EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 September 2022
EMA/789715/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report on group of variations including an extension of indication assessment report

Invented name: Veklury

International non-proprietary name: remdesivir

Procedure No. EMEA/H/C/005622/II/0035/G

Marketing authorisation holder (MAH) Gilead Sciences Ireland UC

Note

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

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List of abbreviations

%CV	percentage coefficient of variation
AE	adverse event
AIDS	acquired immunodeficiency syndrome
AKI	acute kidney injury
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC_{tau}	area under the concentration versus time curve over the dosing interval
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CLcr	creatinine clearance
CMA	conditional marketing authorisation
CoV	coronavirus
COVID-19	coronavirus disease 2019
CSR	clinical study report
ECMO	extracorporeal membrane oxygenation
eGFR	estimated glomerular filtration rate
GMR	geometric mean ratio
ET	endotracheal tube
EUA	Emergency Use Authorization
ICU	intensive care unit
ie	that is
INR	international normalized ratio
IV	intravenous
ITT	intent-to-treat
m	Module
MAV	medically attended visit
max	maximum
min	median
MERS	Middle East respiratory syndrome
NA	not applicable

NP	nasopharyngeal
OP	oropharyngeal
O2	oxygen
PCR	polymerase chain reaction
PD	pharmacodynamics
PK	pharmacokinetic(s)
PEWS	Paediatric Early Warning Score
PK	pharmacokinetic(s)
PopPK	population pharmacokinetic
Q1	first quartile
Q2	second quartile
Q3	third quartile
Q4	fourth quartile
RDV	remdesivir (GS-5734™)
RNA	ribonucleic acid
SBECD	sulfobutylether β-cyclodextrin sodium
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
SD	standard deviation
SmPC	summary of product characteristics
SpO_2	oxygen saturation
TBD	to be determined
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
US	United States
V_c	central volume of distribution
V_p	peripheral volume of distribution
WT	body weight

* This is a general list of abbreviations. Not all abbreviations will be used or are included.

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Gilead Sciences Ireland UC submitted to the European Medicines Agency on 2 February 2022 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Grouped application of two Extensions of indication to include:
- treatment of 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, based on interim results from Study GS-US-540-5823; a phase 2/3 single-arm, open-label study to evaluate the safety, tolerability, pharmacokinetics, and
efficacy of Remdesivir in participants from birth to <18 years of age with COVID-19;
- treatment of 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, based on data from 8 adolescent patients who were included in Study GS-US-540-9012, which was initially assessed by the CHMP as part of procedure II/16 (Extension of Indication to include treatment of adults).
As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet as well as the instructions for healthcare professionals have been updated accordingly. Version 3.2 of the RMP has also been submitted.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0060/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0060/2021 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Derogation(s) of market exclusivity

Not applicable

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Janet Koenig Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	2 February 2022
Start of procedure:	21 March 2022
CHMP Rapporteur Assessment Report	29 April 2022
PRAC Rapporteur Assessment Report	2 May 2022
PRAC members comments	26 April 2022
PRAC Outcome	5 May 2022
CHMP members comments	10 May 2022
Updated CHMP Rapporteur Assessment Report	12 May 2022
Request for supplementary information (RSI)	19 May 2022
CHMP Rapporteur Assessment Report	15 August 2022
PRAC Rapporteur Assessment Report	19 August 2022
PRAC members comments	24 August 2022
Updated PRAC Rapporteur Assessment Report	25 August 2022
PRAC Outcome	1 September 2022
CHMP members comments	05 September 2022
Updated CHMP Rapporteur Assessment Report	08 September 2022
Opinion	15 September 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

As of 17 February 2022, approximately 12.5 million children aged 0 to 17 years in the US had tested positive for COVID-19 since the onset of the pandemic {American Academy of Pediatrics 2022}. Although children with COVID-19 frequently have mild or moderate symptoms {Gotzinger 2020, Liguoro 2020, Zimmermann 2020}, COVID-19 can result in severe disease.

Although the minority of children display severe COVID-19, reports of hospitalized paediatric patients from neonates to adolescents are increasing. In those with severe disease, symptoms and radiological findings are similar to those of adults. Furthermore, underlying conditions such as pulmonary disease, immunocompromised state, or coexisting respiratory infections might predispose to severe respiratory disease.

While vaccination against COVID-19 infection is effective in preventing COVID-19, vaccines are not yet available for all children and breakthrough cases of COVID-19 can occur in those who are vaccinated. Thus, a treatment for pediatric patients with COVID-19 is needed.

Disease or condition

A novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in December of 2019 in Wuhan, China as causing a respiratory illness designated as coronavirus disease 2019, or COVID-19. On 30 January 2020, the International Health Regulations Emergency Committee of the WHO declared the COVID-19 outbreak a Public Health Emergency of International Concern {World Health Organization (WHO) 2020, https://www.who.int/news-room/detail/27-04-2020-who-timeline---covid-19} Since then, there has been rapid spread of the virus, leading to a global pandemic of COVID-19.

The human disease caused by SARS-CoV-2 has been designated COVID-19. In most (~80%) cases, COVID-19 presents as a mild-to-moderately severe, self-limited acute respiratory illness with fever, cough, and shortness of breath. Symptoms are thought to appear 2 to 14 days after exposure. COVID-19 can be severe, resulting in pneumonia, severe acute respiratory syndrome, hypercoagulation, kidney failure, and death.

The vulnerability of children to infection with SARS-CoV-2 is expected to be equivalent to that of adults; however, similar to SARS-CoV and Middle East respiratory syndrome-CoV, SARS-CoV-2 infection appears to be less common in children {Cruz 2020, Dong 2020, Lee 2020, Zimmermann 2020}. With moderate to severe COVID-19, both populations display similar symptoms. Although COVID-19 infections usually lead to mild or moderate symptoms in children, some progress to severe disease and require hospitalization (49.7 per 100,000 cases at Coronavirus Disease 2019 Associated Hospitalization Surveillance Network sites in the US from 01 March 2020 to 14 August 2021 and 0.1%-0.2% in Europe from 04 January to 20 June 2021) {Delahoy 2021, European Centre for Disease Prevention and Control 2021}. Although the minority of children display severe COVID-19, reports of hospitalized paediatric patients from neonates to adolescents are increasing. In those with severe disease, symptoms and radiological findings are similar to those of adults. Furthermore, underlying conditions such as pulmonary disease, immunocompromised state, or coexisting respiratory infections

might predispose to severe respiratory disease. A statistically higher chance of severe lower respiratory tract disease has been noted in children infected with human CoVs and underlying pulmonary disorders, an immunocompromised state, and coinfection with a respiratory copathogen(s).

State the claimed the therapeutic indication

The following therapeutic indication is proposed:

Veklury is indicated for the treatment of coronavirus disease 2019 (COVID-19):

- adults and paediatric patients adolescents (aged at least 4 weeks of age 12 to less than 18 years and weighing at least 40 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 section 5.1)

The extension of the current indication pertains to the following:

- treatment of 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.
- treatment of 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.

Epidemiology and risk factors

On 12 January 2020 it was announced that a novel coronavirus had been identified in samples obtained from cases and that initial analysis of virus genetic sequences suggested that this was the cause of the outbreak. This virus is referred to as SARS-CoV-2, and the associated disease as COVID-19. On 30 January 2020, the International Health Regulations Emergency Committee of the WHO declared the COVID-19 outbreak a Public Health Emergency of International Concern {World Health Organization (WHO (https://www.who.int/news-room/detail/27-04-2020-who-timeline---covid-19) 2020c}. Globally, as of 7 September 2022, there have been 603,711,760 confirmed cases of COVID-19, including 6,484,136 deaths, reported to WHO. In Europe, 249,105,808 case were confirmed {World Health Organization (WHO) 2022}.

Recently, the world has experienced a switch from a predominant delta variant pandemic to an omicron variant pandemic. Globally, from 5 August to 5 September 2022, 118,028 SARS-CoV-2 sequences were shared through GISAID. Among these, 117,317 sequences were the Omicron variant of concern (VOC), accounting for 99.4% of sequences reported globally in the past 30 days. A comparison of sequences submitted to GISAID in epidemiological week 34 (22 to 28 August 2022) and week 33 (15 to 21 August 2022) shows that BA.5 Omicron descendent lineages continue to be dominant globally, with an increase in weekly prevalence from 84.8% to 86.8%. The prevalence of BA.4 descendent lineages decreased from 6.8% in week 33 to 4.2% in week 34 including BA.4.6 descendent lineage, which decreased from 3.5% to 2% within the same time period. The prevalence of BA.2 descendent lineages (BA.2.X) remained stable in week 34 compared to week 33 (2.6% in week 33 and 2.5% in week 34). BA.2.75, an Omicron descendent lineage under monitoring, still shows a relatively low (0.9% and 1.2% in weeks 33 and 34 respectively) prevalence globally, but a number of countries have observed recent increasing trends {taken from World Health Organization (WHO) 2022}.

Most infections are self-limiting. However, approximately 15% of adults with COVID-19 develop severe pneumonia that requires treatment with supplemental oxygen, and an additional 5% of adults with COVID-19 progress to critical illness, with hypoxemic respiratory failure, acute respiratory distress syndrome, and multiorgan failure, potentially requiring ventilator oxygen support for several weeks {Chen 2020a, Wu 2020, Zhou 2020}.

The cumulative incidence of COVID-19-associated hospitalizations in children and adolescents aged 0 to 17 years from 01 March 2020 to 14 August 2021 was 49.7 per 100,000 at Coronavirus Disease 2019-Associated Hospitalization Surveillance Network sites in the US {Delahoy 2021}. Among 3,116 hospitalized children and adolescents with COVID-19 from 01 March 2020 to 19 June 2021, 26.5% (827 patients) were admitted to an intensive care unit (ICU), 6.1% (190 patients) required invasive mechanical ventilation, and 0.7% (21 patients) died. In Europe, children made up an increasing proportion of weekly reports of cases of COVID-19 infection during the period from 04 January to 20 June 2021, coinciding with the availability of vaccines for adults, although the percentage of children across different age groups from 1 to 18 years who were admitted to hospital remained low (0.1%-0.2%) {European Centre for Disease Prevention and Control 2021}. In those with severe disease, symptoms and radiological findings are similar to those of adults. Furthermore, as said underlying conditions such as pulmonary disease, immunocompromised state, or coexisting respiratory infections might predispose children to severe respiratory disease {Ogimi 2019}. Risk factors identified in children with COVID-19 infection for hospitalization and/or ICU admission include complex chronic diseases, type 1 diabetes, obesity, and cardiac and circulatory congenital anomalies {Kompaniyets 2021}. Prematurity has been identified as a risk factor for severe disease in children under 2 years old.

Biologic feature, Aetiology and pathogenesis

Coronaviruses are a group of highly diverse, enveloped, positive-sense, single-stranded ribonucleic acid (RNA) viruses that belong to two subfamilies, Coronaviridae and Toroviridae, in the family of Coronaviridae. These viruses were first discovered in the 1960s and can be further classified into four main genera: Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus, based on their phylogenetic relationships and genomic structures. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped, positive-sense, single-stranded ribonucleic acid (RNA) beta coronavirus causing coronavirus disease-2019 (COVID-19). Phylogenetic analysis of the complete viral genome revealed that the virus, SARS-CoV-2, is part of the subgenus Sarbecovirus of the genus Betacoronavirus and is most closely related (approximately 88% identity) to a group of SARS CoV-like coronaviruses previously sampled from bats in China. Currently, there are seven strains of coronaviruses that are known to infect humans, including the recently identified SARS-CoV-2, human coronavirus 229E (HCoV-229E), OC43 (HCoV-OC43), NL63 (HCoV-NL63), HKU1 (HCoV-HKU1), severe acute respiratory syndrome coronavirus (SARS-CoV), and Middle East respiratory syndrome coronavirus (MERS-CoV).

The virus causes respiratory illness in people and can spread from person to person {Center for Disease Control (CDC) 2020, Center for Disease Control and Prevention (CDC) 2020}. While most people infected with SARS-CoV-2 have mild upper respiratory tract disease, older individuals and adults with comorbidities are more likely to have severe progressive pneumonia and multiorgan failure.

Accumulating evidence has suggested that inflammatory responses play a critical role in the progression of COVID-19, and several markers have some tracing and detecting accuracy for disease severity (Mehta et al., 2020, Stebbing et al., 2020, Wu C. et al., 2020). Immune-mediated lung injury

and acute respiratory distress syndrome (ARDS) are associated with adverse outcomes in patients with COVID-19.

The natural course of COVID-19 is classified into 3-stage, recognizing that COVID-19 illness exhibits 3 grades of increasing severity, which correspond with distinct clinical findings, response to therapy, and clinical outcome. Stage 1 is the early infection stage, with mild symptoms and high viral load. The second stage is characterised by pulmonary involvement with or without hypoxia, established pulmonary disease, viral multiplication and localized inflammation in the lung. A minority of COVID-19 patients will transition into the third and most severe stage of the illness, which manifests as an extrapulmonary systemic hyperinflammation syndrome and systemic hyperinflammation.

The efficacy of antiviral agents may vary depending on whether a patient presents early or late in the course of COVID-19 (i.e., during viral pathogenesis versus after immunopathologic manifestations) {Harrington 2020}. Although research into COVID-19 continues to evolve, it is expected that the impact of antiviral agents such as RDV is likely to be greatest early in the course of COVID-19 (i.e., prior to the need for advanced respiratory support).

Clinical presentation, diagnosis

Common signs of infection include fever, cough, shortness of breath, breathing difficulties, and other respiratory symptoms. In severe cases, SARS-CoV-2 can cause pneumonia, severe acute respiratory syndrome, kidney failure, and death {World Health Organization (WHO) 2020a}.Therefore, while most people with COVID-19 develop only mild or moderate disease, approximately 15% develop severe disease that requires oxygen support, and 5% have critical disease with complications such as respiratory failure, acute respiratory distress syndrome (ARDS), sepsis and septic shock, thromboembolism, and/or multiorgan failure, including acute kidney injury and cardiac injury.

Older age, and underlying non-communicable diseases, such as diabetes, hypertension, cardiac disease, chronic lung disease and cancer, have been reported as risk factors for severe disease and death.

COVID-19 has been also associated with mental and neurological manifestations, including delirium or encephalopathy, agitation, stroke, meningoencephalitis, impaired sense of smell or taste, etc.

Regarding pregnant women, some studies have suggested that women with SARS CoV-2 infection during pregnancy are at increased risk of adverse pregnancy and neonatal outcomes like preterm birth or pre-eclampsia. {Ipek Gurol-Urganci eat al 2021}

Clinical manifestations of COVID-19 are generally milder in children compared with adults. Although COVID-19 infections usually lead to mild or moderate symptoms in children, some progress to severe disease and require hospitalization. In those with severe disease, symptoms and radiological findings are similar to those of adults. Most recently, an acute presentation with a hyperinflammatory syndrome leading to multiorgan failure and shock has been described named as multisystem inflammatory syndrome temporally associated with COVID-19 in children and adolescents.

