EU Risk Management Plan for
Veklury (Remdesivir)

EU RISK MANAGEMENT PLAN FOR VEKLURY (REMDESIVIR)

RMP version to be assessed as part of this application:

Version number:	Data lock point for this RMP:	Date of final sign off:
8.0	04 January 2023	Refer to ELECTRONIC SIGNATURES

Rationale for submitting an updated RMP:	Removal of the completed Category 3 additional pharmacovigilance activity Study GS-US-540-9014. Removal of the missing information Safety in patients with hepatic impairment as there are no outstanding additional pharmacovigilance activities following the completion of Study GS-US-540-9014.

Summary of significant changes in this RMP:

Part	Module/Annex	Significant changes to RMP
Part I Product Overview		Information updated
Part II Safety Specification	Part II: Epidemiology of the indication and target populations(s)	Information updated
	Part II: Module SII: Nonclinical part of the safety specification	None
	Part II: Module SIII: Clinical study exposure	Information updated to include study GS-US-540-9014
	Part II: Module SIV: Populations not studied in clinical studies	Information updated to include exposure in patients with hepatic impairment
	Part II: Module SV: Postauthorization experience	Postauthorization exposure updated
	Part II: Module SVI: Additional EU requirements for the safety specification	None
	Part II: Module SVII: Identified and potential risks	Removed the missing information Safety in patients with hepatic impairment
	Part II: Module SVIII: Summary of the safety concerns	Updated per Part II Module SVII
Part III Pharmacovigilance Plan		Removed completed Category 3 additional pharmacovigilance activity Study GS-US-540-9014
Part IV Plan for postauthorization efficacy studies		None
Part V Risk Minimization Measures		Updated to reflect changes in Parts II and III
Part VI Summary of RMP		Updated to reflect changes in Parts II and III
Part VII Annexes		Annexes updated to reflect changes in Parts II and III.

Other RMP versions under evaluation:

Not Applicable.

Details of the currently approved RMP:

Version number:	Approved with procedure	Date of approval (opinion date)
7.0	EMEA/H/C/005622/II/0046/G	22 June 2023

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	Adverse Drug Reaction
AKI	Acute kidney injury
ARDS	acute respiratory distress syndrome
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CI	Confidence Interval
CKD	Chronic kidney disease
CLD	Chronic Liver Disease
CNS	Central Nervous System
CoV	coronavirus
COVID-19	Coronavirus disease 2019
CU	Compassionate Use
CYP	Cytochrome 450
DHHS	Department of Health & Human Services
DIC	Disseminated Intravascular Coagulation
DLP	Data lock point
ECDC	European Centre for Disease Prevention and Control
ECMO	Extracorporeal membrane oxygenation
EEA	European Economic Area
EPAR	European Public Assessment Report
EU	European Union
EU-RMP	EU Risk Management Plan
FDA	Food and Drug Administration
ICU	Intensive Care Unit
IM	intramuscular
INR	International normalized ratio
IV	intravenous
KRT	Kidney Replacement Therapy
MIS-C	multisystem inflammatory syndrome in children
NOAEL	no observed adverse effect level
OAT3	organic anion transporter-3
OR	odds ratio
P-gp	P-glycoprotein
PK	Pharmacokinetics
PL	Patient Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	Prothrombin time
PV	Pharmacovigilance
RDV	remdesivir
RMP	Risk Management Plan

RNA	Ribonucleic acid
RSV	Respiratory syncytial virus
SARS	Severe Acute Respiratory Syndrome
SmPC	Summary of Product Characteristics
WHO	World Health Organisation
UK	United Kingdom
US	United States

PART I: PRODUCT OVERVIEW

Table Part I.1. Product Overview

Active substance(s) (INN or common name):	Remdesivir
Pharmaco-therapeutic group(s) (ATC Code):	Nucleosides and nucleotides excl. reverse transcriptase inhibitors (J05AB)
Marketing Authorization Holder:	Gilead Sciences Ireland UC
Medicinal products to which this RMP refers:	1
Invented name(s) in the European Economic Area (EEA)	Veklury™
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class Prodrug of a nucleoside reverse transcriptase inhibitor
	Summary of mode of action Remdesivir is a single diastereomer monophosphoramidate prodrug that is intracellularly metabolized into an analog of adenosine triphosphate that inhibits viral ribonucleic acid (RNA) polymerases and has broad-spectrum activity against members of the coronaviruses (CoVs) including Severe Acute Respiratory Syndrome (SARS) SARS-CoV-2.
	Important information about its composition Contains betadex sulfobutyl ether sodium
Hyperlink to the Product Information	Remdesivir Summary of Product Characteristics (SmPC)
Indication(s) in the EEA	Current: Veklury is indicated for the treatment of coronavirus disease 2019 (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.
	Proposed (if applicable): Not applicable

Dosage in the EEA	Current: Posology The recommended dosage of remdesivir in adults and paediatric patients (weighing at least 40 kg) is: • Day 1 – single loading dose of remdesivir 200 mg given by intravenous infusion • Day 2 onwards – 100 mg given once daily by intravenous infusion. The recommended dosage of remdesivir in paediatric patients at least 4 weeks of age and weighing at least 3 kg but less than 40 kg is: • Day 1 – single loading dose of remdesivir 5 mg/kg given by intravenous infusion • Day 2 onwards – 2.5 mg/kg given once daily by intravenous infusion. Treatment duration *Patients with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment):* *Adults:* Daily for at least 5 days and not more than 10 days. *Paediatric patients (weighing at least 40 kg):* Daily for at least 5 days and not more than 10 days. *Paediatric patients at least 4 weeks old (weighing at least 3 kg but less than 40 kg):* Daily for up to a total of 10 days. *Patients who do not require supplemental oxygen and are at increased risk of progressing to severe COVID-19:* *Adults and paediatric patients (weighing at least 40 kg):* Daily for 3 days, starting as soon as possible after diagnosis of COVID-19 and within 7 days after the onset of symptoms.
	Proposed (if applicable): Not applicable
Pharmaceutical form(s) and strengths	Current: Veklury 100 mg powder for concentrate for solution for infusion: • The lyophilized formulation of remdesivir contains remdesivir to be reconstituted with sterile water for injection and diluted into IV infusion fluids prior to IV administration. It is supplied as a sterile product in a single-use, clear glass vial. Following reconstitution, each vial contains a 5 mg/mL remdesivir concentrated solution with sufficient volume to allow withdrawal of 20 mL (100 mg of remdesivir).
	Proposed (if applicable): Not applicable
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. Coronavirus Disease 2019 (COVID-19)

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel enveloped, positive-sense, single-stranded ribonucleic acid (RNA) beta-coronavirus that is genetically related to the coronavirus responsible for the 2003 SARS global outbreak {Fehr 2015, Gorbalenya 2020, World Health Organization (WHO) 2020c}. In December 2019, an outbreak of COVID-19 began in Wuhan, China where the virus was detected in three pneumonia patients who were connected to a cluster of cases with acute respiratory illness {Wu 2020a}. The virus subsequently became widespread throughout mainland China via suspected person to person transmission {Li 2020}.

The primary route of transmission is through close contact (i.e., within approximately two meters) with an infected person mainly through respiratory droplets {Meyerowitz 2021}. The recommended practices to limit direct viral transmission include respiratory etiquette and proper hand hygiene, cleaning and disinfecting surfaces regularly, maintaining physical distances, avoiding those with fever or respiratory symptoms, and for healthcare workers to follow droplet and contact precautions when caring for COVID-19 patients in the clinical setting {World Health Organization (WHO) 2020a}.

The introduction of COVID-19 vaccines, which began at the end of 2020, provided an additional tool for lowering risk of transmission and attenuating disease severity in infected individuals. The first COVID-19 vaccine that became available under emergency use authorization was the Pfizer-BioNTech mRNA vaccine (nucleoside modified), which was authorized in December 2020 for individuals from 12 years of age and older in European Union and European Economic Area (EU/EEA), United States (US), Canada, and several other countries. At the end of 2021 there were ten COVID-19 vaccines authorized for use by the WHO under Emergency Use Listing, and several other vaccines have been approved for use by individual countries via domestic emergency use authorization based on national regulations {World Health Organization (WHO) 2022c}. Currently, monovalent vaccines are also available for children from 6 months through 11 years of age. Estimates of vaccination rates vary widely worldwide, with over 70% of the population being fully vaccinated in high and upper middle-income countries, about 38% in lower middle-income countries and about 5% in low-income countries {Our World in Data 2022}.

Over time, mutations in the SARS-CoV-2 genome have occurred, and certain variant strains emerged rapidly with evidence of increased transmissibility, clinical implications, and/or impact on effectiveness of public health measures, termed as variants of concern {World Health Organization (WHO) 2022d}. The Delta variant (B.1.617.2 lineage) was first identified in December 2020 in India and thereafter became the most prevalent globally. It was reported that Delta was more transmissible and has posed an increased risk of hospitalization {World Health

Organization (WHO) 2022d}. In November 2021, the original Omicron variant (B.1.1.529 lineage), sublineage BA.1, was first reported in Botswana and South Africa, and surpassed the Delta variant as the most prevalent strain in several areas including the US, United Kingdom (UK), and EU/EEA as of January 2022 {Centers for Disease Control and Prevention (CDC) 2022a, European Centre for Disease Prevention and Control (ECDC) 2022a, UK Health Security Agency 2021}. Currently, sublineages BA.2, BA.4, and BA.5 are the dominant strains circulating worldwide {World Health Organization (WHO) 2022b}, and sublineage BQ.1 is emerging in France, Belgium, Ireland, The Netherlands, and Italy {European Centre for Disease Prevention and Control (ECDC) 2022c}. As new mutations occur, data on clinical implications are being identified, monitored, and new evidence is emerging.

SI.1.1. Incidence and Prevalence

As COVID-19 testing strategies and availability vary by worldwide and change over time, assessment of global incidence and prevalence are not robust{Kalish 2021} {Lipsitch 2020}. Reliable estimates on true incidence and prevalence in populations are also lacking and are considered underestimates, as mild cases may not be tested and reported, and symptomatic cases that resolve and recover are not enumerated systematically {Clarke 2022, Verity 2020}. Despite these challenges, passive surveillance of reported cases across geographies in a timely manner provide meaningful information on the pandemic's progress overtime and regional variation.

