EU RISK MANAGEMENT PLAN FOR VILOBELIMAB

RMP version to be assessed as part of this application:

RMP Version number:	0.5
Data lock point for this RMP	26th March 2023
Date of final sign off	3rd December 2024
Rationale for submitting an RMP This is an initial EU RMP in support of first marketing authorisation application for vilobelimab.	
Summary of significant changes in this RMP: Not applicable-Initial RMP	
Other RMP versions under evaluation: Not applicable	
QPPV Name	Delphine Cossard
QPPV Oversight Declaration The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.	

ABBREVIATIONS

ADA	Anti-drug antibody
AE	Adverse Event
ANCA	Anti-neutrophil cytoplasmatic antibodies
ARDS	Acute respiratory distress syndrome
C5a	Complement factor 5a
CH50	Total haemolytic complement activity
CHMP	Committee for Medicinal Products for Human Use
COVID-19	Coronavirus disease 2019
CT	Computer tomography
DNA	Deoxyribonucleic acid
ECDC	European Centre for Disease Control
ECMO	Extra-corporal membrane oxygenation
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
EUA	Emergency Use Authorisation
FDA	Food and Drug Administration
HS	Hidradenitis Suppurativa
ICU	Intensive care unit
IG	Immunoglobulin
IMV	Invasive mechanical ventilation
INN	International Non-proprietary Name
IV	Intravenous
MA	Marketing Authorization
MAC	Membrane attack complex
NIH	National Institutes of Health [US]
NYHA	New York Heart Association
PaO_2/FiO_2	Ratio of arterial oxygen partial pressure to fractional inspired oxygen
PD	Pharmacodynamics
PG	Pyoderma Gangrenosum
PIP	Paediatric investigation plan
PK	Pharmacokinetics
PL	Package Leaflet
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SmPC	Summary of Product Characteristics
US	United States
VR	Residual volume [lung]
WHO	World Health Organisation

CONTENT

PART I: PRODUCT(S) OVERVIEW

Table 1: Product(s) Overview

Active substance (INN or common name)	Vilobelimab
Pharmacotherapeutic group(s) (ATC Code)	Not yet assigned
Marketing Authorisation Applicant	InflaRx GmbH Winzerlaer Strasse 2 07745 Jena, Germany
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Gohibic
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Vilobelimab is a chimeric monoclonal immunoglobulin (Ig) G4 antibody that specifically binds to the soluble human complement cleavage product C5a. Vilobelimab is composed of 1,328 amino acids and has an approximate molecular weight of 148 kDa. Summary of its mode of action: The binding of vilobelimab to human complement factor 5a (C5a) facilitates an effective blockade of C5a induced biological effects by disabling C5a binding to, and reacting with, its corresponding cell-bound receptors. Important information about its composition: Vilobelimab is expressed in a mammalian cell line as recombinant protein and finally formulated in a phosphate buffered saline and polysorbate containing solution for intravenous (IV) administration.
Hyperlink to the Product Information	Summary of Product Characteristics (Module 1.3.1)
Indication(s) in the EEA	Gohibic is indicated for 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)).
Dosage in the EEA	800 mg administered by IV infusion after dilution for a maximum of 6 (six) doses. 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]).
Pharmaceutical form(s) and strengths	Concentrate for solution for infusion. Each vial contains 200 mg of vilobelimab in 20 mL (10 mg/mL).
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II: SAFETY SPECIFICATION

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

SI.1 Indication

Vilobelimab is indicated for 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)).

Incidence and Prevalence: Since the end of 2019 the SARS-CoV-2 pandemic is present with highly varying numbers of infection, hospitalisation, and death cases. As of 29 May 2023, 767,364,883 cumulative cases and 6,938,353 cumulative deaths have been reported worldwide (World Health Organisation [WHO] Covid-19 Dashboard).

Table 2 is based on the death cases published by the European Centre for Disease Control (ECDC, COVID-19 situation update for the EU/EEA, as of 26 March 2023) and shows the incidence of death in the populations of the individual countries of the European Economic Area (EEA) out of which the estimated incidences for SARS-CoV-2 requiring invasive ventilation can be generated, if the intensive care unit (ICU) mortality is 43% (Patel et al., 2021) and it is assumed that SARS-CoV-2 overall mortality can be approximated to ICU mortality. The incidence of SARS-CoV-2 requiring IMV is then calculated by death cases / population / 0.43:

Table 2: Death cases per country population up to the end of Week 12 (26 March 2023) (unless otherwise indicated)

Country	Population	Death cases	Incidence SARS-CoV-2 requiring invasive mechanical ventilation
Austria	8,978,929	22,325	0.58 %
Belgium	11,617,623	38,191	0.76 %
Bulgaria	6,838,937	38,194	1.30 %
Croatia	3,862,305	5,432	0.33 %
Cyprus	904,705	1,621	0.42 %
Czechia	10,516,707	42,544	0.94 %
Denmark	5,873,420	8,158	0.32 %
Estonia	1,331,796	2,840	0.50 %
Finland	5,548,241	8,948	0.38%
France	67,871,925	169,558	0.58 %
Germany	83,237,124	172,411	0.48 %
Greece	10,459,782	36,606	0.81 %
Hungary	9,689,010	47,501	1.14 %

Country	Population	Death cases	Incidence SARS-CoV-2 requiring invasive mechanical ventilation
Iceland	376,248	186[1]	0.11 %
Ireland	5,060,004	8302	0.38 %
Italy	59,030,133	197006	0.78 %
Latvia	1,875,757	7249	0.90 %
Liechtenstein	39,308	89	0.53 %
Lithuania	2,805,998	9432	0.78 %
Luxembourg	645,397	1000	0.36 %
Malta	520,971	852	0.38 %
Netherlands	17,590,672	22986[2]	0.30 %
Norway	5,425,270	2031[3]	0.87 %
Poland	37,654,247	119666	0.74 %
Portugal	10,352,042	26405	0.59 %
Romania	19,042,455	65572	0.80 %
Slovakia	5,434,712	19530	0.84 %
Slovenia	2,107,180	9227	1.02 %
Spain	47,432,893	120605	0.59 %
Sweden	10,452,326	23880	0.53 %

[1] Last data from Week 4, 2023

[2] Last data from Week 52, 2022

[3] Last data from Week 40, 2022

Source: European Centre for Disease Control and Prevention, COVID-19 data set

The incidence of SARS-CoV-2 requiring IMV is in the range of 0.09% and 1.30%.