The diagnosis of COVID-19 can be established based on a suggestive clinical history and the detection of SARS-CoV-2 RNA in respiratory secretions. Nucleic acid tests that detect the SARS-CoV-2 RNA genome are now widely employed to diagnose coronavirus disease 2019 (COVID-19). In addition, serological assays measure antibody responses and determine seroconversion although they are not well suited to detect acute infections.

Management

In the EU currently two vaccines against SARS-CoV-2 infection are approved for paediatric patients. Comirnaty for children aged five years and older and Spikevax for children aged six years and older.

Dexamethasone can be used in the EU to treat COVID-19 in adolescents aged 12 years and older and weighing at least 40 kg after EMA's CHMP completed its review under Article 5(3). Treatment with Dexamethasone have been proven effective and safe in the treatment of severe COVID-19 of severe COVID-19 in adolescents aged 12 years and older and weighing at least 40 kg and require supplemental oxygen. Furthermore, Remdesivir is approved for the treatment of COVID-19 in adolescent patients with pneumonia aged 12 years and older and weighing at least 40 kg who require low-flow oxygen, high-flow oxygen or non-invasive mechanical ventilation at the start of therapy.

Currently, several monoclonal antibodies are approved for the treatment of mild and moderate COVID-19 infection in adolescent patients outside the hospital setting, Xevudy (sotrovimab) and Ronapreve (casirivimab/imdevimab) and Evusheld (tixagevimab/cilgavimab). Xevudy and Ronapreve are indicated for treating COVID-19 in adults and adolescents (from 12 years of age and weighing at least 40 kilograms) who do not require supplemental oxygen and who are at increased risk of their disease becoming severe. Ronapreve can also be used for preventing COVID-19 in people aged 12 years and older weighing at least 40 kilograms. Evushed was also approved for preventing COVID-19 in people aged 12 years and older weighing at least 40 kilograms.

Currently, there are no approved antiviral treatments for the treatment of COVID-19 in children and adolescents below the age of 12 or weighing less than 40 kg.

In addition, paediatric patients with COVID-19 are treated with relevant supportive care, including e.g., oxygen, mechanical ventilation and other life support, as required.

There is a high medical need for an effective agent for treatment of COVID-19 for children and adolescents especially for those below 12 years of age or weighing less than 40 kg.

2.1.2. About the product

Veklury received a 'conditional marketing authorisation' in the EU on 3 July 2020 and was initially indicated for the treatment of COVID-19 in adults and adolescents from 12 years of age with pneumonia who require supplemental oxygen.

On 21 December 2020, the CHMP concluded that the benefit/risk has not been shown to be positive in patients on IMV or ECMO and restricted the indication of remdesivir accordingly (please refer to procedure EMEA/H/C/005622/II/0012). Veklury® is now indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment).

On 16 December 2021, the CHMP adopted a positive opinion recommending the use of remdesivir in adult patients with COVID-19 who do not require supplemental oxygen and who are at increased risk for progressing to severe disease (please refer to procedure EMEA/H/C/005622/II/0016). Veklury® is now also indicated for the treatment of COVID-19 in adult patients who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID 19.

Remdesivir is a nucleotide prodrug that is intracellularly metabolized into an analogue of adenosine triphosphate that inhibits viral RNA polymerases. Remdesivir competes with the natural ATP substrate for incorporation into nascent RNA chains by the SARS-CoV 2 RNA-dependent RNA polymerase, which

results in delayed chain termination during replication of the viral RNA. Remdesivir triphosphate can also inhibit viral RNA synthesis following its incorporation into the template viral RNA by compromising the efficiency of incorporation of the complementary natural nucleotide. Remdesivir has broad-spectrum activity against members of the coronaviruses (CoVs; eg, severe acute respiratory syndrome coronavirus-2 [SARS-CoV-2], SARS-CoV, Middle East respiratory syndrome [MERS]-CoV), filoviruses (e.g., Ebola virus, Marburg virus), and paramyxoviruses (e.g., respiratory syncytial virus [RSV], Nipah virus, Hendra virus).

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

No CHMP scientific advice was given on the Remdesivir development programme.

2.1.4. General comments on compliance with GCP

The MAH has provided statements that clinical trials were conducted in accordance with GCP.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The MAH provided an updated ERA regarding the PECsurfacewater values for remedesivir and for GS 441524, the environmentally relevant active substance. Remdesivir is a prodrug of the nucleoside analog GS-441524.

PECsurfacewater values have been refined by modifying the Fpen using estimated potential patient population and the fixed treatment regime of the product.

GS 441524: Doseai = 96.7 mg/d, Fpen = 0.0000425
PECsurfacewater-refined = 0.00205 [µg/L]

Remdesivir: Doseai = 200 mg/d, Fpen = 0.0000425
PECsurfacewater-refined = 0.00425 [µg/L]

The PECsurface water value for GS 441524 or remdesivir is below the trigger value of 0.01 µg·L-1 and therefore a Phase II assessment is not required.

GS-441524 has a logK_{ow} < 4.5 and therefore a PBT assessment is not necessary.

Substance (INN/Invented Name): GS-441524			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	Shake-flask method	-0.58 pH 5 -0.56 pH 7 -1.90 pH 9	Potential PBT (N)
Phase I			

Calculation	**Value**	**Unit**	**Conclusion**
PECsurfacewater, *refined with treatment regime and prevalence data*	0.00205	µg/L	> 0.01 threshold N
Substance (INN/Invented Name): Remdesivir (GS-5734)			
CAS-number (if available): 1809249-37-3			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	Shake flask Method (study not available)	3.2	Potential PBT (N)
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PECsurfacewater, *refined with treatment regime and prevalence data*	0.00425	µg/L	> 0.01 threshold N

2.2.2. Discussion on non-clinical aspects

Not applicable, as no new non-clinical data have been submitted. For the conclusion on the ecotoxicity/environmental risk assessment please see below.

2.2.3. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of Remdesivir.

Considering the above data, Remdesivir is not expected to pose a risk to the environment. Remdesivir should be used according to the precautions stated in the SmPC in order to minimize any potential risks to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Type of Study	Study Number	Study Objective	Design	Study Drug Regimens	Duration of Treatment	Participant Population			Study Status; Type of Report
						Age/Weight Group	Number of Participants	Entry Criteria	
Uncontrolled clinical studies pertinent to the claimed indication	GS-US-540-5823[a]	To evaluate the safety, tolerability, PK, and efficacy of RDV in pediatric participants from birth to < 18 years with COVID-19	Phase 2/3, single-arm, open-label, multicenter study	IV RDV 200 mg on Day 1 followed by IV RDV 100 mg daily	Up to 10 days	Cohort 1 ≥ 12 years to < 18 years and weight ≥ 40 kg	Enrolled: 12 Treated: 12 Completed study treatment: 3	Male or nonpregnant female pediatric participants 0 days to < 18 years of age who had SARS-CoV-2 infection confirmed by PCR, were hospitalized and required medical care for COVID-19	Interim CSR
				IV RDV 5 mg/kg on Day 1 followed by IV RDV 2.5 mg/kg daily	Up to 10 days	Cohort 2 ≥ 28 days to < 18 years and weight ≥ 20 kg to < 40 kg	Enrolled: 12 Treated: 12 Completed study treatment: 2		
				IV RDV 5 mg/kg on Day 1 followed by IV RDV 2.5 mg/kg daily	Up to 10 days	Cohort 3 ≥ 28 days to < 18 years and weight ≥ 12 kg to < 20 kg	Enrolled: 12 Treated: 12 Completed study treatment: 2		
				IV RDV 5 mg/kg on Day 1 followed by IV RDV 2.5 mg/kg daily	Up to 10 days	Cohort 4 ≥ 28 days to < 18 years and weight ≥ 3 kg to < 12 kg	Enrolled: 12 Treated: 12 Completed study treatment: 4		

Type of Study	Study Number	Study Objective	Design	Study Drug Regimens	Duration of Treatment	Participant Population			Study Status; Type of Report
						Age/Weight Group	Number of Participants	Entry Criteria	
				IV RDV 5 mg/kg on Day 1 followed by IV RDV 2.5 mg/kg daily	Up to 10 days	Cohort 5[a] ≥ 14 days to < 28 days of age, gestational age > 37 weeks and weight at screening ≥ 2.5 kg[a]	--		--
				RDV at a dose TBD	Up to 10 days	Cohort 6[a] 0 days to < 14 days of age, gestational age > 37 weeks, and birth weight ≥ 2.5 kg[a]	--		--
				RDV at a dose TBD	Up to 10 days	Cohort 7[a] 0 days to < 56 days of age, gestational age ≤ 37 weeks, and birth weight ≥ 1.5 kg[a]	--		--
				IV RDV 200 mg on Day 1 followed by IV RDV 100 mg daily	Up to 10 days	Cohort 8 < 12 years and weight ≥ 40 kg	Enrolled: 5 Treated: 5 Completed study treatment: 2		Interim CSR

Type of Study	Study Number	Study Objective	Design	Study Drug Regimens	Duration of Treatment	Participant Population			Study Status; Type of Report
						Age/Weight Group	Number of Participants	Entry Criteria	
Randomized, placebo-controlled studies pertinent to the claimed indication	GS-US-540-9012[b]	To evaluate treatment with IV RDV in an outpatient setting in participants with confirmed COVID-19 who were at risk for disease progression	Phase 3, randomized, double-blind, placebo-controlled, multicenter study	IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2 and 3	3 days	≥ 12 years and weight ≥ 40 kg	Overall Enrolled: 630 Treated: 562 Completed study treatment: 542 Adolescent participants, ≥ 12 to <18 years and weight ≥ 40 kg Enrolled: 8 Treated: 8 Completed study treatment: 8	Male or female participants ≥ 12 years of age weighing ≥ 40 kg who had SARS-CoV-2 infection confirmed by molecular testing and with at least 1 preexisting risk factor for progression to hospitalization	Completed; Final CSR

COVID-19 = coronavirus disease 2019; CSR = clinical study report; IV = intravenous; PCR = polymerase chain reaction; RDV = remdesivir; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TBD = to be determined.
a The study is ongoing. The results of these cohorts are not included in this submission.
b Data from participants ≥ 18 years of age are not included in this submission.

Study GS GS-US-540-5823: Uncontrolled clinical study pertinent to the claimed indication.

Study GS-US-540-5823 is a phase 2/3, single-arm, open-label, multicentre study to evaluate the safety, tolerability, PK, and efficacy of RDV in paediatric participants from birth to < 18 years with COVID-19 Phase 2/3, single-arm, open-label, multicentre study.

Study GS-US-540-9012: Randomized, placebo-controlled study pertinent to the claimed indication.

Study GS-US-540-9012 is a Phase 3, randomized, double-blind, placebo-controlled, multi-center study to evaluate treatment with IV RDV in an outpatient setting in participants with confirmed COVID-19 who were at risk for disease progression.

2.3.2. Pharmacokinetics

New pharmacokinetic studies were submitted.

New pharmacokinetic studies were submitted.

Study GS-US-540-5823

PK was evaluated in study GS-US-540-5823. Only design features concerning the PK-outcome are presented here. For further information on the study design, please refer to the clinical efficacy and safety section.

Statistical analysis of pharmacokinetics

The primary end point was the PK of RDV and its metabolites (GS-441524 and GS-704277). By-participant concentration data listings that included PK concentrations and PK sampling details (procedures, differences in scheduled and actual draw times, and sample age) were provided for all enrolled participants.

Pharmacokinetic parameters from population PK modelling of RDV and metabolites were listed and summarized using descriptive statistics. Summary statistics (numbers of participants, mean, SD, percentage coefficient of variation [%CV], median, minimum, maximum, Q1, and Q3) were presented by cohort and overall.

Plasma concentrations of SBECD were also analysed (where possible) as a secondary end point. However, these data have not been submitted yet.

Sample size and power, Cohorts 1 through 4 and Cohort 8

Twelve participants for each cohort in Cohorts 1 through 4 were planned for enrolment in this study. The PK data from 12 participants from each cohort in Cohorts 1 through 4 provided greater than 99% power for each cohort to conclude exposure equivalence of RDV AUC_{tau} in adolescents and children in this study compared with 25 healthy adult participants from Study GS-US-399-5505. Two 1-sided tests were used, each performed at an alpha level of 0.05.

It was assumed that the geometric mean ratio of AUC_{tau} between the adolescents and children versus the adult group was equal to 1, the inter-subject SD (natural log scale) of RDV AUC_{tau} was 0.18 ng•h/mL, and the equivalency boundary was 70% to 143%. The PK data from 12 participants from each cohort in Cohorts 1 through 4 also provided greater than 99% power for each cohort to conclude exposure equivalence of RDV C_{max} in adolescents and children in this study compared with 26 healthy adult participants from Study GS-US-399-5505, assuming the expected geometric mean ratio of C_{max} between the adolescents and children group and the adult group was equal to 1, the intersubject SD (natural log scale) of C_{max} was 0.19 ng•h/mL, and the equivalency boundary was 70% to 143%.

Plasma PK parameters by dose for RDV and its metabolites following 30-minute IV infusion in adult participants from Study GS-US-399-5505 is provided in the Table 1-2 of the SAP (Appendix 16.1.9).

Sample size and power calculations were made using the software package nQuery Advisor® Version 8.5 (Cork, Ireland).

Pharmacokinetic Analysis Sets

The RDV PK Analysis Set included all participants who were enrolled and received at least 1 dose of RDV, and for whom PK concentrations of RDV were available.

The Metabolites (GS-441524 and GS-704277) PK Analysis Set included all participants who were enrolled and received at least 1 dose of RDV, and for whom PK concentrations of the metabolite(s) (analytes) were available.

Pharmacokinetic Assessments

Plasma samples were collected to determine the PK parameters of RDV and its metabolites (GS-441524 and GS-704277) according to the schedule of the study

As many of the specified PK time points was to be obtained from each participant as was feasible.

<u>Cohorts 1 through 4 (12 participants in each cohort) and Cohort 8 (all available):</u>

- ☐ Day 2: end of infusion (± 15 minutes) and 4 hours (± 30 minutes) after end of infusion
- ☐ Day 3: pre-infusion (≤ 60 minutes) and 2 hours (± 15 minutes) after end of infusion
- ☐ Day 5: middle of infusion and 6 hours (± 60 minutes) after end of infusion (optional)

<u>Cohorts 5 (minimum of 4 participants), 6, and 7 (all available), Day 2 or Day 3:</u>

- ☐ Day 2: end of infusion (± 15 minutes) and 4 hours (± 30 minutes) after end of infusion
- ☐ Day 3: pre-infusion (≤ 60 minutes) and 2 hours (± 15 minutes) after end of infusion

Drug Concentration Measurements

Concentrations of RDV, GS-704277, and GS-441524 in plasma samples were determined using fully validated high-performance liquid chromatography-tandem mass spectroscopy (LC-MS/MS) bioanalytical methods. All samples were analysed in the timeframe supported by frozen stability storage data. The assays for RDV, GS-704277, and GS-441524 were all performed and validated by QPS, LLC. (Newark, DE, USA). Bioanalytical sample analysis reports are provided in Appendix 16.1.10.

