n	(%)	n	(%)
Any AE	159	(90.9%)	172	(91.0%)	331	(90.9%)
Mild	14	(8.0%)	12	(6.3%)	26	(7.1%)
Moderate	25	(14.3%)	29	(15.3%)	54	(14.8%)
Severe	26	(14.9%)	19	(10.1%)	45	(12.4%)
Life-threatening	32	(18.3%)	27	(14.3%)	59	(16.2%)
Fatal	62	(35.4%)	85	(45.0%)	147	(40.4%)
Any treatment-related AE	20	(11.4%)	16	(8.5%)	36	(9.9%)
Mild	5	(2.9%)	4	(2.1%)	9	(2.5%)
Moderate	4	(2.3%)	4	(2.1%)	8	(2.2%)
Severe	7	(4.0%)	3	(1.6%)	10	(2.7%)
Life-threatening	4	(2.3%)	4	(2.1%)	8	(2.2%)
Fatal	0	(0.0%)	1	(0.5%)	1	(0.3%)
Any serious AE	103	(58.9%)	120	(63.5%)	223	(61.3%)
Any serious treatment-related AE	8	(4.6%)	9	(4.8%)	17	(4.7%)
Any fatal AE	62	(35.4%)	85	(45.0%)	147	(40.4%)
Any non-serious AE	147	(84.0%)	152	(80.4%)	299	(82.1%)
Any AE of special interest	111	(63.4%)	109	(57.7%)	220	(60.4%)
Any serious AE of special interest	66	(37.7%)	63	(33.3%)	129	(35.4%)
Any AE leading to premature study termination for reasons other than death	0	(0.0%)	0	(0.0%)	0	(0.0%)
Any AE leading to drug withdrawal	5	(2.9%)	3	(1.6%)	8	(2.2%)
Any AE leading to interrupted/omitted/postponed infusion	2	(1.1%)	7	(3.7%)	9	(2.5%)
Any pre-treatment AE	16	(9.1%)	16	(8.5%)	32	(8.8%)
Any AE with onset after hospital discharge	6	(3.4%)	7	(3.7%)	13	(3.6%)
Any AE with onset after Day 60	1	(0.6%)	0	(0.0%)	1	(0.3%)

AE = adverse event, SoC = standard of care
Percentages were based on number of patients with at least one AE of the specified AE type / total number of patients in the treatment group.

Table 39: Summary of AEs (PANAMO study, phase II COVID-19 study)

	Total (N=30)			Vilobelimab + BSC (N=15)			BSC (N=15)		
Category	N	(%)	Ev. N	n	(%)	Ev. n	N	(%)	Ev. N
Any AE	28	(93.3%)	282	14	(93.3%)	152	14	(93.3%)	130
Mild	0	(0.0%)	NA	0	(0.0%)	NA	0	(0.0%)	NA
Moderate	8	(26.7%)	NA	3	(20.0%)	NA	5	(33.3%)	NA
Severe	9	(30.0%)	NA	6	(40.0%)	NA	3	(20.0%)	NA
Life-threatening	5	(16.7%)	NA	3	(20.0%)	NA	2	(13.3%)	NA
Fatal	6	(20.0%)	7	2	(13.3%)	2	4	(26.7%)	5
Any related AE	9	(30.0%)	34	9	(60.0%)	34	NA	NA	NA

Category	Total (N=30)			Vilobelimab + BSC (N=15)			BSC (N=15)		
	N	(%)	Ev. N	n	(%)	Ev. n	N	(%)	Ev. N
Mild	0	(0.0%)	NA	0	(0.0%)	NA	NA	NA	NA
Moderate	4	(13.3%)	NA	4	(26.7%)	NA	NA	NA	NA
Severe	4	(13.3%)	NA	4	(26.7%)	NA	NA	NA	NA
Life-threatening	1	(3.3%)	NA	1	(6.7%)	NA	NA	NA	NA
Fatal	0	(0.0%)	0	0	(0.0%)	0	NA	NA	NA
Any non-serious AEs	28	(93.3%)	240	14	(93.3%)	129	14	(93.3%)	111
Any related non-serious AEs	9	(30.0%)	27	9	(60.0%)	27	NA	NA	NA
Any SAE	16	(53.3%)	42	9	(60.0%)	23	7	(46.7%)	19
Any related SAEs	4	(13.3%)	7	4	(26.7%)	7	NA	NA	NA
Any non-related SAEs	15	(50.0%)	35	8	(53.3%)	16	7	(46.7%)	19
Any AEs leading to drug withdrawal/dose reduction	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0
Any AEs leading to premature study termination	0	(0.0%)	0	0	(0.0%)	0	0	(0.0%)	0
Any AESI	15	(50.0%)	24	9	(60.0%)	17	6	(40.0%)	7
Any ICU AEs	23	(76.7%)	220	12	(80.0%)	110	11	(73.3%)	110
Any IMC AEs	18	(60.0%)	44	10	(66.7%)	32	8	(53.3%)	12
Any normal ward AEs	5	(16.7%)	15	3	(20.0%)	10	2	(13.3%)	5
Any follow-up AEs	2	(6.7%)	3	0	(0.0%)	0	2	(13.3%)	3
Any fatal AEs	6	(20.0%)	7	2	(13.3%)	2	4	(26.7%)	5

AE = adverse event, AESI = adverse event of special interest, BSC = best supportive care, Ev. n = number of events, ICU = intensive care unit, IMC = intermediate care ward, N = total number of patients in the corresponding treatment group, n = number of patients with available values, NA = not available or not applicable, SAE = serious adverse event. Percentages are based on the number of patients in the respective cohort.

90.9% in the vilobelimab group and 91.0% in the placebo group experienced an AE in the phase III trial and 93.3 % in both groups experienced an AE in the phase II trial. Mild and moderate AEs were balanced between vilobelimab and placebo treated patients, while severe and life-threatening AEs were overrepresented in the vilobelimab treated group. Fatal AEs on the other hand, were overrepresented in the placebo-treated group, in accordance with the nominally increased survival rate observed in the vilobelimab group (Phase III: 62 patients; 35.4% in the vilobelimab group vs 85 patients; 45.0% in the placebo group. Phase II: 2 patients; 13.3% in the vilobelimab group vs. 6 patients; 20.0% in the placebo group).

o AE by SOC

The majority of AEs were reported in the SOCs of 'Infections and infestations' and 'Respiratory, thoracic and mediastinal disorders'. PTs where imbalances were seen in AEs between vilobelimab treatment and placebo treatment were the following:

Pneumonia: 21.7% in the VILO group versus 13.8% in the placebo group experienced pneumonia. Approximately half of these patients (21 patients; 12.0%, in the vilobelimab group and 12 patients; 6.3% in the Placebo group) had SAEs of pneumonia. A further post-hoc analysis of all PTs coded to the system organ class of infections and infestations when grouped by high level group term showed that a few more patients in the VILO group experienced fungal infections or viral infections, whereas bacterial infections occurred in a similar proportion of patients. Further analyses of the incidence rates of pneumonia confirmed the observed imbalances. Pneumonia is listed an AE of vilobelimab in the SmPC.

Vascular disorders: Overall, there was an imbalance regarding thrombotic and embolic events; being increased in the vilobelimab treated patients (21.5 vs 18.5%). At the PT level, there were similar imbalances for thrombosis, (1.1 vs 0.5%), deep vein thrombosis (6.3 vs. 4.8%), jugular vein thrombosis (1.7 vs. 0.5%), phlebitis 2.3 vs. 0.5%), and distributive shock (1.1 vs. 0.5%). The overall incidence rate for based on the output of the SMQ "embolic and thrombotic" events was slightly increased in the vilobelimab group compared to the control group (0.94 vs. 0.89), which is considered a borderline finding. The applicant has therefore been requested to add venous thrombosis as a potential risk in the list of safety concerns in the RMP.

Thrombocytopenia: Thrombocytopenia was overrepresented in the vilobelimab group compared to the placebo treated group (4.6 vs 1.1%). which was confirmed in the analyses of incidence rates (0.16 vs. 0.03). Thrombocytopenia is labelled in the SmPC.

Cardiac disorders: There was an imbalance in the PTs cardiac arrest (2.9 vs. 1.1%), supraventricular tachycardia (4.0 vs.0.5%), ventricular extrasystoles (1.1 vs. 0%) and ECG abnormalities (1.1 vs. 0.5%). Whether mechanistic link exists between cardiac disorders and C5a inhibition is currently unknown. Due to the obvious imbalance seen in supraventricular tachycardia also with time adjusted data (incidence rate 0.16 vs. 0.03 events per100 patient days) supraventricular tachycardia is labelled as an AE in the SmPC.

Sepsis and urinary tract infections as PTs were overrepresented in the vilobelimab group compared to the placebo treated group (5.1 vs 2.1% and 5.1 vs. 3.2%, respectively). Sepsis and urinary tract infections were imbalanced also as AESIs and SAEs.

A causal relation between sepsis and vilobelimab treatment is plausible given the overrepresentation in the vilobelimab treated group together with the immunomodulatory nature of vilobelimab. The risk of secondary infections is a major concern upon immunomodulatory treatment of ARDS. Sepsis is therefore labelled as an AE in section 4.8 of the SmPC.

The broad term urinary tract infection, however, is not interpretable in the same way. Patients will have indwelling catheters and bacterial colonisation will be near-ubiquitous, why a causal relationship between vilobelimab treatment and urinary tract infection is not obvious.

Liver toxicity: ALT and AST levels were elevated in the vilobelimab treated patients (1.1 vs 0.5% both for ALT and AST). Cases of DILI, and unspecified liver injury and abnormal liver function were observed as SAEs, (see SAE section). The difference in incidence rate, was however negligible between the vilobelimab and placebo treated groups (0.04 vs. 0.03 events per 100 patient days).

Table 40: AEs reported for at Least 10% of patients in any treatment group by MedDRA system organ class and preferred term (safety analysis set)

System Organ Class	Vilobelimab + SoC (N = 175)		Placebo + SoC (N = 189)		Total (N = 364)	
Preferred Term	N	(%)	n	(%)	n	(%)
Total	159	(90.9%)	172	(91.0%)	331	(90.9%)
Infections and infestations	110	(62.9%)	112	(59.3%)	222	(61.0%)
Pneumonia	38	(21.7%)	26	(13.8%)	64	(17.6%)
Septic shock	24	(13.7%)	31	(16.4%)	55	(15.1%)
Respiratory, thoracic, and mediastinal disorders	63	(36.0%)	69	(36.5%)	132	(36.3%)
Respiratory failure	22	(12.6%)	25	(13.2%)	47	(12.9%)
Pulmonary embolism	19	(10.9%)	17	(9.0%)	36	(9.9%)
General disorders and administration site conditions	51	(29.1%)	53	(28.0%)	104	(28.6%)
Multiple organ dysfunction syndrome	17	(9.7%)	21	(11.1%)	38	(10.4%)
Vascular disorders	53	(30.3%)	43	(22.8%)	96	(26.4%)
Renal and urinary disorders	42	(24.0%)	51	(27.0%)	93	(25.5%)
Acute kidney injury	35	(20.0%)	40	(21.2%)	75	(20.6%)
Cardiac disorders	43	(24.6%)	43	(22.8%)	86	(23.6%)
Atrial fibrillation	13	(7.4%)	19	(10.1%)	32	(8.8%)
Metabolism and nutrition disorders	35	(20.0%)	49	(25.9%)	84	(23.1%)
Psychiatric disorders	36	(20.6%)	43	(22.8%)	79	(21.7%)
Investigations	37	(21.1%)	36	(19.0%)	73	(20.1%)
Gastrointestinal disorders	39	(22.3%)	32	(16.9%)	71	(19.5%)
Blood and lymphatic system disorders	27	(15.4%)	23	(12.2%)	50	(13.7%)
Skin and subcutaneous tissue disorders	22	(12.6%)	17	(9.0%)	39	(10.7%)

MedDRA = Medical Dictionary for Regulatory Activities, SoC = standard of care Coding was based on MedDRA version 24.1. Percentages were based on the number of patients with at least one adverse event of the specified MedDRA preferred term or MedDRA System Organ Class type / total number of patients in the treatment group.

o Treatment-related Adverse Events

Treatment-related AEs were reported in 36 of 364 treated patients (9.9%), most commonly in the system organ class of ‘infections and infestations’. The frequency of treatment-related AEs was

slightly higher in the VILO group (20 of 175 patients; 11.4%) compared to the Placebo group (16 of 189 patients; 8.5%). In terms of severity of treatment-related AEs, the majority were severe in severity (10 patients) followed by mild and moderate severity (8 patients each). Four patients (2.3%) in the vilobelimab + SoC group and 4 patients (2.1%) in the placebo + SoC group had life-threatening AEs that were considered related to study treatment; all of these AEs were reported in the SOC of 'Infections and infestations'. One patient in the placebo + SoC group had a fatal AE of herpes simplex pneumonia that was considered related to study treatment.