Demographics of the population in the proposed indication and risk factors for the disease: The main COVID-19 characterizing clinical features are age greater than 50 years and presence of comorbidities such as hypertension and diabetes, whereas main laboratory findings show hepatic and renal dysfunction in the presence of leukopenia, lymphopenia, increase of D-dimers, and strong inflammatory cytokine activation (Guan et al. 2020; Huang et al. 2020; Liu et al. 2020; Garg et al. 2020; Wiersinga et al. 2020). Elevated D-dimer values have been shown to be strongly associated with poorer prognosis. It is also reported that the complement cascade is highly activated (Gao et al. 2020). One hallmark of progressed disease in patients who become severely diseased is the association of blood neutrophil increases with disease severity, and neutrophil infiltration in heart and liver. Nicholson et al. 2021 found 4 factors to be independently predictive for mechanical ventilation requirement: diabetes mellitus, the ratio of arterial oxygen partial pressure to fractional inspired oxygen, C-reactive protein and lactate dehydrogenase, and 10 factors to be predictors of in-hospital mortality: age, male sex, coronary artery disease, diabetes mellitus, chronic statin use, the

ratio of arterial oxygen partial pressure to fractional inspired oxygen, body mass index, neutrophil to lymphocyte ratio, platelet count, and procalcitonin.

There is an increasing risk with age. The risk of in-hospital and case mortality increased per age year by 5.7% and 7.4%, respectively, while the risk of hospitalisation increased by 3.4% per age year. No increased risk was observed for ICU admission and intubation by age year. There was no evidence of a specific age threshold at which the risk accelerates considerably (Starke et al. 2021). A review of epidemiological data by Gebhard et al. 2020 on confirmed COVID-19 cases shows that there were 50% more men requiring hospitalisation compared to women, with ICU admission being 3- to 4-fold higher, creating a male bias in severity and mortality (Alwani et al. 2021).

There is disparity concerning race and ethnicity as to the risk of severe illness (CDC, June 2nd, 2022). While Asian populations compare to White populations by a rate ratio of 0.8 for both hospitalisation and death, Black/Afro-American populations do so by a rate ratio 2.3 and 1.7, respectively.

SI.2 The main existing treatment options

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 appears to be driven by a dysregulated immune/inflammatory response to SARS-CoV-2 that leads to tissue damage (United States [US] National Institutes of Health [NIH], 2023). Based on this understanding, it is anticipated that therapies that directly target SARS-CoV-2 would have the greatest effect early in the course of the disease, while immunosuppressive/anti-inflammatory therapies are likely to be more beneficial in the later stages of COVID-19. Vilobelimab is indicated in the later stages only.

As of May 2023, the following 8 treatments of COVID-19 have been granted a marketing authorisation in the EU (European Medicines Agency [EMA], 2023) (see Table 3). Only one of them (RoActemra) is indicated for treatment in the same patient population as vilobelimab requiring mechanical ventilation; the other 7 treatments do not address the population with severe COVID-19 pneumonia requiring mechanical ventilation.

Table 3: EU Marketing Authorisations for COVID-19 Treatments (May 2023)

Product name (INN)	COVID-19 indication	Date of approval
RoActemra (tocilizumab)	For the treatment of COVID-19 in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation.	07 December 2021
Evusheld (tixagevimab / cilgavimab)	*Pre-exposure prophylaxis:* for the pre-exposure prophylaxis of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40kg. *Treatment:* for the treatment of adults and adolescents (aged 12 years and older weighing at least 40kg) with COVID-19, who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.	25 March 2022

Product name (INN)	COVID-19 indication	Date of approval
Kineret (anakinra)	For the treatment of COVID-19 in adult patients with pneumonia requiring supplemental oxygen (low- or high-flow oxygen) who are at risk of progressing to severe respiratory failure determined by plasma concentration of soluble urokinase plasminogen activator receptor ≥ 6 ng/ml	17 December 2021
Paxlovid (nirmatrelvir / ritonavir)	For the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19	28 January 2022 (conditional)
Regkirona (regdanvimab)	For the treatment of adults with COVID-19 who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19	12 November 2021
Ronapreve (casirivimab / imdevimab)	Indicated for: • treatment of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19. • prevention of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg.	12 November 2021
Veklury (remdesivir)	For the treatment of COVID-19 in: • adults and paediatric patients (at least 4 weeks of age and weighing at least 3 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment) • adults and paediatric patients (weighing at least 40 kg) who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19	08 August 2022 (conditional MA 03 July 2020)
Xevudy (sotrovimab)	For the treatment of adults and adolescents (aged 12 years and over and weighing at least 40 kg) with COVID-19 who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19	17 December 2021

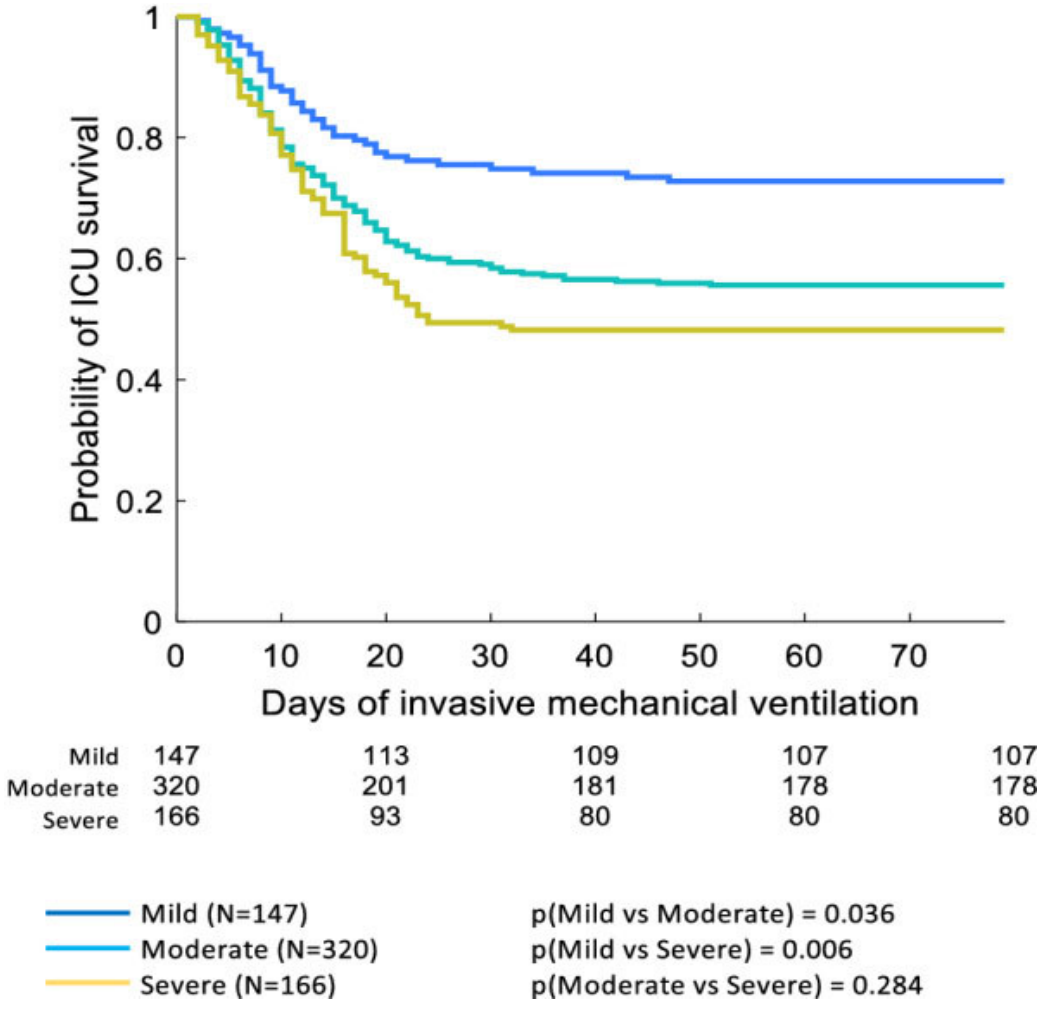
In addition, EMA's Committee for Medicinal Products for Human Use (CHMP) has concluded that dexamethasone can be considered a treatment option for patients who require oxygen therapy (from supplemental oxygen to mechanical ventilation), based on its review of results from the RECOVERY study arm that involved the use of the corticosteroid medicine dexamethasone in the treatment of patients with COVID-19 admitted to hospital.