Table 1: GS-US-540-5823: Bioanalytical assay validation for Remdesivir, GS-704277, and GS-441524 in formic acid-treated human plasma

Parameter	Remdesivir	GS-704277	GS-441524
Calibrated range (ng/mL)	4 to 4000	2 to 2000	2 to 2000
Interassay precision (%CV)	2.3 to 3.8	2.1 to 3.8	3.5 to 5.3
Interassay accuracy range (%RE)	0 to 9.5	−9.8 to −3.5	−0.6 to 8.0
Stability in frozen matrix (days)	3 Days at −20 °C and 392 Days at −70 °C	257 Days at −70 °C	3 Days at −20 °C and 392 Days at −70 °C

%CV = percentage coefficient of variation; %RE = percentage relative error
Source: Appendix 16.1.10

Absorption, Distribution, Elimination

No new information was submitted.

2.3.3. Pharmacodynamics

New pharmacodynamics studies were submitted.

2.3.4. PK/PD modelling

New popPK modelling data were submitted.

The previous popPK model describing PK data of RDV and its metabolites in adults was based on three phase 1 studies. This model is now updated and refined with data derived from one paediatric phase 3 study (-5823) and the two studies (9012 and -5844/REMDACTA/WA42511).

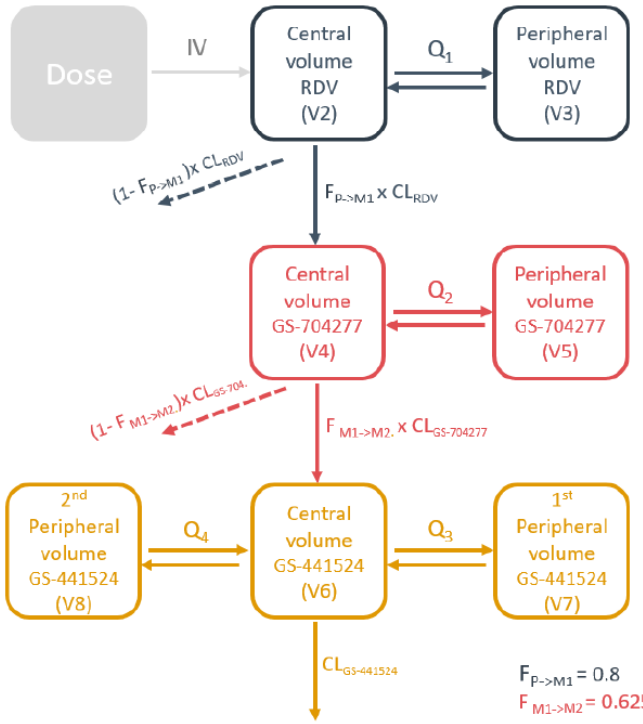
Model Development

The popPK analysis dataset included RDV, GS-704277, and GS-441524 concentrations. A total of 14588 PK samples were available (4875 for RDV, 4846 for GS-704277, and 4867 for GS-441524) from 611 subjects. Of the total 14588 PK samples, 654 were paediatric samples, and 13934 were adult PK samples of which 4103 were samples from COVID-19 patients and 9831 were samples from healthy volunteers.

The development of the popPK model for RDV and its metabolites was performed sequentially, starting with the parent RDV data, then moving onto GS-704277 data, and ending with GS-441524 data. Aside from the parent model, each model was informed by the post hoc popPK parameters from the previous model or models. Plasma concentration-time data were analysed using a NONMEM approach (NONMEM

software, version 7.4.3). The first-order conditional estimation method of NONMEM with interaction method was used for PK model development.

The previous final popPK models, were used as a starting point to develop the models for RDV, GS-704277, and GS-441524, as applicable. However, the previous final model did not adequately describe the newly added data from studies GS-US-540-5823, GS-US-540-9012 and WA42511 (REMDACTA). Therefore, a further modelling development was implemented. The parameters were re-estimated using all data available from Studies GS-US-399-1812, GS-US-399-1954, GS US-399 5505, GS-US 540-5823, GS-US-540-9012, and REMDACTA (WA42511) for evaluation.



CL_{RDV} = clearance for RDV; $CL_{GS-704277}$ = clearance for CL-GS-704277; $CL_{GS-441524}$ = clearance for CL-GS-441524;
$F_{P->M1}$ = fraction of RDV metabolized to GS-704277; $F_{M1->M2}$ = fraction of GS-704277 metabolized to GS-441524;
IV = intravenous; PopPK = population pharmacokinetic; Q_1 = intercompartment clearance for RDV;
Q_2 = intercompartment clearance for GS-704277; Q_3 = first intercompartment clearance for GS-441524;
Q_4 = second intercompartment clearance for GS-441524; RDV = remdesivir.

Figure 1: PopPK Model Diagram for RDV, GS-704277, and GS-441524

To determine the full covariate model, each covariate that was identified as a significant covariate during the screening was added to the base model using a stepwise forward addition method. First, each covariate was added to the base model one at a time. All significant covariates at $P < 0.01$ with difference in objective function value (OFV) > 6.64 were retained. The most significant covariate was retained in the model, and the forward addition was repeated with the remaining significant covariates. Finally, all significant covariates were included to form a full popPK model. The error models for IIV and RV in the full multivariable model were evaluated following completion of forward selection. This evaluation included the addition of new IIV terms to other parameters in the model, reevaluation of the appropriateness of the functional form for each IIV term and the RV model, and assessment of possible correlations between eta (η) variables. The backward step started with the full popPK model. Each covariate was removed one at a time, and the least significant covariate that did not reach the P

< 0.001 level of significance (> 10.83) was dropped from the model. This process was repeated until all remaining covariates were significant when removed one at a time.

Table 2: Covariates in all subjects to be evaluated

Covariate	Possible Values	Reference Value	Parameter
Age	< 60 years old/≥ 60 years old	< 60 years old	CL, V_c
Sex	Male/female	Male	CL, V_c
Race	White, Black, Asian, Other	Caucasian	CL, V_c
Study population	Patient status within all subjects Hospitalization status (if patient) Patient status within adults	Patient Hospitalized Patient	CL
Ethnicity	Hispanic or Latino vs Not	Hispanic or Latino	CL

CL = clearance; V_c = central volume.

Table 3: Covariates in the paediatric data to be evaluated

Covariate	Possible Values	Reference Value	Parameter
Baseline AST	> 0 U/L	45 U/L (median)	CL
Baseline ALT	> 0 U/L	22 U/L (median)	CL
Baseline total bilirubin	> 0 mg/dL	0.20 mg/dL (median)	CL
Baseline albumin	> 0 g/dL	3.2 g/dL (median)	CL
Baseline eGFR by Bedside Schwartz	> 0 mL/min/1.73 m^2	111 mL/min/1.73 m^2 (median)	CL
Baseline eGFR by Schwartz	> 0 mL/min/1.73 m^2	111 mL/min/1.73 m^2 (median)	CL
Baseline ferritin	> 0 ng/mL	180 ng/mL (median)	CL
Baseline C-reactive protein	> 0 mg/dL	6.95 mg/dL (median)	CL
Oxygen support status	1 - Death 2 - Hospitalized, on invasive mechanical ventilation or ECMO 3 - Hospitalized, on noninvasive ventilation or high-flow oxygen devices 4 - Hospitalized, requiring low flow supplemental oxygen 5 - Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise) 6 - Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care (other than per protocol RDV administration) 7 - Not hospitalized 8 - Not assessed	5 - Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise)	CL

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CL = clearance; COVID-19 = coronavirus disease 2019; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate.

Allometric scaling was chosen as superior to modelled weight exponents. In the previously developed model for HV, CL- and Q-related weight exponents were fixed to 0.75, and V-related weight exponents were fixed to 1.0. Modelled weight exponents were explored in subjects aged ≥ 6 years for the RDV base model and compared to the allometric scaling mentioned. The sparsity of data in subjects aged < 6 years and the potential impact of maturation may have obscured the impact of modelled weight exponents and was not considered for initial tests.

A maturation function was incorporated for the CL of RDV and GS-704277. Unlike RDV and GS-704277, GS-441524 follows a glomerular filtration. Baseline creatinine clearance (BCRCL) is considered a marker for glomerular filtration. Given that BCRCL was not identified as an impactful covariate, a maturation function was not considered for GS-441524. Various maturation functions identified in the literature were considered, and the selected final form, which adequately recreates the maturation process is as follows:

$$CL_{POP} = \frac{Adult_{max} - F_{birth}}{AGE50^{nexp} + age^{nexp}} \cdot age^{nexp} + F_{birth}$$
$$= \frac{1 - 0.205}{0.542^{0.977} + age^{0.977}} \cdot age^{0.977} + 0.205$$

Where $CLPOP$ is a factor that decreases CL as a function of AGE expressed in years. The effect of including this maturation function was investigated on subjects aged ≥ 6 years in addition to allometric scaling and modelled weight exponents. In both cases, the impact of adding a maturation function was minor in terms of OFV (< 1.5 difference in both cases) and parameter estimates. Additionally, even with the inclusion of a maturation function, the allometric weight scaling was deemed preferable given the small difference on OFV, the instability caused by the added parameters, and the unrealistic estimates for modelled weight exponents. Moreover, to further improve the fit on younger subjects, the estimation of $AGE50$ was evaluated. However, given the sparsity of data in the youngest age groups compared to adults, $AGE50$ was estimated to approach 0. Given the small penalty on OFV (< 3 points), $AGE50$ was fixed to 0.542.

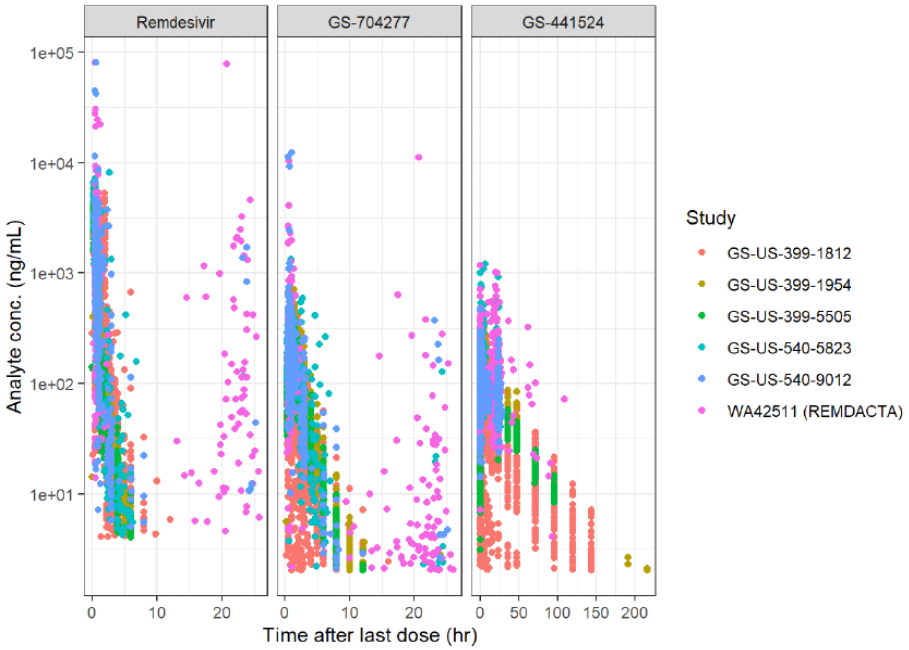
A significant fraction of the data was BLQ; thus, a censored-data likelihood method (M3 method in NONMEM) was evaluated. However, it is known that some of the limiting factors for using M3 methods are the longer runtimes, unsuccessful minimizations, and general instability of the models. Thus, when the M3 method was proven to be too unstable to move forward to a covariate step, a left censoring method was considered (M6 method in NONMEM). To implement the M6 method, the first BLQ sample was imputed to half of the lower limit of quantification, and all other BLQ samples were ignored. The change resulted in increased stability of the model, and the M6 method was selected moving forward.

Given the discrepancy in variability between Phase 3 studies (GS-US-540-9012 and WA42511) and the other studies, different IIVs were considered for Phase 3 studies. Variance of residual errors was also estimated separately, depending on phase study.

Simulations were conducted to evaluate RDV, GS-704277, and GS-441524 exposures at Day 1 (area under the concentration versus time curve from time 0 to 24 hours [AUC0-24], maximum observed concentration [C_{max}]); steady-state exposures (area under the concentration versus time curve over the dosing interval [AUC_{tau}], C_{max} at steady state, observed drug concentration at the end of the dosing interval [C_{tau}], and t1/2); as well as the sum of volume of distribution of all compartments and CL.

Model Results

The figure below displays semi-logarithmic plots of RDV, GS-704277, and GS-441524 concentration over time. The plots show, in general, a monoexponentially decline in all analyte concentrations after administration. For RDV and GS-704277 high variability is described for later timepoints in paediatric patients (pink circles).



PK = pharmacokinetic; RDV = remdesivir.
Each circle represents an individual PK observation for RDV (left), GS-704277 (middle), and GS-441524 (right), with circles colored based on study.
Source: EDA_POPPK.html

Figure 2: RDV, GS-704277, and GS-441524 concentration-time after dose profiles

Plasma concentrations of RDV, GS-704277, and GS-441524 were described following a sequential modelling approach by 2-compartment models for RDV and GS-704277 and a 3-compartment model for GS-441524 with first-order elimination. The effect of body weight was described by fixed allometry by fixing CL-related body weight exponents to 0.75 and volume of distribution-related body weight exponents to 1.0. A maturation function was added to accurately describe the CL of RDV and GS-704277 on the youngest subjects.

Hospitalised COVID-19 patients, adult and paediatric, had a lower CL (28.1% decrease) of GS-704277. Given the lack of non-hospitalised paediatric COVID-19 patient data, it was assumed that the effect of hospitalization was the same between adult and paediatric patients. Within the paediatric population, baseline ferritin was found to impact the CL (20.1% decrease) of GS-704277, and baseline bilirubin was found to impact the CL (25% decrease) of GS-441524. IIV was separately included for Phase 3 participants versus Phase 1 or Phase 2/3 participants.