Table 41: Treatment-related adverse events reported for at least two patients in the vilobelimab group by MedDRA system organ class and preferred term (safety analysis set)

System Organ Class	Vilobelimab +SoC (N = 175)		Placebo + SoC (N = 189)		Total (N = 364)	
Preferred Term	n	(%)	n	(%)	n	(%)
Total	13	(7.4%)	2	(1.1%)	15	(4.1%)
Infections and infestations*						
Pneumonia**	5	(2.9%)	1	(0.5%)	6	(1.6%)
Septic shock	3	(1.7%)	0	(0.0%)	3	(0.8%)
Bronchopulmonary aspergillosis	2	(1.1%)	0	(0.0%)	2	(0.5%)
Herpes simplex	2	(1.1%)	0	(0.0%)	2	(0.5%)
Investigations						
Hepatic enzyme increased	2	(1.1%)	2	(1.1%)	4	(1.1%)
Skin and subcutaneous tissue disorders						
Rash	2	(1.1%)	0	(0.0%)	2	(0.5%)
Renal and urinary disorders						
Acute kidney injury	2	(1.1%)	0	(0.0%)	2	(0.5%)

MedDRA = Medical Dictionary for Regulatory Activities, SoC = standard of care Coding was based on the MedDRA version 24.1. Percentages were based on the number of patients with at least one adverse event of the specified MedDRA preferred term / total number of patients in the treatment group. This table shows adverse reactions derived from treatment-related AEs that occurred in at least in 2 patients in the vilobelimab arm of the PANAMO Phase III clinical trial. *Overall detected treatment-related AEs that were reported under MedDRA SOC 'Infections and infestations' were comparable between treatment arms with 24 patients affected (13.7%) in the vilobelimab arm and 23 patients affected (12.2%) in the placebo arm. **All treatment-related AEs subsumed under the category 'Pneumonia' including single-patient occurrences showed comparable frequency in the vilobelimab arm (5.1% [n=9]) compared to the placebo arm (4.8% [n=9]) when pooled. Hence, they were not considered adverse reactions. Source: CSR IFX-1-P2.9 Phase III Table 14.3.2.16.

2.5.8.2. Serious adverse events, deaths, and other significant events

SAEs

In the phase III study, the SAE frequency was overall lower in the VILO group (58.9%) compared to the Placebo group (63.5%). Particularly common SOCs were 'Infections and infestations' (40% vs 37%) and 'Respiratory, thoracic and mediastinal disorders' (24.6% vs 26.5%).

Of note are imbalances regarding lung infections seen with the product in the SAE section. Cases of pneumonia (12.0% vs. 8,5%) and specified subtypes of pneumonia, i.e. pneumonia induced by

klebsiella (3.4% vs 2.1%), staphylococcus (5.7% vs 1.6%), acinetobacter (2,9% vs 1.6%) or E. coli (1.1% vs 0,5%). This is accompanied by an overrepresentation COVID pneumonia (1.1% vs 0.0%) in the VILO group. As mentioned in the AE section, pneumonia is reflected in the SmPC section 4.8 Small imbalances are seen for lung complications such as ARDS (2.3% vs. 1.6%), hypoxia (2,9% vs 1,6%) and pneumomediastinum (1.7% vs. 0.0%).

A slight increased risk for a worsening of infections is reflected in a higher rate of sepsis (2.9% vs. 0.5%), pulmonary sepsis (8,0% vs 5,8%) and specific types of sepsis induced by staphylococcus, enterococcal bacteria (2,9% vs. 0.5% and 2,3% vs 0.5%) or Acinetobacter (1.1% vs. 0%), pseudomonas sepsis (1.1 vs. 0.5%) and urosepsis (1.7% vs. 1.1%).

Imbalances are observed in the SOC vascular disorders (6.3% vs. 2.1%) for the PTs haemorrhagic and distributive shock (1.7% vs. 0.5% and 1.1% vs 0.5%) and thrombosis (1.1% vs 0.0%) as well as for cardiac arrest (2.9% vs.1.1%). These events are discussed in depth in the chapter AESIs (see above).

1 SAE of DILI, 2 SAEs of (not further specified) liver injury and 1 case of abnormal liver function is noted within the VILO group. As the numerical difference in ALT increases are not striking and there is little mechanistic suspicion of that a mAb specific for C5a would be hepatoxic, a causal relationship between liver toxicity and vilobelimab treatment is not inferred. Furthermore, 2 SAEs of pancreatitis (acute and necrotizing) are noted in in the same patient treated with vilobelimab. The single case occurred in a severely ill patient with concomitant Covid-19 infection and aspergillosis complicated by septic shock. A causal relationship between pancreatitis and vilobelimab is not sufficiently plausible and should therefore not be listed in the SmPC.

2 vs 0 SAEs of thrombocytopenia are seen in the VILO group (1.1% vs 0.0%). In light of imbalances seen in the AE section and isolated severe shifts observed in the laboratory section, this term is reflected in the SmPC.

In the phase II study, the frequency of SAEs within each SOC was similar between treatment groups, with the exception of General Disorders and Administration Site Conditions including the SAE of multiple organ dysfunction syndrome that was reported only in the BSC group (4 of 15 patients, 26.7%). SAEs in the Infections and Infestations SOCs including Pneumonia as well as the PT pulmonary embolism (most frequently reported SAE) were reported less frequently in the IFX-1 group.

Table 42: All SAEs by MedDRA SOC and PT; SAS - Phase III study

	Total (N=364)			Vilo + SOC (N = 175)			Placebo + SOC (N=189)		
MedDRA System Organ Class MedDRA Preferred Term	Pat. n	(Pat. %)	Events	Pat. n	(Pat. %)	Events	Pat. n	(Pat. %)	Events
Total	223	(61.3%)	729	103	(58.9%)	374	120	(63.5%)	355
Infections and infestations	140	(38.5%)	360	70	(40.0%)	196	70	(37.0%)	164
Septic shock	54	(14.8%)	63	24	(13.7%)	29	30	(15.9%)	34
Pneumonia	37	(10.2%)	47	21	(12.0%)	29	16	(8.5%)	18
Pulmonary sepsis	25	(6.9%)	35	14	(8.0%)	21	11	(5.8%)	14
Klebsiella infection	13	(3.6%)	13	4	(2.3%)	4	9	(4.8%)	9
Pneumonia staphylococcal	13	(3.6%)	14	10	(5.7%)	11	3	(1.6%)	3
Bronchopulmonary aspergillosis	12	(3.3%)	12	6	(3.4%)	6	6	(3.2%)	6
Pneumonia klebsiella	10	(2.7%)	11	6	(3.4%)	6	4	(2.1%)	5
Staphylococcal infection	9	(2.5%)	9	4	(2.3%)	4	5	(2.6%)	5
Urinary tract infection	9	(2.5%)	11	6	(3.4%)	8	3	(1.6%)	3
Acinetobacter infection	8	(2.2%)	8	4	(2.3%)	4	4	(2.1%)	4
Pneumonia Acinetobacter	8	(2.2%)	8	5	(2.9%)	5	3	(1.6%)	3
Pneumonia pseudomonal	6	(1.6%)	7	3	(1.7%)	3	3	(1.6%)	4
Sepsis	6	(1.6%)	6	5	(2.9%)	5	1	(0.5%)	1
Staphylococcal sepsis	6	(1.6%)	8	5	(2.9%)	7	1	(0.5%)	1
Enterococcal sepsis	5	(1.4%)	5	4	(2.3%)	4	1	(0.5%)	1
Urosepsis	5	(1.4%)	5	3	(1.7%)	3	2	(1.1%)	2
Aspergillus infection	4	(1.1%)	4	1	(0.6%)	1	3	(1.6%)	3
Tracheobronchitis	4	(1.1%)	4	2	(1.1%)	2	2	(1.1%)	2
Device related bacteraemia	3	(0.8%)	3	2	(1.1%)	2	1	(0.5%)	1
Enterococcal infection	3	(0.8%)	3	2	(1.1%)	2	1	(0.5%)	1
Herpes simplex pneumonia	3	(0.8%)	3	0	(0.0%)	0	3	(1.6%)	3
Pneumonia Escherichia	3	(0.8%)	4	2	(1.1%)	3	1	(0.5%)	1
Pseudomonal sepsis	3	(0.8%)	3	2	(1.1%)	2	1	(0.5%)	1
Stenotrophomonas infection	3	(0.8%)	3	2	(1.1%)	2	1	(0.5%)	1
Urinary tract infection enterococcal	3	(0.8%)	3	0	(0.0%)	0	3	(1.6%)	3
Vascular device infection	3	(0.8%)	3	1	(0.6%)	1	2	(1.1%)	2
Acinetobacter sepsis	2	(0.5%)	2	2	(1.1%)	2	0	(0.0%)	0
COVID-19 pneumonia	2	(0.5%)	2	2	(1.1%)	2	0	(0.0%)	0
Citrobacter infection	2	(0.5%)	2	1	(0.6%)	1	1	(0.5%)	1
Enterobacter pneumonia	2	(0.5%)	3	1	(0.6%)	2	1	(0.5%)	1
Enterococcal bacteraemia	2	(0.5%)	2	0	(0.0%)	0	2	(1.1%)	2
Escherichia infection	2	(0.5%)	2	1	(0.6%)	1	1	(0.5%)	1
Escherichia urinary tract infection	2	(0.5%)	2	1	(0.6%)	1	1	(0.5%)	1
Klebsiella sepsis	2	(0.5%)	2	1	(0.6%)	1	1	(0.5%)	1
Lung abscess	2	(0.5%)	2	2	(1.1%)	2	0	(0.0%)	0
Nosocomial infection	2	(0.5%)	2	1	(0.6%)	1	1	(0.5%)	1
Pneumonia aspiration	2	(0.5%)	2	1	(0.6%)	1	1	(0.5%)	1
Pneumonia bacterial	2	(0.5%)	2	1	(0.6%)	1	1	(0.5%)	1
Pneumonia cytomegaloviral	2	(0.5%)	2	1	(0.6%)	1	1	(0.5%)	1
Pneumonia serratia	2	(0.5%)	2	1	(0.6%)	1	1	(0.5%)	1
Pseudomonas infection	2	(0.5%)	2	1	(0.6%)	1	1	(0.5%)	1
Superinfection bacterial	2	(0.5%)	3	1	(0.6%)	2	1	(0.5%)	1
Tracheobronchitis bacterial	2	(0.5%)	2	0	(0.0%)	0	2	(1.1%)	2
Bacteraemia	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Bacterial infection	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Bronchitis	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Candida sepsis	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Cholangitis infective	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Corynebacterium sepsis	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Device related infection	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Device related sepsis	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Empyema	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Enterobacter infection	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Enterobacter sepsis	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Enterobacter tracheobronchitis	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Epstein-Barr virus infection	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Herpes simplex reactivation	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Infectious pleural effusion	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Klebsiella bacteraemia	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Liver abscess	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Morganella infection	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Peritonitis	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Pneumonia haemophilus	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1