The US Food and Drug Administration (FDA) has issued an Emergency Use Authorisation (EUA) for use of Gohibic (vilobelimab) to treat COVID-19 in hospitalised adults when initiated within 48 hours of receiving IMV or ECMO (US FDA Fact Sheet: EUA for Gohibic).

SI.3 Natural history of the indicated condition in the (untreated) population, including mortality and morbidity

The natural course of severe SARS-CoV-2 requiring mechanical ventilation was described by Patel et al. 2021, with an ICU mortality of 43% and 57% ICU survivors. The outcome depends on cardiopulmonary factors (e.g., pulmonary consolidation, thrombosis, fibrosis and right ventricular compromise) but also on responsiveness to interventions (many of which aim to reduce ventilator-induced lung injury). The longitudinal natural history shows that key modalities associated with pulmonary dysfunction, i.e., PaO_2/FiO_2, residual volume (VR) and peak pressure, had the highest importance in predicting mortality across the entire first week. Patients with progressive hypoxaemia over the first week suffered a mortality of 59.4% versus 16.3% in those that resolved hypoxaemia. Over 75% of patients remained in either static or worse hypoxemic categories, despite an increased application of adjunctive acute respiratory distress syndrome (ARDS) interventions suggesting that many patients were refractory to traditional ARDS interventions, ultimately dying with refractory hypoxaemia. The survival rates are depicted in Figure 1.

Figure 1: ICU Survival Curves Based on Admission Severities of Hypoxaemia as defined by the Berlin Definition of ARDS



ARDS = acute respiratory distress syndrome; ICU = intensive care unit
Source: Patel et al. 2021

The progression from ARDS to requiring mechanical ventilation and ICU admission and the median time to requiring mechanical ventilation and ICU admission is 10 days (Asokan, 2020; Tang, 2020). This most severe phase of infection is largely extra-pulmonary and occurs within 2-3 weeks of initial symptom presentation. Notable features include extra-pulmonary systemic hyperinflammatory syndrome, severe pneumonia, septic shock, respiratory failure, cardiac arrest, and multiple organ failure. (Gouveia, 2020; Malik, 2020). Irregular reticular opacities mixed with ground glass opacities can be identified by computer tomography (CT) in the 4th week (Sheervalilou, 2020). Late-stage complications include Multisystem Inflammatory Syndromes (Feldstein, 2020; Morris, 2020), characterized by severe auto-inflammatory disorders involving 2 or more multiple organ systems: cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological (Malik, 2020). While this most severe form of COVID-19 requiring invasive mechanical ventilation usually takes weeks or months for recovery, in some cases long or post-acute COVID-19 is reported after the acute COVID-19 illness has resolved. Long-COVID is not restricted to severe cases but can occur even after relatively mild acute illness. There is no consistent definition of long COVID yet, making it difficult to differentiate between sequelae of the disease or of the treatment and reactions to the disease. Depending on the definitions, population studied, setting, and the study design, between 13% to 87% of patients report ≥1 persistent symptom(s) 3 or more weeks following initial symptoms (Nalbandian, 2021; Sudre, 2021). Reported symptoms of long COVID-19 include fatigue, feeling unwell, headache, dyspnea, loss of smell or taste, and cognitive issues such as trouble concentrating (Carfi, 2020; Garrigues, 2020; Logue, 2021; Sudre, 2021), but also, acute kidney injury, or new or worsening of existing diabetes mellitus (Nalbandian, 2021).

Invasively ventilated septic patients are generally known to be highly susceptible to the development of secondary pulmonary and other infections such as ventilator-associated pneumonia, systemic viral re-activations (e.g., herpes and others) as well as fungal infections and others because of their compromised immune status and because of invasive procedures (Grasselli et al. 2021). The duration of mechanical ventilation and the ICU lengths of stay of these patients are therefore often prolonged (up to 19 days for mechanical ventilation and up to 49 days for ICU length of stay (Grasselli et al. 2020, Schmidt et al. 2021). In addition, applied therapies such as corticosteroids or immunomodulators are known to further increase the risk of infection. Based on literature review, critical COVID-19 and its treatment with IMV is also linked to higher co-infection rates (Grasselli et al. 2021). Also, COVID-19 per se is associated with significant dysfunction of the patient's immune system. Multiple studies have shown the involvement of both innate and acquired immunity as a response to SARS-CoV-2 infection (Qin et al. 2020, Xiong et al. 2020, Zhang et al. 2020, Zheng et al. 2020, Liu et al. 2020a).

SI.4 Important co-morbidities

Important co-morbidities in patients suffering from severe COVID-19 are hypertension (64.1%) and diabetes (41.2%) (Oliveira et al. 2021). A systematic review and meta-analysis to evaluate comorbidities associated with severe and fatal cases of COVID-19 were conducted (Gold et al. 2020). In this review and meta-analysis, hypertension, diabetes and respiratory diseases were found to be more frequent among the deceased patients compared to total cases. Patients enrolled in Study IFX-1-P2.9 (PANAMO COVID-19 study) showed comorbidities

typical of the target population; the most commonly reported comorbidities were hypertension, obesity, and diabetes.