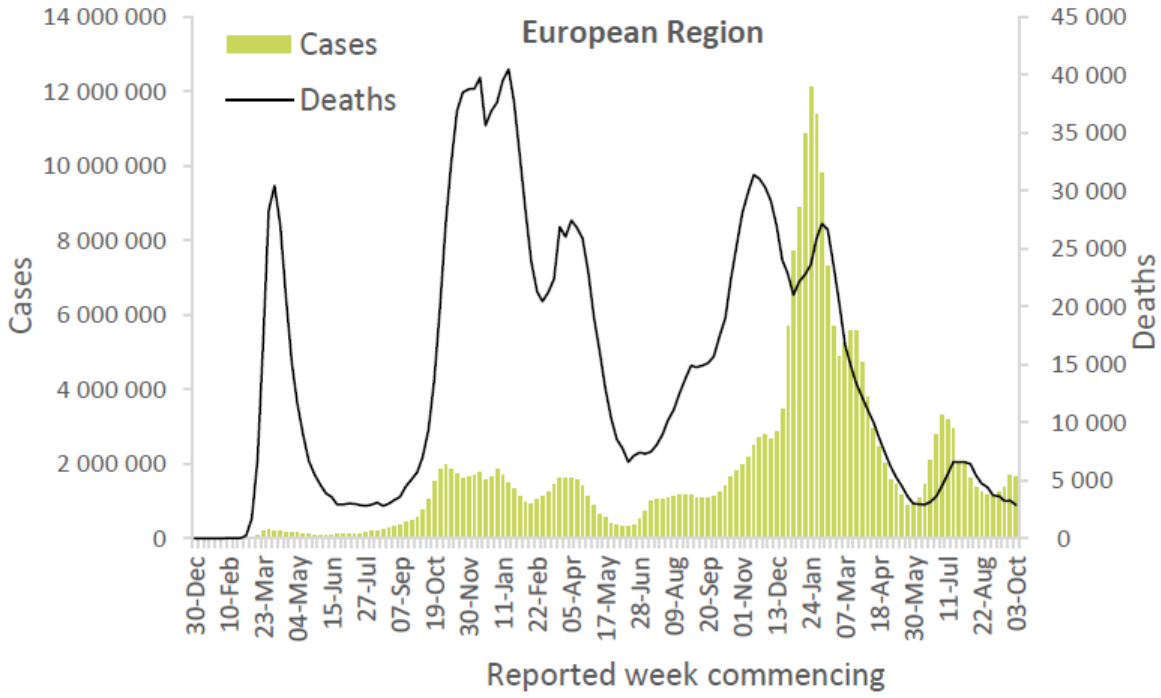
As of 09 October 2022, there were 618,507,182 cumulative cases reported according to local case definitions and testing strategies and reported by the World Health Organization (WHO). Increased weekly case reporting was observed globally during times of increased transmission due to seasonality and emergence of variants of concern, however regional variability exists. For example, the circulation of the COVID-19 Delta variant and rapidly increasing emergence of the Omicron variant resulted in increases of reported cases in the WHO regions of Africa, Europe, and the US at the end of 2021, while the number of cases in the South-East Asia and Eastern Mediterranean regions declined during that time and rose in early 2022 {World Health Organization (WHO) 2022a}. Since then, cases have declined overall since the initial spike due to the emergence of the Omicron variant. By WHO region, Europe has the largest number of cases reported (256,019,483 [41%]), followed by the Americas (178,832,851 [29%]), Western Pacific (90,869,335 [15%]), South-east Asia (60,339,540 [10%]), Eastern Mediterranean (23,107,748 [4%]), and Africa (9,337,461 [2%]) {World Health Organization (WHO) 2022b}.

The numbers of COVID-19 cases and deaths reported in the European region from December 2019 to October 2022 are presented in Figure SI.1. The following European countries reported the highest number of cumulative cases as of 28 October 2022: France (36,750,554), Germany (35,523,412), United Kingdom (23,898,485), Italy (23,475,187), and Russian Federation (21,409,815) {European Centre for Disease Prevention and Control (ECDC) 2022d}.

Overall, the 14-day incidence rate reached a peak in the weeks of November 2020 (624.0 per 100,000 population), and subsequently decreased to 286.7 per 100,000 before surging to a second peak of 496.0 per 100,000 in March 2021 {European Centre for Disease Prevention and Control (ECDC) 2021a}. Since then, the 14-day incidence rate steadily declined through June 2021, coinciding with gradual vaccine uptake in EU/EEA countries, though rates increased

thereafter due to the emergence of the Delta and Omicron variants, reaching a new peak of over 1,000 per 100,000 at the start of 2022 {European Centre for Disease Prevention and Control (ECDC) 2021c}. Since then, incidence rates have declined overall, and as of 09 October 2022, in the EU/EEA, the 14-day incidence rate was 636 per 100,000 population; the lowest rate per 100,000 population was reported in Norway (18.2), and the highest rate was reported in Austria (2,550) {European Centre for Disease Prevention and Control (ECDC) 2022b}.

Figure SI.1. Number of reported COVID-19 cases and deaths in the European Region, December 2019 to October 2022



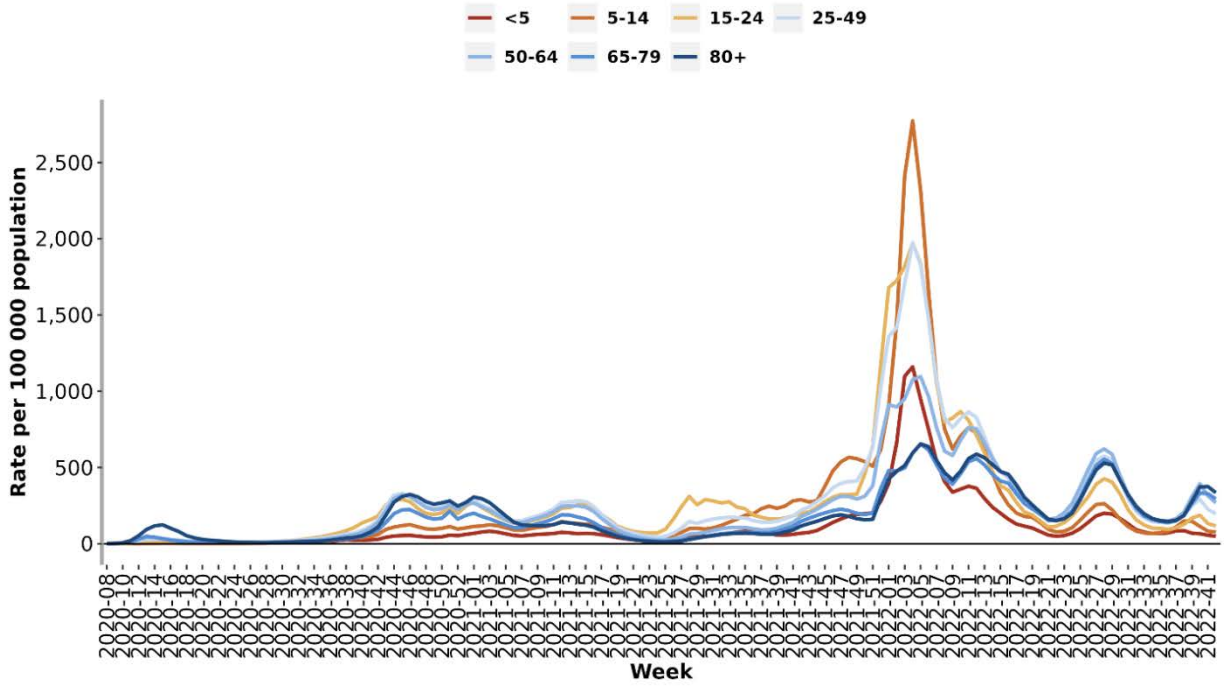
Source: {European Centre for Disease Prevention and Control (ECDC) 2022b}

SI.1.2. Demographics of the Population in the Authorized Indication

Persons of all ages are susceptible to SARS-CoV-2 infection. Weekly incidence rates in the European region from August 2020 to October 2022 are presented in Figure SI.2 {European Centre for Disease Prevention and Control (ECDC) 2022d}. At the beginning of the pandemic, incidence was highest among those aged 65 years old and above. As targeted public health measures were adopted to protect older individuals, such as improved infection control measures in nursing homes and vaccination programs targeting the ≥65 age group first, reported cases among those 65 years and older declined, while cases among those between 15 and 64 years old increased {European Centre for Disease Prevention and Control (ECDC) 2022a}. At the end of 2021, incidence was highest among age groups below 65 years, with steep increases among the 25 to 29, 15 to 24 and less than 15 age groups as the Delta and Omicron variants emerged (Figure SI.2). Currently, incidence rates are highest among older age groups in Europe,

with a 14-day case notification rate of 669 per 100,000 among those aged 65 years and above {European Centre for Disease Prevention and Control (ECDC) 2022b}. Rates of severe disease, hospitalization, and death are higher compared to the below age 65 group. {Centers for Disease Control and Prevention (CDC) 2021, European Centre for Disease Prevention and Control (ECDC) 2022a}.

Figure SI.2. Weekly COVID-19 incidence rates in the European Region by age group, August 2020 to October 2022



Source: {European Centre for Disease Prevention and Control (ECDC) 2022d}

Overall children comprise a small proportion of the reported cases worldwide, though over time this portion has steadily increased {Cai 2020, Qiu 2020, U. S. Department of Health & Human Services (DHHS) 2020}. In the US, the proportion of cases among children below age 12 increased from less than 4% at the start of the pandemic to approximately 15% in mid-2021, at which time hospitalizations among the paediatric population in the US increased {Centers for Disease Control and Prevention (CDC) 2021, Jones 2021}. In EU/EEA, 14-day incidence rates were lowest among children younger than 15 years compared to all other age groups for most of the pandemic and did not surpass 500 cases per 100,000 population until the emergence of the Delta and Omicron variants in 2021 (Figure SI.2) {European Centre for Disease Prevention and Control (ECDC) 2022a}. At the end of 2021, the rate exceeded 1,000 cases per 100,000 among children younger than 15 years and was the highest of all age groups, with evidence of greater burden among the 5 to 9 age group {European Centre for Disease Prevention and Control (ECDC) 2022a, UK Health Security Agency 2021}. Further, as testing is less likely to occur among those with mild symptoms or asymptomatic infection, estimates on the true burden of COVID-19 among this age group are not known.

In the EU/EEA and the UK, hospitalization rates vary by age. Among those aged 29 or younger, 1.3% result in hospitalization, 3.9% among those aged 30 to 59 years, 12.8% among those aged 60 to 69 years, 26.1% among those aged 70 to 79 years, and 34.9% among those 80 years and older {European Centre for Disease Prevention and Control (ECDC) 2021b}.

Globally, rates of SARS-CoV-2 infection among pregnant women admitted to or receiving care at a hospital for any reason vary by region and country income level. Overall, the estimated infection rate among this patient population is 8% (95% Confidence Interval [CI] 7% to 9%), with highest rates of infection observed in the Latin America and Caribbean region (19%, 95% CI 12% to 27%) and lower-middle-income countries (13%, 95% CI 6% to 23%). The lowest rates of infection were observed in the East Asia and Pacific region (0.4%, 95% CI 0% to 2%) and upper-middle income countries (5.7%, 95% CI 5.6% to 5.9%) {Sheikh 2022}.

Although early studies observed males comprised a higher proportion of reported COVID-19 cases compared to females {Chen 2020b, European Centre for Disease Prevention and Control (ECDC) 2020, Onder 2020, Yang 2020, Zhou 2020} and a higher proportion of COVID-19 deaths compared to females among reported cases {Wu 2020a}, current literature does not note any significant differences in COVID-19 diseases by gender.

SI.1.3. Main Existing Treatment Options

Treatment of COVID-19 varies depending upon stage and severity of disease. Those with mild illness tend to recover on an outpatient basis, with supportive care and isolation to prevent disease transmission.