	Total (N=364)			Vilo + SOC (N = 175)			Placebo + SOC (N=189)		
MedDRA System Organ Class MedDRA Preferred Term	Pat. n	(Pat. %)	Events	Pat. n	(Pat. %)	Events	Pat. n	(Pat. %)	Events
Pneumonia streptococcal	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Providencia infection	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Pseudomonal bacteraemia	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Severe acute respiratory syndrome	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Staphylococcal bacteraemia	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Stenotrophomonas sepsis	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Streptococcal sepsis	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Systemic candida	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Urinary tract infection pseudomonal	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Respiratory, thoracic and mediastinal disorders	93	(25.5%)	125	43	(24.6%)	62	50	(26.5%)	63
Respiratory failure	44	(12.1%)	48	20	(11.4%)	23	24	(12.7%)	25
Pulmonary embolism	22	(6.0%)	22	10	(5.7%)	10	12	(6.3%)	12
Pneumothorax	10	(2.7%)	11	4	(2.3%)	4	6	(3.2%)	7
Hypoxia	8	(2.2%)	8	5	(2.9%)	5	3	(1.6%)	3
Acute respiratory distress syndrome	7	(1.9%)	8	4	(2.3%)	4	3	(1.6%)	4
Laryngeal oedema	3	(0.8%)	3	1	(0.6%)	1	2	(1.1%)	2
Pneumomediastinum	3	(0.8%)	3	3	(1.7%)	3	0	(0.0%)	0
Aspiration	2	(0.5%)	2	2	(1.1%)	2	0	(0.0%)	0
Haemoptysis	2	(0.5%)	2	1	(0.6%)	1	1	(0.5%)	1
Respiratory distress	2	(0.5%)	2	0	(0.0%)	0	2	(1.1%)	2
Acute respiratory failure	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Anoxia	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Bronchial obstruction	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Bronchopleural fistula	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Cough	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Haemothorax	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Hypercapnia	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Lung opacity	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Mediastinal shift	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Organising pneumonia	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Pleural effusion	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Pulmonary fibrosis	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Pulmonary hypertension	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Pulmonary infarction	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Pulmonary necrosis	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Sputum retention	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Renal and urinary disorders	53	(14.6%)	57	21	(12.0%)	22	32	(16.9%)	35
Acute kidney injury	45	(12.4%)	46	16	(9.1%)	16	29	(15.3%)	30
Renal failure	5	(1.4%)	5	3	(1.7%)	3	2	(1.1%)	2
Renal impairment	4	(1.1%)	4	2	(1.1%)	2	2	(1.1%)	2
Anuria	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Oliguria	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
General disorders and administration site conditions	40	(11.0%)	42	19	(10.9%)	21	21	(11.1%)	21
Multiple organ dysfunction syndrome	37	(10.2%)	37	16	(9.1%)	16	21	(11.1%)	21
Hyperthermia	2	(0.5%)	2	2	(1.1%)	2	0	(0.0%)	0
Fibrosis	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Medical device site haemorrhage	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Oedema peripheral	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Cardiac disorders	30	(8.2%)	39	11	(6.3%)	16	19	(10.1%)	23
Cardiac arrest	7	(1.9%)	7	5	(2.9%)	5	2	(1.1%)	2
Cardio-respiratory arrest	5	(1.4%)	7	1	(0.6%)	1	4	(2.1%)	6
Acute myocardial infarction	3	(0.8%)	3	0	(0.0%)	0	3	(1.6%)	3
Bradycardia	2	(0.5%)	2	1	(0.6%)	1	1	(0.5%)	1
Cardiogenic shock	2	(0.5%)	2	0	(0.0%)	0	2	(1.1%)	2
Ventricular tachycardia	2	(0.5%)	2	0	(0.0%)	0	2	(1.1%)	2
Arrhythmia	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Atrial fibrillation	1	(0.3%)	3	1	(0.6%)	3	0	(0.0%)	0
Atrioventricular block	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Atrioventricular block complete	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Cardiac failure	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Cardiac failure acute	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Cardiac perforation	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Cardiomyopathy	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Cardiopulmonary failure	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Myocardial infarction	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Supraventricular tachycardia	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Ventricular arrhythmia	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1

	Total (N=364)			Vilo + SOC (N = 175)			Placebo + SOC (N=189)		
MedDRA System Organ Class MedDRA Preferred Term	Pat. n	(Pat. %)	Events	Pat. n	(Pat. %)	Events	Pat. n	(Pat. %)	Events
Ventricular extrasystoles	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Ventricular fibrillation	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Nervous system disorders	17	(4.7%)	21	9	(5.1%)	12	8	(4.2%)	9
Depressed level of consciousness	8	(2.2%)	8	4	(2.3%)	4	4	(2.1%)	4
Cerebral infarction	3	(0.8%)	3	2	(1.1%)	2	1	(0.5%)	1
Autonomic nervous system imbalance	2	(0.5%)	2	2	(1.1%)	2	0	(0.0%)	0
Ischaemic stroke	2	(0.5%)	2	1	(0.6%)	1	1	(0.5%)	1
Haemorrhagic cerebral infarction	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Seizure	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Stroke in evolution	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Subarachnoid haemorrhage	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Toxic encephalopathy	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Transient ischaemic attack	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Vascular disorders	15	(4.1%)	19	11	(6.3%)	13	4	(2.1%)	6
Shock haemorrhagic	4	(1.1%)	5	3	(1.7%)	3	1	(0.5%)	2
Distributive shock	3	(0.8%)	3	2	(1.1%)	2	1	(0.5%)	1
Deep vein thrombosis	2	(0.5%)	2	1	(0.6%)	1	1	(0.5%)	1
Jugular vein thrombosis	2	(0.5%)	2	1	(0.6%)	1	1	(0.5%)	1
Thrombosis	2	(0.5%)	2	2	(1.1%)	2	0	(0.0%)	0
Circulatory collapse	1	(0.3%)	2	1	(0.6%)	2	0	(0.0%)	0
Hypertensive crisis	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Obstructive shock	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Shock	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Hepatobiliary disorders	13	(3.6%)	14	5	(2.9%)	5	8	(4.2%)	9
Liver injury	4	(1.1%)	4	2	(1.1%)	2	2	(1.1%)	2
Acute hepatic failure	2	(0.5%)	2	1	(0.6%)	1	1	(0.5%)	1
Hepatic failure	2	(0.5%)	2	0	(0.0%)	0	2	(1.1%)	2
Ischaemic hepatitis	2	(0.5%)	2	0	(0.0%)	0	2	(1.1%)	2
Cholangitis sclerosing	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Drug-induced liver injury	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Hepatic function abnormal	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Hepatic infarction	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Gastrointestinal disorders	9	(2.5%)	13	5	(2.9%)	7	4	(2.1%)	6
Intra-abdominal haemorrhage	2	(0.5%)	2	1	(0.6%)	1	1	(0.5%)	1
Large intestine perforation	2	(0.5%)	2	1	(0.6%)	1	1	(0.5%)	1
Diverticulum intestinal haemorrhagic	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Duodenal ulcer haemorrhage	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Gastrointestinal haemorrhage	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Gastrointestinal necrosis	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Intestinal ischaemia	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Mouth haemorrhage	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Pancreatitis acute	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Pancreatitis necrotising	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Rectal haemorrhage	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Investigations	9	(2.5%)	17	5	(2.9%)	12	4	(2.1%)	5
Bronchoalveolar lavage abnormal	3	(0.8%)	5	2	(1.1%)	4	1	(0.5%)	1
Aspergillus test positive	2	(0.5%)	2	1	(0.6%)	1	1	(0.5%)	1
Herpes simplex test positive	2	(0.5%)	2	2	(1.1%)	2	0	(0.0%)	0
Blood culture positive	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Glutamate dehydrogenase increased	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Hepatic enzyme abnormal	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Hepatic enzyme increased	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Klebsiella test positive	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Sputum culture positive	1	(0.3%)	2	1	(0.6%)	2	0	(0.0%)	0
Transaminases increased	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Blood and lymphatic system disorders	6	(1.6%)	6	3	(1.7%)	3	3	(1.6%)	3
Anaemia	2	(0.5%)	2	1	(0.6%)	1	1	(0.5%)	1
Thrombocytopenia	2	(0.5%)	2	2	(1.1%)	2	0	(0.0%)	0
Heparin-induced thrombocytopenia	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Splenic infarction	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Metabolism and nutrition disorders	5	(1.4%)	7	0	(0.0%)	0	5	(2.6%)	7
Hyperkalaemia	2	(0.5%)	3	0	(0.0%)	0	2	(1.1%)	3
Acid-base balance disorder mixed	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Acidosis	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Hyperglycaemic hyperosmolar nonketotic syndrome	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Hypovolaemia	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Injury, poisoning and procedural complications	4	(1.1%)	4	3	(1.7%)	3	1	(0.5%)	1

	Total (N=364)			Vilo + SOC (N = 175)			Placebo + SOC (N=189)		
MedDRA System Organ Class MedDRA Preferred Term	Pat. n	(Pat. %)	Events	Pat. n	(Pat. %)	Events	Pat. n	(Pat. %)	Events
Endotracheal intubation complication	2	(0.5%)	2	1	(0.6%)	1	1	(0.5%)	1
Post procedural complication	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Post procedural haemorrhage	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Skin and subcutaneous tissue disorders	2	(0.5%)	2	1	(0.6%)	1	1	(0.5%)	1
Subcutaneous emphysema	2	(0.5%)	2	1	(0.6%)	1	1	(0.5%)	1
Musculoskeletal and connective tissue disorders	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Muscle haemorrhage	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Product issues	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Device dislocation	1	(0.3%)	1	0	(0.0%)	0	1	(0.5%)	1
Psychiatric disorders	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0
Agitation	1	(0.3%)	1	1	(0.6%)	1	0	(0.0%)	0

Source: Table 14.3.2.11 Serious TEAEs by MEdDRA SOC and PT- SAF

Related SAEs

In the phase III trial, treatment-related SAEs were overall in same frequencies reported in the VILO and in the placebo group (4.6% vs. 4.8%). The majority of treatment-related SAEs were reported in the SOC 'Infections and infestations'. As noted already in the section "all SAEs", the cases of thrombocytopenia have been evaluated as related by the study physician. Imbalances of pneumonia (2.3% vs 0%) and sepsis/septic shock (1.7% vs 0%) is reflected in the SmPC, section 4.8, as mentioned in the AE section. A slight imbalance of bronchopulmonary aspergillosis is seen. Aspergillosis is included in the SmPC, section 4.8.

In the phase II trial, seven SAEs in 4 patients in the IFX-1 group were considered to be possibly related to IFX-1 treatment by the Investigator: pneumonia, Pseudomonas infection, Staphylococcal infection and vascular device infection in 1 patient; and device related sepsis, end-tidal CO2 decreased, and UTI in 1 patient each.

Table 43: All treatment-related serious adverse events reported by MedDRA system organ class and preferred term (SAS) - phase III study

System Organ Class (SOC) Preferred Term (PT)	VILO+SOC (N = 175) n	(%)	Placebo+SOC (N = 189) n	(%)	Total (N = 364) n	(%)
Total	8	(4.6%)	9	(4.8%)	17	(4.7%)
Infections and infestations	6	(3.4%)	6	(3.2%)	12	(3.3%)
Pneumonia	4	(2.3%)	0	(0.0%)	4	(1.1%)
Klebsiella infection	0	(0.0%)	3	(1.6%)	3	(0.8%)
Pneumonia klebsiella	1	(0.6%)	2	(1.1%)	3	(0.8%)
Septic shock	3	(1.7%)	0	(0.0%)	3	(0.8%)
Bronchopulmonary aspergillosis	2	(1.1%)	0	(0.0%)	2	(0.5%)
Pneumonia staphylococcal	1	(0.6%)	1	(0.5%)	2	(0.5%)
Acinetobacter infection	0	(0.0%)	1	(0.5%)	1	(0.3%)
Aspergillus infection	0	(0.0%)	1	(0.5%)	1	(0.3%)
Bronchitis	1	(0.6%)	0	(0.0%)	1	(0.3%)
Device related bacteraemia	1	(0.6%)	0	(0.0%)	1	(0.3%)
Escherichia infection	1	(0.6%)	0	(0.0%)	1	(0.3%)
Escherichia urinary tract infection	1	(0.6%)	0	(0.0%)	1	(0.3%)
Herpes simplex pneumonia	0	(0.0%)	1	(0.5%)	1	(0.3%)
Herpes simplex reactivation	0	(0.0%)	1	(0.5%)	1	(0.3%)
Infectious pleural effusion	0	(0.0%)	1	(0.5%)	1	(0.3%)
Liver abscess	0	(0.0%)	1	(0.5%)	1	(0.3%)
Nosocomial infection	0	(0.0%)	1	(0.5%)	1	(0.3%)
Pneumonia cytomegaloviral	0	(0.0%)	1	(0.5%)	1	(0.3%)
Pneumonia escherichia	1	(0.6%)	0	(0.0%)	1	(0.3%)
Pneumonia haemophilus	0	(0.0%)	1	(0.5%)	1	(0.3%)
Pneumonia streptococcal	1	(0.6%)	0	(0.0%)	1	(0.3%)
Pulmonary sepsis	0	(0.0%)	1	(0.5%)	1	(0.3%)
Staphylococcal sepsis	1	(0.6%)	0	(0.0%)	1	(0.3%)
Tracheobronchitis bacterial	0	(0.0%)	1	(0.5%)	1	(0.3%)
Hepatobiliary disorders	1	(0.6%)	1	(0.5%)	2	(0.5%)
Drug-induced liver injury	1	(0.6%)	0	(0.0%)	1	(0.3%)
Liver injury	0	(0.0%)	1	(0.5%)	1	(0.3%)
Investigations	1	(0.6%)	1	(0.5%)	2	(0.5%)
Glutamate dehydrogenase increased	0	(0.0%)	1	(0.5%)	1	(0.3%)
Transaminases increased	1	(0.6%)	0	(0.0%)	1	(0.3%)
Blood and lymphatic system disorders	1	(0.6%)	0	(0.0%)	1	(0.3%)
Thrombocytopenia	1	(0.6%)	0	(0.0%)	1	(0.3%)

System Organ Class (SOC)	VILO+SOC (N = 175)		Placebo+SOC (N = 189)		Total (N = 364)	
Preferred Term (PT)	n	(%)	n	(%)	n	(%)
Gastrointestinal disorders	1	(0.6%)	0	(0.0%)	1	(0.3%)
Pancreatitis acute	1	(0.6%)	0	(0.0%)	1	(0.3%)
Pancreatitis necrotising	1	(0.6%)	0	(0.0%)	1	(0.3%)
Metabolism and nutrition disorders	0	(0.0%)	1	(0.5%)	1	(0.3%)
Hyperkalaemia	0	(0.0%)	1	(0.5%)	1	(0.3%)

MedDRA = Medical Dictionary for Regulatory Activities, SOC = standard of care, VILO = vilobelimab. Coding was based on the MedDRA version 24.1. Percentages were based on the number of patients with at least one adverse event of the specified MedDRA preferred term or MedDRA system organ class type / total number of patients in the treatment group.