Part II: Module SII - Non-clinical part of the safety specification

Pharmacology

Vilobelimab displays a high species-specificity, a high binding affinity to complement factor 5a (C5a) and a clearly defined mode of action, with high blocking activity of C5a-induced effects in *ex vivo* and *in vitro* models. No immunotoxicity effects or inhibition of the membrane attack complex (MAC) were observed *in vitro* in the presence of vilobelimab.

Repeated Dose Toxicity

The sub-chronic and chronic effects of vilobelimab have been evaluated for up to 26 weeks in monkeys after IV infusion (1 hour) up to 50 mg/kg. The only remarkable finding was a slight reduction of total haemolytic complement activity (CH50) in male and female animals when compared to controls. However, no clinical correlation could be detected. The observed effect was therefore judged as minor and without clinical relevance.

Genotoxicity

Standard genotoxicity studies are not considered relevant for vilobelimab, which is a human/mouse chimeric immunoglobulin (Ig)G4 anti human complement C5a monoclonal antibody. It is not anticipated that a monoclonal antibody will directly interact with desoxyribonucleic acid (DNA) or other chromosomal materials. Furthermore, no signals regarding genotoxicity have been identified in any toxicological studies employing vilobelimab or based on its mode of action.

Carcinogenicity

No carcinogenicity studies have been performed since standard carcinogenicity bioassays are generally inappropriate for biotechnology-derived pharmaceuticals, including monoclonal antibodies. Based on its mechanism of action, it is not anticipated that vilobelimab will directly support or induce proliferation of transformed cells and clonal expansion leading to neoplasia.

Reproductive and Developmental Toxicity

Fertility, embryo-foetal development and peri- and postnatal development reproduction studies have been conducted in cynomolgus monkeys. These studies did not reveal any evidence of reproduction toxicity or developmental toxicity related to vilobelimab.

Other Toxicity Studies

The tissue cross-reactivity study in cynomolgus monkeys and humans with different tissues from unrelated donors demonstrated a wide range of vilobelimab-positive staining in almost all organs/tissues. However, no toxicological findings were detected during the repeated-dose toxicity studies in any organ system in cynomolgus monkeys to indicate compromised safety. C5 is largely present and C5a is generated after death by unspecific complement activation

(e.g., *via* 3 well-known pathways and extrinsic cleavage during coagulation) in the circulation and within the tissues in the post-mortem subjects, and subsequently deposited on tissues and on cells. In conclusion, the anticipated and observed wide range of staining in the tissue cross-reactivity study is likely due to a post-mortem effect linked to the nature of C5a and the high specificity of vilobelimab to bind to C5a. These results are not considered to be clinically relevant because toxicological testing in cynomolgus monkeys did not reveal any potentially vilobelimab -related organ dysfunction or other safety concerns.

Summary

Table 4: Key safety findings and relevance to human usage

Key safety findings (from non-clinical studies)	Relevance to human usage
Repeated dose toxicity • slight reduction of total haemolytic complement activity (CH50)	Reduction was within normal range of variation. No clinical relevance.
Reproductive and developmental toxicity	Vilobelimab is not predicted to cause any harm to the foetus or the mother when used during pregnancy.
Genotoxicity	Standard genotoxicity studies are not considered relevant for monoclonal antibodies as it is not anticipated they will directly interact with desoxyribonucleic acid (DNA) or other chromosomal materials. There are no concerns about a genotoxic potential.
Carcinogenic potential; long-term data missing.	Standard carcinogenicity bioassays are generally inappropriate for biotechnology-derived pharmaceuticals. There are no concerns about a carcinogenic potential inherent to vilobelimab based on the pharmacological mode of action and the acute use of the indication.

Part II: Module SIII – Clinical trial exposure

To date, one Phase II/III clinical study ("PANAMO", Study IFX-1-P2.9) with vilobelimab has been completed for the COVID-19 indication. A total of 8 other clinical studies in healthy volunteers and different indications (septic organ dysfunction, complex cardiac surgery, hidradenitis suppurativa (HS), anti-neutrophil cytoplasmatic antibodies (ANCA)-associated vasculitis, and pyoderma gangrenosum (PG) have been completed (Studies IFX-1-P1.1, IFX-1-P2.1, IFX-1-P2.2, IFX-1-P2.3, IFX-1-P2.4, IFX-1-P2.5, IFX-1-P2.6, and IFX-1-P2.7). Two studies are currently ongoing in cutaneous squamous cellular carcinoma and PG (Studies IFX-1-P2.8 and IFX-1-P3.4). Due to differences in indications, study designs, administered doses, and dosing schedules, the safety data were not pooled and are presented separately by study.

Across all 9 completed studies of vilobelimab, a total of 587 subjects or patients received at least one dose of vilobelimab: 97 subjects/patients received single vilobelimab doses ranging from 0.02 to 8 mg/kg, and 490 patients received multiple doses, with administered doses ranging from 2 mg/kg to 2400 mg, dosing frequencies ranging from twice daily to every

2 weeks, and treatment durations ranging from 1 day to 40 weeks (Table 5). An additional 25 patients have been treated in the ongoing study. In total, 587 subjects or patients have been treated to date with vilobelimab or vilobelimab in combination with glucocorticoids or pembrolizumab, as summarized in Table 6. In studies involving treatment with vilobelimab over several weeks or more, treatment with vilobelimab was initiated with a fractionated loading dose.

Table 5: Overall Cumulative Patient Exposure in Completed Clinical Trials

Study Number	Study Population	Vilobelimab Dose Cohort	Number of Patients Receiving Vilobelimab
IFX-1-P1.1	Healthy volunteers	0.02, 0.1, 0.5, 2 or 4 mg/kg bw (single dose)	15
IFX-1-P2.1	Adults with early septic organ dysfunction	2 x 2 mg/kg bw	16
		2 x 4 mg/kg bw	16
		3 x 4 mg/kg bw	16
IFX-1-P2.2	Adults who underwent complex cardiac surgery	1 mg/kg bw	23
		2 mg/kg bw	18
		4 mg/kg bw	21
		8 mg/kg bw	20
IFX-1-P2.3	Adults with moderate to severe Hidradenitis Suppurativa (HS)	9 x 800 mg (consecutive treatment)	12
IFX-1-P2.4	Adults with moderate to severe HS	Main phase (blinded, 16 weeks): 6 x 400 mg (Cohort 2) 7 x 800 mg (Cohort 3 and 4) 3 x 800 mg and 8 x 1200 mg (Cohort 5)	175
		Extension phase (open-label, up to Week 40): Responders: 800 mg q4w (from Week 20 to Week 40) Non-responders: 800 mg q2w (from Week 18 to Week 40)	
IFX-1-P2.5	Adults with active granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA).	11 x 800 mg + reduced-dose GC (RDGC)	15
		11 x 800 mg IFX-1 + placebo-GC (No GC)	18
IFX-1-P2.6	Adults with GPA and MPA	11 x 400 mg	7
		11 x 800 mg	6