Moderate illness among patients with COVID-19 requires monitoring for progression of symptoms and may require hospitalization. Those with severe illness require hospitalization, and specific treatments for use against SARS-CoV-2 infection vary by disease stage {Gandhi 2020}.

To treat symptoms associated with COVID-19, patients are given supportive care and oxygen supplementation via non-invasive or mechanical ventilation. In patients with COVID-19 pneumonia who require supplemental oxygen or mechanical ventilation, dexamethasone or systemic corticosteroid + tocilizumab are available treatment options as well as anakinra which is recommended for patients who require supplemental oxygen (low- or high-flow) and are at increased risk of progression to severe respiratory failure (as determined by plasma concentration of soluble urokinase plasminogen activator receptor $\geq$ 6 ng/ml). In critically ill patients with extremely low blood pressure or secondary bacterial infections, vasopressors and/or antibiotics may be prescribed, respectively {European Centre for Disease Prevention and Control (ECDC) 2020}.

For patients who do not require supplemental oxygen but are at increased risk of progression to severe COVID-19 based on underlying risk factors the following alternative treatment strategies are available: antiviral nirmatrelvir/ritonavir and monoclonal antibodies (tixagevimab/cilgavimab, casirivimab/indivimab, regdanvimab and sotrovimab). Also, an antiviral molnupiravir and monoclonal antibodies (bamlanivimab/etesevimab) were recommended for this patient population following review under Article 5(3).

To see the current status of Article 5(3) reviews as well as the list of currently authorized products, please see https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/treatments-covid-19/covid-19-treatments-article-53-reviews and https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/treatments-covid-19/covid-19-treatments-authorised.

SI.1.4. Natural History of the Indicated Condition including Mortality and Morbidity

The manifestation of COVID-19 among persons with SARS-CoV-2 infection varies widely, from asymptomatic infection to severe illness that may result in respiratory failure and multiorgan dysfunction leading to hospitalization and death. The onset of symptoms due to SARS-CoV-2 infection appears after an initial incubation period that ranges from one to 14 days, with most cases occurring approximately four to six days after exposure {Backer 2020, Guan 2020, Li 2020}. Symptomatic infection severity ranges from mild or moderate (including those without pneumonia or with mild pneumonia), reported in 81% of cases, to severe disease (14%), critical disease (5%), and death (2.3% overall) {Wu 2020b}. Common symptoms among mild cases included those related to viral pneumonia such as dry cough, fatigue, fever, and lymphopenia. Severe cases have dyspnea or hypoxia, and critical cases result in respiratory failure, shock or multiorgan dysfunction. Some studies have reported that approximately half of mild cases progressed to develop dyspnea over five to eight days after initial symptom onset, and to mechanical ventilation in 10 days {Deng 2020, Huang 2020a, Wu 2020b}. Other symptoms include headache, hemoptysis, diarrhea, anosmia, dysgeusia, and upper respiratory symptoms, such as sputum production {Giacomelli 2020, Huang 2020a, Rothan 2020}.

While most COVID-19 cases result in mild illness, defined as mild symptoms (e.g., fever, cough, anosmia/dysgeusia) without dyspnea and clinical/radiological evidence of lower respiratory tract infection (with oxygen saturations ≥94%), literature describing the detailed clinical course among these patients is lacking {Gandhi 2020}. Recent studies following adult outpatients via phone survey or non-hospitalized isolation have found that among patients with mild illness, symptoms at presentation were similar to those of patients who eventually required hospitalization. However, symptoms lasted one to two weeks after initial diagnosis among those with mild illness, compared to three to four weeks amongst those with moderate illness who eventually required hospitalization, notably for lower respiratory symptoms such as chest pain and dyspnea {Blair 2021}. Several retrospective analyses, have shown that up to 75% of adult outpatients who had never been hospitalized reported persistent symptoms one to two months after initial symptom onset, with approximately 5% of outpatients in one study seeking medical care for chronic COVID-19 symptoms at four weeks after initial symptom onset {Blair 2021, Carvalho-Schneider 2021, Vahey 2021}.

Worldwide, rates of disease severity and hospitalization vary based on a combination of factors, including outbreak response, testing availability, population demographics, and characteristics of circulating variants within a geography. Complications observed during disease progression have been reported, though frequencies observed are mainly based on smaller patient cohorts. Among patients with severe disease, acute respiratory distress syndrome (ARDS) is a major

complication, developing in 20% of those with mild illness a median of eight days after initial symptom onset, with greater risk among patients with diabetes, hypertension, or are greater than 65 years old {Wang 2020a, Wu 2020a}. Among patients with severe disease, elevated inflammatory markers and proinflammatory cytokines have been associated with progressing onto more critical infection or death {Huang 2020a}.

Chronic kidney disease (CKD) patients at various stages have an increased risk of COVID-19 infection {Kunutsor 2020}. CKD patients also tend to have more severe outcomes than those who do not have CKD {Zhou 2020, Henry 2020}. A meta-analysis of patients with CKD found that incidence of COVID-19 was higher in people with CKD treated with dialysis than those not requiring kidney replacement therapy (KRT) or in kidney or pancreas/kidney transplant recipients {Chung 2021}. Acute kidney injury (AKI) patients requiring KRT is common among hospitalized, critically ill COVID-19 patients (5-9%) and increases the overall hospital mortality rate {Robbins-Juarez 2020, Zhou 2020}.

Early evidence didn't appear to indicate an association between Chronic Liver Disease (CLD) and prognosis of COVID-19 with respect to disease severity and mortality {Wu 2020c}. However, a recent systematic review and meta-analysis of 40 studies including more than 900,000 patients demonstrated that COVID-19 patients with CLD experience more severe disease and higher mortality compared to COVID-19 patients without CLD. Namely, for mortality the pooled odds ratio (OR) was 2.35 (95% CI, 1.84–3.00) in CLD versus non CLD patients; The odds of developing severe disease among COVID-19 patients with CLD were 2.44 times higher than among patients without CLD{Nagarajan 2022}. These findings are in line with the results of a meta-analysis of nine studies with a total of 2115 patients, showing that patients with COVID-19 have a high prevalence of liver injury and that liver injury is associated with an increased risk of severity and mortality of COVID-19 {Yadav 2021}.

SI.1.4.1. Specific complications among hospitalized patients with COVID-19

One study in the UK found renal (24.3%), gastrointestinal (including liver) (10.8%), cardiovascular (12.3%), neurological (4.3%) and respiratory (18.4%) as well as systemic (16.3%) in-hospital complications among patients {Drake 2021}.

Cardiac issues, such as myocardial injury, viral myocarditis, cardiac injury, heart failure arrhythmias, and other issues related to coronary artery disease, are common complications among hospitalized patients with COVID-19{Tersalvi 2020, Lalani 2022, Zhao 2021}. The frequency of acute cardiac injury ranges from 15% to 33% {Peiris 2022}. Among hospitalized patients, myocardial injury (ie, electrocardiographic abnormalities or elevated cardiac troponin levels) has been observed in 7.2% to 27.8% and was independently associated with an increased rate of in-hospital mortality {Guo 2020, Shi 2020, Wang 2020a}. Cardiomyopathy (33% among critically ill patients), arrhythmias (7.4% to 18% among hospitalized patients and 44% among ICU patients), shock (7% to 9% among hospitalized patients and 31% among ICU patients), and cardiac arrest (14% among critically ill hospitalized patients) have also been reported {Arentz 2020, Goyal 2020, Huang 2020a, Shi 2020, Wang 2020a}. Cardiac arrest has been attributed not only to the virus but also inflammation and systemic illness among ICU patients and is associated with in-hospital mortality {Bhatla 2020}. For patients with existing heart disease,

in-hospital mortality was strongly associated with heart failure {CAPACITY-COVID Collaborative Consortium and LEOSS Study Group 2022}. SARS-CoV2 down-regulates ACE-2 expression, which may create a pro-inflammatory environment that can lead to arrhythmias {Ni 2020}. Myocarditis and pericarditis, which are potential manifestations of the infection, can precipitate arrythmias {Varney 2022}.

The onset of acute kidney injury is a common complication among patients with severe SARS-CoV-2 infection and has been associated with increased risk of in-hospital mortality compared to those who do not experience AKI during hospitalization {Ng 2020, Robbins-Juarez 2020}. It has been observed among patients requiring hospitalization (5% to 37%), ICU care (23% to 78%) and among fatalities (25% to 50%){Chen 2020b, Cheng 2020, Hirsch 2020, Huang 2020a, Pei 2020, Richardson 2020, Wang 2020a, Zhou 2020}. In a meta-analysis, the incidence of AKI was estimated to be 17% among cohorts across geographies consisting mostly of hospitalized COVID-19 patients, which ranged widely from 0.5 to 80%, likely due to the varying proportions of critically ill patients included in each study {Robbins-Juarez 2020}. For example, in one study based in New York City, USA, AKI was more frequent among patients who experienced respiratory failure, in which 89.7% of patients who required mechanical ventilation developed AKI, compared to 21.7% of those who were non-ventilated {Hirsch 2020}. Further, proteinuria and hematuria have been reported among COVID-19 patients at the time of hospital admission (43.9% to 65.8% and 26.7% to 41.7%, respectively), in addition to elevated creatinine and blood urea nitrogen (14.4% and 13.1%, respectively) {Cheng 2020, Pei 2020}. Acute kidney injury has a pooled incidence of 12.3% in hospitalized COVID-19 patients {Yang 2021}. COVID-19-related acute kidney injury is associated with poor disease outcomes and higher mortality {Xu 2021}. The cause of renal injury may be glomerulonephritis, thrombotic microangiopathy, tubular injury or interstitial nephritis {Farouk 2020}.

Liver injury, characterized broadly by abnormal alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels and slightly elevated bilirubin levels, has also been reported among 14% to 58% of hospitalized COVID-19 cases {Chen 2020a, Fan 2020, Huang 2020a, Huang 2020b, Ponziani 2020, Shi 2020, Wu 2020a, Yang 2020}. Severe acute liver injury (>20 times upper limit of normal transaminase levels) are uncommon, occurring in <0.1% of infected patients {Sobotka 2022}. In a meta-analysis including over 12,000 COVID-19 patients, the overall prevalence of acute kidney injury, elevated AST levels, and elevated ALT levels was 26.5%, 41.1%, and 29.1%, respectively; and the presence of acute liver injury or elevated AST/ALT levels was independently associated with greater odds of negative outcomes, including ICU admission, mechanical ventilation, and in-hospital mortality {Sharma 2020}. A large, multicenter retrospective study of hospitalized COVID-19 patients in China found the median day of acute liver injury occurrence to be day 17 (interquartile range, 13 to 23) among the total patient population {Lei 2020}. The study also found that patients with severe COVID-19 experienced elevated levels of AST more frequently and to a greater severity compared to ALT. The wide ranges of reported liver injury prevalence may also be due to the use of different clinical treatments across the various studies, such as steroids and antivirals, which may also impact the liver to varying degrees and has not been fully assessed {Xu 2020, Yang 2020}. SARS-CoV-2 infection has been associated with an inflammatory cytokine storm, which may contribute to hepatologic abnormalities. However, liver injury is most likely multifactorial, including immune response, vascular damage and coagulopathy {Dufour 2022}.