Deaths

In the phase III study, fatal AEs were reported in 147 of 364 patients (40.4%). The frequency of fatal AEs was higher in the placebo group (85 of 189 patients [45.0%]) than the VILO group (62 of 175 patients [35.4%]). The most commonly reported fatal AEs (in ≥ 10% of patients in any treatment group) were:

• Multiple organ dysfunction syndrome: 16 patients (9.1%) in the VILO group versus 20 patients (10.6%) in the Placebo group

• Septic shock: 11 patients (6.3%) in the VILO group versus 20 patients (10.6%) in the Placebo group

• Respiratory failure: 11 patients (6.3%) in the VILO group versus 20 patients (10.6%) in the Placebo group

While the vast majority of SOCs and PTs were in higher frequency observed in the placebo group, a slight imbalance of patients in disadvantage for the VILO group is seen for vascular disorders (2.3% vs 1.1%) composed of PTs such as different forms of shock (unspecified/distributive/obstructive; 3 vs 1 cases) and thrombosis (1 vs 0 cases) and neurological disorders with 1 vs 0 event of stroke. Vascular events are further discussed in the sections AESIs.

In the phase II study, a total of 6 of 30 patients (20.0%) died by Day 28: 2 of 15 patients (13.3%) in the IFX-1 group and 4 of 15 patients (26.7%) in the BSC group.

2.5.8.3. Laboratory findings

Laboratory values presented by the applicant are mainly derived from the phase III study. Values that have been also analysed in the phase II study, have been added to the specific sub sections as indicated and are treated as supportive data.

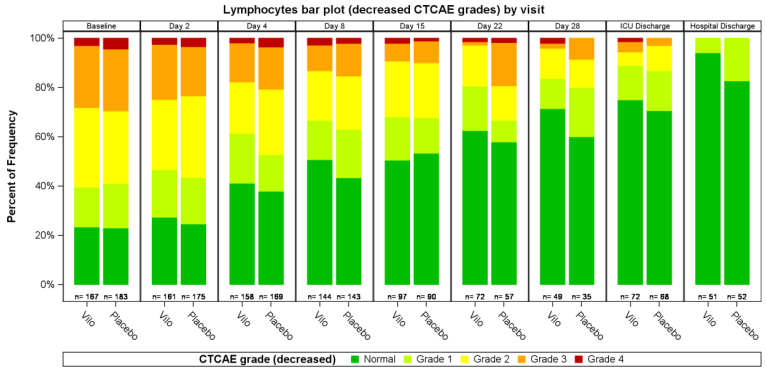
Haematology

Leukocytes were overall comparable between VILO and placebo group at baseline in the phase III study (increased in both groups) and at discharge (normalised in both groups).

Basophils and Eosinophils were overall within normal ranges at baseline, during study run and at discharge in both study groups in the phase III study. A slight neutrophilia was present in almost all patients at baseline, with a median of 10.1 × 10^9/L in the VILO group and 9.6× 10^9/L in the Placebo group, which normalised up to ICU discharge in both treatment groups and which were within the normal range by hospital discharge. Similar observations were made in the phase II trial, where neutrophilia was present in many patients at the time of enrolment, with median neutrophil counts of 7.260 × 10^9/L in the IFX-1 group and 8.310 × 10^9/L in the BSC group at baseline. The proportion of patients with neutrophil counts within normal limits remained constant throughout the study in both groups. Mean changes in neutrophil counts were also not significantly different between the two groups at the other time points.

Patients in both groups showed to a certain degree lymphopenia at baseline in the phase III study, which normalised stepwise up to discharge. Monocytes were overall comparable between VILO and placebo group at baseline and discharge with normal or near normal values over time. Lymphocytopenia (defined as < 1.5 × 10^9/L) was present in almost all patients at the time of enrolment in the phase II study. Shift plots show that the proportion of patients with lymphocyte counts within normal limits increased in both groups, with a numerically higher proportion of patients in the IFX-1 group at Day 15 (87% vs. 47%). Mean changes in lymphocyte counts were not significantly different between the two groups at the other time points.

Figure 14: Lymphocytes bar plot (decreased CTCAE grades) by visit (SAS) phase III study



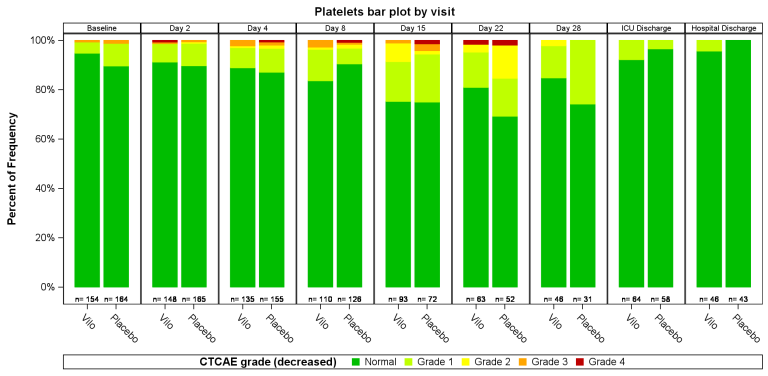
CTCAE = Common Terminology Criteria for Adverse Events, Hosp Dis = hospital discharge, ICU = intensive care unit, SOC = standard of care, VILO = vilobelimab; Percentages were based on the number of patients in the respective group and visit.

Erythrocytes were normal at baseline and discharge and temporarily decreased during study run on both groups in the phase III study. Haematocrit and haemoglobin were in both groups decreased at baseline and normalised again up to discharge in both treatment group. MCV was normal in both treatment groups Overall, changes from baseline in haematology parameters during the study were transient and mild.

Platelets and coagulation

Platelets were roughly in normal ranges during the phase III study.

Figure 15: Platelet bar plot (decreased CTCAE grades) by visit (SAS) phase III study



Percentages are based on the number of patients in the respective treatment group and visit

Vilo = Vilobelimab + SOC, Placebo = Placebo + SOC, SOC = Standard of care, SAF = Safety analysis set, FAS = Full analysis set , PPS = Per-protocol set

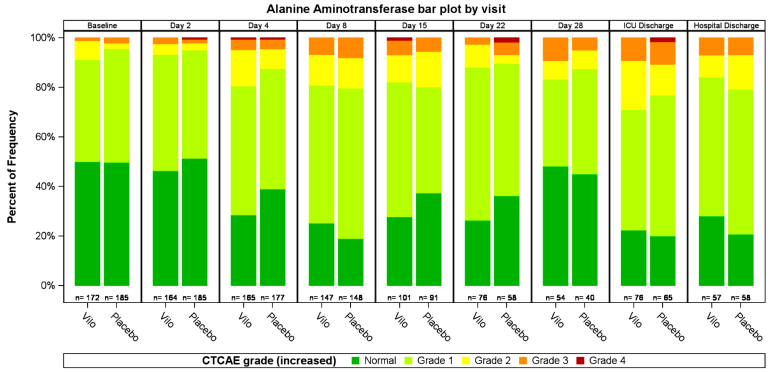
Overall, no significant differences regarding shifts in coagulation parameters, i.e., d-dimers, aPTT, PT and INR were observed between the study groups in the phase III study. In the phase II study, D-dimer concentrations were increased at baseline in both study arms. Of note, temporary elevations of d-dimers were observed at Days 2 and 4 in the IFX.1 group (day 2 increase of 169.6% in the IFX-1 group versus 23.3% in the BSC group; p=0.0282; and at day 4 (267.8% versus 54.0%, respectively; p=0.0286). The observation reverted at day 15 with higher values ins the BSC group (222.9%) compared with the IFX-1 group (196.2%), without reaching statistical significance (difference -26.7% [95% CI -420.6;367.2], p=0.8904). The view of the applicant that the increase in D-dimer levels may be a result of an earlier resolution of coagulation activity with IFX-1 in the context of COVID-19 can be supported.

Clinical Chemistry

Liver values

Overall, ALT behaved comparable in the two study groups during the phase III study run. ALT increases were mainly seen at baseline and became better during the study. Shifts from 0 or 1 to grade 3 are in several cases observed in the VILO group at all days, the proportion of patients showing these shifts seems, however, overall balanced between VILO and placebo group. Two 2 cases shifting from grade 0 or 1 to grade 4 are seen in the VILO group.

Figure 16: Alanine aminotransferase bar plot by visit – SAS, phase III study



Percentages are based on the number of patients in the respective treatment group and visit
Vilo = Vilobelimab + SOC, Placebo = Placebo + SOC, SOC = Standard of care, SAF = Safety analysis set, FAS = Full analysis set, PPS = Per-protocol set

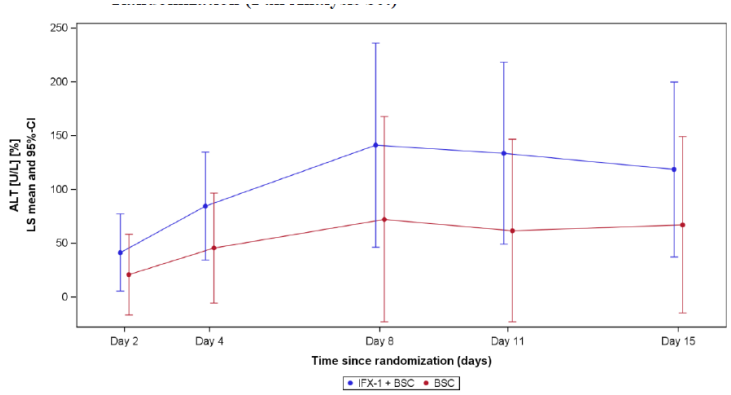
Table 44: ALT shifts phase III study (extract)

Baseline	CTCAE Grades Day 4 Normal	Grade 1	Grade 2	Grade 3	Grade 4
Vilo + SOC (N=175) (nmiss=13)					
Normal (n=82)	40 (22.9%)	37 (21.1%)	2 (1.1%)	2 (1.1%)	1 (0.6%)
Grade 1 (n=66)	6 (3.4%)	41 (23.4%)	16 (9.1%)	3 (1.7%)	0
Grade 2 (n=12)	0	7 (4%)	4 (2.3%)	1 (0.6%)	0
Grade 3 (n=2)	0	1 (0.6%)	0	1 (0.6%)	0
Grade 4 (n=0)	0	0	0	0	0
Placebo + SOC (N=189) (nmiss=14)					
Normal (n=88)	52 (27.5%)	32 (16.9%)	3 (1.6%)	1 (0.5%)	0
Grade 1 (n=79)	15 (7.9%)	50 (26.5%)	9 (4.8%)	5 (2.6%)	0
Grade 2 (n=4)	0	3 (1.6%)	1 (0.5%)	0	0
Grade 3 (n=4)	0	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)
	Day 15				
Vilo + SOC (N=175) (nmiss=74)					
Normal (n=45)	15 (8.6%)	27 (15.4%)	3 (1.7%)	0	0
Grade 1 (n=47)	12 (6.9%)	23 (13.1%)	6 (3.4%)	5 (2.9%)	1 (0.6%)
Grade 2 (n=7)	0	5 (2.9%)	2 (1.1%)	0	0
Grade 3 (n=2)	1 (0.6%)	0	0	1 (0.6%)	0
Grade 4 (n=0)	0	0	0	0	0
Placebo + SOC (N=189) (nmiss=101)					
Normal (n=44)	20 (10.6%)	18 (9.5%)	4 (2.1%)	2 (1.1%)	0
Grade 1 (n=39)	12 (6.3%)	17 (9%)	8 (4.2%)	2 (1.1%)	0
Grade 2 (n=3)	0	3 (1.6%)	0	0	0
Grade 3 (n=2)	0	0	1 (0.5%)	1 (0.5%)	0
Grade 4 (n=0)	0	0	0	0	0
Grade 4 (n=0)	0	0	0	0	0