Study Number	Study Population	Vilobelimab Dose Cohort	Number of Patients Receiving Vilobelimab
IFX-1-P2.7	Adults with an ulcerative form of Pyoderma Gangrenosum (PG)	3 x 800 mg (initial dose), 3 x 800 mg (maintenance), 9 x 800 mg q2w (uptitration) (option to increase to 9 x 1600 mg q2w for uptitration)	6
		3 x 800 mg (initial dose), 3 x 1600 mg q2w (maintenance), 9 x 1600 mg q2w (uptitration) (option to increase to 9 x 2400 mg q2w for uptitration)	6
		3 x 800 mg (initial dose), 3 x 2400 mg q2w (maintenance) + 9 x 2400 mg q2w (uptitration)	7
IFX-1-P2.9 PANAMO (Phase II: Open Label)	Adults with severe pneumonia in context of COVID-19	7 x 800 mg over 29 days + BSC	15
IFX-1-P2.9 PANAMO (Phase III: Blinded)	COVID-19 adult patients requiring mechanical ventilation or ECMO	6 x 800 mg over 22 days + SoC	175
		Total	**587**

BSC = best supportive care; bw = body weight; EOT = end of treatment; GC = glucocorticoid (prednisone); q2w = every 2 weeks; q4w = every 4 weeks; q6w = every 6 weeks; RDGC = reduced-dose glucocorticoid; SoC = standard of care.

Table 6: Overall Cumulative Patient Exposure in Completed Clinical Trials with Vilobelimab

Study Drug	Patients	Healthy Volunteers	Total
Vilobelimab	539	15	**564**
Vilobelimab plus glucocorticoid	33	-	**33**
Total	**572**	**15**	**587**

For the intended indication (COVID-19 treatment), clinical trial exposure has been rather homogeneous regarding treatment duration and dosing (Table 7 and Table 8).

Table 7: Duration of Exposure Across All Indications from Completed Clinical Trials with Vilobelimab

Cumulative for all indications (person time)		
Duration of exposure (months)	**Patients**	**Person time (month)**
<1 m	351	104.90
1 to <3 m	27	55.75
3 to <6 m	103	453.22
≥6 m	106	951.36
Total person time	587	1565.24

Table 8: Duration and Doses of Exposure for COVID-19 Indication

Duration of time on study medication	**Number of Patients**
7 x 800 mg over 22 days	3
6 x 800 mg over 22 days	73
5 x 800 mg over 22 days	44
Less than 5 x 800 mg over 22 days	70

In the trials in healthy volunteers and in other indications, there was a broad spectre of age groups covered (Table 9 and Table 10). As for gender, approximately 63% of patients were males.

Table 9: Cumulative Patient Exposure to Vilobelimab and Placebo or Comparator from Completed Clinical Trials by Age and Sex

Name of Study	**Age Range [years]**	**Number of Patients**		
		Male	**Female**	**Total**
Phase I study	18-40	26	0	**26**
IFX-1-P2.1	any age	46	26	**72**
IFX-1-P2.2	40-86	76	28	**104**
IFX-1-P2.3	29-62	4	8	**12**
IFX-1-P2.4	18-85	79	98	**177**
IFX-1-P2.5	27-83	40	17	**57**
IFX-1-P2.6	33-82	6	13	**19**
IFX-1-P2.7	24-73	9	10	**19**
IFX-1-P2.9 Phase II	41-75	22	8	**30**

(PANAMO COVID-19 study)				
IFX-1-P2.9 Phase III (PANAMO COVID-19 study)	22-81	248	116	**364**
Total		**556**	**324**	**880**

Table 10: Cumulative Patient Exposure to Vilobelimab from IFX-1-P2.9 (PANAMO Phase II/III COVID-19 Study) by Age and Sex

Age categories	**Vilobelimab (N = 190)**
≥ 18 and ≤ 65 years	135 (71.1%) Male: 98 Female: 37
> 65 and ≤ 85 years	55 (28.9%) Male: 36 Female: 19
> 85 years	0 (0.0%)
≥ 18 and < 40 years	22 (11.6%) Male: 17 Female: 5
≥ 40 and < 50 years	33 (17.4%) Male: 30 Female: 3
≥ 50 and < 60 years	48 (25.3%) Male: 29 Female: 19
≥ 60 and < 70 years	52 (27.4%) Male: 38 Female: 14
≥ 70 and < 80 years	33 (7.4%) Male: 20 Female: 13
≥ 80 years	2 (1.1%) Male: 0 Female: 2

Note, the number (percentage of patients) is derived from the Phase II and Phase III parts of the PANAMO COVID-19 study.

While the age distribution was within the trials' expected range for the indication, the sex distribution was unbalanced towards the male sex. This is in line with the higher risk of ICU admission due to COVID-19 for the male sex (Nachtigall et al., 2021).

The overall exposure has also been reviewed by racial group for all completed studies is presented in Table 11 and also for the COVID-19 study individually in Table 12. The PANAMO COVID-19 study enrolled a broad range of ethnic groups.

Table 11: Cumulative Patient Exposure to Vilobelimab, Placebo or Comparator from Completed Trials by Racial Group

Racial group	**Number of Patients (%)**
Asian	18 (2.1%)
Black or African American	36 (4.2%)
Caucasian/White	679 (79.5%)
American Indian or Alaska Native	46 (5.4%)
Multiple	4 (0.5%)
Other	41 (4.8%)
Missing	30 (3.5%)
Total	**854**

Note: Data for Phase I study (IFX-1-P1.1) is not available (N=26).

Table 12: Cumulative Patient Exposure to Vilobelimab by Racial / Ethnic Group in IFX-1-P2.9 (PANAMO Phase II/III COVID-19 Study)

	Vilobelimab (N = 190)
Race (n [%])	
White	123 (64.7%)
American Indian or Alaskan Native	21 (11.1%)
Other	16 (8.4%)
Not reported	13 (6.8%)
Black or African American	7 (3.7%)
Asian	9 (4.7%)
Multiple	1 (0.5%)
Ethnicity (n [%])	
Not Hispanic or Latino	85 (44.7%)
Hispanic or Latino	59 (31.1%)
Not reported	28 (14.7%)
Unknown	11 (5.8%)
Missing	7 (3.7%)

Note, the number (percentage of patients) is derived from the Phase II and Phase III parts of the PANAMO COVID-19 study.