Respiratory complications found in hospitalized patients include suspected bacterial pneumonia and likely acute respiratory distress syndrome (ARDS) {Drake 2021}. The average incidence of stroke in one meta-analysis of COVID-19 patients was 1.74% {Siow 2021}. Case reports and case series of cerebral venous thrombosis have also been described {Ghosh 2021}. Delirium is found in as many as 55% of hospitalized patients {Pun 2021}. Psychiatric complications are also common in hospitalized patients {Steardo 2020}.

Hospitalized patients have developed thrombotic and hemorrhagic complications {Gomez-Mesa 2021}. Increased inflammatory response, hypoxia, immobilization and disseminated intravascular coagulation (DIC) can lead to both venous and arterial thromboembolism {John 2021}.

COVID-19 infection can precipitate diabetic ketoacidosis, hyperosmolar hyperglycemic state and severe insulin resistance {Kim 2020}.

Changes in hematological indices can be seen in 20-50% of hospitalized COVID-19 patients, who may develop thrombotic and hemorrhagic complications {Gomez-Mesa 2021}. An Italian study found venous and arterial thromboembolism in 27.6% of patients in the ICU and 6.6% of patients in the general wards {Lodigiani 2020}.

SI.1.4.2. Specific complications among paediatric patients with COVID-19

Paediatric patients experience similar clinical manifestations of SARS-CoV-2 infection compared to adult patients, and cases in children are usually mild and many asymptomatic {Dong 2020}. In rare cases, however, children may experience severe disease, particularly among those with underlying conditions {Wanga 2021}. Symptoms of SARS-CoV-2 infection among children range from mild to moderate, and although the majority of laboratory confirmed cases among children are not severe, cases requiring hospitalization have occurred {Cai 2020, Qiu 2020, U. S. Department of Health & Human Services (DHHS) 2020}. Among a sample of hospitalized paediatric patients (<18 years) in the US during a period of increased paediatric cases due to the Delta variant, approximately 68% had one or more underlying conditions, and 16% had a viral coinfection, the majority having respiratory syncytial virus {Wanga 2021}. Half of these hospitalized paediatric patients received oxygen support, 30% were admitted to the ICU, 1.1% required extracorporeal membrane oxygenation, and 1.5% died.

Clinical manifestations unique to paediatric cases exist, such as multisystem inflammatory syndrome in children (MIS-C), a condition with features like Kawasaki disease and toxic shock syndrome that occurs two to six weeks after SARS-CoV-2 infection {Belay 2021, Feldstein 2020}. The case definition of MIS-C varies by geography, but clinical presentation generally includes persistent fever with abdominal pain, vomiting, diarrhea, skin rash, and/or mucocutaneous lesions, evidence of inflammation, multisystem involvement, and no other apparent cause of systemic inflammation among paediatric patients with SARS-CoV-2 infection {Centers for Disease Control and Prevention (CDC) 2022b, Jiang 2020, World Health Organization (WHO) 2020b}. Initial reports of MIS-C emerged in April 2020 from the UK, with other global regions, including the Europe, North America, Asia, and Latin America, also reporting similar cases since then {Jiang 2020, World Health Organization (WHO) 2020b}. The incidence of MIS-C is rare, and estimates range from approximately 5.1 to 20 per 1,000,000

persons younger than 21 years {Dufort 2020, Payne 2021}. Studies in the UK and US have found 60-79% of MIS-C patients are admitted to the ICU, and 1-3.5% die {Bowen 2021, Davies 2020, Feldstein 2020, Jiang 2020, Radia 2021, Swann 2020}.

SI.1.4.3. Mortality

As of 09 October 2022, there have been over 6.5 million cumulative deaths reported globally, with the highest percentage being reported from the WHO region of the Americas (43%), followed by Europe (32%), South-east Asia (12%), Eastern Mediterranean (5%), Western Pacific (4%), and Africa (3%) {World Health Organization (WHO) 2022b}. In the EU/EEA, the 14-day death rate due to COVID-19 (based on official reporting from 30 countries) as of 09 October 2022 was 7.3 deaths per million population, ranging from 0 (Iceland and Liechtenstein) to 35.9 (Latvia) per million across all reporting countries {European Centre for Disease Prevention and Control (ECDC) 2022b}.

Reported measures of mortality due to COVID-19 vary geographically due to differing population demographics and early mitigation response. Case fatality ratios, defined as the percentage of individuals with symptomatic or confirmed COVID-19 who die from the disease, have been estimated using various statistical modeling methods among different patient cohorts.

There is also strong evidence for increased mortality among older age groups. In an analysis adjusting for demographic characteristics and under-ascertainment of cases, the age-specific case fatality ratios in China were estimated to be 0.32%, 6.4%, and 13.4% among those 60 years and younger, greater than 60 years old, and 80 years and older, respectively {Verity 2020}. Estimates from the same study for cases occurring outside of China also showed the same trend. In EU/EEA countries, higher crude case-fatality rates are observed with increasing age among cases reported, where 1% of diagnosed cases aged 59 and younger are fatal, 2% of those aged 60 to 69 years, 7.4% of those aged 70 to 79 years, and 19% of those 80 years and older{European Centre for Disease Prevention and Control (ECDC) 2021c}.

There is no evidence of increased in-hospital mortality due to SARS-CoV-2 infection among pregnant women {Hsu 2022, Leung 2022}. However, higher rates of maternal mortality among pregnant people with SARS-CoV-2 infection who were admitted to or received care at a hospital for any reason have been observed in upper-middle-income countries and the Latin America and Caribbean region {Sheikh 2022}.

SI.1.5. Important Co-morbidities

Although severe illness due to COVID-19 can occur in individuals of any age without preexisting health conditions, increased risk of hospitalization, severe disease and/or death due to COVID-19 has been identified among patients with the following co-morbidities.

- Cancer {Venkatesulu 2021}
- Cardiovascular disease {Luo 2021, Liu 2021}
- Chronic kidney disease {Jdiaa 2022, Singh 2021}

- Chronic obstructive pulmonary disease {Kumasaka 2021, Lippi 2020, Singh 2022}
- Chronic respiratory disease {Centers for Disease Control and Prevention (CDC) 2019}
- Diabetes mellitus {Wei 2021}
- Hypertension {Wassef 2021}
- Immunocompromised state {Morford 2021, Jakharia 2022}
- Obesity (body-mass index ≥30) {Morais 2021}
- Sickle cell disease {Centers for Disease Control and Prevention (CDC) 2019}

Other co-morbidities related to high-risk populations include:

- Chronic liver disease {Hofmeister 2021}
- Disabilities {So 2021}
- Mental health conditions {Ceban 2021}
- Neurological conditions {Herman 2020, Zuin 2020, Liu 2020}
- Physical inactivity {Hill 2021}
- Pregnancy and recent pregnancy {Yang 2022}
- Smoking, current and former {Lippi 2020}
- Tuberculosis {Kumasaka 2021}
- Use of corticosteroids or other immunosuppressive medications {Yekeduz 2020}

PART II: MODULE SII- NONCLINICAL PART OF THE SAFETY SPECIFICATION

Table SII.1. Table of Key Safety Findings from Nonclinical Studies

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Use
Renal findings	
Following repeated dosing in rats and monkeys, the kidney was identified as the only target organ of toxicity. In the repeat dose studies with remdesivir (RDV), toxicity findings were consistent with dose-dependent and reversible kidney injury and dysfunction at doses greater than 3 mg/kg/day in rats and 5 mg/kg/day in rhesus monkeys. There were no observable kidney changes in cynomolgus monkeys administered intravenous (IV) RDV at 10 mg/kg/day. In rats, clinical chemistry and urinalysis findings, including increases in blood urea nitrogen and serum creatinine, and increases in urinary biomarkers of kidney injury, eg, total protein, n-acetyl-glucosaminidase, cystatin C, beta-2-microglobulin, and kidney injury molecule-1, were predictive of the microscopic changes observed in the kidney. Microscopic findings included a spectrum of degenerative, necrotic and regenerative changes to the renal tubular epithelium in the cortex. In the 2-week study (TX-399-2003), the changes in the kidney were reversible after a 4-week recovery period and correlated with the reversibility of the clinical chemistry, urinalysis and urinary biomarker findings. In the 4-week toxicity study (TX-399-2016), the no observed adverse effect level (NOAEL) was 3 mg/kg/day, based on the nature and severity of the kidney changes at the 10 mg/kg/day dose level. The sensitivity of rats to renal effects of RDV may be related to the active tubular transport of RDV metabolites by rat renal organic anion transporter-3 (OAT3); this interaction has not been detected with human renal OAT3 (PC-399-2020). In cynomolgus monkeys administered RDV via daily IV (slow bolus) injection for up to 4 weeks, there were no changes indicative of an effect in the kidney, and the NOAEL was the high dose of 10 mg/kg/day (TX-399-2017). After daily intramuscular (IM) injections of 15 mg/kg/day GS-466547 (diastereomeric mixture) to cynomolgus monkeys, similar microscopic changes were observed in the proximal tubules of the kidney to those noted in rats; clinical pathology changes correlated with the renal changes at the 15 mg/kg/day IM dose (TX-399-2001). Exposures at the NOAEL in the 7-day IM-study were slightly higher than at the NOAEL in the 4-week IV study. In a 7-day IV study in (Indian-origin) rhesus monkeys, adverse kidney changes were observed at $\geq$ 5 mg/kg/day, with mortality noted in 1 animal administered 20 mg/kg/day (TX-399-2021). The reason for the possible increased sensitivity of rhesus monkeys compared to cynomolgus monkeys is unknown.	Although the kidney was identified as the only target organ of toxicity in nonclinical studies, the available clinical data do not suggest a confirmed renal safety signal.