Source: Table 14.3.3.4.1.3

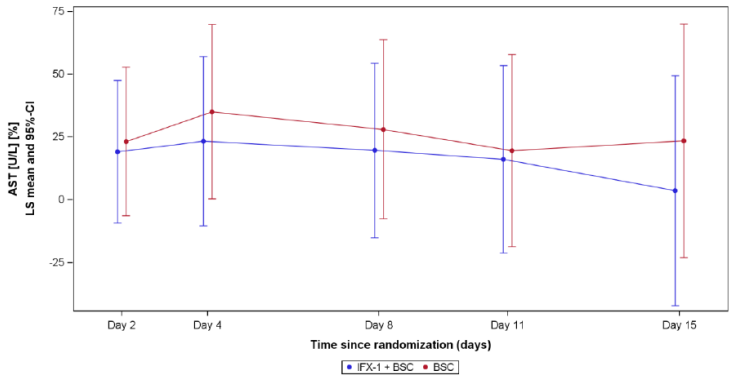
Of note, ALT levels increased to a stronger extent over time in the phase II study compared to the placebo group with a peak at day 8 and increases of 118% vs 67% compared to baseline.

Figure 17: mean ALT and AST levels phase II study



BSC = best supportive care, CI = confidence interval, LS = least square
Solid lines interpolate between the LS-means (dots) at the study days of interest; 95% CIs included (vertical lines).
Source: Figure 14.2.10.1.8

Figure 10-5 LS-means Plot of Relative Change in AST [%]by Day Since Randomization (Full Analysis Set)



BSC = best supportive care, CI = confidence interval, LS = least square
Solid lines interpolate between the LS-means (dots) at the study days of interest; 95% CIs included (vertical lines).
Source: Figure 14.2.10.2.8

AST behaved comparable in the two study groups during the phase III study run and no major shifts/increases are seen compared to study baseline in the VILO group. As seen for ALT, Grade 3 shifts of AST from grades 0 or 1 are in isolated cases seen on the majority of days monitored, however, in overall balanced proportion in VILO and placebo group. One case of Grade 1 to Grade 4 increase of AST is seen in the VILO group. No relevant differences for AST are seen in the phase II study.

Table 45: AST shifts phase III study (extract)

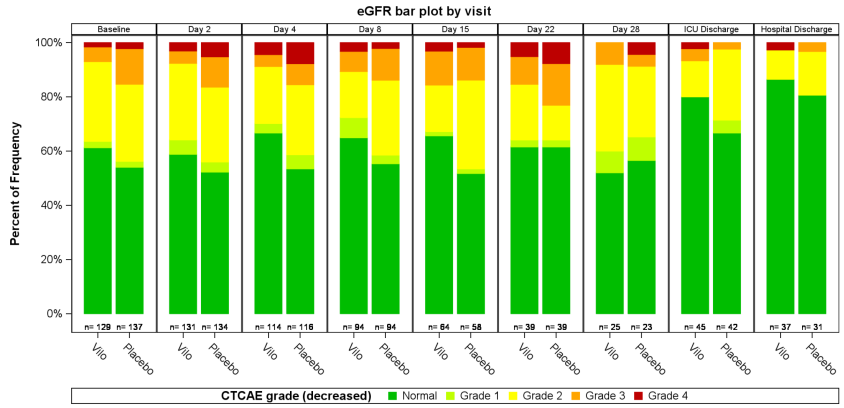
Baseline	Day 4 Normal	Grade 1	Grade 2	Grade 3	Grade 4
Vilo + SOC (N=175) (nmiss=13)					
Normal (n=64)	28 (16%)	34 (19.4%)	1 (0.6%)	1 (0.6%)	0
Grade 1 (n=87)	17 (9.7%)	59 (33.7%)	9 (5.1%)	1 (0.6%)	1 (0.6%)
Grade 2 (n=8)	0	5 (2.9%)	3 (1.7%)	0	0
Grade 3 (n=3)	1 (0.6%)	0	0	2 (1.1%)	0
Grade 4 (n=0)	0	0	0	0	0
Placebo + SOC (N=189) (nmiss=13)					
Normal (n=68)	30 (15.9%)	34 (18%)	3 (1.6%)	1 (0.5%)	0
Grade 1 (n=100)	20 (10.6%)	70 (37%)	8 (4.2%)	2 (1.1%)	0
Grade 2 (n=5)	1 (0.5%)	3 (1.6%)	0	1 (0.5%)	0
Grade 3 (n=3)	0	2 (1.1%)	0	1 (0.5%)	0
Grade 4 (n=0)	0	0	0	0	0

Median and mean bilirubin levels were in average within the normal range at baseline in both groups in the phase III study. Bilirubin decreased further after day 15 and in the placebo group after Day 28, staying within normal ranges. No grade 4 and only isolated cases of grade 3 elevations from normal values at baseline (1 case, day 15; vs 4 cases in the placebo group) were seen in the VILO group.

Kidney values

Creatinine concentrations were slightly lower than normal range at baseline of the phase III study Patients with creatinine levels above normal range were numerically higher in the BSC group at Day 15. Mean changes from baseline in creatinine increased in both groups, with a numerically larger increase in the BSC group. At Day 15, a 11.7% increase from baseline was observed in the IFX-1 group versus a 43.2% increase in the BSC group, which was not significantly different.
Mean and median eGFR values were in the normal range in both treatment groups at baseline in the phase III study. Shift plots show that eGFR in patients in the IFX-1 group in the majority remained within normal limits or decreased mild to moderately. Shifts from grade 0/1 to 4 appear to be numerically higher in the VILO group compared to placebo between day 8 to day 22 (7 vs. 2 cases). However, mean e GFR values overall were comparable at all study days.

Figure 18: eGFR bar plot by visit – phase III study



Percentages are based on the number of patients in the respective treatment group and visit
Vilo = Vilobelimab + SOC, Placebo = Placebo + SOC, SOC = Standard of care, SAF = Safety analysis set, FAS = Full analysis set , PPS = Per-protocol set

In the phase II study, creatinine values were at all time points higher in the placebo group and GFR values lower in the placebo group compared to IFX-1 treated individuals. One of 15 patients (6.7%) in the IFX-1 group and 4 of 15 patients (26.7%) in the BSC group experienced a worsening of eGFR values (at least moderately decreased [< 45 mL/min per 1.73 m²]). Two patients received renal

replacement therapy (i.e., continuous hemodiafiltration) due to vancomycin renal toxicity (IFX-1 group) and kidney failure in the BSC group. Overall, no safety concern is detected here.

CRP and LDH

CRP was initially high in both study arms in the phase III study and decreased stepwise during study run up to discharge. LDH levels were increased at baseline in both treatment groups and decreased in both treatment groups evenly up to discharge. In the phase II study, LDH concentrations were similarly increased at baseline in both treatment groups with 34.4% decrease in the IFX-1 group versus a 12.6% decrease in the BSC group. Mean changes in LDH were also not significantly different between the two groups at the other time points. No safety concern is detected here.

Blood pressure and ECG

No relevant differences in systolic and diastolic blood pressure were seen between VILO and placebo group. No shifts of concern were detected in the VILO group over time in the phase III study.
No differences in ECG outcome were seen when comparing baseline and discharge in the phase III study.

Table 46: ECG outcomes at baseline and at discharge – phase III study

Baseline value	Abnormal, clinically significant	Last reported value Abnormal, not clinically significant	Normal
Total (N=364) (nmiss=245)			
Abnormal, clinically significant	0 (0.0%)	2 (0.5%)	0 (0.0%)
Abnormal, not clinically significant	4 (1.1%)	26 (7.1%)	9 (2.5%)
Normal	5 (1.4%)	19 (5.2%)	54 (14.8%)
Placebo + SOC (N=189) (nmiss=131)			
Abnormal, clinically significant	0 (0.0%)	2 (1.1%)	0 (0.0%)
Abnormal, not clinically significant	1 (0.5%)	10 (5.3%)	6 (3.2%)
Normal	2 (1.1%)	10 (5.3%)	27 (14.3%)
Vilo + SOC (N=175) (nmiss=114)			
Abnormal, clinically significant	0 (0.0%)	0 (0.0%)	0 (0.0%)
Abnormal, not clinically significant	3 (1.7%)	16 (9.1%)	3 (1.7%)
Normal	3 (1.7%)	9 (5.1%)	27 (15.4%)

2.5.8.4. In vitro biomarker test for patient selection for safety

N/A

2.5.8.5. Safety in special populations

A breakdown of all TEAEs by age subgroups (<65/≥65 years old) was performed. A summary of the difference in the frequency of the events (overall) between both age groups, and the difference in terms of higher frequency in patients who are ≥65 years old for relevant events (infections and hypersensitivity) is presented below.

Treatment emergent adverse events (TEAEs)

Overall, no differences in the proportion of patients with TEAEs in patients ≥65 years old and <65 years old were observed in the vilobelimab group (91.7% vs 90.4%) while being significantly higher in the placebo group (98.4% vs 87.3%). On the individual PT level, considering TEAEs relevant for the product, there was a higher frequency in patients ≥65 years than in those <65 years for the following PTs (data presented for PTs with a frequency of >5% in patients ≥65 in any study group):

Table 47: TEAEs

Event incidences per patient age group **(≥65** years versus <65 years)		
Preferred Term	Vilobelimab **(≥65** years vs <65 years)	Placebo **(≥65** years vs <65 years)
Vascular device infection	8.3% vs 2.6%	7.9% vs 6.3%
Staphylococcal sepsis	6.7% vs 1.7%	3.2% vs 0.8%
Respiratory tract infection	6.7% vs 2.6%	3.2% vs 2.4%
Hypotension	6.7% vs 2.6%	4.8% vs 1.6%
Aspergillus test positive	5.0% vs 0.9%	4.8% vs 0.8%
Herpes simplex test positive	5.0% vs 0.9%	3.2% vs 1.6%
Enterococcal sepsis	5.0% vs 0.9%	1.6% vs 0.0%
Staphylococcal test positive	3.3% vs 2.6%	9.5% vs 1.6%
Pneumonia Staphylococcal	10.0% vs 3.5%	0.0% vs 4.0%
Staphylococcal infection	8.3% vs 3.5%	7.9% vs 8.7%
Bronchopulmonary aspergillosis	8.3% vs 4.3%	3.2% vs 4.0%
Herpes simplex	8.3% vs 5.2%	1.6% vs 3.2%
Herpes simplex reactivation	5.0% vs 0.9%	0.0% vs 1.6%
Bronchitis	5.0% vs 0.0%	0.0% vs 1.6%
Rash	5.0% vs 2.6%	0.0% vs 0.0%
Enterococcal infection	3.3% vs 7.0%	7.9% vs 2.4%

Serious TEAEs

Overall, the proportion of patients ≥65 years with serious TEAEs was higher than those <65 years in the vilobelimab group (63.3% vs 56.5%) and significantly higher in the placebo group (79.4% vs 55.6%).