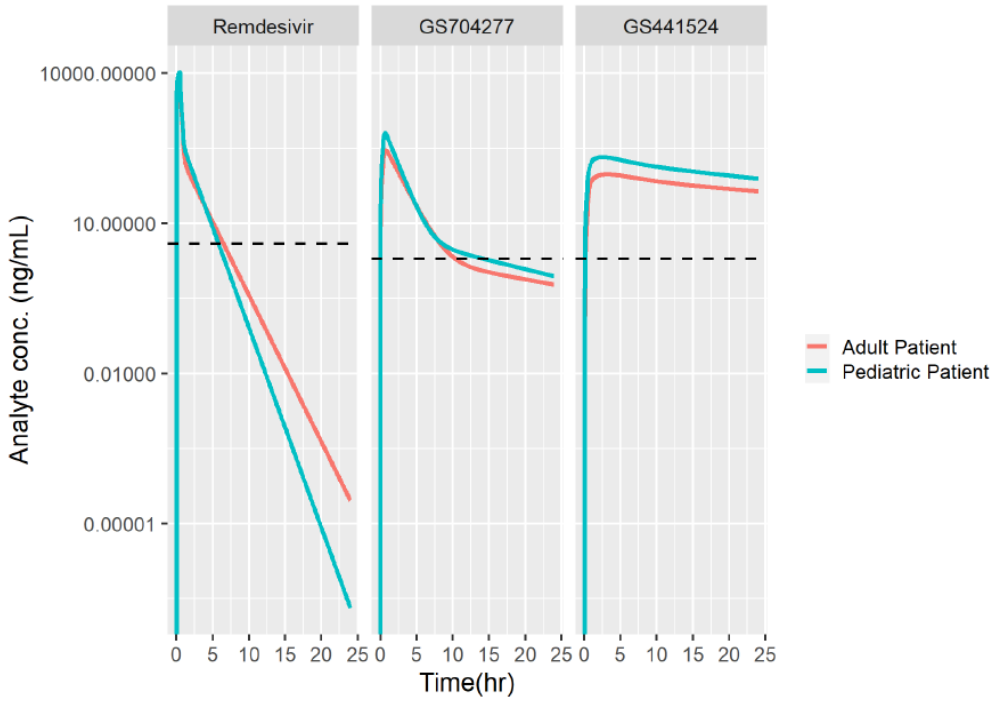
For a 90-kg, 58-year old, hospitalised adult with COVID-19 (a typical adult patient) receiving IV RDV 200 mg on Day 1 followed by IV RDV 100 mg once daily, the typical RDV CL, intercompartmental CL of central compartment (Q), Vc, and peripheral volume of distribution (Vp) values were 59.1 L/h, 6.18 L/h, 9.11 L, and 8.20 L, respectively. The t1/2 of RDV was 1.03 hours. The typical GS-704277 CL, Q, Vc, and Vp values were 247 L/h, 13.7 L/h, 367 L, and 215 L, respectively. The t1/2 of GS-704277 was 11.5 hours. The typical GS-441524 CL, Q, intercompartmental CL of peripheral compartment (Q2), Vc, Vp, and second peripheral volume.

(Vp2) values were 31.3 L/h, 638 L/h, 55.6 L/h, 193 L, 479 L, and 383 L, respectively. The t1/2 of GS-441524 was 25.5 hours. It is worth noting that for GS-704277, the calculated t1/2 based on post hoc estimations (11.5 hours) was higher than the previously reported t1/2 (2 hours).

For a 25.4-kg, 8-year old, child with COVID-19 (a typical paediatric patient) (receiving a 5-mg/kg loading dose followed by 4 maintenance doses at 2.5 mg/kg of RDV, the typical RDV CL, Q, Vc, and Vp

values were 21.8 L/h, 2.39 L/h, 2.57 L, and 2.31 L, respectively. The t1/2 of RDV was 0.753 hours. The typical GS-704277 CL, Q, Vc, and Vp values were 91.2 L/h, 5.31 L/h, 104 L, and 60.7 L, respectively. The t1/2 of GS-704277 was 8.43 hours. The typical GS-441524 CL, Q, Q2, Vc, Vp, and Vp2 values were 12.1 L/h, 247 L/h, 21.5 L/h, 54.3 L, 135 L, and 108 L, respectively. The t1/2 of GS-441524 was 18.6 hours.

The simulation of RDV, GS-704277, and GS-441524 concentration-time profiles for this reference 90-kg, 58-year old, hospitalised adult with COVID-19 and for a 25.4-kg, 8-year old child with COVID-19 are shown in the figure below. The table below provides the final parameter estimates and standard errors associated with the final PopPK model.



COVID-19 = coronavirus disease 2019; LLOQ = lower limit of quantitation; RDV = remdesivir.
Notes: Adult Patient represents a 90-kg, 58-year-old, hospitalized adult with COVID-19. Pediatric Patient represents a 25.4-kg, 8-year-old, child with COVID-19 receiving a 5-mg/kg loading dose following protocol. Dotted lines represent LLOQ of each analyte: RDV (4 ng/mL), GS-704277 (2 ng/mL), GS-441524 (2 ng/mL).
Source: PPK-Diagnostics.html

Figure 3: Simulated RDV, GS-704277, and GS-441524 concentration-time profiles for reference adult and paediatric COVID-19 patients

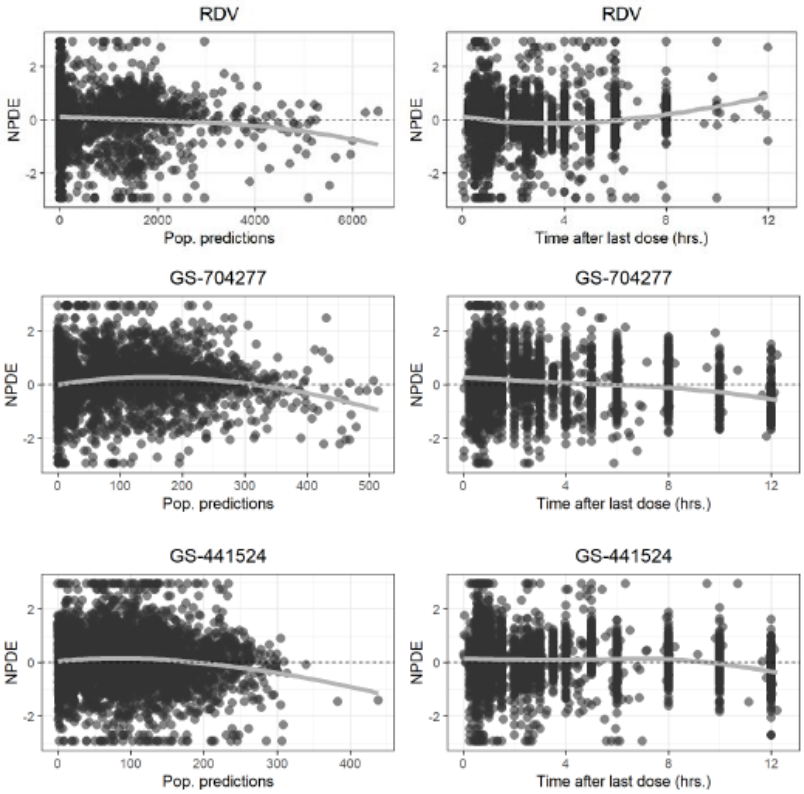
Table 4: Summary of sequential final model PK parameters for Remdesivir (GS-5734), GS-704277, and GS-441524

Parameter – Model	Parameter Description	Population Estimate	RSE%
Structural Model Parameters			
θ_1 – remdesivir	CL - remdesivir (L/h)	49.4	3.1
θ_2 – remdesivir	Central volume - remdesivir (L)	7.09	6.09
θ_3 – remdesivir	Peripheral volume - remdesivir (L)	6.38	4.82
θ_4 – remdesivir	Intercompartment clearance - remdesivir (L/h)	5.12	4.88
θ_1 - GS-704277	CL - GS-704277 (L/h)	287	4.67
θ_2 - GS-704277	Central volume - GS-704277 (L)	285	6.66
θ_3 - GS-704277	Peripheral volume - GS-704277 (L)	167	28.1
θ_4 - GS-704277	Intercompartment clearance - GS-704277 (L/h)	11.4	13.4
θ_7 - GS-704277	Effect of baseline ferritin for pediatric subjects on clearance	−0.201	42.4
θ_8 - GS-704277	Effect of hospitalization for patients on clearance	−0.281	18.7
θ_9 - GS-704277	Effect of age for subjects 60 years or older on central volume	−0.324	21.7
θ_1 - GS-441524	Clearance - GS-441524 (L/h)	26	2.62
θ_2 - GS-441524	Central volume - GS-441524 (L)	150	6.53
θ_3 - GS-441524	First peripheral volume - GS-441524 (L)	373	3.77
θ_4 - GS-441524	Intercompartment clearance to first periph. Cmt. GS-441524 (L/h)	529	5.41
θ_5 - GS-441524	Second peripheral volume - GS-441524 (L)	298	5.94
θ_6 - GS-441524	Intercompartment clearance to second periph. Cmt. GS-441524 (L/h)	46	6.8
θ_9 - GS-441524	Effect of age for subjects 60 years or older on clearance	−0.341	10.2
θ_{10} - GS-441524	Effect of baseline bilirubin for pediatric subjects on clearance	−0.25	56
Interindividual Variability Parameters			
ω^2_{11} – remdesivir	IIV on CL-remdesivir, Phases 1 and 2/3 (%CV)	15.7%	36.9
ω^2_{22} – remdesivir	IIV of V_c -remdesivir, Phases 1 and 2/3 (%CV)	15.2%	78.9
ω^2_{33} – remdesivir	IIV of CL-remdesivir, Phase 3 (%CV)	111%	38
ω^2_{44} – remdesivir	IIV of V_c -remdesivir, Phase 3 (%CV)	157%	25.3
ω^2_{11} - GS-704277	IIV on CL-GS-704277, Phases 1 and 2/3 (%CV)	17.2%	19.6
ω^2_{22} - GS-704277	IIV of V_c -GS-704277, Phases 1 and 2/3 (%CV)	28.6%	27.3
ω^2_{33} - GS-704277	IIV of CL-GS-704277, Phase 3 (%CV)	53%	32.9
ω^2_{44} - GS-704277	IIV of V_c -GS-704277, Phase 3 (%CV)	123%	22.1
ω^2_{11} - GS-441524	IIV on CL-GS-441524, Phases 1 and 2/3 (%CV)	17.5%	20.7
ω^2_{22} - GS-441524	IIV of V_c -GS-441524, Phases 1 and 2/3 (%CV)	88%	20.7

Parameter – Model	Parameter Description	Population Estimate	RSE%
ω^2_{33} - GS-441524	IIV of Vp1-GS-441524, Phases 1 and 2/3 (%CV)	21.6%	20.1
ω^2_{44} - GS-441524	IIV of Vp2-GS-441524, Phases 1 and 2/3 (%CV)	30.3%	40.1
ω^2_{55} - GS-441524	IIV on CL-GS-441524, Phase 3 (%CV)	32.8%	15.5
ω^2_{66} - GS-441524	IIV of V_c -GS-441524, Phase 3 (%CV)	98.2%	25.9
ω^2_{77} - GS-441524	IIV of Vp1-GS-441524, Phase 3 (%CV)	128%	21
ω^2_{88} - GS-441524	IIV of Vp2-GS-441524, Phase 3 (%CV)	187%	20.2
Residual Variability Parameters			
σ_1 – remdesivir	Variance of residual error - remdesivir, Phases 1 and 2/3	0.6	14.1
σ_2– remdesivir	Variance of residual error - remdesivir, Phase 3	1.78	8.28
σ_1 – GS-704277	Variance of residual error - GS-704277, Phases 1 and 2/3	0.125	29.1
σ_2– GS-704277	Variance of residual error - GS-704277, Phase 3	0.782	45
σ_1 – GS-441524	Variance of residual error - GS-441524, Phases 1 and 2/3	0.231	8.59
σ_2– GS-441524	Variance of residual error - GS-441524, Phase 3	0.929	10.5
sqrt(θ5) – remdesivir	Proportional residual error - remdesivir (%CV)	40.4%	7.11
θ6 – remdesivir	Additive residual error - remdesivir (ng/mL)	1.78	1.64
sqrt(θ5) - GS-704277	Proportional residual error - GS-704277 (%CV)	75.8%	15.6
θ6 - GS-704277	Additive residual error - GS-704277 (ng/mL)	1	
sqrt(θ7) - GS-441524	Proportional residual error - GS-441524 (%CV)	21.9%	0.56
θ8 - GS-441524	Additive residual error - GS-441524 (ng/mL)	1	

θ = absolute value of the estimate; %CV = percentage coefficient of variation; IIV = interindividual variability; OFV = objective function value; periph. Cmt. = peripheral compartment; PK = pharmacokinetic; RDV = remdesivir; RSE = relative standard error; σ = variance of residual error; ω = interindividual variability; V_c = central volume; Vp1 = first peripheral volume; Vp2 = second peripheral volume.
OFV–remdesivir = 25248.242, OFV–GS-704277= 20924.235, OFV–GS-441524 = 26379.828
Condition number– Remdesivir = 58.56, Condition number – GS-704277= 993.9, Condition number – GS-441524 = 119.4
Source: PPK-Diagnostics.html

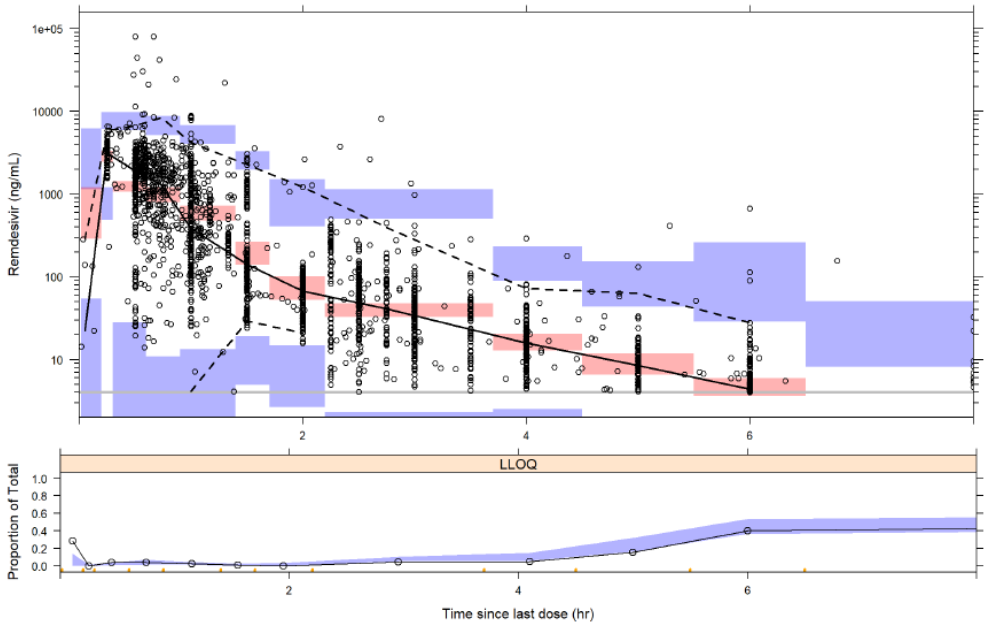
The NPDEs of RDV, GS-704277, and GS-441524 plasma concentration-time profiles are shown in the figure below.