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Table 13: Exclusion criteria in pivotal clinical studies within the development programme

Exclusion Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
Known hypersensitivity to vilobelimab or any other ingredient in the study medication	To minimise risk to the patient and to minimise confounding of the assessment of both safety and efficacy data in the study population.	No	Hypersensitivity to the active substance or to any of the excipients is included as a contraindication in the SmPC.
Children and adolescents <18 years of age	IFX-1-P2.9 COVID-19 study was the first study conducted in the indication and safety and efficacy has in children has not been established. Evaluation of safety and efficacy in paediatric patients is subject to a Paediatric Investigation Plan (PIP) in the EU.	Yes	
Intubated > 48 hrs at time of randomisation	To minimise risk of confounding variables for the assessment of both safety and efficacy data in the study population.	No	No anticipated impact on safety for the indicated population.
Expected stop of invasive ventilation or expected extubation in the next 24 hrs without additional intervention according to the	To minimise risk of confounding variables for the assessment of both safety and efficacy data in the study population.	No	No anticipated impact on safety for the indicated population.

Exclusion Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
judgement of the investigator			
Known history of chronic dialysis or received renal replacement therapy in past 14 days or anticipated to receive renal replacement therapy within 24 hrs after randomisation	To minimise risk to the patient and to minimise confounding of the assessment of both safety and efficacy data in the study population.	No	Due to the small number of patients within this sub-population, a study is not deemed possible. The SmPC provides appropriate information for patients with renal impairment.
Treatment of COVID-19 with investigational antibodies which are not approved or not included into locally adapted treatment guidelines for this indication in the past 7 days	To minimise risk of confounding variables for the assessment of both safety and efficacy data in the study population.	No	No anticipated impact on safety for the indicated population.
Received cytokine adsorption therapy in past 3 days	To minimise risk to the patient and to minimise confounding of the assessment of both safety and efficacy data in the study population.	No	No anticipated impact on safety for the indicated population.
Serum or urine pregnancy test positive	To minimise risk to the patient and the offspring.	Yes	
Received organ or bone marrow transplantation in past 3 months	To minimise risk of confounding variables for the assessment of both safety and efficacy data in the study population.	No	There were no data generated on organ or bone marrow transplantation. Due to the small number of patients within this sub-population, a study is not deemed possible.
Known cardio-pulmonary resuscitation in past 14 days	To minimise risk of confounding variables for the assessment of both safety and efficacy	No	No anticipated impact on safety for the indicated population.

Exclusion Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
	data in the study population.		
Patient moribund or expected to die in 24 hours according to investigator judgement	To minimise risk of confounding variables for the assessment of both safety and efficacy data in the study population.	No	No anticipated impact on safety for the indicated population.
Known to have received anti-cancer therapy for hemato-oncological disease in past 4 weeks or known to have malignant disease at the point of randomisation	To minimise risk of confounding variables for the assessment of both safety and efficacy data in the study population.	No	No anticipated impact on safety for the indicated population.
Known severe congestive heart failure NYHA Class III – IV	To minimise risk of confounding variables for the assessment of both safety and efficacy data in the study population.	No	No anticipated impact on safety for the indicated population.
Known history of chronic liver disease, Child-Pugh B or C	To minimise risk of confounding variables for the assessment of both safety and efficacy data in the study population.	No	Due to the small number of patients within this sub-population, a study is not deemed possible. The SmPC provides appropriate guidance.
Known history of progressed COPD as evidenced by use of daily maintenance treatment with long-acting bronchodilators or inhaled/oral corticosteroids for > 2 months	To minimise risk of confounding variables for the assessment of both safety and efficacy data in the study population.	No	No anticipated impact on safety for the indicated population.

COPD = chronic obstructive pulmonary disease; EU = European Union; NYHA = New York Heart Association

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions and adverse reactions with a long latency.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 14: Limitations in respect to populations typically under-represented in clinical trial development programmes

Type of special population	Exposure
Pregnant women There are no data from the use of vilobelimab in pregnant women.	Female participants were excluded from the clinical trial programme if they were pregnant.
Breastfeeding women There is insufficient information on the excretion of vilobelimab in human milk. A risk to the newborns/infants cannot be excluded.	Female participants were excluded from the clinical trial programme if they were breastfeeding. There was, however, one case in the IFX-1-P2.9 COVID-19 study where breastfeeding was allowed after a thorough benefit-risk analysis for both the mother and the child. No adverse events occurred in the child.
Paediatric patients	Patients <18 years old were excluded from the clinical trial programme. Further characterisation and studies will be conducted according to the paediatric investigation plan (PIP) (EMEA-003080-PIP03-22) which includes a clinical study in patients from birth to less than 18 years of age in the intended indication, as well as population pharmacokinetic (PK) modelling and PK/pharmacodynamic (PD) exposure and extrapolation from the adult studies.
Elderly	During the IFX-1-P2.9 COVID-19 study, 30% of the patients were in the >65 and ≤85 years age category. There are currently no data for treatment with vilobelimab for patients > 85 years and above.
Different racial and / or ethnic origin	Cumulative patient exposure shows that a higher percentage of White/Caucasian patients were treated with vilobelimab. With regards to race, there were 65% White/Caucasian patients who received vilobelimab during the IFX-1-P2.9 COVID-19 study. 12.4% of patients were American Indian/Alaskan Native and the remaining racial groups were Black/African American (2.8%), Asian (2.3%), multiple (0.6%), other (9.0%), or not reported (7.9%).

Type of special population	Exposure
Patients with relevant comorbidities: Patients with hepatic impairment Vilobelimab is degraded by widely distributed proteolytic enzymes, not restricted to hepatic tissue, therefore changes in hepatic function are unlikely to have any effect on the elimination of vilobelimab. However, hepatic impairment according to the Child-Pugh B and C has been excluded from the IFX-1-P2.9 study. No dose adjustment is expected to be required in patients with lesser hepatic impairment.	A specific exclusion criterion excluded Child Pugh B and C cases from the IFX-1-P2.9 COVID-19 study.
Patients with relevant co-morbidities: Patients with renal impairment Vilobelimab, like other immunoglobulins, is too large to be excreted renally, thus renal impairment is not expected to have any effect on the elimination of vilobelimab. However, patients with chronic dialysis or kidney transplantation less than 3 months prior to the IFX-1-P2.9 study were excluded. No dose adjustment is expected to be required in patients with lesser renal impairment.	A specific exclusion criterion excluded patients with chronic dialysis or kidney transplantation less than 3 months ago from the IFX-1-P2.9 COVID-19 study.

Part II: Module SV – Post authorisation experience

SV.1: Post-authorisation exposure

Not applicable.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

A potential for misuse for illegal purposes or abuse has not been identified for vilobelimab and is considered unlikely from the knowledge on vilobelimab.

Potential for transmission of infectious agents

Vilobelimab is produced in Chinese hamster ovary cells by recombinant DNA technology. Potential viral and nonviral adventitious agents such as contaminating bacteria, fungi, and transmissible spongioform encephalopathy are controlled at several levels. The introduction of such agents is prevented or minimised by controls on starting materials, including raw

materials, excipients, and cell source. The vilobelimab drug substance undergoes a purification process to remove or inactivate potential viruses.