On the individual PT level, considering TEAEs relevant for the product, there was a higher frequency of serious TEAEs in patients ≥65 than in those <65 years for the following PTs (data presented for PTs with a frequency of >5% in patients ≥65 in any study group):

Table 48: Serious TAEs

Event incidences per patient age group **(≥65** years versus <65 years)		
Preferred Term	Vilobelimab **(≥65** years vs <65 years)	Placebo **(≥65** years vs <65 years)
Pneumonia	13.3% vs 11.3%	9.5% vs 7.9%
Pneumonia staphylococcal	10.0% vs 3.5%	0.0% vs 2.4%
Enterococcal sepsis	5.0% vs 0.9%	1.6% vs 0.0%
Staphylococcal sepsis	5.0% vs 1.7%	1.6% vs 0.0%
Klebsiella infection	0.0% vs 3.5%	6.3% vs 4.0%

Higher frequencies of serious events in patients ≥65 years were reported for “Pneumonia staphylococcal”, “Enterococcal sepsis”, and “Staphylococcal sepsis” in the vilobelimab group. The PT “Klebsiella infection” frequency was relatively higher in the placebo group.

2.5.8.6. Immunological events

Please see section on Clinical pharmacology and additional information on adverse events under Clinical safety above.

2.5.8.7. Safety related to drug-drug interactions and other interactions

N/A

2.5.8.8. Concomitant Medications and Procedures

Concomitant medications

All 368 patients in the FAS received concomitant medications during the study. The most frequently reported concomitant medications (in ≥ 80% of all patients) belonged to the following classes, with an even distribution between the treatment groups for each class: antithrombotic agents (362 patients [98.4%]; VILO group 99,4%and placebo group 97,4%), corticosteroids for systemic use (356 patients [96.7%]), antibacterials for systemic use (350 patients [95.1%] , VILO group 95,1%, placebo group 93,7%), anaesthetics (325 patients [88.3%]), psycholeptics (322 patients [87.5%]), analgesics (308 patients [83.7%]), and cardiac therapy (302 patients [82.1%]).

Antivirals (systemic) were used in 64 patients (17.4%; 31 patients (17.5%) in the VILO group and 33 patients (17.3%) in the placebo group). The majority (44 patients [12.0%]) received acyclovir.

Antifungal therapy was used in 26,6% vs 23,6 in the placebo group.

Immunosuppressants were used in 27 patients (7.3%): 15 patients (8.5%) in the VILO group and 12 patients (6.3%) in the Placebo group. 10 of these patients (2.8%) received interleukin-6 inhibitors (tocilizumab or levilimab). No major safety concern is detected here.

No imbalances were seen regarding concomitant medications for COVID-19.

Table 49: Concomitant medications for COVID-19 reported for at least 3% of patients in any treatment group by WHO drug global ATC2 level (full analysis set, phase III study)

ATC Classification (2nd level)	VILO+SOC (N = 177)		Placebo+SOC (N = 191)		Total (N = 368)	
Preferred Name	N	(%)	N	(%)	n	(%)
Total	176	(99.4%)	187	(97.9%)	363	(98.6%)
CORTICOSTEROIDS FOR SYSTEMIC USE	171	(96.6%)	181	(94.8%)	352	(95.7%)
DEXAMETHASONE	155	(87.6%)	149	(78.0%)	304	(82.6%)
METHYLPREDNISOLONE	43	(24.3%)	51	(26.7%)	94	(25.5%)
HYDROCORTISONE	21	(11.9%)	19	(9.9%)	40	(10.9%)
PREDNISONE	21	(11.9%)	16	(8.4%)	37	(10.1%)
PREDNISOLONE	11	(6.2%)	13	(6.8%)	24	(6.5%)
ANTITHROMBOTIC AGENTS	159	(89.8%)	165	(86.4%)	324	(88.0%)
ENOXAPARIN	88	(49.7%)	84	(44.0%)	172	(46.7%)
NADROPARIN	45	(25.4%)	48	(25.1%)	93	(25.3%)
HEPARIN	35	(19.8%)	31	(16.2%)	66	(17.9%)
DALTEPARIN	16	(9.0%)	16	(8.4%)	32	(8.7%)
RIVAROXABAN	12	(6.8%)	10	(5.2%)	22	(6.0%)
IMMUNOSUPPRESSANTS	12	(6.8%)	9	(4.7%)	21	(5.7%)
BARICITINIB	5	(2.8%)	6	(3.1%)	11	(3.0%)
TOCILIZUMAB	6	(3.4%)	3	(1.6%)	9	(2.4%)
ANTIBACTERIALS FOR SYSTEMIC USE	6	(3.4%)	8	(4.2%)	14	(3.8%)
AZITHROMYCIN	5	(2.8%)	6	(3.1%)	11	(3.0%)

ATC = anatomical therapeutic chemical, COVID-19 = coronavirus disease 2019, SOC = standard of care, VILO = vilobelimab, WHO = World Health Organization; Coding was based on the WHODrug Global B3 2021 March. Percentages were based on the number of patients with at least one medication of the specified type / total number of patients.
Source: Table 14.3.10.1

No imbalances regarding medication were seen in the phase II trial.

Concomitant procedures

Numerical differences were seen regarding median duration of invasive mechanical ventilation/intubation which was higher in the VILO group (alive at the end of the procedure (12.0 vs. 9.0 days; including also deceased patients: 13.0 versus 11.0 days). The same trend was seen for tracheostomy (including deceased patients: VILO 15.0 days, Placebo 13.0 days; alive at end of procedure: VILO 21.0 vs 14.0 days). The median duration of ECMO and RRT appeared to be similar between the treatment groups. While a greater proportion of patients were extubated alive in the VILO group (70.3% vs. 57.7%), re-intubation was more often seen in the VILO group (3.4% vs 0.5%). than in the placebo group (0.5%). This may be a result of the positive trend in mortality seen for the VILO group.

Table 50: Number of patients with ECMO, RRT, or tracheostomy initiated after randomisation until day 28 (safety analysis set, phase III study)

Up to day 28						
	Total (N=364)		Vilo + SOC (N=175)		Placebo + SOC (N=189)	
Term	Pat. n	(Pat. %)	Pat. n	(Pat. %)	Pat. n	(Pat. %)
Total	102	(28.0%)	47	(26.9%)	55	(29.1%)
Tracheostomy	60	(16.5%)	32	(18.3%)	28	(14.8%)
Renal replacement therapy	47	(12.9%)	17	(9.7%)	30	(15.9%)
ECMO	16	(4.4%)	7	(4.0%)	9	(4.8%)
After day 28						
	Total (N=364)		Vilo + SOC (N=175)		Placebo + SOC (N=189)	
Term	Pat. n	(Pat. %)	Pat. n	(Pat. %)	Pat. n	(Pat. %)
Total	16	(4.4%)	12	(6.9%)	4	(2.1%)
Tracheostomy	12	(3.3%)	8	(4.6%)	4	(2.1%)
Renal replacement therapy	4	(1.1%)	4	(2.3%)	0	(0.0%)
ECMO	1	(0.3%)	1	(0.6%)	0	(0.0%)

ECMO = extracorporeal membrane oxygenation, RRT = renal replacement therapy, SOC = standard of care, VILO = vilobelimab.

Table 51: Organ support summary table (SAS) – phase III study

	VILO+SOC (N = 175)	Placebo+SOC (N = 189)	Total (N = 364)
Duration of invasive mechanical ventilation / intubation (ended alive) [days]			
n	123	109	232
Mean (SD)	15.2 (11.6)	12.1 (8.2)	13.7 (10.3)
Min – Max	2 – 60	2 – 46	2 – 60
Median (Q1 – Q3)	12.0 (8.0 – 20.0)	9.0 (7.0 – 15.0)	10.5 (7.0 – 16.0)
Patients with documented extubation alive	123 (70.3%)	109 (57.7%)	232 (63.7%)
Patients with at least one re-intubation after first extubation	23 (13.1%)	20 (10.6%)	43 (11.8%)
Patients with more than one re-intubation	6 (3.4%)	1 (0.5%)	7 (1.9%)
Duration of invasive mechanical ventilation / intubation (including deceased) [days]			
n	170	181	351
Mean (SD)	15.7 (10.8)	13.6 (9.2)	14.6 (10.1)
Min – Max	2 – 60	2 – 50	2 – 60
Median (Q1 – Q3)	13.0 (8.0 – 20.0)	11.0 (7.0 – 17.0)	12.0 (7.0 – 19.0)
Duration of tracheostomy (ended alive) [days]			
n	18	19	37
Mean (SD)	23.1 (10.9)	17.8 (11.9)	20.4 (11.6)
Min – Max	3 – 45	2 – 52	2 – 52
Median (Q1 – Q3)	21.0 (16.0 – 31.0)	14.0 (12.0 – 24.0)	19.0 (13.0 – 25.0)
Duration of tracheostomy (including deceased) [days]			
n	30	30	60
Mean (SD)	17.0 (11.8)	14.7 (11.4)	15.8 (11.6)
Min – Max	2 – 45	2 – 52	2 – 52
Median (Q1 – Q3)	15.0 (6.0 – 23.0)	13.0 (5.0 – 19.0)	14.0 (5.5 – 22.5)
Duration of mechanical ventilation (ended alive) [days]			
n	122	109	231
Mean (SD)	16.6 (13.7)	13.4 (11.0)	15.1 (12.6)
Min – Max	2 – 60	2 – 58	2 – 60
Median (Q1 – Q3)	12.0 (7.0 – 21.0)	9.0 (7.0 – 16.0)	10.0 (7.0 – 18.0)
Duration of mechanical ventilation (including deceased) [days]			
n	167	179	346
Mean (SD)	17.0 (12.8)	14.7 (10.8)	15.8 (11.8)
Min – Max	2 – 60	2 – 58	2 – 60
Median (Q1 – Q3)	13.0 (8.0 – 22.0)	11.0 (7.0 – 19.0)	12.0 (7.0 – 20.0)
Duration of ECMO (ended alive) [days]			
n	6	7	13
Mean (SD)	20.3 (13.8)	21.7 (17.6)	21.1 (15.3)
Min – Max	5 – 43	1 – 50	1 – 50
Median (Q1 – Q3)	17.0 (12.0 – 28.0)	16.0 (12.0 – 42.0)	16.0 (12.0 – 28.0)
Duration of ECMO (including deceased) [days]			
n	7	9	16
Mean (SD)	17.9 (14.2)	19.6 (15.8)	18.8 (14.6)
Min – Max	3 – 43	1 – 50	1 – 50
Median (Q1 – Q3)	12.0 (5.0 – 28.0)	14.0 (12.0 – 17.0)	13.5 (11.5 – 25.0)
Duration of renal replacement therapy (ended alive) [days]			
n	16	22	38
Mean (SD)	7.3 (7.6)	8.0 (7.0)	7.7 (7.2)
Min – Max	1 – 31	2 – 26	1 – 31
Median (Q1 – Q3)	6.0 (2.0 – 8.5)	5.5 (3.0 – 11.0)	6.0 (2.0 – 9.0)
Duration of renal replacement therapy (including deceased) [days]			
n	20	30	50
Mean (SD)	6.8 (6.9)	9.4 (9.0)	8.4 (8.3)
Min – Max	1 – 31	2 – 34	1 – 34
Median (Q1 – Q3)	6.0 (2.0 – 7.5)	6.5 (3.0 – 13.0)	6.0 (3.0 – 9.0)

ECMO = extracorporeal membrane oxygenation, Max = maximum, Min = minimum, Q1 = first quartile, Q3 = third quartile, SD = standard deviation, SOC = standard of care, VILO = vilobelimab
Percentages were based on the total number of patients in the Safety Analysis Set.
Source: Table 14.3.16.2

In the phase II trial, the median number of ventilator-free days was numerically higher in the IFX-1 group (17.8 days) compared with all patients in the BSC group (15.3 days), without reaching statistical significance (p=0.9000). Similar results were observed for the median number of ICU-free days (17.0 vs. 14.0 days; p=0.7680) in phase II.

Duration of Hospitalisation

The median time of hospitalisation was longer in the VILO group (28.0 vs. 22.0 days) in the phase III trial, which can be explained by the higher survival rates. Consistent with this the median duration of ICU and IMC stay was also longer in the VILO group than the Placebo group.

In the phase II trial, the median time to ICU discharge was 16.82 days (95% CI 10.87; 54.94) for the 10 patients in the IFX-1 group and 14.00 days (95% CI 5.09; 23.91) for the 7 patients in the BSC group, with no significant difference between the two groups (p=0.8222)

2.5.8.9. Discontinuation due to adverse events

No patient had an AE that led to premature study termination for reasons other than death in the phase II study.