NPDE = normalized prediction distribution error; PopPK = population pharmacokinetic; RDV = remdesivir.
NPDE versus Pop. Predictions (left), time after the last dose (right), for RDV (upper), GS-704277 (middle), and GS-441524 (lower) are presented in the plots. Points are individual NPDE. The gray line is the LOESS smooth curve.
Source: PPK-Diagnostics.html

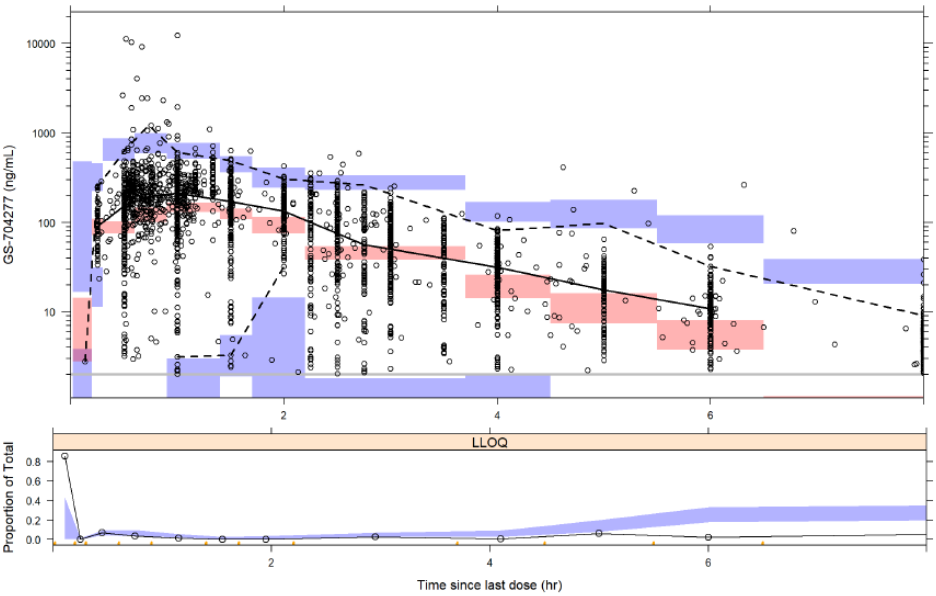
Figure 4: NPDE of the final sequential RDV, GS-704277, and GS-441524 PopPK model

The overall VPCs of RDV, GS-704277, and GS-441524 plasma concentration-time profiles are shown in Figure 5, Figure 6, and Figure 7, respectively. VPCs of RDV, GS-704277, and GS-441524 plasma concentration-time profiles stratified by age for RDV are also presented in Figure 8.



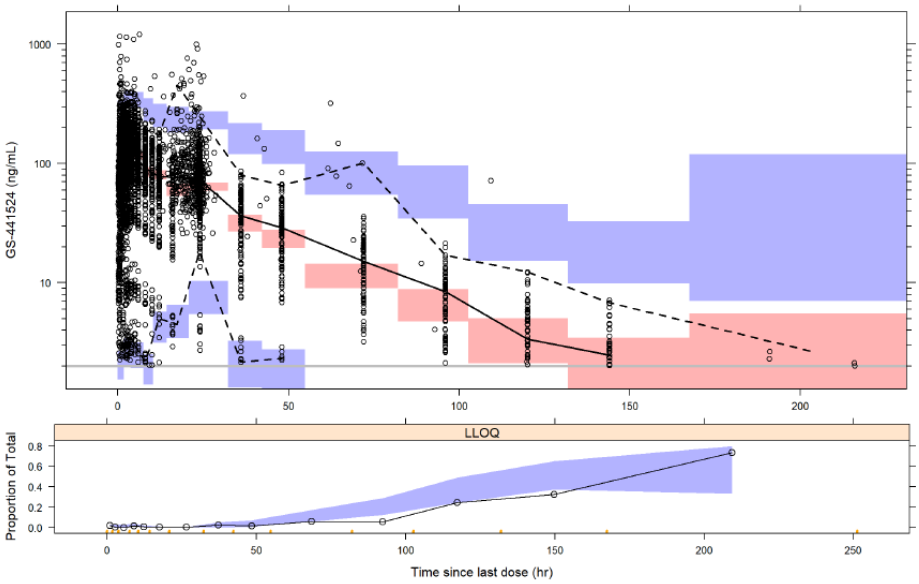
BLQ = below the limit of quantitation; CI = confidence interval; DV = observed concentrations; LLOQ = lower limit of quantitation; VPC = visual predictive check.
The VPC plots show the median (solid black lines) and spread (5th to 95th percentiles, dashed black line) of the DV (open circles) in all subjects. The red area is the 95% CI of the simulated median, and the blue area is the 95% CI of the simulated 5th and 95th percentiles. For the LLOQ panel, open circles and black solid lines show the observed proportion of BLQ samples, whereas the blue area shows the 95% CI of the simulated BLQ samples.
Source: PPK-Diagnostics.html

Figure 5: Overall VPC of the final Remdesivir (GS-5734) model



BLQ = below the limit of quantitation; CI = confidence interval; DV = observed concentrations; LLOQ = lower limit of quantitation; VPC = visual predictive check.
The VPC plots show the median (solid black lines) and spread (5th to 95th percentiles, dashed black line) of the DV (open circles) in all subjects. The red area is the 95% CI of the simulated median, and the blue area is the 95% CI of the simulated 5th and 95th percentiles. For the LLOQ panels, open circles and black solid lines show the observed proportion of BLQ samples, whereas the blue area shows the 95% CI of the simulated BLQ samples.
Source: PPK-Diagnostics.html

Figure 6: Overall VPC of the final GS-704277 model



BLQ = below the limit of quantitation; CI = confidence interval; DV = observed concentrations; LLOQ = lower limit of quantitation; VPC = visual predictive check.
The VPC plots show the median (solid black lines) and spread (5th to 95th percentiles, dashed black line) of the DV (open circles) in all subjects. The red area is the 95% CI of the simulated median, and the blue area is the 95% CI of the simulated 5th and 95th percentiles. For the LLOQ panels, open circles and black solid lines show the observed proportion of BLQ samples, whereas the blue area shows the 95% CI of the simulated BLQ samples.
Source: PPK-Diagnostics.html

Figure 7: Overall VPC of the final GS-441524 model

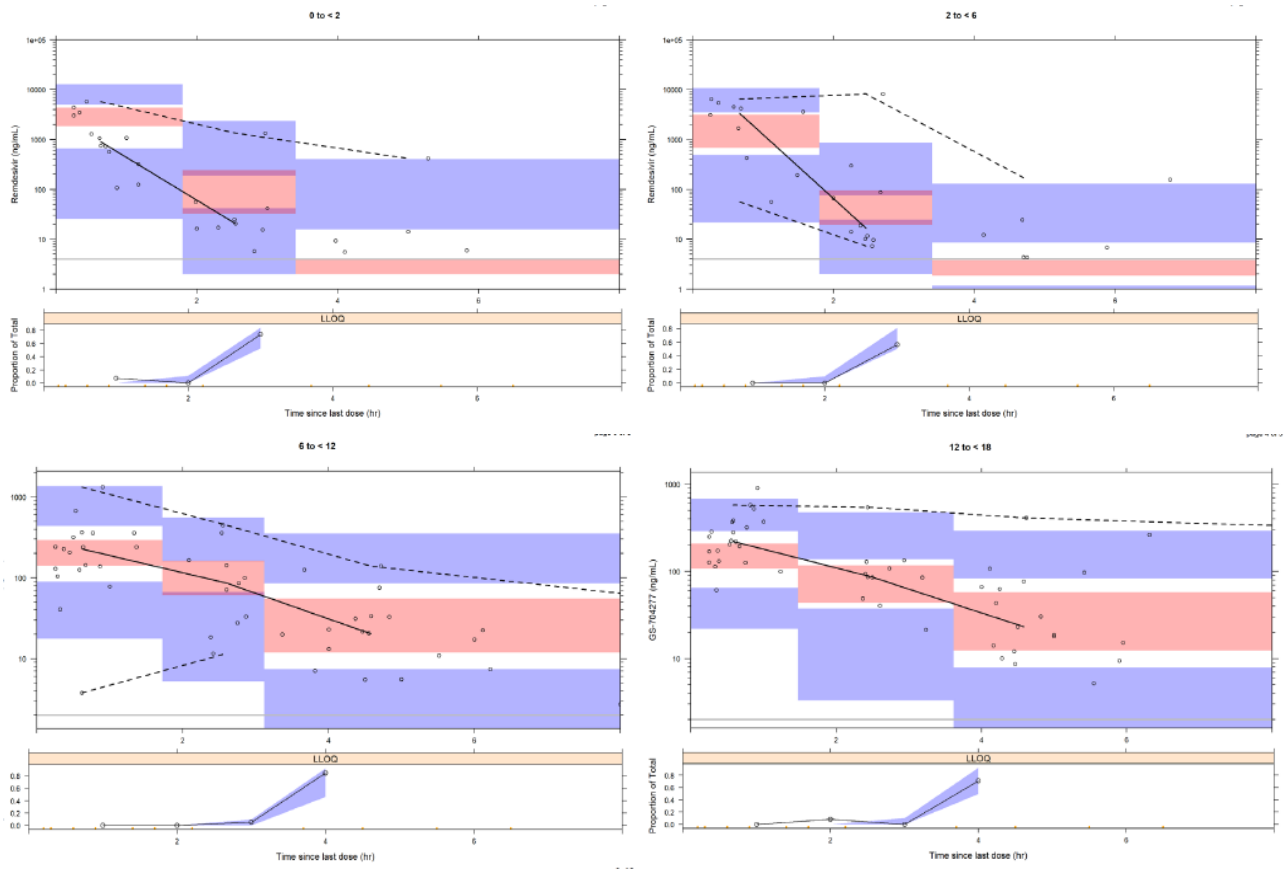


Figure 8: VPC Stratified by age of the final Remdesivir (GS-5734) model

The univariate analysis to identify significant covariates for the expected steady-state exposure of GS-704277 in paediatric subjects was evaluated in a sensitivity analysis. The AUC_{tau} and C_{max} of GS-704277 were computed for each of the scenarios based on the final PopPK model. The sensitivity analysis results are shown in Figure 9. The range of simulated exposures presented in the black shaded bars were based on a dose regimen following protocol specifications. Specifically, subjects in Cohorts 1 and 8 were simulated to receive IV RDV 200mg on Day 1 followed by IV RDV 100 mg once daily; subjects in Cohorts 2 to 5 were simulated to receive IV RDV 5 mg/kg on Day 1 followed by IV RDV 2.5 mg/kg once daily. The exposure of those subjects in Cohorts 1 and 8 was scaled to match a weight-base dose regimen.

Each blue shaded bar represents the influence of single or combined covariates on the steady-state exposure. All simulated exposures presented in the blue shaded bars were based on a dose regimen of IV RDV 5 mg/kg on Day 1 followed by IV RDV 2.5 mg/kg once daily. The sensitivity analysis identified baseline ferritin as the most influential covariate, with a maximum percent change in GS-704277 exposures ranging from −24.5% to +66.6% (relative to the median exposures) for subjects with extreme covariate values. The covariate effect WT was also influential, resulting in GS-704277 exposures ranging from −37% to +40.9% in paediatric subjects for a body weight based dosing regimen.

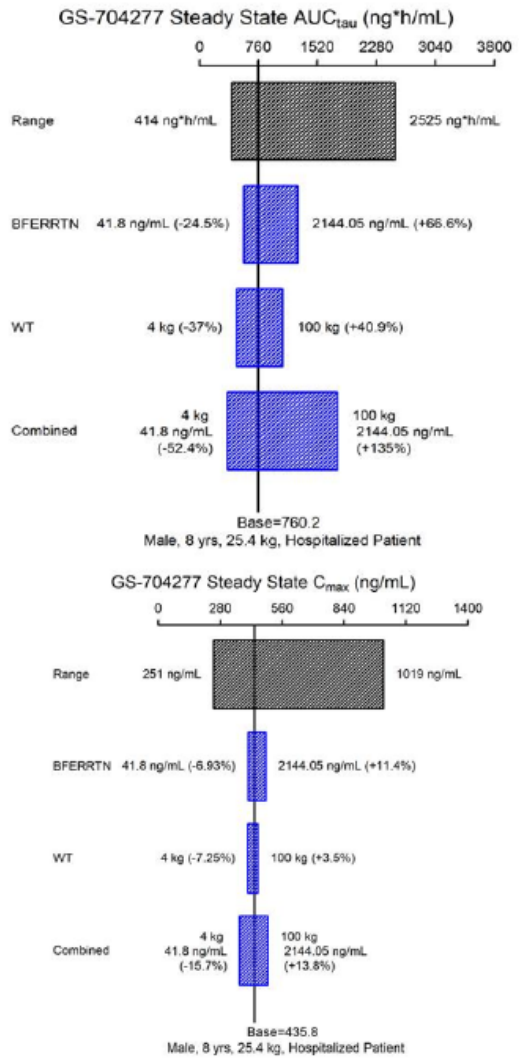


Figure 9: Sensitivity plot comparing the effect of covariates on GS-704277 steady-state AUC_{tau} and C_{max} in paediatric subjects

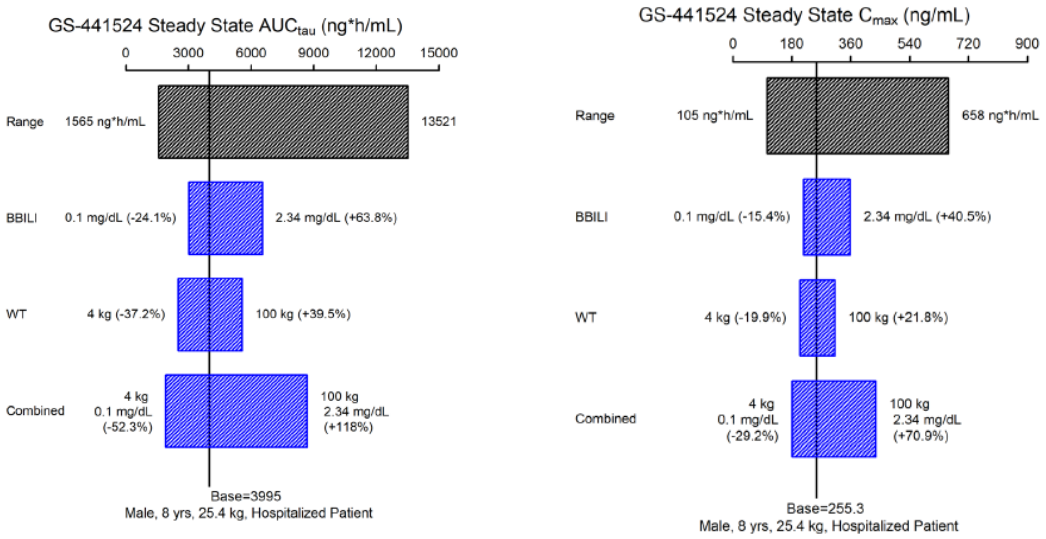


Figure 10: Sensitivity plot comparing the effect of covariates on GS-441524 steady-state AUC_{tau} and C_{max} in paediatric subjects

Similarly, the sensitivity analysis was conducted for GS-441524; the analysis showed that the effect of WT and baseline bilirubin was similar, with a maximum percent change in GS-441524 exposures ranging from −37.2% to +39.5% (relative to the median exposures) for subjects with extreme WT values at the body weight-based dosing regimen and −24.1% to +63.8% for subjects with extreme baseline bilirubin values. The identified covariates, including WT and baseline bilirubin on GS-441524 exposures, accounted for the majority of the observed PK variability, with approximately −52.3% to +118% change in AUC_{tau} and approximately −29.2% to +70.9% change in C_{max} for subjects with extreme covariate values relative to the median exposures.