The manufacturing process and facility are designed to prevent contamination during production of vilobelimab drug substance and drug product. Manufacturing takes place on a campaign basis in suites which are, during production, dedicated to the production of vilobelimab. Validation of the cleaning procedures confirms that cleaning is effective.

In-process controls ensure that purity requirements are met. Release testing of drug substance and drug product assures purity and quality of the product.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

Table 15: Important Risks

SVII 1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Vilobelimab is used in an ICU setting with a population facing a life-threatening disease and health professionals closely monitoring these patients and are prepared to handle these types of reactions.

SVII

SVII 1.1.1 Risk not considered as important: immunogenicity

Across the non-clinical studies, one unexplained death of a cynomolgus monkey retrospectively showed development of anti-drug antibodies (ADAs). The death occurred in an animal treated with 50 mg/kg during the 26-week chronic toxicity study. After comprehensive examination, it was found that this animal was the only one exhibiting a high level of ADA in the blood, and it was concluded that an immune-mediated reaction caused by ADA-induced immune complex formation may have contributed to the death. However, anti-drug antibody related reactions occurring in animals have been described to not be predictive of such reactions in humans.

In the Phase III PANAMO COVID-19 study, one patient in each treatment group had treatment-induced ADAs; however, no AEs related to immunogenicity or other safety findings were observed. Across the remaining completed clinical studies, few patients tested positive for ADAs. No indication of increased immunogenicity was found after vilobelimab treatment at various doses and during long-term administration, and therefore immunogenicity is not considered an important risk.

SVII 1.1.2. Risk not considered as important: infusion reactions including rash

At this stage we consider that this risk is not considered as important. A warning is included in SmPC section 4.4. Rash is considered causally related to Gohibic, but not as an important risk, since in the context of an ICU, rash can be easily managed. It is listed as adverse reaction in SmPC section 4.8. We consider routine pharmacovigilance activities are sufficient to

further monitor this risk. Rash and other infusion-related reactions occurred with a low frequency across the clinical studies and are acceptable in relation to the severity of the indication treated and in the context of the ICU setting in which they are occurring where measures are available to handle them. These are known risks which require no further characterisation and are followed up via routine pharmacovigilance activities namely through signal detection and adverse reaction reporting.

SVII 1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk

Serious infections

Serious infections were observed more frequently in the vilobelimab group than in the placebo group and are considered an important identified risk.

Risk-benefit impact

The specialist nature of the ICU setting ensures that infections are closely monitored

Important Potential Risks

Venous thrombosis.

Venous thrombosis rate was slightly higher in the vilobelimab group compared to the placebo group.

Risk-benefit impact

Vilobelimab is indicated for the treatment of adult patients with SARS-CoV2-induced acute respiratory distress syndrome (ARDS) who are receiving invasive mechanical ventilation (IMV). The impact of venous thromboembolism varies from mild to severe systemic life-threatening conditions. However, the risk of venous thrombosis is well-known to health professionals especially to those managing the targeted patient population in an ICU setting and they have the appropriate measures in place as part of clinical practice.

Missing Information: Use during pregnancy

There are currently no data on the use of vilobelimab in patients who are pregnant.

SVII.2 New safety concerns and reclassification with a submission of in updated RMP

Not applicable

SVII.3 Details of important identified risks, important potential risks, missing information

SVII.3.1 Presentation of important identified risks and important potential risks

Important identified risks: Serious infections

Potential mechanisms:

Serious infections have been observed as adverse reactions while these infections are known co-morbidities of the ICU setting. Its mechanism of action, however, targeting C5a and leaving the membrane attack complex (MAC) intact, is not suggestive of promoting these infections.

Evidence source and strength of evidence:

Study IFX-1-P2.9 (PANAMO, COVID-19) and studies for other indications listed in this RMP.

Characterisation of the risk:

The incidence of infections in hospitalised patients with severe acute respiratory syndrome coronavirus type 2 (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)) is high in general. The medical condition and ventilation situation significantly increases the risk of bacterial, fungal, and viral co-infections, and increased occurrence of these nosocomial infections has been associated with length of ICU stay (Buehler et al. 2021, Musuuza, et al. 2021, Chastre and Fagon 2001, Malekifar et al. 2021, Bardi et al. 2020, Raffaelii et al. 2022).

Risk factors and risk groups:

None beyond those at risk of serious complications of severe COVID-19 infection.

Preventability:

The SmPC warns of the risk of infection other than COVID-19 in section 4.4. A patient who develops a new infection during treatment with vilobelimab should undergo diagnostic investigations. Appropriate treatment should be initiated, and the patient should be closely monitored.
Additionally, this risk is followed up in the PSURs and monitored in an ongoing way.

Impact of the risk-benefit balance of the product:

The specialist nature of the ICU setting ensures that infections are closely monitored.

Public health impact:

There is no public health impact.

Important potential risk: Venous thrombosis

Potential mechanisms:

There is no known plausible mechanism through which vilobelimab could trigger venous thrombosis in patients with Covid-19. However, COVID-19 itself causes endothelial injury, activation of the coagulation system and thrombosis via an inflammatory response driven by the host immune system, a phenomenon called “thrombo-inflammation”. There is available evidence that supports the inclusion of C5 activation as one of the drivers of COVID-19-associated thrombo-inflammation. Accordingly, there is a potential role of inhibitors targeting C5, C5a or C5aR1 in preventing and controlling COVID-19 induced thromboembolic complications. Hence, vilobelimab’s mechanism of action does not include any pro-thrombotic component, on the contrary, it inhibits C5a being known for activating the tissue factor coagulation pathway.

Evidence source and strength of evidence:

In Study IFX-1-P2.9 (PANAMO, COVID-19), the overall frequency of embolic and thrombotic events was higher in the vilobelimab group (25.1%) than in the placebo group (18.5%). However, the incidence rate (number of patients with the event over a specific period of time in hospital) was only slightly higher in the vilobelimab group (0.94 vs 0.89) indicating that the longer observation times for the patients in the vilobelimab group, associated with improved survival, significantly contributed to the higher reporting of embolic and thrombotic events.

Characterisation of the risk:

In the randomised placebo-controlled phase III clinical trial (PANAMO), embolic and thrombotic adverse events occurred at a higher rate in the vilobelimab group (44/175 patients [25.1%]) than in the placebo group (35/189 patients [18.5%]), but embolic and thrombotic serious adverse events were evenly distributed (20/189 patients [10.6%] in the placebo group and 19/175 [10.9%] in the vilobelimab group). One patient in the placebo group and three in the vilobelimab group had a fatal serious thromboembolic adverse event. None of the thromboembolic events was considered related to vilobelimab except one non-serious event of thrombophlebitis.