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Use
Hepatic findings	
In the nonclinical program, there were no changes in the liver in rats or monkeys based on clinical chemistry parameters, liver weight, or microscopic observations. Data from in vitro studies with liver cell culture systems (m2.6.6, Section 9.3.1) demonstrated that human hepatocytes are more susceptible to toxicity from RDV than from its metabolites GS-704277 and GS-441524, likely due to high cellular permeability and effective intracellular metabolism of the drug. While GS-704277 and GS-441524 are in vivo metabolites, and can be readily detected in plasma, these metabolites are unlikely to contribute significantly to changes in liver enzymes observed in humans administered repeated doses of RDV due to their low toxicity on hepatocytes observed in vitro.	In clinical studies with RDV in healthy subjects, transient elevations in ALT and AST have been observed with single doses of RDV up to 225 mg and multiple once-daily doses of RDV 150 mg for up to 14 days, with mild, reversible prothrombin time (PT) prolongation in some subjects but without any clinically relevant change in international normalized ratio (INR) or other evidence of hepatic effects. In 2 placebo-controlled clinical studies in patients with COVID-19, liver-related AEs were reported at a lower or similar incidence for RDV versus placebo {Beigel 2020a, Beigel 2020b, Wang 2020b}.
Genotoxicity	
Remdesivir and the nucleoside metabolite, GS-441524, were non-mutagenic in the in vitro Ames mutagenicity assay (TX-399-2005 and TX-195-2006, respectively), and RDV was negative in the rat micronucleus assay (TX-399-2003). In the in vitro chromosome aberrations assay with human lymphocytes, RDV was negative without metabolic activation, and equivocal in the 3-hour treatment with metabolic activation (TX-399-2006).	Remdesivir is nongenotoxic.
Carcinogenicity	
Carcinogenicity studies have not been conducted.	Current regulatory guidance does not require carcinogenicity studies with RDV for the COVID-19 indication with a dosing duration of less than 3 months.
Effects on respiratory, Central Nervous System (CNS), and cardiovascular systems	
Safety pharmacology studies were conducted to examine the potential effects of RDV on the respiratory, CNS, and cardiovascular systems after IV administration (PC-399-2004, PC-399-2003, and PC-399-2005, respectively). In a respiratory safety study in rats, RDV had no effect on tidal volume or minute volume; however, respiration rates were transiently increased in animals administered ≥ 20 mg/kg and returned to control levels by 24 hours postdose, resulting in a NOEL for respiratory function in male rats of 5 mg/kg, at exposures approximately 2.2-fold above the GS-441524 C_{max} at the 200 mg clinical dose. Remdesivir had no effect on the CNS of rats and no effect on cardiovascular parameters in monkeys. At the CNS NOEL of 50 mg/kg, exposures in rats were approximately 19-fold above the GS-441524 C_{max} at the 200-mg clinical dose. At the cardiovascular NOEL of 10 mg/kg, exposures in monkeys were approximately 0.3-fold and 2.7-fold for RDV and GS-441524, respectively, compared to the respective C_{max} values at the 200-mg clinical dose. The lack of in vivo cardiovascular effect is consistent with the weak in vitro inhibition of the hERG channel by RDV (IC_{50} 28.9 µM) and GS-441524 and GS-704277 (IC_{50}'s > 30 µM).	The potential for CNS, respiratory, or cardiovascular effects is considered low.

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Use
Local Tolerance	
Remdesivir is intended for IV administration. In the repeat-dose studies, injection site reactions, such as red discoloration, were observed in rats. There were no similar reactions in monkeys. Remdesivir is not an irritant to skin, was classified as non-irritant to eyes, and is unlikely to be phototoxic based on the absence of binding to melanin-containing tissues (AD-399-2017), and its photochemical properties.	Infusion site reactions are not considered a safety concern for RDV due to the low frequency (<1%) and low grade of the events (mostly grade 1/2) reported in Studies GS-US-540-5773 and GS-US-540-5774. Hypersensitivity including infusion-related reactions are noted in the SmPC.
Reproductive & Developmental Effects	
A complete reproductive and development toxicity program has been completed with RDV. There were no effects on embryofetal development in rats and rabbits, and the NOAELs were 20 mg/kg/day in both species. There were no adverse effects in the pre- and postnatal toxicity study in rats, and the NOAEL was 10 mg/kg/day. There were no effects on male reproductive performance and spermatogenesis, and the NOAEL for male reproductive toxicity was 10 mg/kg/day. For females the NOAEL for reproductive toxicity and embryonic toxicity was 3 mg/kg/day, based on decreases in corpora lutea, numbers of implantation sites and viable embryos at the 10 mg/kg/day dose associated with systemic maternal toxicity. Remdesivir and/or its metabolites were detected in the plasma of nursing pups likely due to the presence of RDV and/or its metabolites in milk.	No reproductive or developmental effects are anticipated. It is unknown if RDV or its metabolites are excreted in human milk. The decreases in corpora lutea, and consequent decreases in implantation sites and viable embryos, are considered a consequence of stress/maternal toxicity at this dose level in rats. The female rodent is fairly sensitive to agents that cause decreased body weight gain and reduced food intake (negative energy balance) and respond with decreased weights of ovary, uterus, and cervix and reduced ovarian follicles and corpora lutea {Everds 2012, Rudmann 2013}. These findings can be expected to be fully reversible in animals. In the absence of significant toxicity to the patient (eg, severe weight loss), these changes in the fertility study in female rats are not considered clinically relevant at the doses to be administered to humans, and by inference, the potential effects on patients are not considered clinically relevant.
Drug-drug interaction liability assessment	
The liability for RDV to cause pharmacokinetic (PK) drug interactions was assessed using current Food and Drug Administration (FDA) Guidelines (AD-540-2006) and representative clinical PK data. In vitro, remdesivir is a weak inhibitor of cytochrome 3A4 (CYP3A4), organic anion transporting polypeptide 1B1 (OATP1B1), OATP1B3, bile salt export pump (BSEP), multidrug resistance-associated protein 4 (MRP4), and sodium-taurocholate cotransporting polypeptide (NTCP). The clinical relevance of these in vitro drug assessments has not been established. Remdesivir may transiently increase plasma concentrations of medicinal products that are substrates of CYP3A or OATP 1B1/1B3. The inhibitory effects are weak and, due to the short half-life of RDV, the effects would only be manifest briefly. Further evaluation of GS-704277 and GS-441524 for possible interactions with drug metabolizing enzymes and transporters is ongoing. In vitro, remdesivir is a substrate for drug metabolizing enzymes CYP2C8, CYP2D6, and CYP3A4, and is a substrate for OATP1B1 and P-glycoprotein (P-gp) transporters. The use of strong inducers of P-gp (eg, rifampicin) that may decrease plasma concentrations of remdesivir is not recommended.	The overall potential for interactions is currently unknown; patients should remain under close observation during the days of remdesivir administration.

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Use
Antagonism with chloroquine phosphate	
The antiviral activity of remdesivir was antagonized by chloroquine phosphate in a dose-dependent manner when the two drugs were co-incubated at clinically relevant concentrations in HEp-2 cells infected with respiratory syncytial virus (RSV). Higher remdesivir EC_{50} values were observed with increasing concentrations of chloroquine phosphate. Increasing concentrations of chloroquine phosphate or hydroxychloroquine sulphate reduced formation of remdesivir triphosphate in A549-hACE2, HEp-2, and normal human bronchial epithelial cells.	Due to potential antagonism based on in vitro observations, concomitant use of remdesivir with chloroquine phosphate or hydroxychloroquine sulphate is not recommended.

PART II: MODULE SIII - CLINICAL STUDY AND COMPASSIONATE USE EXPOSURE

SIII.1. Gilead-Sponsored Clinical Study and Compassionate Use Exposure

The tables in this section present exposure data to remdesivir in healthy volunteer participants and other volunteer participants without COVID-19 infection from Phase 1 studies, the compassionate use program in patients with COVID-19, and Gilead-sponsored clinical studies in patients with COVID-19:

Healthy Volunteer Participants:

- GS-US-399-1812
- GS-US-399-1954
- GS-US-399-4231
- GS-US-399-5505

Hospitalized COVID-19 Participants:

- IN-US-540-5755
- GS-US-540-5773
- GS-US-540-5774
- GS-US-540-5823
- GS-US-540-5912

COVID-19 Participants not requiring Supplemental Oxygen:

- GS-US-540-9012

Other Volunteer Participants without COVID-19 infection:

- GS-US-540-9014
- GS-US-540-9015

Table SIII.1. Number of Participants in Gilead-Sponsored Clinical Studies and Compassionate Use Exposure

Duration of Exposure (Days)	Persons (n)	Person Days
Healthy Volunteer Participants		
GS-US-399-1812	78	78
GS-US-399-1954	16	165
GS-US-399-4231	8	8
GS-US-399-5505	29	237
Total	**131**	**488**
Hospitalized COVID-19 Participants		
IN-US-540-5755	240	2080
GS-US-540-5773	4838	35406
GS-US-540-5574	887	5261
GS-US-540-5823	53	306
GS-US-540-5912	163	744
Total	**6181**	**43,797**
COVID-19 Participants not requiring Supplemental Oxygen		
GS-US-540-9012	279	829
Total	**279**	**829**
Other Volunteer Participants without COVID-19 infection		
GS-US-540-9014	32	32
GS-US-540-9015	75	81
Total	**107**	**113**
Grand Total	**6698**	**45,227**

Table SIII.2. Duration of Exposure

Duration of Exposure (Days)	Persons (n)	Person Days
Healthy Volunteer Participants		
≥1-3	87	87
4-5	9	43
≥6-10	27	246
>10	8	112
Total	**131**	**488**
Hospitalized COVID-19 Participants		
≥1-3	883	2062
4-5	1496	7007
≥6-10	3723	33,781
>10	79	947
Total	**6181**	**43,797**
COVID-19 Participants not requiring Supplemental Oxygen		
≥1-3	278	824
4-5	1	5
≥6-10	0	0
>10	0	0
Total	**279**	**829**
Other Volunteer Participants without COVID-19 infection		
≥1-3	107	113
4-5	0	0
≥6-10	0	0
>10	0	0
Total	**107**	**113**
Grand Total	**6698**	**45,227**

Table SIII.3. Exposure by Age and Gender

Age Group (Years)	Persons (n)		Person Days	
	Male	**Female**	**Male**	**Female**
Healthy Volunteer Participants				
Birth – 27 Days (Neonate)	0	0	0	0
28 Days – 11 Months (Infant)	0	0	0	0
12 – 23 Months (Toddler)	0	0	0	0
2 – 11 Years (Children)	0	0	0	0
12 – 17 (Adolescent)	0	0	0	0
18 – 64 Years	88	43	352	136
65 – 74 Years	0	0	0	0
75 – 84 Years	0	0	0	0
≥ 85 Years	0	0	0	0
Total	**88**	**43**	**352**	**136**
Hospitalized COVID-19 Participants				
Birth – 27 Days (Neonate)	0	0	0	0
28 Days – 11 Months (Infant)	13	11	90	73
12 – 23 Months (Toddler)	2	2	12	20
2 – 11 Years (Children)	23	18	162	128
12 – 17 (Adolescent)	43	39	296	290
18 – 64 Years[a]	2571	1456	17,991	10,016
65 – 74 Years	750	481	5735	3492
75 – 84 Years	353	261	2515	1922
≥ 85 Years	80	77	595	450
Total	**3835**	**2345**	**27,396**	**16,391**
COVID-19 Participants not requiring Supplemental Oxygen				
Birth – 27 Days (Neonate)	0	0	0	0
28 Days – 11 Months (Infant)	0	0	0	0
12 – 23 Months (Toddler)	0	0	0	0
2 – 11 Years (Children)	0	0	0	0
12 – 17 (Adolescent)	2	1	6	3
18 – 64 Years	122	114	363	339
65 – 74 Years	21	10	61	30
75 – 84 Years	3	4	9	12
≥ 85 Years	0	2	0	6
Total	**148**	**131**	**439**	**390**

Age Group (Years)	Persons (n)		Person Days	
	Male	Female	Male	Female
Other Volunteer Participants without COVID-19 infection				
Birth – 27 Days (Neonate)	0	0	0	0
28 Days – 11 Months (Infant)	0	0	0	0
12 – 23 Months (Toddler)	0	0	0	0
2 – 11 Years (Children)	0	0	0	0
12 – 17 (Adolescent)	0	0	0	0
18 – 64 Years	45	37	48	40
65 – 74 Years	16	6	16	6
75 – 84 Years	1	2	1	2
≥ 85 Years	0	0	0	0
Total	**62**	**45**	**65**	**48**
Grand Total	**4,133**	**2564**	**28,252**	**16,965**

a Missing gender for 1 patient (10 person days)