In adults, simulations showed that RDV, GS-704277, and GS-441524 exposures were inversely correlated with weight, with a percent change in exposures ranging from −33.5% to +44.2% for adult patients with extreme covariate values. Weight was found to be the most influential covariate. The univariate analysis to identify significant covariates for the expected steady-state exposure of GS-704277 in adult subjects was evaluated in a sensitivity analysis. The AUC_{tau} and C_{max} of GS-704277 were computed for each of the scenarios based on the final PopPK model. The sensitivity analysis results are shown in Figure 11. The sensitivity analysis identified WT as the most influential covariate, with a maximum percent change in GS-704277 exposures ranging from −30.1% to +32.2% (relative to the median exposures) for subjects with extreme covariate values (i.e., 5^{th} and 95^{th} WT percentiles, respectively). The covariate effect of hospitalisation resulted in approximately 28.1% increase in GS-704277 exposures compared to non-hospitalised patients. The categorical effect of age for subjects aged ≥ 60 years had the smallest impact on GS-704277 exposures.

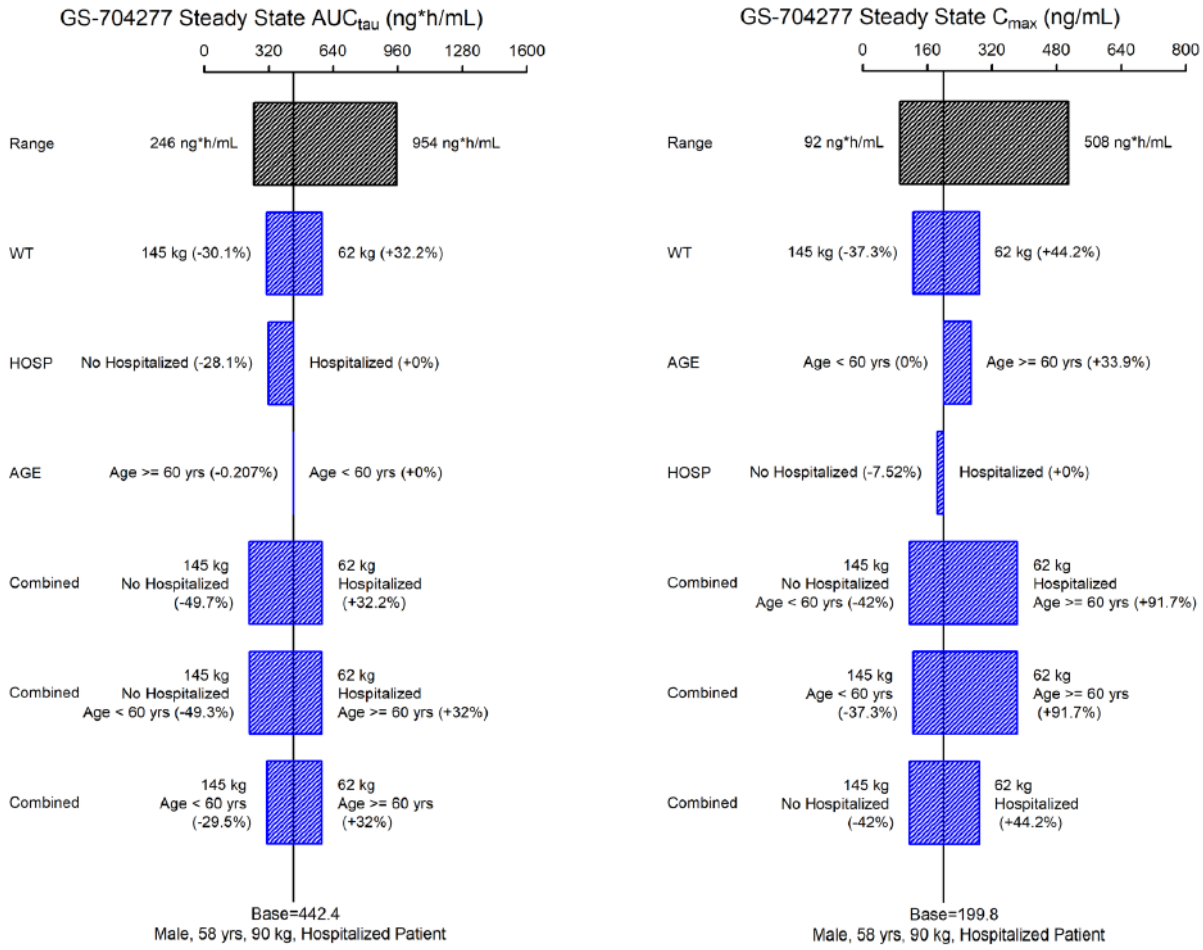


Figure 11: Sensitivity plot comparing the effect of covariates on GS-704277 steady-state AUC_{tau} and C_{max} in adult patients

Age as a continuous covariate was not identified as a statistically significant covariate for RDV, GS-704277, or GS-441524 in the final model in adults. However, age as a categorical covariate (subjects 60 years or older) was identified as a significant covariate on central volume of GS-704277 and CL of GS-441524. The impact of age as a continuous covariate on RDV, for adult COVID-19 patients is shown in the table below.

Table 5: Impact of age on mean (%CV) steady-state RDV exposure in adult COVID-19 patients who received RDV in studies GS-US-540-9012 and REMDACTA

Characteristics	Age				Median Q4 – Q1 % Difference
	Q1	Q2	Q3	Q4	
Age (years: min, median, max)	19, 37, 46	47, 53, 57	58, 61, 65	66, 71, 90	--
Number of subjects	109	103	106	106	--
RDV AUC_{tau} (h•ng/mL)	5731.7 (683.5)	10475.4 (569.4)	1849.5 (78.2)	2473.7 (116.4)	-20.7
RDV C_{max} (ng/mL)	3195.1 (136)	3952.2 (143)	3024.2 (52)	3654.1 (64.7)	-25.7

%CV = percentage coefficient of variation; AUC_{tau} = area under the concentration-time curve over 1 dosing interval; C_{max} = maximum steady-state concentration; COVID-19 = coronavirus disease 2019; max = maximum; min = minimum; Q = quartile;

The impact of age as a categorical covariate on RDV for adult COVID-19 patients is shown below.

Table 6: Impact of age as a categorical covariate on mean steady-state RDV exposure in adult COVID-19 patients who received RDV in studies GS-US-540-9012 and REMDACTA

Characteristics	Age		GMR (90% CI) (%)
	Age < 60 Years	Age ≥ 60 Years	
Number of subjects	245	179	
RDV AUC_{tau} (h•ng/mL)	1564.11	1720.00	90.94 (78.17, 105.79)
RDV C_{max} (ng/mL)	2504.69	2915.64	85.91 (76.41, 96.58)

AUC_{tau} = area under the concentration-time curve over 1 dosing interval; CI = confidence interval; C_{max} = maximum steady-state concentration; GMR = geometric mean ratio calculated by age < 60 and age ≥ 60 years old; No. = number; RDV = remdesivir.
Source: TFLs_Gilead_Oct8.html

The following Boxplots in *Figure 12*, *Figure 14*, and *Figure 13* show AUC_{tau} values by age/weight cohort.

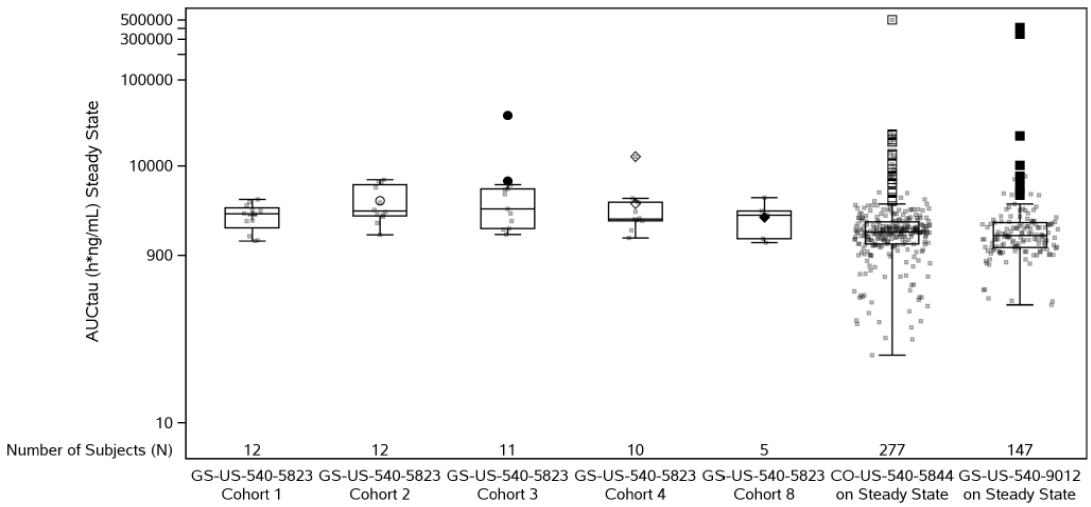


Figure 12: Boxplots of steady-state plasma RDV PK parameters from population PK modelling RDV PK analysis Set GS-US-540-5823 Cohort 1, 2, 3, 4 and 8 vs. CO-US-540-5844 and GS-US-540-9012 on steady state

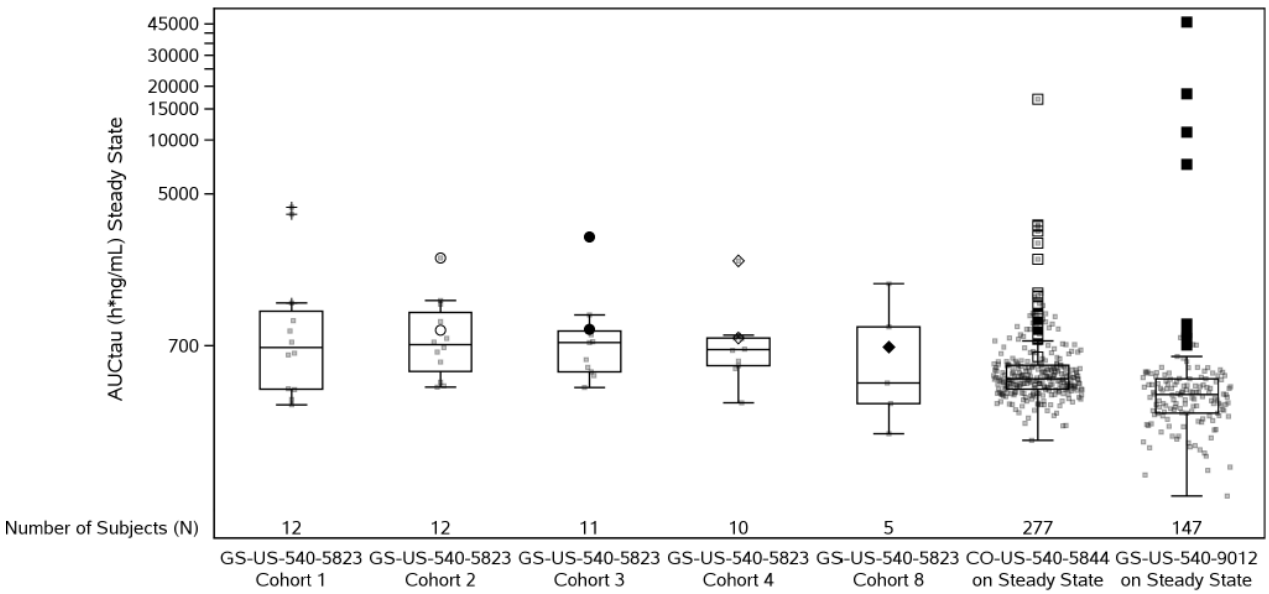


Figure 13: Boxplots of steady-state plasma GS-704277 metabolite PK parameters from population PK modelling metabolites PK analysis set GS-US-540-5823 Cohort 1, 2, 3, 4 and 8 vs. CO-US-540-5844 and GS-US-540-9012 on steady state

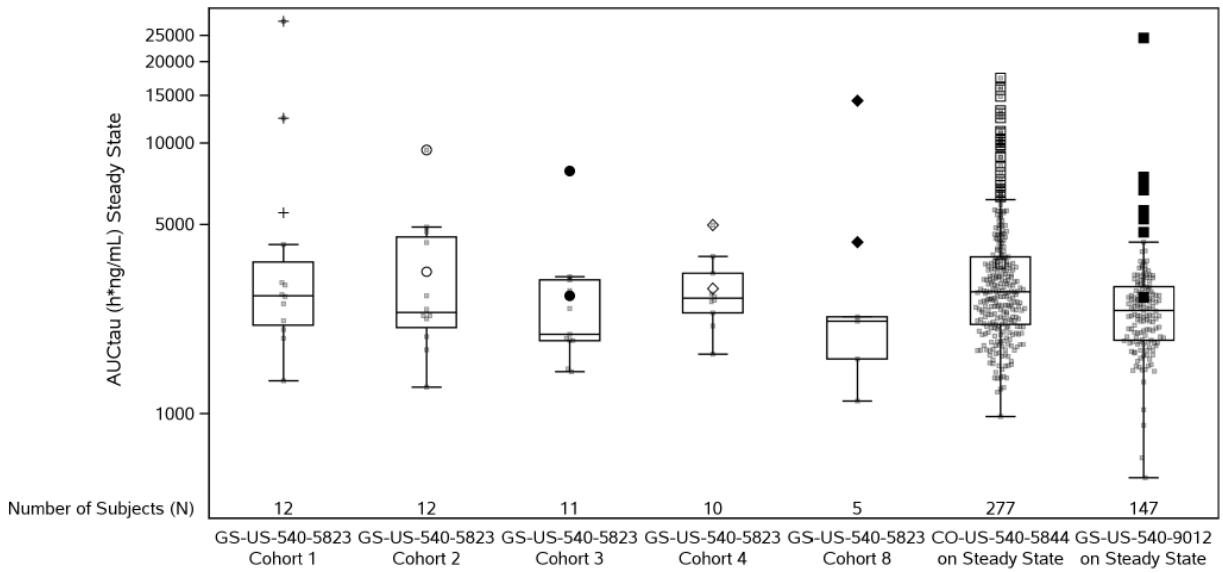


Figure 14: Boxplots of steady-state plasma GS-441524 metabolite PK parameters from population PK modelling metabolites PK analysis set GS-US-540-5823 Cohort 1, 2, 3, 4 and 8 vs. CO-US-540-5844 and GS-US-540-9012 on steady state

2.3.5. Discussion on clinical pharmacology

The previous preliminary population PK model was updated and refined using paediatric data and adult phase 3 data. The popPK model was developed using plasma concentrations for Remdesivir and two metabolites (GS-704277 and GS-441524) using sequential 2-compartment models for RDV and GS-704277, and a 3-compartment model for GS-441524. Allometric scaling and a maturation function were used in the model.