Risk factors and risk groups:

The targeted patient population is at higher risk of developing venous thrombosis due to Covid-19 itself, the severity of the condition and the potential prolonged stay in hospital.

Preventability:

Venous thrombosis may be prevented with antithrombotic therapy.

Impact of the risk-benefit balance of the product:

Vilobelimab is indicated for the treatment of adult patients with SARS-CoV2-induced acute respiratory distress syndrome (ARDS) who are receiving invasive mechanical ventilation (IMV). The impact of venous thromboembolism varies from mild self-limiting local symptoms such as leg-swelling and tenderness to severe systemic life-threatening conditions such as pulmonary embolism and stroke. The risk of venous thrombosis is well-known to health professionals

especially to those managing the targeted patient population and they have the appropriate measures in place as part of clinical practice. The core element of the management of such a risk is the use of antithrombotic therapy which is part of the standard therapy/routine clinical care for those patients.

Public health impact:

Considering the very specific targeted patient population the impact on public health is likely to be low.

SVII.3.2 Presentation of the missing information

Use during pregnancy:

Evidence Source:

The safety of vilobelimab in pregnant women is unknown as there is no experience in pregnant women.

Anticipated risk/consequence of the missing information:

The intended use of vilobelimab is in an ICU setting and will be used in conjunction with other medicinal products given the seriousness of the patient's condition. As a precautionary measure, it is preferable to avoid the use of Gohibic during pregnancy.

Part II: Module SVIII – Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	Serious infections
Important potential risks	Venous thrombosis
Missing information	Use during pregnancy

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection

Specific adverse reaction follow-up questionnaires:

A specific adverse reaction follow-up questionnaire will not be used.

Other forms of routine pharmacovigilance activities for serious infections and venous thrombosis:

- Cumulative reviews of serious infections and venous thrombosis will be performed within the Safety Management Team at regular intervals.

- Traceability

  The SmPC Section 4.4 includes the following instructions to healthcare providers:

  "In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded."

III.2 Additional Pharmacovigilance activities

None.

III.3 Summary table of additional Pharmacovigilance activities

Not applicable

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Table 16: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Planned Just Breathe (Vilobelimab cohort)	In order to further investigate the efficacy and safety of vilobelimab in the treatment of adult patients with SARS-CoV2-induced acute respiratory distress syndrome (ARDS) who are receiving systemic corticosteroids, the MAH shall submit results for the vilobelimab cohort in 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.	Long-term efficacy	Protocol submission	NA
			Interim reports	To be submitted with annual re-assessment
			Final report	31/12/2029
Ongoing	In order to ensure the adequate monitoring of efficacy and safety of vilobelimab in the treatment of adult patients with SARS-CoV2-induced 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.	Long term efficacy and safety	Interim Reports	Annually with annual re-assessment

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

V.1. Routine Risk Minimisation Measures

Table 17: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Serious infections (important identified risk)	Routine risk communication: SmPC Section 4.4 and Section 4.8 PL Section 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for management and monitoring are included in SmPC Section 4.4. Other routine risk minimisation measures beyond the Product Information: Legal status of the product is “Medicinal product subject to medical prescription”
Venous thrombosis (important potential risk)	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Legal status of product is “Medicinal product subject to medical prescription”
Use during pregnancy (missing information)	Routine risk communication: SmPC Section 4.6 PL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation on usage during pregnancy is included in SmPC Section 4.6. Other routine risk minimisation measures beyond the Product Information: Legal status of product is “Medicinal product subject to medical prescription”

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Table 18: 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 minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Cumulated 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 minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Cumulated 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

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

This is a summary of the risk management plan (RMP) for Gohibic. The RMP details important risks of Gohibic, how these risks can be minimised, and how more information will be obtained about Gohibic's risks and uncertainties (missing information).

Gohibic’s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Gohibic should be used.

This summary of the RMP for Gohibic should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Gohibic's RMP.

I. The medicine and what it is used for:

Gohibic is authorised for the treatment of adult patients with severe acute respiratory syndrome coronavirus type 2 (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)). It contains vilobelimab as the active substance and it is given by intravenous infusion.

Further information about the evaluation of Gohibic’s benefits can be found in Gohibic’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/gohibic

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Gohibic, together with measures to minimise such risks and the proposed studies for learning more about Gohibic's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine’s packaging
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine’s legal status - the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Gohibic is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of vilobelimab are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential.

Identified risks are concerns for which there is sufficient proof of a link with the use of vilobelimab. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the use of the medicine in paediatric populations).

Summary of Safety Concerns	
Important identified risks	Serious infections
Important potential risks	Venous thrombosis
Missing information	Use during pregnancy

II.B Summary of important risks

Important identified risk: Serious infections	
Evidence for linking the risk to the medicine	Study IFX-1-P2.9 (PANAMO, COVID-19) and studies for other indications listed in this RMP.
Risk factors and risk groups	None beyond those at risk of serious complications of severe COVID-19 infection.
Risk minimisation measures	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
Important potential risk: Venous thrombosis	
Evidence for linking the risk to the medicine	In Study IFX-1-P2.9 (PANAMO, COVID-19), the overall frequency of embolic and thrombotic events was higher in the vilobelimab group (25.1%) than in the placebo group (18.5%). However, the incidence rate

	(number of patients with the event over a specific period of time in hospital) was only slightly higher in the vilobelimab group (0.94 vs 0.89) indicating that the longer observation times for the patients in the vilobelimab group, associated with improved survival, significantly contributed to the higher reporting of embolic and thrombotic events.
Risk factors and risk groups	The targeted patient population is at higher risk of developing venous thrombosis due to Covid-19 itself, the severity of the condition and the potential prolonged stay in hospital.
Risk minimisation measures	Routine risk minimisation measures: None Legal status of product is “Medicinal product subject to medical prescription” Additional risk minimisation measures: None

Missing information: Use during Pregnancy	
Risk minimisation measures	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

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of vilobelimab.

II.C.2 Other studies in post-authorisation development plan

A study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of vilobelimab for the treatment of COVID-19 in paediatric patients from birth to less than 18 years of age who are on IMV or ECMO is planned according to an agreed paediatric investigation plan (EMEA-003080-PIP03-22).

PART VII: ANNEXES

Annex 1: EudraVigilance Interface

Not applicable

Annex 2: Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Not applicable

Annex 3: Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Not applicable

Annex 4: Specific adverse drug reaction follow-up forms

Not applicable

Annex 5: Protocols for proposed and on-going studies in RMP part IV

Not applicable

Annex 6: Details of proposed additional risk minimisation activities

Not applicable

Annex 7: Other supporting data (including referenced material)

Refer to References (below).

Annex 8: Summary of changes to the risk management plan over time

Not applicable.

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