Table SIII.4. Exposure by Dose

Dose	Persons (n)	Person Days
Healthy Volunteer Participants[a]		
200/100 mg[b]	29	237
Hospitalized COVID-19 Participants		
200/100 mg[c]	6115	43,344
5/2.5 mg/kg[d]	66	453
COVID-19 Participants not requiring Supplemental Oxygen		
200/100 mg[e]	279	829
Other Volunteer Participants without COVID-19 infection		
20 mg	4	4
40 mg	24	24
40/20 mg	6	12
100 mg	73	73
Grand Total	**6596**	**44,976**

a 102 participants (251 person days) received between 3 – 225 mg
b Participants received 200 mg loading dose on Day 1, followed by 100 mg daily for either 4 days or 9 days. Includes 1 participant from GS-US-399-5505 randomized to be administered RDV, but only received 200 mg of RDV on Day 1
c Participants received 200 mg loading dose on Day 1, followed by 100 mg daily for up to 9 days
d Participants ≤ 40 kg received a weight-based dosing regimen of 5 mg/kg on Day 1, followed by 2.5 mg/kg daily for 9 days
e Participants received 200 mg loading dose on Day 1, followed by 100 mg daily for 2 days

Table SIII.5. Exposure by Ethnic Origin

Ethnic origin	*Healthy Volunteer Participants*		*Hospitalized COVID-19 Participants*[a]		*COVID-19 Participants not requiring Supplemental Oxygen*		*Other Volunteer Participants without COVID-19 infection*	
	Persons (n)	**Person Days**	**Persons (n)**	**Person Days**	**Persons (n)**	**Person Days**	**Persons (n)**	**Person Days**
White	105	374	3180	22,506	228	681	86	90
Black or African American	25	109	1040	6778	20	57	16	16
Asian	1	5	576	4326	6	18	0	0
American Indian or Alaska Native	0	0	53	367	15	43	0	0
Native Hawaiian or Other Pacific Islander	0	0	45	319	1	3	3	4
Other	0	0	774	5523	3	9	2	3
Not permitted	0	0	273	1898	6	18	0	0
Missing	0	0	240	2080	0	0	0	0
Grand Total	**131**	**488**	**6181**	**43,797**	**279**	**829**	**107**	**113**

a Ethnic origin not reported for 240 participants (2080 person days) from the Compassionate use program

SIII.2. Non-Gilead Sponsored Clinical Study Exposure

Exposure data from one non-Gilead sponsored study is presented below:

- CO-US-540-5776: A Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy Study of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Adults (ACTT-1) {Beigel 2020a, Beigel 2020b}

- CO-US-540-5961: Pharmacokinetics and Safety of Remdesivir for Treatment of COVID-19 in Pregnant and Non-Pregnant Women in the United States (IMPAACT 2032)

Table SIII.6. Duration of Exposure

Duration of Exposure	Persons (n)	Person Days
CO-US-540-5776[a]		
≥1-3 Days	98	231
4-5 Days	92	415
6-10 Days	342	3074
>10 Days	0	0
Total	**532**	**3720**
CO-US-540-5961		
≥1-3 Days	5	13
4-5 Days	43	205
≥6-10 Days	5	34
Total	**53**	**252**
Grand Total	**585**	**3972**

a As treated population

Table SIII.7. Exposure by Age and Gender

	Persons (n)		Person Days	
Age Group	**Male**	**Female**	**Male**	**Female**
CO-US-540-5776[a]				
Birth – 27 Days (Neonate)	0	0	0	0
28 Days – 11 Months (Infant)	0	0	0	0
12 – 23 Months (Toddler)	0	0	0	0
2 – 11 Years (Children)	0	0	0	0
12 – 17 (Adolescent)	0	0	0	0
18 – 64 Years	238	111	1559	777
65 – 74 Years	67	40	518	299
75 – 84 Years	30	26	216	196
> 85 Years	12	8	89	66
Total	**347**	**185**	**2382**	**1338**
CO-US-540-5961				
Birth – 27 Days (Neonate)	0	0	0	0
28 Days – 11 Months (Infant)	0	0	0	0
12 – 23 Months (Toddler)	0	0	0	0
2 – 11 Years (Children)	0	0	0	0
12 – 17 (Adolescent)	0	0	0	0
18 – 64 Years	0	53	0	252
65 – 74 Years	0	0	0	0
75 – 84 Years	0	0	0	0
> 85 Years	0	0	0	0
Total	**0**	**53**	**0**	**252**
Grand Total	**347**	**238**	**2382**	**1590**

a As treated population

Table SIII.8. Exposure by Dose

Dose	Persons (n)	Person Days
CO-US-540-5776[a]		
200/100 mg	532	3720
CO-US-540-5961		
200/100 mg	53	252
Grand Total	**585**	**3972**

a As treated population

Table SIII.9. Exposure by Ethnic Origin/Race

Ethnicity/Race	Persons (n)	Person Days
CO-US-540-5776[a]		
White	273	1912
Black or African American	105	648
Asian	79	615
American Indian or Alaska Native	4	24
Native Hawaiian or Other Pacific Islander	2	13
Other	0	0
Not Permitted	0	0
Multiple	2	11
Unknown	67	497
Total	**532**	**3720**
CO-US-540-5961		
White	16	72
Black or African American	22	106
Asian	1	5
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Other	0	0
Not permitted	0	0
Multiple	1	5
Missing	0	0
Unknown	13	64
Total	**53**	**252**
Grand Total	**585**	**3972**

a As treated population

Table SIII.10. Exposure by Baseline Ordinal Score

Baseline Ordinal Score[a]	Persons (n)	Person Days
CO-US-540-5776[b]		
4. Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care	75	459
5. Hospitalized, requiring supplemental oxygen	231	1497
6. Hospitalized, on noninvasive ventilation or high-flow oxygen devices	94	663
7. Hospitalized, on invasive mechanical ventilation or ECMO	132	1101
Grand Total	**532**	**3720**

a Baseline Ordinal Score information was not provided for Study CO-US-540-5961
b As treated population

PART II: MODULE SIV- POPULATIONS NOT STUDIED IN CLINICAL STUDIES AND COMPASSIONATE USE PROGRAM

SIV.1. Exclusion Criteria in Clinical Studies within the Development Program and Compassionate Use Program

Table SIV.1. Important Exclusion Criteria in Pivotal Studies in the Development Program and Compassionate Use Program

Criterion	Reason for Exclusion	Considered to be Missing Information
Patients with alanine aminotransferase (ALT) ≥ 5 times the upper limit of normal (ULN)	RDV has been associated with transaminase elevations in healthy volunteers.	No Rationale: Completion of study GS-US-540-9014 in patients with hepatic impairment.
Patients with severe renal impairment	Impact of severe renal impairment on RDV pharmacokinetics (PK) is not known.	No Rationale: Completion of GS-US-540-5912 and GS-US-540-9015 in patients with severe renal impairment.
Pregnant females and females who are breastfeeding*	Limited patient exposure to RDV. It is not known if RDV is excreted in human milk.	Pregnant females: Yes Breastfeeding females: No Rationale: Breastfeeding women are no longer considered a missing information population based on the data presented in literature {Bertrand 2022, Wada 2022}.

* Pregnant and lactating women are excluded from Gilead-sponsored clinical trials and were excluded from the original protocol for the compassionate use program. Amendments to the compassionate use program allow pregnant women to receive remdesivir.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Study Development Programs and Compassionate Use Program

Table SIV.2. Ability of the Clinical Development Program and Compassionate Use Program to Detect Adverse Drug Reactions

Ability to Detect Adverse Reactions	Limitation of Program	Discussion of Implications for Target Population
Which are rare	7283 COVID-19 patients have been exposed to RDV in clinical studies and the CU dataset.	The ability to detect rare reactions in the datasets available to date is limited.
Due to prolonged exposure	RDV has a maximum 10-day dosing regimen.	Prolonged exposure to the drug is not expected.
Due to cumulative effects	RDV and its metabolites are rapidly metabolized.	Cumulative effects are not expected.
Which have a long latency	RDV and its metabolites are rapidly metabolized.	Adverse drug reactions (ADRs) with a long latency are not expected.

SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Study Development Programs and Compassionate Use Program

Table SIV.3. Exposure of Special Populations Included or not in Clinical Development Programs and Compassionate Use Program

Type of special population	Exposure	Considered to be Missing Information
Pregnant women	Not included in the clinical development program[a]	Yes
Breastfeeding women	Not included in the clinical development program	No Rationale: Breastfeeding women are no longer considered a missing information population based on the data presented in literature {Bertrand 2022, Wada 2022}.
Patients with hepatic impairment	As of 04 January 2023, 32 patients with hepatic impairment were included in Study GS-US-540-9014	No Rationale: Completion of study GS-US-540-9014 in patients with hepatic impairment.

Type of special population	Exposure	Considered to be Missing Information
Patients with severe renal impairment	As of 01 November 2022, 163 patients with severe renal impairment were included in Study GS-US-540-5912 and 20 were included in Study GS-US-540-9015	No Rationale: Removal of the missing information Safety in patients with severe renal impairment as there are no outstanding additional pharmacovigilance activities following the completion of Studies GS-US-540-5912 and GS-US-540-9015. The safety profile of RDV, metabolites and excipients in patients with severe renal impairment is generally safe and well tolerated.
Paediatric patients	As of 29 October 2021, 77 paediatric patients were included in the compassionate use program, 21 were included in Study GS-US-540-5773 and GS-US-540-5774, 3 were included in Study GS-US-540-9012, 53 were included in GS-US-540-5823	No Rationale: The safety profile in adolescents aged 12 to < 18 years is not anticipated to differ from that in adults. Paediatric patients of at least 4 weeks of age and >3 kg are included in the indication.

a Subsequent amendments to the compassionate use program allow pregnant women to receive remdesivir.

PART II: MODULE SV - POSTAUTHORIZATION EXPERIENCE

SV.1. Postauthorization Exposure

SV.1.1. Method Used to Calculate Exposure

Patient exposure to marketed Veklury for the treatment of COVID-19 is estimated from sales data and is reported in PSURs.

SV.1.2. Exposure

Cumulative global patient exposure to Veklury since first marketing approval in Japan on 07 May 2020 to 31 October 2022 is estimated to be 4,392,082 patients, including 912,960 patients in the EU, based on a 5-day regimen.

PART II: MODULE SVI- ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1. Potential for Misuse for Illegal Purposes

There are no data to suggest that there is potential for remdesivir to be misused for illegal purposes.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1. Identification of Safety Concerns in the Initial RMP submission

SVII.1.1. Risk(s) not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Based on the current data for COVID-19 population, no risks not considered important have been identified for RDV.

SVII.1.2. Risk(s) Considered Important for Inclusion in the List of Safety Concerns in the RMP

SVII.1.2.1. Important Identified Risks

Table SVII.1. Important Identified Risks

Important Identified Risks	Risk-Benefit Impact
Hypersensitivity including Infusion-Related Reaction	Cases of hypersensitivity including infusion-related reaction following administration of RDV have been reported. Signs and symptoms ranged from throat itching to significant hypotension. Where the final outcome was described, all cases described event resolution or improvement.