The dose selection for children was based on simulations from the PBPK model from 2020, including limited adult data and plasma concentrations (without paediatric data). The PBPK model was not updated with the new studies (-5823 and -9012), instead exposure in children and adolescents were evaluated with the popPK model. Based on the clinical data, the predictions of the old PBPK model are not reflective of the measured concentrations in paediatric patients, as plasma concentrations and exposures determined in paediatric patients revealed higher values than expected compared to adults. However, the interpretation of this data was difficult due to small sample size and high variability in phase 3 data. In addition, data from the popPK model indicate that exposure (C_{max} and AUC) were two-fold higher in paediatric patients compared to adults questioning the dosing strategy or the aimed target exposure in paediatric patients. Upon request simulations were provided which the dose strategy that would lead to plasma concentrations in paediatric patients that were comparable to adults. In addition, boxplots comparing exposure in between children and adults using a linear scale were also provided. In light of the information provided, the increase of remdesivir and GS-704277 concentrations are expected to be transient due to their short half-lifes and on the other hand, the concentration of the intracellularly formed metabolite GS-441524 was only slightly affected. Moreover, there is no clear correlation between exposure and weight/age and thus the MAH´s conclusion that no dose reduction is required is supported from the PK view. However, it was considered more adequate to compare the paediatric PK data with the PK data from hospitalised adult patients and the respective data were requested for the final conclusion on exposure in paediatric patients. The comparison of PK parameters AUC, C_{max} and C_{min} between the hospitalized paediatric patients (from Study GS-US-540-5823) and hospitalized adult patients (from Study CO-US-540-5844) were submitted. For the most relevant compound (GS-441524), paediatric exposure was comparable to adult exposure in an acceptable range. The differences observed seem probably due the uncertainties in exposure parameters resulting from very sparse sampling in hospitalized patients.

From a safety point of view, it is agreed that RDV was well tolerated during clinical studies in paediatric patients and the safety data reported during study GS-US-540-5823 are comparable to the studies in adults. Overall, no safety signal was identified based on the data provided.

Baseline ferritin (for GS-704277) and baseline bilirubin (for GS-441524) were revealed as most influential covariates in paediatric patients, this was not considered regarding dosing recommendations but might be an option to reduce variability.

2.3.6. Conclusions on clinical pharmacology

The MAH was asked to justify the higher exposure seen in paediatric patients above 4 weeks of age and weighing at least 3.5 kg especially in terms of safety and SBECD exposure. Simulations were provided which dose strategy led to plasma concentrations in paediatric patients that are comparable to adults. In light of the complementary information provided, the MAH´s conclusion that no dose reduction is required is supported from the PK view. The safety data reported during study GS-US-540-5823 are comparable to the studies in adults. Overall, no safety signal was identified based on the data provided.

2.4. Clinical efficacy

2.4.1. Dose response studies

No additional dose response studies have been submitted.

2.4.2. Main studies

1.-The study supporting the clinical efficacy and safety of RDV for the treatment of COVID-19 in paediatric patients aged ≥ 28 days to < 18 years of age and weighing ≥ 3 kg with pneumonia requiring oxygen (low- or high-flow oxygen or other non -invasive ventilation at start of treatment) is the ongoing Phase 2/3 uncontrolled, open-label, single arm study (GS-US-540-5823) evaluating the safety, tolerability, PK, and efficacy of RDV in paediatric participant in 53 participants from birth to < 18 years of age.

2.-The study supporting the clinical efficacy and safety of remdesivir in paediatric patients >12 years of age weighing at least 40 kg who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19 is the phase 3, randomized, double-blind, placebo-controlled, multicenter study (GS-US-540-9012) evaluating the efficacy and safety of treatment of early stage COVID-19 with IV-administered Remdesivir in an outpatient setting in 584 participants with confirmed COVID-19 who were at increased risk for disease progression.

For study GS-US-540-9012 only the subset of eight adolescents with COVID-19 were considered.

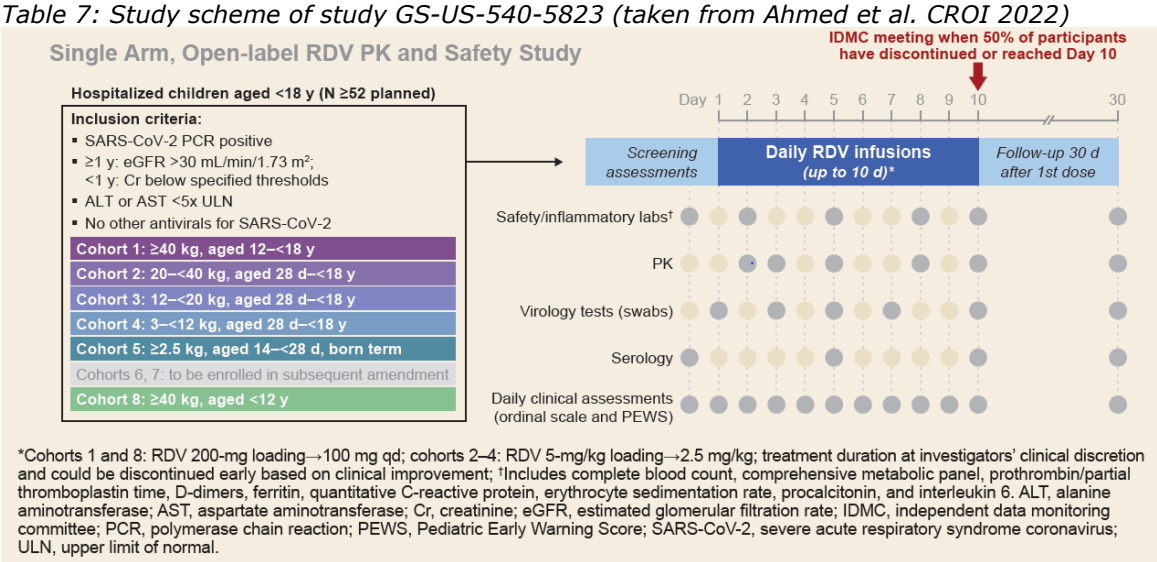
Study GS-US-540-5823 (CARAVAN study)

A Phase 2/3 single-arm, open-label study to evaluate the safety, tolerability, pharmacokinetics, and efficacy of Remdesivir (GS-5734™) in participants from birth to < 18 years of age with COVID-19.

Methods

Study GS-US-540-5823 is an open-label, single-arm study to evaluate the safety, tolerability, pharmacokinetics, and efficacy of Remdesivir (GS-5734™) in participants from birth to < 18 years of age with laboratory-confirmed COVID-19. The study is a multi-centre trial, conducted at 19 sites globally, including two sites in the EU, one site in the UK and 13 sites in the US.

Table 7: Study scheme of study GS-US-540-5823 (taken from Ahmed et al. CROI 2022)



*Cohorts 1 and 8: RDV 200-mg loading→100 mg qd; cohorts 2–4: RDV 5-mg/kg loading→2.5 mg/kg; treatment duration at investigators' clinical discretion and could be discontinued early based on clinical improvement; †Includes complete blood count, comprehensive metabolic panel, prothrombin/partial thromboplastin time, D-dimers, ferritin, quantitative C-reactive protein, erythrocyte sedimentation rate, procalcitonin, and interleukin 6. ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; eGFR, estimated glomerular filtration rate; IDMC, independent data monitoring committee; PCR, polymerase chain reaction; PEWS, Pediatric Early Warning Score; SARS-CoV-2, severe acute respiratory syndrome coronavirus; ULN, upper limit of normal.

Cohorts 1 through 5 and 8 were enrolled in parallel. Participants in Cohorts 6 and 7 will only be enrolled once RDV exposures have been evaluated from Cohort 5 and a dose has been determined.

Study participants

Main inclusion criteria:

Children and adolescents < 18 years who had SARS-CoV-2 infection confirmed by PCR, were hospitalized and required medical care for COVID-19, and had the following body weight criteria were included:

- Weight at screening ≥ 40 kg for ≥ 12 years to < 18 years of age
- Weight at screening ≥ 3 kg to < 40 kg for ≥ 28 days to < 18 years of age
- Weight at screening ≥ 2.5 kg for ≥ 14 days to < 28 days of age or gestational age > 37 weeks
- Birth weight ≥ 2.5 kg for 0 days to < 14 days of age/gestational age > 37 weeks
- Birth weight ≥ 1.5 kg for 0 days to < 56 days of age/gestational age ≤ 37 weeks
- Weight at screening ≥ 40 kg for < 12 years of age

Main exclusion criteria:

- Concurrent treatment with other agents with actual or possible direct antiviral activity against SARS-CoV-2 < 24 hours prior to study drug dosing
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 x upper limit of normal (ULN)
- Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m2 using Schwartz formula for participants ≥ 1 year of age
- Creatinine above thresholds in table below for < 1 year of age

Gestational Age	Chronological Age	Creatinine Value Cutoff in mg/dL
24-27 weeks	0-28 days	≥ 1.6
28-29 weeks	0-14 days	≥ 1.1
30-32 weeks	0-7 days	≥ 1.0
	≥ 7 days to 1 month	≥ 0.8[a]
	≥ 1-2 months	≥ 0.6[a]
	≥ 2 months to < 1 year	≥ 0.5[a]
≥ 32 weeks	0-2 days	≥ 1.0[a]
	≥ 2-7 days	≥0.8[a]
	≥ 7 days to 2 months	≥ 0.6[a]
	≥ 2 months to < 1 year	≥ 0.5[a]

a Creatinine values exceed the 97.5th percentile {Vieux 2010} or upper limit {Colantonio 2012} of creatinine for age. Critical serum creatinine values for preterm infants {Bruel 2013, Kastl 2017}.

- If < 28 days of age, any major congenital renal anomaly
- On renal replacement therapies (intermittent haemodialysis [iHD], peritoneal dialysis [PD], and continuous renal replacement therapy [CRRT])
- Positive pregnancy test at screening only for female of childbearing potential

Prior and concomitant drugs:

Concomitant use of the following was prohibited in participants receiving RDV:

- Investigational agents for COVID-19 with direct antiviral effect including approved HIV protease inhibitors such as lopinavir (LPV)/ritonavir (RTV), chloroquine, interferon, etc. due to lack of evidence on additive or synergistic effects and potential for an increased risk of transaminase elevations
- Strong inducers of P-glycoprotein (e.g., rifampicin, rifabutin, carbamazepine, phenytoin or herbal medications)

Immune modulators are allowed as well as intravenous immunoglobulin (IVIG) and convalescent plasma.

Treatments

Regimens:

Remdesivir for injection, 100 mg, was administered as shown in the table below.

Shortly, patients below 12 years of age and weighing less than 40 kg received remdesivir according to their body weight.

Table 8: GS-US-540-5823: Study treatments

Cohort	Description	Dose
Pediatric participants ≥ 28 days to < 18 years old		
1	≥ 12 years to < 18 years and weight ≥ 40 kg	IV RDV 200 mg on Day 1 followed by IV RDV 100 mg daily up to 10 days
2	≥ 28 days to < 18 years and weight ≥ 20 kg to < 40 kg	IV RDV 5 mg/kg on Day 1 followed by IV RDV 2.5 mg/kg daily up to 10 days
3	≥ 28 days to < 18 years and weight ≥ 12 kg to < 20 kg	
4	≥ 28 days to < 18 years and weight ≥ 3 kg to < 12 kg	
Term neonatal participants 0 days to < 28 days old		
5	≥ 14 days to < 28 days of age, gestational age > 37 weeks, and weight at screening ≥ 2.5 kg	IV RDV 5 mg/kg on Day 1 followed by IV RDV 2.5 mg/kg daily up to 10 days
6	0 days to < 14 days of age, gestational age > 37 weeks, and birth weight ≥ 2.5 kg	RDV at a dose to be determined up to 10 days
Preterm neonates and infants 0 days to < 56 days old		
7	0 days to < 56 days of age, gestational age ≤ 37 weeks, and birth weight ≥ 1.5 kg	RDV at a dose to be determined up to 10 days
Exploratory cohort for pediatric participants < 12 years		
8	< 12 years and weight ≥ 40 kg	IV RDV 200 mg on Day 1 followed by IV RDV 100 mg daily up to 10 days

IV = intravenous; RDV = remdesivir (GS-5734™)

Duration of treatment:

The duration of treatment was up to 10 days. Those participants who demonstrated clinical improvement may have been considered for a shorter treatment period.

Justification of dose and duration of treatment:

The proposed clinical regimen for the treatment of patients weighing ≥ 40 kg with COVID-19 was as follows: single RDV 200 mg IV loading dose on Day 1 followed by RDV 100 mg IV once-daily maintenance doses for up to 9 days (Days 2 to 10).

The proposed clinical regimen for the treatment of patients weighing < 40 kg with COVID-19 (14 days old, born full term [gestational age (GA) > 37 weeks]) and with serum creatinine < 0.6 mg/dL) was as follows: single RDV 5 mg/kg IV loading dose on Day 1 followed by RDV 2.5 mg/kg IV once-daily maintenance doses for up to 9 days (Days 2 to 10).

Selection of this dosing regimen is based on the PK bridge from animal data to human doses and efficacy using the results of *in vivo* efficacy studies conducted in SARS-CoV-2- and Middle East respiratory syndrome (MERS)-CoV-infected rhesus monkeys, available PK data in healthy rhesus monkeys, and Phase 1 studies in healthy participants.