Two patients (1.1%) in the VILO group and seven patients (3.7%) in the Placebo group had AEs that led to interrupted, omitted, or postponed study drug infusion in the phase III study. Five patients (2.9%) in the VILO group and three patients (1.6%) in the Placebo group had AEs that led to study drug discontinuation. Rash and bronchopulmonary aspergillosis led to drug discontinuation in one vilobelimab treated patient and eczema in another patient. Rash and bronchopulmonary aspergillosis are listed as adverse effects in the SmPC and likely related to vilobelimab treatment, Furthermore, one

case of severe thrombocytopenia led to discontinuation, which was considered related by the study physician.

2.5.8.10. Post marketing experience

Not applicable

2.5.9. Discussion on clinical safety

The total safety database consists of 190 patients receiving vilobelimab and 204 patients receiving placebo. The phase III trial with 175 vilobelimab treated patients is considered pivotal while the phase II trial with 15 vilobelimab treated patients is considered supportive. Additional safety data from other indications currently under development have also been provided; these data are considered informative and are not the focus of this assessment. Thus, the number of patients with Covid 19 that have received 800 mg x 6 doses is limited but considered sufficient, rare side effects may not be identified.

The overall population included in the phase III part of the study is considered representative of patients with severe COVID-induced ARDS (100% category ≥ 6 in the 8-point WHO scale (100% requiring mechanical ventilation). Demographics and baseline characteristics in terms of ethnicity, age and BMI were balanced between the vilobelimab and the placebo treated groups, as was the use of anticoagulants and other supportive treatments.

90% in the vilobelimab group and 91% in the placebo group experienced an AE. Mild and moderate AEs were balanced between vilobelimab and placebo treated patients, while severe and life-threatening AEs were overrepresented in the vilobelimab treated group. This observation should be seen in the context of a numerically higher mortality, and therefore a shorter observation time in the control arm. Fatal AEs on the other hand, were overrepresented in the placebo-treated group, in accordance with the increased survival observed in the vilobelimab group. This pattern was discerned both in phase II and III trials of PANAMO.

Differences between both treatment groups were noted in certain SOCs. In particular, patients in the vilobelimab group reported AEs more frequently in the SOCs infections (63% vs. 59.3%), vascular disorders (30.3% vs. 22.3%), cardiac disorders (24.6% vs. 22.8%), GI disorders (22.3% vs. 16.9%), investigations (21.1% vs. 19%), blood disorders (15.4% vs. 12.2%) and skin disorders (12.6% vs. 9%).

AEs by PT in the context of infections, included pneumonia (22% vs 14%), sepsis (5.1 vs 2.1%) and urinary tract infection (5.1 vs. 3.2%). These imbalances were also seen after controlling for the longer observation time in the vilobelimab group (number of events per 100 patient days: pneumonia 1.23 vs. 0.84, sepsis 0.20 vs. 0.10 and urinary tract infection 0.25 vs. 0.15). The over representation of infections in the vilobelimab treated group suggests that the mode of action of the product may have an impact on the infection risk. Therefore, serious infections are listed as important identified risks in the RMP. While the limited safety database is acknowledged, this is considered acceptable. The CHMP concluded that the increased risk for infections, is adequately addressed and sufficiently characterised at present. A warning for the risk of infections is considered adequate and has been included in the section 4.4 of the SmPC.

Regarding vascular disorders, an increase in the PTs, thrombosis, (1.1 vs 0.5%), deep vein thrombosis (6.3 vs. 4.8%), jugular vein thrombosis (1.7 vs. 0.5%) and phlebitis (2.3 vs. 0.5%) are noted. Additionally, small imbalances of thrombocytosis (2.3 vs 1.1%) and pulmonary embolism (10.9 vs. 9.0%) are observed. When calculating incidence rates of “embolism and thrombosis”, slightly higher rates were observed in the vilobelimab group (0.54 vs. 0.41 events per 100 patient days). Thus, the applicant has been requested to add thrombosis as an important potential risk as a safety concern in the RMP.

As to cardiac disorders, an imbalance in the PTs cardiac arrest (2.9 vs. 1.1%), supraventricular tachycardia (4.0 vs.0.5%), ventricular extrasystoles (1.1 vs. 0%) and ECG abnormalities (1.1 vs. 0.5%) is seen. Supraventricular tachycardia is included in the SmPC, section 4.8.

An imbalance in the AE “thrombocytopenia” is observed (4,6 vs. 1.1%). Haemorrhagic shock (1.7 vs. 0.5%) is numerically imbalanced between the VILO and placebo group. The applicant has therefore included thrombocytopenia in the SmPC, section 4.8.

One case of acute pancreatitis and one case of necrotizing pancreatitis occurred in the same patient. As this single case occurred in a severely ill patient a causal relationship cannot be concluded at present. Thus, pancreatitis is not listed in the SmPC.

An analysis of hypersensitivity was submitted by the applicant. Rash (1.1% vs 0%) is imbalanced and has been included in section 4.8 of the SmPC which is endorsed by CHMP. Moreover, the applicant proposed a warning against potential hypersensitivity reactions in section 4.4 which is accepted by CHMP.

The number of patients receiving ECMO is very small (7 and 9, in the vilobelimab and placebo groups, respectively), which is a limitation for the characterisation of vilobelimab safety in this population subset. This has been adequately reflected in the introductory part of the SmPC, section 4.8.

Separate safety information in elderly patients (≥65 years old) was provided. Overall, SAEs, severe AEs and TEAEs of interest for the product occurred more frequently in the patients >65 years than in those<65 years. Also, in the age group AEs were higher in the vilobelimab group than in the placebo treated controls. This is a matter of concern. The applicant has therefore implemented these observations as a warning for vilobelimab-associated infections in elderly patients, under section 4.4 of the SmPC.

In terms of laboratory values, leucocytes were overall comparable between VILO and placebo group. Basophils and eosinophils were within normal ranges. Slight neutrophilia was present in almost all patients at baseline, which normalised up to ICU discharge in both treatment groups and were within the normal range by hospital discharge.

Patients in both groups showed to a certain degree lymphopenia at baseline which normalised stepwise up to discharge. Monocytes were overall comparable between VILO and placebo group at baseline and discharge with normal or near normal values over time. Platelets were roughly in normal ranges during the study. A few cases of severe thrombocytopenia shifts were observed, in line with observations made for thrombocytopenia in the AE/SAE section (please see above). Overall, no significant shifts in coagulation parameters, i.e., d-dimers, aPTT, PT and INR are seen.

No safety concerns are detected with renal values, i.e., creatinine and eGFR or proinflammatory and biochemical parameters such as CRP or LDH, which behaved similarly in both treatment arms. No relevant differences in systolic and diastolic blood pressure were seen between VILO and placebo group. No general differences in the frequency of abnormal ECG outcomes were seen at baseline and discharge.

2.5.10. Conclusions on clinical safety

In conclusion, the safety profile appears acceptable in the studied population who were critically ill and where limited treatment options are available. The size of the safety database remains limited and will be further characterised in the post marketing setting. An increased risk of secondary infections has been identified, as might be anticipated for an immunomodulator. This risk is adequately addressed in the SmPC sections 4.4 and 4.8.

The CHMP considers the following measures necessary to address the missing safety data in the context of a MA under exceptional circumstances:

In addition to providing results from the Just Breathe study, the MAH shall provide yearly updates on any new information concerning the efficacy and safety of Gohibic in adult patients with SARS-CoV2-induced acute respiratory distress syndrome (ARDS) who are receiving systemic corticosteroids.

2.6. Risk Management Plan

2.6.1. Safety concerns

The applicant identified the following safety concerns in the RMP (v 0.5):

Table 52: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Serious infections
Important potential risks	Venous Thrombosis
Missing information	Use during pregnancy

2.6.2. Pharmacovigilance plan

There are no additional pharmacovigilance activities.

2.6.3. Risk minimisation measures

The risk minimisation measures agreed are described below

Table 53: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Serious infections	Routine risk minimisation measures: SmPC section 4.4 and 4.8 PL section 2 and 4 Legal status of product is 'Medicinal product subject to medical prescription' Additional risk minimisation measures: none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection. Cumulative review on a regular basis Additional pharmacovigilance activities: none
Venous thrombosis	Routine risk minimisation measures: None Legal status of product is 'Medicinal product subject to medical prescription' Additional risk minimisation measures: none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection. Cumulative review on a regular basis Additional pharmacovigilance activities: none
Use during pregnancy	Routine risk minimisation measures: SmPC section 4.6 PL section 2 Legal status of product is 'Medicinal product subject to medical prescription' Additional risk minimisation measures: none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: none

2.6.4. Conclusion

The CHMP considers that the risk management plan version 0.5 is acceptable

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD) which is 04 April 2023. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Gohibic (Vilobelimab) is included in the additional monitoring list as

- it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU,
- It is a biological product that is not covered by the previous category and authorised after 1 January 2011;
- It is approved under exceptional circumstances [REG Art 14(8), DIR Art (22)]

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The therapeutic indication presently claimed by the applicant is:

Gohibic is indicated for the treatment of adult patients with SARS-CoV-2-induced acute respiratory distress syndrome (ARDS) who are receiving systemic corticosteroids as part of Standard of Care and receiving invasive mechanical ventilation (IMV) (with or without extracorporeal membrane oxygenation (ECMO)).

3.1.2. Available therapies and unmet medical need

Coronavirus disease 2019 (COVID-19) is a highly contagious infectious disease which can be life-threatening in certain patient populations. Severe COVID-19 is characterised by acute respiratory failure requiring mechanical ventilation, septic shock, and multiple organ failure.

For treatment of severe and critical COVID-19 disease systemic corticosteroids and interleukin-6 (IL-6) receptor blockers such as tocilizumab, and/or baricitinib (Janus kinase inhibitor, not approved for COVID-19 in the EU are recommended in hospitalised patients who require mechanical ventilation with or without ECMO. It is also recommended to use venous thromboembolism prophylaxis. Despite available treatments, the mortality in patients mechanically ventilated due to COVID-19 is high.

3.1.3. Main clinical studies

The main evidence of efficacy submitted is the single pivotal phase III study PANAMO. This was a double-blind, placebo-controlled, 1:1 randomised study comparing vilobelimab + standard of care (SOC) versus Placebo + SOC.

The SOC included venous thromboembolism (VTE) prophylaxis at a minimum, and other international and country-specific recommended treatments for COVID-19 per the locally adopted treatment recommendations. Moreover, almost all patients were treated with corticosteroids.

There were 178 patients in the vilobelimab group and 191 in the placebo group.

Patients were treated with a maximum of 6 intravenous (IV) doses of vilobelimab 800 mg + SOC or Placebo + SOC at Days 1, 2, 4, 8, 15, and 22, as long as the patient was still hospitalised.

Participants had to be at least 18 years of age with a positive SARS-CoV-2 test within 14 days of randomisation. The study included adult patients with Sars-Cov-2 who were mechanically ventilated and had been so for less than 48 hours at the time of randomisation. Moreover, patients had a PaO2 / FiO2 ratio of < 200 and > 60 at randomisation.

The primary efficacy endpoint was 28-day all-cause mortality analysed using site-stratified Cox regression adjusting for age. Secondary endpoints included 60-day all-cause mortality and other parameters to assess improvement or worsening in condition.

3.2. Favourable effects

In the prespecified primary analysis using site-stratified Cox regression analysis and adjusting for age, the proportion of patients with 28-day mortality was 31.65% vs. 41.59% in the vilobelimab and placebo groups, respectively (HR 0.728 [95% CI: 0.502, 1.056], p-value =0.0941).

This study did not show a statistically significant reduction in 28-day all-cause mortality in the primary analysis. However, several post hoc, unblinded analyses of the primary endpoint showed a reduced 28-day mortality in patients treated with vilobelimab compared to placebo.

The applicant's initial plan was to analyse the primary endpoint using a Cox regression model adjusted for age, without considering the site-stratified randomisation procedure. This analysis resulted in a HR of 0.674 (95% CI:0.476, 0.955) with a nominal two-sided p-value=0.0266.

The change of this analysis in the statistical analysis plan to a site-stratified model was introduced based on a recommendation received from US FDA. The stratification by site was chosen because it was anticipated that even within region and country, variability in background mortality by site could be high.

The applicant conducted several post-hoc analyses, exploring different ways of pooling sites. One approach was to pool small sites with less than 4 or 5 participants within each country (pooling sites with n<4; HR 0.691 [95% CI: 0.490;0.974], nominal p-value=0.0346). This approach could be considered a preferable way of handling small sites without completely ignoring variation in mortality between sites.