SVII.1.2.2. Important Potential Risks

Table SVII.2. Important Potential Risks

Important Potential Risks	Risk-Benefit Impact
Hepatotoxicity	In Phase 1 studies in healthy participants, low-grade and transient increases in transaminases were observed, which were not associated with hepatic AEs. In the context of COVID-19, hepatic safety appears comparable between RDV and placebo or standard of care (SOC) based on the safety data from controlled studies {Beigel 2020a, Beigel 2020b, Wang 2020b} (Study GS-US-540-5774). Evaluation of hepatic events from Study GS-US-540-5773 and the compassionate use cohort (IN-US-540-5755) consistently demonstrates that Grade 3 and above hepatic AEs occurred either in the context of clinical deterioration from COVID-19, involved concomitant use of medications associated with hepatic adverse reactions, or involved laboratory abnormalities that peaked and then decreased while RDV was continued. Limited patient-level data are currently available from the placebo-controlled studies to fully exclude this potential risk {Beigel 2020a, Beigel 2020b, Wang 2020b}.
Nephrotoxicity	The kidney was identified as the only target organ of toxicity in nonclinical studies. In the context of COVID-19, renal safety appears comparable between RDV and placebo or SOC based on the safety data from controlled studies {Beigel 2020a, Beigel 2020b, Wang 2020b} (Study GS-US-540-5774). Evaluation of renal-related AEs from Study GS-US-540-5773 and the compassionate use cohort (IN-US-540-5755) consistently demonstrated that renal AEs occurred in the context of clinical deterioration from COVID-19 or concomitant use of medications associated with renal adverse effects. Limited patient-level data are currently available from the placebo-controlled studies to fully exclude this potential risk {Beigel 2020a, Beigel 2020b, Wang 2020b}.

SVII.1.2.3. Missing Information

Table SVII.3. Missing Information

Missing Information	Risk-Benefit Impact
Safety in patients with hepatic impairment	It is not known if the PK of RDV and its metabolite(s) is affected by hepatic impairment as RDV has not been studied in patients with hepatic impairment. The relevance of the low-grade and transient increases in transaminases observed in healthy participants in Phase 1 studies is unknown in patients with hepatic impairment.
Safety in patients with severe renal impairment	It is not known if the PK of RDV and its metabolite(s) is affected by severe renal impairment as no studies have been conducted in patients with severe renal impairment. The safety of the excipient betadex sulfobutyl ether sodium is unknown in COVID-19 patients with severe renal impairment; betadex sulfobutyl ether sodium is renally cleared and accumulates in patients with decreased renal function.
Safety in pregnant and lactating women	The safety of RDV in pregnant women and lactating women is unknown as no studies have been conducted in pregnant women and it is not known whether RDV is excreted in human milk and effects the breast-fed infant.

SVII.2. New Safety Concerns and Reclassification with a Submission of an updated RMP

No new safety concerns have been identified or reclassified since the submission of the last RMP.

Safety in patients with hepatic impairment previously classified as missing information is removed from the list of safety concerns. The rationale for the removal is that there are no outstanding additional PV activities for this safety concern. The Category 3 additional PV activity Study GS-US-540-9014 has been completed.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

SVII.3.1.1. Important Identified Risks

There are no important identified risks for Veklury.

SVII.3.1.2. Important Potential Risks

There are no important potential risks for Veklury.

SVII.3.2. Presentation of the Missing Information

Table SVII.4. Missing Information

Missing Information:	Evidence source
Safety in pregnant women	Population in need of further characterization: Limited amount of safety data of RDV in pregnant women is available.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1. Summary of Safety Concerns

Important Identified Risks	None
Important Potential Risks	None
Missing Information	Safety in pregnant women

PART III: PHARMACOVIGILANCE PLAN

III.1. Routine Pharmacovigilance Activities

Routine Pharmacovigilance Activities Beyond ADRs Reporting and Signal Detection:

Specific Adverse Reaction Follow-up Questionnaires

Table Part III.1. Specific Adverse Reaction Follow-up Questionnaires

Name of Questionnaire	Description
Postmarketing pregnancy report form	The questionnaire is designed to obtain information including maternal profile, maternal risk factors, contraception, previous pregnancies, medications used on current pregnancy, prenatal test, paternal details, male partner medical history, and medication used at time of conception.
Postmarketing pregnancy outcome report form	The questionnaire is designed to obtain information including maternal details, course and outcome of pregnancy, comedications, characteristics of baby (general appearance, clinical condition, follow-up examination, test/procedures for baby/fetus).

Monitoring of data on treatment failure due to emerging variants

As requested by Pharmacovigilance Risk Assessment Committee (PRAC), as part of the enhanced signal detection activities for the duration of the COVID-19 pandemic, data on treatment failure due to emerging variants will be monitored from all available data sources, including but not limited to:

- Nonclinical data (antiviral activity and viral resistance) on new emerging variant of concerns or variant of interest (as defined by the WHO or ECDC)
- Spontaneous reports (retrieved by using Standardized Medical Dictionary for Regulatory Activities Queries Lack of efficacy/effect)
- Literature reports
- Marketing authorisation holder´s and partners clinical trial data
- Studies conducted by public health authorities

Cumulative data from the review will be summarized in a dedicated section of the PSUR. A dedicated paragraph will be included to present data from immunocompromised patients with the treatment duration of three days as there is a concern of potential development of viral resistance. If the review of the data leads to an impact on the benefit risk profile of RDV, appropriate variation (including the data, a benefit-risk discussion and any warranted product information updates) will be submitted to the agency within one month.

Other Forms of Routine Pharmacovigilance Activities

Gilead has in place a general Business Continuity Plan (BCP) and annexed to this is a pandemic specific BCP setting forth the principles by which Gilead responds to increasing demand and/or decreasing capacity of its Pharmacovigilance (PV) system through active prioritization with a focus on critical products and key PV activities. At the same time and in order to manage through the pandemic and resource restraint situations without compromising compliance overall capacity enhancement and resource expansion is a key element of the preparedness and business continuity planning activity.

III.2. Additional Pharmacovigilance Activities

Table Part III.2. Ongoing and Planned Additional Pharmacovigilance Activities

Title	Rationale and Objectives	Design and Populations	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
CO-US-540-6127 COVID-19 International Drug Pregnancy Registry (COVID-PR)	Safety concern addressed: Safety in pregnancy (missing information) Objectives: To evaluate obstetric, neonatal, and infant outcomes among women treated with monoclonal antibodies or antiviral drugs indicated for mild, moderate, or severe COVID-19 from the first day of the last menstrual period to end of pregnancy	Post-marketing cohort study in pregnant women	Submission of study report	Interim results due at the time of the PSUR submissions, and final results due January 2027 (or within 6 months of the study completion in November 2026)

III.3. Summary Table of additional Pharmacovigilance Activities

Table Part III.3. Ongoing and Planned Additional Pharmacovigilance Activities

Activity (Status)	Summary of Objectives	Safety Concerns Addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
CO-US-540-6127 COVID-19 International Drug Pregnancy Registry (COVID-PR)	Safety concern addressed: Safety in pregnancy (missing information) Objectives: To evaluate obstetric, neonatal, and infant outcomes among women treated with monoclonal antibodies or antiviral drugs indicated for mild, moderate, or severe COVID-19 from the first day of the last menstrual period to end of pregnancy	Post-marketing cohort study in pregnant women	Submission of study report	Interim results due at the time of the PSUR submissions, and final results due January 2027 (or within 6 months of the study completion in November 2026)

PART IV:
PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

There are no planned postauthorization efficacy studies.

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

V.1. Routine Risk Minimization Measures

Table Part V.1. Description of Routine Risk Minimization Measures by Safety Concern

Safety concern	Routine risk minimization activities
Safety in pregnant women	Routine risk minimization measures: SmPC section 4.6 PL section 2

V.2. Additional Risk Minimization Measures

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

V.3. Summary Risk Minimization Measures

Table Part V.2. Summary Table of Pharmacovigilance and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important identified risk(s)		
None		
Important potential risk(s)		
None		
Missing information		
Safety in pregnant women	Routine risk minimization measures: SmPC section 4.6 PL section 2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Postmarketing pregnancy report form Postmarketing pregnancy outcome report form Additional pharmacovigilance activities: Study CO-US-540-6127 (COVID-19 International Drug Pregnancy Registry [COVID-PR]) Submission of study report: interim results due at the time of the PSURs submissions, and final results due January 2027 (or within 6 months of the study completion in November 2026)

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR VEKLURY (REMDESIVIR)

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

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

This summary of the RMP for Veklury 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 Veklury's RMP.

I. The Medicine and What is it Used for

Veklury is indicated for the treatment of coronavirus disease 2019 (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 (see SmPC for the full indication).

It contains remdesivir as the active substance and it is given by intravenous infusion.

Further information about the evaluation of Veklury's benefits can be found in Veklury'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/veklury.

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

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

Measures to minimize 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 authorized 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 public (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including periodic safety update report (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 Veklury is not yet available, it is listed under 'missing information' below.

II.A. List of important risks and missing information

Important risks 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 Veklury. 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 (eg, on the long-term use of the medicine).

Table Part VI.1. List of Important Risks and Missing Information

Important Identified Risks	None
Important Potential Risks	None
Missing Information	Safety in pregnant women

II.B. Summary of Important Risks and Missing Information

Table Part VI.2. Summary of Important Risk(s) and Missing Information

Missing information	Safety in pregnant women
Risk Minimization Measure(s)	Routine risk minimization measures: SmPC section 4.6 PL section 2
Additional Pharmacovigilance activities	Additional pharmacovigilance activities: Study CO-US-540-6127 (COVID-19 International Drug Pregnancy Registry [COVID-PR]) See Section II.C.2 of this summary for an overview of the postauthorization development plan.

II.C. Postauthorization Development Plan

II.C.1. Studies which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligations for Veklury.

II.C.2. Other Studies in Postauthorization Development Plan

Table Part VI.3. Other Studies in Postauthorization Development Plan

Program Name	Purpose of the Program
Study CO-US-540-6127 COVID-19 International Drug Pregnancy Registry (COVID-PR)	*Safety concern addressed:* Safety in pregnancy (missing information) *Objectives:* To evaluate obstetric, neonatal, and infant outcomes among women treated with monoclonal antibodies or antiviral drugs indicated for mild, moderate, or severe COVID-19 from the first day of the last menstrual period to end of pregnancy.

PART VII: ANNEXES

Table of Contents

Annex 1. EudraVigilance Interface

This XML file is submitted electronically and can be provided on request.

Annex 2. Tabulation Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program

Annex 3. Protocols for Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan

Annex 4. Specific Adverse Drug Reaction Follow-up Forms

Postmarketing pregnancy report form

Postmarketing pregnancy outcome report form

Annex 5. Protocols for Proposed and Ongoing Studies in RMP Part IV

None.

Annex 6. Details of Proposed Additional Risk Minimization Measures (if applicable)

None.

Annex 7. Other Supporting Data (Including Referenced Material)

The following information is included in this annex:

- Referenced material (Refer to REFERENCES)

Annex 8. Summary of Changes to the Risk Management Plan over Time

GILEAD	POST MARKETING PREGNANCY REPORT FORM	FRM-13564 (1.0)

Please enter all dates in the following format: DD/MMM/YYYY (e.g. 01/JAN/2018) **Gilead MCN:** ___

EFFECTIVE

Maternal Profile

Initials

Patient ID

Program/Study Name or No.:

Birth Date (DD/MMM/YYYY) / /

Or, if unknown, Age

Race: ☐ Caucasian ☐ Hispanic ☐ Of African Descent ☐ Asian ☐ Aboriginal / TSI ☐ Other (specify)

Last Menstrual Period (DD/MMM/YYYY) / /

Weight ☐ LB ☐ KG

Expected Date of Delivery (DD/MMM/YYYY) / /

Height ☐ IN ☐ CM

Occupation

Education Level

Were there any relevant maternal risk factors in the home/work environment (such as chemical exposure, x-rays, decreased pregnancy rate, etc.)? ☐ Yes ☐ No

If yes, please describe ___

Maternal Risk factors:

Alcohol? ☐ Yes ☐ No ☐ Unknown

Tobacco? ☐ Yes ☐ No ☐ Unknown

Recreational drugs? ☐ Yes ☐ No ☐ Unknown

Other? ☐ Yes ☐ No ☐ Unknown

Is there any family history of malformation, significant obstetrical outcome or heredity disorders? ☐ Yes ☐ No

If YES, please describe

Please describe the mother's medical history (include any endocrinological problems, recent infections or diseases which needed treatment, any fertility problems or use of fertility methods):

___

Contraception (may choose more than one)

None ☐ Condom ☐ Surgical Sterilization (Male) ☐ (Female) ☐

Withdrawal ☐ Spermicide ☐ Infertility (Male) ☐ (Female) ☐

Unknown ☐ Diaphragm ☐ Contraceptive Medication ☐ Rhythm ☐

Pregnancy due to:

Unsuccessful at abstinence ☐

Used ineffective contraception ☐

Used contraception inconsistently ☐

Unexpected sexual activity ☐

Contraceptive failure ☐

Other (please specify) ☐

If applicable, please provide HIV/HBV viral load, CD4+T Cell count and Hepatitis Severity Indicator at the beginning of pregnancy:

	Date (DD/MMM/YYYY)	Result	Units		Not Applicable	Not Available
Serum HBV DNA	/ /		☐ Log 10copies/ml	☐ Copies/ml	☐	☐
Plasma HIV RNA	/ /		☐ Log 10copies/ml	☐ Copies/ml	☐	☐
CD4+TCell Count	/ /		☐ Log 10cells/mm³	☐ Cells/mm³	☐	☐

Hepatitis Severity Indicator:

☐ Compensated liver disease (Child - Pugh - Turcotte score < 7)

☐ Decompensated liver disease (Child - Pugh - Turcotte score ≥ 7)

☐ Not Applicable

Previous Pregnancies

Provide the number for each pregnancy category

Gravida (# of times pregnant)	**Para** (# of successful deliveries > 20 weeks gestation)	**Abortus** (# of fetal losses < 20 weeks gestation)

Please describe any abnormal outcomes (include elective abortions, miscarriages, and malformations) including dates if known:

Doc. Status Effective Doc
Effective Date 28 Apr 2021 GVault Ver. No. 1.0
Date Printed 21 Dec 2021 Legacy Doc. No.

In case of a previous abnormal pregnancy outcome, list all known medications used:

Present Pregnancy

Gilead Product(s) (Please Specify):

Gilead product exposure via: ☐ Male Partner ☐ Maternal Exposure

Product	Route	Dose	Start Date	Stop Date	Indication	Lot Number
			/ /	/ /		
			/ /	/ /		

What other medications has the mother used since last menses date? (Include Rx, OTC, and vitamins)

Medication	Indication	Start Date (DD/MMM/YYYY)	End Date/ Ongoing (DD/MMM/YYYY)
		/ /	/ /
		/ /	/ /

Was a prenatal test done? ☐ Yes (complete below) ☐ No ☐ Unknown

Test (Check all tests performed)	Date (DD/MMM/YYYY)	Evidence of structural defect?		If yes, describe structural defect
☐ Ultrasound	/ /	☐ No	☐ Yes	
☐ Amniocentesis	/ /	☐ No	☐ Yes	
☐ MSAFP/serum markers	/ /	☐ No	☐ Yes	
☐ Other: (e.g. Chorionic Villi sampling, serology tests)	/ /	☐ No	☐ Yes	

What is the status of the current pregnancy?

☐ Continuing ☐ Spontaneous abortion

☐ Elective abortion ☐ Threatened abortion

☐ Missed abortion ☐ Ectopic pregnancy

☐ Unknown ☐ False positive pregnancy test

Please complete **Post Marketing Pregnancy Outcome Report Form** -**FRM-13586** for outcome details of this pregnancy

☐ Date of abortion / /

Paternal Details (To be completed only for Gilead product exposure via male partner)

Initials

Birth Date (DD/MMM/YYYY) / /

Race ☐ Of African Descent ☐ Hispanic ☐ Caucasian ☐ Asian ☐ Aboriginal / TSI ☐ Other (specify)

Occupation

Education Level

Male Partner Medical History

☐ Unknown ☐ Smoking ☐ Alcohol ☐ Allergies (specify) _____ ☐ Drug abuse (specify) _____ ☐ Other relevant history (specify) _____

What medication was the Father using at the time of conception? (include Rx, OTC, and vitamins)

Drug Name	Route	Dosage Regimen	Start Date	Stop Date	Indication for Use
			/ /	/ /	
			/ /	/ /	
			/ /	/ /	

Reporter Information

Reporter Name _____

Type ☐ Physician (specify) _____ ☐ Pharmacist ☐ Consumer ☐ Other (specify) _____

Contact Address

City, State _____ Telephone Number _____ Fax Number _____

Postal / Zip Code _____ Email _____

Signature _____ Date

Please provide contact details of healthcare provider (HCP) involved in the patient's prenatal or postnatal care (e.g., Obstetrician/Gynaecologist).

HCP Name: _____ HCP Telephone No./Fax No.: _____

HCP Email: _____

Send completed form to: Email: <Add applicable Company details> Fax: <Add applicable Company details> Address: <Add applicable Company details>

Please be aware that information provided to Gilead relating to you, may be used to comply with applicable laws and regulations. Gilead processes your personal or sensitive data in accordance with applicable data protection laws and the Gilead Privacy Statement, available to you either on www.gilead.com/privacy or upon request.

GILEAD	POST MARKETING PREGNANCY OUTCOME REPORT FORM	FRM-13586 (1.0)

EFFECTIVE

Please enter all dates in the following format: DD/MMM/YYYY (e.g. 01/JAN/2018) **Gilead MCN:____**

Maternal Information

Initials | Patient ID | Program/Study Name or No.:

Birth Date (DD/MMM/YYYY) | Or, if unknown, Age:

Last Menstrual Period (DD/MMM/YYYY) | Weight ☐ LB ☐ KG

Race: ☐ Caucasian ☐ Hispanic ☐ Of African Descent ☐ Asian ☐ Aboriginal / TSI ☐ Other ____ (specify)

Expected Date of Delivery (DD/MMM/YYYY) | Height ☐ IN ☐ CM

Occupation | Education Level

Course and Outcome of Pregnancy

Did the mother experience any medical problems during this pregnancy? ☐ No ☐ Yes (complete below)

Event	Trimester of occurrence (check all that apply):
	☐ 1 ☐ 2 ☐ 3
	☐ 1 ☐ 2 ☐ 3
	☐ 1 ☐ 2 ☐ 3

Did the mother take any medications during this pregnancy? (include Rx, OTC and vitamins, but exclude medications used during labour and delivery)

☐ No ☐ Yes (complete below)

Gilead Product(s) (Please Specify): Product exposure via: ☐ Male Partner ☐ Maternal Exposure

Medication	Indication	Trimester of occurrence (check all that apply)
		☐ 1 ☐ 2 ☐ 3
		☐ 1 ☐ 2 ☐ 3
		☐ 1 ☐ 2 ☐ 3

Other Product(s) (Please Specify)

Medication (preferably generic name)	Indication	Trimester of occurrence (check all that apply)
		☐ 1 ☐ 2 ☐ 3
		☐ 1 ☐ 2 ☐ 3
		☐ 1 ☐ 2 ☐ 3

Did the mother receive any medication during labour and delivery? (include anaesthesia) ☐ No ☐ Yes (complete below)

Medication (preferably generic name)	Start Date	End Date / Ongoing	Indication

Specify the outcome of pregnancy and complete the rest of the form as applicable

☐ Interrupted pregnancy

☐ Spontaneous abortion Date: / / Possible Cause

☐ Induced abortion Date: / /

Delivery Date ____/____/____ ☐ Spontaneous ☐ Forceps ☐ Vacuum extract

☐ Uninterrupted Delivery Method

Gestational age _____ Weeks ☐ Caesarean section ☐ Induced ☐ Other _____

Were there any labour/delivery complications (e.g. fetal distress, amniotic fluid abnormal, abnormal placenta)

☐ No ☐ Yes Please descr be: _____

Characteristics of the Baby

General Appearance: **Sex** ☐ Male ☐ Female

☐ Term **Weight** _____ ☐ bs/oz ☐ grams

☐ Preterm **Length** _____ ☐ in ☐ cm

☐ Post-term **Head circumference:** _____ ☐ in ☐ cm

Apgar score

1 min: _____

5 min: _____

10 min: _____

Clinical condition of the baby:

☐ Healthy Baby

☐ Prematurity Specify gestational age: _____

☐ Congenital abnormality Specify: _____ Possible Cause: _____

☐ Neonatal problem Specify: _____ Possible Cause: _____

☐ Neonatal death Date: ____/____/____ Possible Cause: _____

☐ Stillbirth Date: ____/____/____ Possible Cause: _____

Was a fetal autopsy done? ☐ No ☐ Yes Please describe: (attach copy of report if available) _____

Follow-up Examination of the Baby:

Date: ____/____/____

Findings _____

Paediatrician (in case of referral); Name: _____

Address: _____ Telephone No _____ Fax No _____

E-mail _____

Relevant laboratory Tests / Procedures for Baby / Fetus

Tests	Results (unit and normal values if applicable)	Pending	Start Date (DD/MMM/YYYY)
		☐	
		☐	
		☐	

Additional information:

Was the baby's hospitalization prolonged? ☐ No ☐ Yes please descr be: _____

Did the baby receive any special treatment? ☐ No ☐ Yes please descr be: _____

Was any relationship suspected between the abnormal pregnancy outcome and exposure to the Gilead Product?

☐ No
☐ Yes
☐ Unknown
☐ Other:

Other factors that may have contr buted to this outcome:

☐ Maternal age
☐ Unknown

Was there any relationship between the abnormal pregnancy outcome and the use of concomitant medications?

☐ No ☐ Yes please descr be: _____

Reporter Information

Reporter Name _____

Type ☐ Physician (specify) _____ ☐ Pharmacist ☐ Consumer ☐ Other (specify) _____

Contact Address City, State _____ Telephone Number _____ Fax Number _____

Postal / Zip Code _____ Emai l _____

Signature _____ **Date** ___/___/___

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