Analyses stratifying by region (Western Europe, South America, and South Africa/Russian Federation) or country also indicated a reduced 28-day mortality in patients treated with vilobelimab compared to placebo. These post-hoc analyses all had nominal p-values <0.05.

3.3. Uncertainties and limitations about favourable effects

The analyses mentioned above were performed post-hoc, this means that they are not type-I-error controlled. This limitation means that the level of evidence of efficacy remain lower than normally anticipated.

This application relies on a single pivotal trial. However, as the Covid19 pandemic has ended, a replication of the study enrolling Covid-19 patients is considered not feasible.

3.4. Unfavourable effects

A total of 190 patients in the safety data base received vilobelimab compared to 204 who received placebo.

AE were reported for 90% in the vilobelimab group and 91% in the placebo group, while 11.4% in the vilobelimab group and 8.5% in the placebo group had an AE deemed treatment-related.

The majority of AEs and TAEs were infections, e.g. viral (herpes simplex; 6.3% in vilobelimab treated patients vs. 2.6% in placebo treated patients), fungal (bronchopulmonary aspergillosis; 5.7 vs 3.7%) and bacterial (Acinetobacter 3.4 vs. 2.6%). The frequencies of sepsis (5.1 vs. 2.1%), and pneumonia (21.7 vs. 13.8% were also overrepresented as AEs in the vilobelimab group compared to the placebo group. They were furthermore overrepresented as SAEs. Therefore, serious infections are listed as important identified risks in the RMP.

An increase in the frequency of supraventricular tachycardia was also noted in the vilobelimab treated patients (4.0 vs 0.5%).

An imbalance in the AE thrombocytopenia (4.6% vs. 1.1%) was also seen as an SAE (1.1 vs. 0%). Venous thromboembolism is considered an important potential risk in the RMP.

3.5. Uncertainties and limitations about unfavourable effects

AE imbalances were also seen for vascular disorders overall (30.3 vs. 22.8%). In support of this observation, were increases in the frequencies of thrombotic and embolic events (25 vs. 18.5%) thrombosis (1.1 vs. 0.5%), deep vein thrombosis (6.3 vs. 4.8%), jugular vein thrombosis ((1.7 vs. 0.5%), and phlebitis (2.3 vs. 0.5%) seen in the vilobelimab group, compared to the placebo treated group. Additionally, small imbalances of thrombocytosis (2.3 vs 1.1%) and pulmonary embolism (10.9 vs. 9.0%) were observed. Venous thrombosis is not considered an ADR at this time but is identified as a potential risk.

An increase of rash has been established in response to vilobelimab treatment. However, the risk of more severe hypersensitivity remains hypothetical.

Age may be a risk factor for unfavourable effects of vilobelimab as there was a general increase in vilobelimab associated infections in elderly patients.

The number of patients receiving ECMO is very small (7 and 9, in the vilobelimab and placebo groups, respectively), which is a limitation for the characterisation of vilobelimab safety in this population subset.

3.6. Effects Table

Table 54: Effects table for vilobelimab for treatment of adult patients with SARS-CoV-2 induced septic acute respiratory distress syndrome (ARDS) receiving invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO).

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
28-day all-cause mortality	Proportion of patients deceased by Day 28 from Kaplan-Meier estimates. Site-stratified Cox regression adjusting for age (Full analysis set)	% (Hazard ratio ;95 % CI)	31.65 (0.728; 0.502,1.056)	41.59	Numerically a favourable effect is observed, however, it is not statistically significant,.	
28-day all-cause mortality	Proportion of patients deceased by Day 28. Non-stratified analysis, adjusting for age (All randomised)	% (Hazard ratio ;95 % CI)	30.3 (0.674;0.476;0.955)	40.3	Post-hoc analysis, considered exploratory	
Unfavourable Effects						
Pneumonia		%	21.7	13.8	The imbalance for pneumonia was seen in the AE, AESI, and SAE sections. Pneumonia is included in the SmPC.	
Sepsis	Incidence of Sepsis	%	5.1	3.2	The imbalance in sepsis was seen in the AE, AESI and SAE evaluations. Sepsis is included in the SmPC	
	Staphylococcal sepsis	%	3,4	1.6		
	Enterococcal sepsis	%	2.3	0.5		

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Vascular disorders		%	30.3	22.8	Vascular disorders were overrepresented in the treatment group as AE and SAE. Also, deaths were slightly overrepresented. Venous thrombosis is listed as a potential risk in the RMP.	
	Thrombotic and embolic events	%	25.0	18.5		
	Deep vein thrombosis	%	6.3	4.8		
	Jugular vein thrombosis	%	1.7	0.5		
	phlebitis	%	2.3	0.5		
	Pulmonary embolism	%	10.9	9.0		
	Thrombo cytosis	%	2.3	1.1		
Blood and lymph disorders		%				
	Thrombocyotopenia	%	4.6	1.1	As an SAE, 2 vs 0 cases of thrombocytopenia occurred. Also, isolated cases of severe thrombocytopenia are noted in the laboratory section. Thrombocytopenia is included in the SmPC.	
Cardiac diseases		%	24.6	22.8		
	Supraventricular tachycardia	%	4.0	0.5	Supraventricular tachycardia is included in the SmPC	

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Vilobelimab is a monoclonal antibody that specifically binds to the anafylatoxin C5a.

In a randomised placebo-controlled Phase III study in patients with severe COVID-19, point estimates suggest a survival advantage. Despite that the result of the randomised placebo-controlled Phase III study in patients with severe COVID-19 did not meet statistical significance, point estimates showed a survival advantage for patients treated with vilobelimab.

While the statistical strength of evidence remains lower than what is normally anticipated, the results of the pivotal trial support a reasonable possibility that vilobelimab would provide benefit to patients

with ARDS due to Sars-Cov-2 infection. Further clinical data are desirable to characterise this benefit. Since Sars-Cov-2 pandemic has ended, confirmatory data within the approved indication are not anticipated to be feasible to generate, an approval under exceptional circumstances is therefore considered relevant.

It is acknowledged that this application relies on a single pivotal trial however as the Covid19 pandemic has ended, a replication of the study enrolling Covid-19 patients is considered not feasible. The safety profile appears acceptable in the studied population who were critically ill and where limited treatment options are available. The size of the safety database is considered acceptable. An increased risk of secondary infections has been identified, as might be anticipated for an immunomodulator. Routine pharmacovigilance is recommended in the post approval setting.

Since the Sars-Cov-2 pandemic has ended and it is not feasible to generate confirmatory data within the indication, an approval under exceptional circumstances subject to specific obligations to the applicant is therefore considered relevant. The specific obligations will allow to further characterise the efficacy and safety of vilobelimab. See section 3.7.3.

3.7.2. Balance of benefits and risks

The benefit/risk balance is positive in the context of an approval under exceptional circumstances.

3.7.3. Additional considerations on the benefit-risk balance

Marketing authorisation under exceptional circumstances

As comprehensive data on the product are not available, a marketing authorisation under exceptional circumstances was proposed by the CHMP during the assessment, after having consulted the applicant.

The PANAMO pivotal Phase 3 trial conducted during the COVID-19 pandemic, randomised 369 COVID-19 ARDS patients receiving IMV or ECMO. Under current circumstances where the COVID-19 pandemic has ended, due to the rarity of the indicated population, it is not feasible to conduct another randomised controlled trial in these patients. Therefore, it is deemed that the applicant cannot reasonably be expected to provide comprehensive evidence.

The CHMP considers that the applicant has sufficiently demonstrated that it is not possible to provide comprehensive data on the efficacy and safety under normal conditions of use.

Therefore, a marketing authorisation under exceptional circumstances for Gohibic is acceptable in regard to the fulfilled criteria of rarity of the disease.

As specific obligation, the applicant has committed to submit results for the vilobelimab cohort in the Just Breathe platform study, a double-blind, placebo-controlled study enrolling patients with moderate to severe ARDS caused by COVID-19 and other viral and bacterial pulmonary infections in order to investigate the efficacy and safety of vilobelimab in the treatment of adult patients with SARS-CoV2-induced acute respiratory distress syndrome (ARDS).

In the Just Breathe Platform study funded by BARDA, patients with ARDS due to various causes will be enrolled including COVID-19 ARDS patients. In this study, patients will be stratified by level of ARDS severity. The identified or suspected inciting cause (e.g., viral, bacterial, aspiration) of ARDS at randomisation will be captured allowing for subgroup analyses. Thus, data from the sub population of COVID-19 ARDS patients will be generated despite the study enrolling a broader population.

In addition, as second specific obligation, the applicant will provide yearly updates on any new information concerning the efficacy and safety of Gohibic in adult patients with SARS-CoV2-induced acute respiratory distress syndrome (ARDS).

In conclusion, the applicant has provided enough evidence to support a positive benefit/risk balance for Gohibic. Based on the rarity of the disease, the CHMP concludes that the criteria for a marketing authorisation under exceptional circumstances are met (Annex I, Part II, 6. Directive 2001/83/EC). The CHMP considers that a marketing authorisation under exceptional circumstances can be granted subject to the setting of two specific obligations to further characterise the efficacy and safety of the medicinal product in the approved indication.

3.8. Conclusions

The overall benefit/risk balance of Gohibic is positive, subject to the conditions stated in section 'Recommendations'.

Divergent positions are appended to this report.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the benefit-risk balance of Gohibic is favourable in the following indication:

Gohibic is indicated for the treatment of adult patients with SARS-CoV2-induced acute respiratory distress syndrome (ARDS) who are receiving systemic corticosteroids as part of Standard of Care and receiving invasive mechanical ventilation (IMV) (with or without extracorporeal membrane oxygenation (ECMO)).

The CHMP therefore recommends the granting of the marketing authorisation under exceptional circumstances subject to the following conditions:

Conditions or restrictions regarding supply and use

Treatment should be initiated and monitored by a physician experienced in the management of patients treated in an intensive care unit (ICU) setting.

Other conditions and requirements of the marketing authorisation

- Periodic Safety Update Reports

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

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- Risk Management Plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.
- *Specific Obligation to complete post-authorisation measures for the marketing authorisation under exceptional circumstances*

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall complete within the stated timeframe, the following measures:

Description	Due date
In order to further investigate the efficacy and safety of vilobelimab in the treatment of adult patients with SARSCoV2induced acute respiratory distress syndrome (ARDS) who are receiving systemic corticosteroids, the MAH shall submit results for the vilobelimab cohort in the Just Breathe platform study, a double-blind, placebo controlled study enrolling patients with moderate to severe ARDS caused by COVID-19 and other viral and bacterial pulmonary infections. Protocol submission: NA	annually (within annual reassessments) Final report by Q4 2029
In order to ensure the adequate monitoring of efficacy and safety of vilobelimab in the treatment of adult patients with SARSCoV2induced acute respiratory distress syndrome (ARDS) who are receiving systemic corticosteroids, the MAH shall provide yearly updates on any new information concerning the efficacy and safety of Gohibic. Study design: NA	annually (within annual reassessment)

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that Vilobelimab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

APPENDIX

DIVERGENT POSITION DATED 14 November 2024

DIVERGENT POSITION DATED 14 November 2024

Gohibic EMEA/H/C/006123/0000

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation of Gohibic indicated for

Gohibic is indicated for the treatment of adult patients with SARS-CoV2-induced acute respiratory distress syndrome (ARDS) who are receiving systemic corticosteroids as part of Standard of Care and receiving invasive mechanical ventilation with or without extracorporeal membrane oxygenation (ECMO).

The reasons for divergent opinion were the following:

1. Efficacy for vilobelimab in patients with severe Covid-19 has not been confirmed statistically, especially considering that the degree of statistical significance required for an application based on a single pivotal study should be particularly compelling. Relevant external evidence to support efficacy for the proposed use is lacking. No other vilobelimab trials have shown proof of effect, despite the drug being tested in several different indications. Further, there are several limitations surrounding the safety profile characterisation of vilobelimab, e.g., limited safety database, increased risk for infections, that could only be acceptable in the context of an overwhelming efficacy that has not been shown. Therefore, the balance of benefits and risks in the proposed indication is considered negative. Concluding a positive benefit-risk is a pre-requisite to grant a positive opinion, even in the context of an authorisation under exceptional circumstances.

2. Additionally, it is considered that the conduct of the proposed BARDA study, included as a specific obligation, is unlikely to be feasible once vilobelimab becomes commercially available. Particularly, the capacity to complete recruitment into the COVID-19 cohort, which is placebo-controlled, is seriously questioned.

Antonio Gómez-Outes

Sol Ruiz

Simona Badoi