For the treatment of COVID-19, the approach has been to target exposures (plasma and peripheral blood mononuclear cells [PBMCs]) associated with efficacy at 10 mg/kg and 5 mg/kg in the SARS-CoV-2- and MERS-CoV-infected rhesus monkeys. Using allometric scaling, a clinical maintenance dose of daily 100 mg for adults provides systemic exposure of RDV in plasma and GS-443902 (active triphosphate) in PBMCs similar with that observed in rhesus monkeys at 5 mg/kg IV dose of RDV (Study AD-399-2030, Study GS-US-399-5505) (see table below).

Table 9: Pharmacokinetics of RDV in plasma and nucleoside triphosphate metabolite GS-443902 (PBMCs) following repeat RDV doses (30 min IV infusion) to healthy monkeys (5mg/kg) and healthy humans (100 mg)

	Mean (SD)	
	Healthy Rhesus Monkeys	Healthy Human Participants
PK Parameter (Mean [SD])	RDV 5 mg/kg (N = 8)	RDV 100 mg (N = 26)
Plasma RDV		
AUC[a] (h•ng/mL)	1430 (230)	1590 (264)
C_{max} (ng/mL)	3350 (390)	2230 (427)
PBMC GS-443902		
C_{24} (µM)	7.1 (6.7)	10.2 (5.05)[b]

IV = intravenous; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic(s); RDV = remdesivir (GS-5734™); SD = standard deviation

a AUC: healthy rhesus monkeys AUC_{0-24}; healthy human participants AUC_{tau}; PK data reported to 3 significant figures.

b N = 25.

Source: AD-399-2030, Tables 8 and 10; GS-US-399-5505 CSR, Tables 15.10.1.1.6.1, 15.10.1.1.6.4, and 16

Targeting efficacy seen at 10 mg/kg loading dose in infected rhesus monkeys requires a loading dose of 200 mg in humans. As shown in the table above, the PK of a single dose of 200 mg RDV in healthy participants is similar to the expected exposure in rhesus monkeys at 10 mg/kg (AUC 5 mg/kg ☐ 2 based on dose proportionality; AD-399-2002).

High intracellular trough concentrations of the active triphosphate metabolite GS-443902 have been observed in human PBMCs following a single RDV 200 mg dose or multiple IV doses of RDV 100 mg (Study GS-US-399-5505). These concentrations are approximately 1000-fold above the *in vitro* half-maximal effective concentration (EC_{50}) against SARS-CoV-2 (EC_{50} = 0.0099 µM) and SARS-CoV in primary human airway epithelial cells (EC_{50} = 0.0066 µM). These concentrations are also comparable with those observed in rhesus monkeys receiving RDV 5 mg/kg doses for 7 days, and the doses associated with efficacy in SARS-CoV-2- and MERS-CoV-infected rhesus monkey models.

Table 10: Pharmacokinetics of plasma RDV and nucleoside triphosphate metabolite GS-443902 (PBMCs) following a 200 mg single dose of RDV to healthy volunteers

PK Parameter (Mean [%CV])	Mean (%CV) Healthy Human Participants RDV 200 mg (N = 28)
Plasma RDV	
$AUC_{0\text{-}24}$ (h•ng/mL)	2860 (18.6)
C_{max} (ng/mL)	4380 (23.5)
PBMC GS-443902	
C_{24} (µM)	6.9 (45.8)

%CV = percentage coefficient of variation; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic(s); RDV = remdesivir (GS-5734™)
Source: GS-US- 399-5505 CSR, Table 15.10.1.1.6.1 and Table 15.10.1.1.6.4

Dose selection of RDV in paediatric patients was informed by a physiologically based PK (PBPK) model developed to characterize the PK of RDV and the primary circulating nucleoside metabolite, GS-441524, in adults (SimCYP v.17, Certara). The adult PBPK model was used to predict paediatric patient exposure, accounting for age-dependent changes in organ volume or size (liver and kidney), esterase expression, plasma protein binding, and organ blood flow. Simulations indicated that use of the adult dosage regimen in children ≥ 40 kg was predicted to maintain RDV and GS-441524 exposures generally within the expected adult steady-state exposure range following the adult dosage regimen. For paediatric patients > 14 days old, born full term (GA > 37 weeks) and with serum creatinine below thresholds in the table below, a loading dose of 5 mg/kg followed by 2.5 mg/kg once-daily maintenance doses of RDV was selected.

Gestational Age	Chronological Age	Creatinine Value Cut-off in mg/dL
24-27 weeks	0-28 days	≥ 1.6
28-29 weeks	0-14 days	≥ 1.1
30-32 weeks	0-7 days	≥ 1.0
	≥ 7 days to 1 month	≥ 0.8[a]
	≥ 1-2 months	≥ 0.6[a]
	≥ 2 months to < 1 year	≥ 0.5[a]
≥≥ 32 weeks	0-2 days	≥ 1.0[a]
	≥ 2-7 days	≥ 0.8[a]
	≥ 7 days to 2 months	≥ 0.6[a]
	≥ 2 months to < 1 year	≥ 0.5[a]

a Creatinine values exceed the 97.5th percentile {Vieux 2010} or upper limit {Colantonio 2012} of creatinine for age. Critical serum creatinine values for preterm infants {Bruel 2013, Kastl 2017}

Use of these doses in these paediatric patients was expected to maintain exposures of both RDV and GS-441524 at or below that which was previously observed to be well tolerated in healthy volunteers (N = 24, GS-US-399-1954). These simulations did not account for possible diminished liver or kidney function due to SARS-CoV-2 infection because the impact of infection on the PK of RDV and GS-441524 was unknown.

The efficacy of the proposed clinical regimen was being evaluated in patients with COVID-19 and was supported by clinical safety data in approximately 500 individuals who had received RDV in Phase 1 studies, non-Gilead-sponsored studies, and on an expanded-access basis for multiple indications.

Formulation:

Remdesivir for injection, 100 mg, was provided by the MAH for study 5823. Investigational product specifications are provided below.

Table 11: GS-US-5405823: Summary of investigational products

	Remdesivir (GS-5734™) for Injection	
Part number	PC-12532	
Strength (mg)	100 mg	
Batch No./Expiration date	EW2001A1 EW2002A1	May 2024 May 2024
Manufacturer/Supplier	Jubiliant HollisterStier LLC 3525 North Regal Street Spokane, WA 99207	
Site of release in Europe	Gilead Sciences Ireland UC	

Remdesivir for injection, 100 mg, is a preservative-free, white to off-white or yellow, lyophilized solid containing 100 mg of RDV that is to be reconstituted with sterile water for injection and diluted into 0.9% saline or 5% dextrose prior to administration by intravenous (IV) infusion.

In addition to the active ingredient, RDV for injection, 100 mg, contains the following inactive ingredients: SBECD, water for injection, hydrochloric acid, and sodium hydroxide. Hydrochloric acid and sodium hydroxide are used to adjust the formulation to a pH of 3.0 to 4.0.

Objectives/Endpoints

The primary objectives were to evaluate the safety and tolerability of RDV in participants with laboratory-confirmed COVID-19 aged 0 days to < 18 years and to evaluate the PK of RDV in participants with laboratory-confirmed COVID-19 aged 0 days to < 18 years. Nine additional secondary endpoints were related to efficacy and virology (see table below).

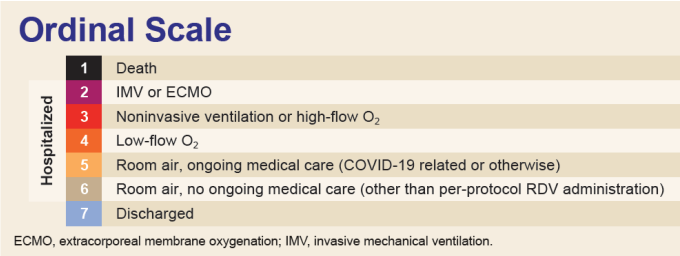
Table 12: Objectives and endpoints of study GS-US-540-9012

Primary Objectives	Primary End Points
• To evaluate the safety and tolerability of RDV in participants with laboratory-confirmed COVID-19 aged 0 days to < 18 years	• The proportion of participants with treatment-emergent adverse events (TEAEs) • The proportion of participants with treatment-emergent graded laboratory abnormalities
• To evaluate the PK of RDV in participants with laboratory-confirmed COVID-19 aged 0 days to < 18 years	• PK assessed by plasma concentrations of RDV and metabolites
Secondary Objectives	**Secondary End Points**
• To evaluate the efficacy of RDV in participants with laboratory-confirmed COVID-19 aged 0 days to < 18 years	• Clinical improvement based on scoring using the 7-point ordinal scale • Time (days) to discharge from hospital
• To determine the antiviral activity of RDV in participants with laboratory-confirmed COVID-19 aged 0 days to < 18 years	• Days to the first confirmed negative polymerase chain reaction (PCR) result, where confirmed is defined as 2 consecutive negative PCR results • Change from baseline in SARS-CoV-2 viral load up to Day 10 or up to the first confirmed negative PCR result (whichever comes first)
• Change from baseline in oxygenation use • Change from baseline in the use of mechanical ventilation or extracorporeal membrane oxygenation (ECMO)	• Oxygen usage and ventilation modality and settings
• To evaluate clinical improvement using the Pediatric Early Warning Score (PEWS) Scale in participants with laboratory COVID-19 aged 0 days to < 18 years	• Clinical improvement based on scoring using the PEWS Scale
• To support primary objective of evaluating the safety and tolerability of RDV in participants with laboratory-confirmed COVID-19 aged 0 days to < 18 years	• Bilirubin concentrations in < 14-day-old participants
• Determine sulfobutylether β-cyclodextrin sodium (SBECD) exposures (where possible)	• Plasma concentrations of SBECD (where possible)
• To provide data on use of medications other than RDV for treatment of COVID-19	• The proportion of participants with concomitant use of medications other than RDV for treatment of COVID-19

Exploratory Objectives	Exploratory End Points
• Determine any correlation between reduction in viral shedding and timing and magnitude of immunoglobulin (Ig) response	• Correlation between duration of SARS-CoV-2 shedding and timing and amplitude of SARS-CoV-2-specific IgG, IgM, and IgA
• To evaluate the emergence of viral resistance to RDV	• Emergence of viral resistance to RDV
• To evaluate the safety, efficacy, and PK of RDV in participants with laboratory-confirmed COVID-19 with body mass index (BMI) for age ≥ 95th percentile as defined by the CDC: https://www.cdc.gov/healthyweight/bmi/calculator.html	• Safety, efficacy, and PK of RDV in overweight participants from Cohort 8 of age < 12 years and weight ≥ 40 kg

The clinical improvement was evaluated based on a scoring using the 7-point Ordinal Scale.

Table 13: 7-point ordinal scale (taken from Ahmed et al., CROI 2022)



Assessor's comment

It is of note that a 7-point ordinal scale instead of the frequently used 11-point ordinal scale was used. The condensation of NIVM and high flow oxygen and IMV and ECMO somewhat limit the impact of improvements in clinical status.

Sample size

Please refer to *Clinical pharmacokinetic.*

Randomisation

This was an uncontrolled, single-arm open-label study. Participants were enrolled in eight Cohorts by age and weight. No other covariates were included in the analyses.

Blinding

This was an uncontrolled, single-arm, open-label study, hence all study drugs were open label.

Statistical methods

Analysis of efficacy end points were performed using the FAS. No formal statistical testing was planned.

One secondary end point of the study was clinical status assessed using a 7-point ordinal scale, which was derived by combining the available death, hospital discharge alive, and ordinal scale assessment reported by the site, where death superseded discharge alive and discharge alive superseded the ordinal scale score reported by the site. The proportion of participants for each ordinal scale category end point was summarized by cohort and expressed as a percentage for presentation purposes.

Every effort was made to obtain clinical status data for all participants prior to discharge alive. The last known clinical status was used for days with missing clinical status (e.g., where the reason for hospital discharge is not "discharged alive" and the participant had not died). All post-baseline days with missing ordinal scale scores, from Day 2 to Day 10, used the previous last known clinical status. Additional details are described in the SAP.

The following secondary efficacy end points were summarized using descriptive statistics for each cohort. Additional details are provided in the SAP.

- Clinical improvement, based on scoring using the 7-point ordinal scale, with improvement in clinical status indicated by increasing scores (i.e., 1 = death and 7 = not hospitalized). Clinical improvement was evaluated by cohort and overall, as follows:
    - Clinical status and change in clinical status by study day and last available assessment

- Time to clinical improvement (days), defined as time to a ≥ 2-point improvement from baseline clinical status or discharged alive on the 7-point ordinal scale, modelled using a competing risk analysis. Time to ≥ 1-point improvement from baseline clinical status or discharged alive on the 7-point ordinal scale, modelled using a competing risk analysis, will also be analysed.
- Percentage of participants with a ≥ 2-point improvement or discharged alive, and percentage of participants with a ≥ 1-point improvement or discharged alive, based on the 7-point ordinal scale on Day 2 through Day 10, and last available assessment
- Time to recovery based on the 7-point ordinal scale, using the definition specified in the SAP, and modelled using a competing risk analysis
- Percentage of participants with recovery based on the 7-point ordinal scale on Day 2 through Day 10, and last available assessment

- Clinical improvement, based on scoring using the PEWS Scale (with improvement indicated by decreasing scores such that 0 = playing and appropriate for behaviour; within normal parameters for age, pink, and/or capillary refill 1 to 2 seconds for cardiovascular; and within normal parameters and no retractions for respiratory) was evaluated as follows:
  - Clinical status and change in clinical status by study day for each category and the total score
  - Time to ≥ 2-point improvement or discharged alive on Day 2 through Day 10, and last available assessment, modelled using a competing risk analysis for each category
  - Percentage of participants with a ≥ 2-point improvement or discharged alive, and percentage of participants with a ≥ 1-point improvement or discharged alive, on Day 2 through Day 10 or discharged alive for each category
  - Time to baseline score improved to 0 based on the PEWS Scale on Day 2 through Day 10, and last available assessment, modelled using a competing risk analysis
  - Percentage of participants with baseline score improved to 0 based on the PEWS Scale on Day 2 through Day 10, and last available assessment
- Time (days) to discharge from hospital. Duration of hospitalization (days) (duration from hospital admission and duration from Day 1) through the Day 30 follow-up visit was also summarized.
- Days to the first confirmed negative PCR result, where confirmed was defined as 2 consecutive negative PCR results, or a negative PCR result at last available sample for participants who completed or discontinued from the study, modelled using a competing risk analysis. The percentage of subjects with confirmed negative PCR result was summarized by sample type.
- SARS-CoV-2 results and change from baseline in SARS-CoV-2 viral load up to Day 10 or up to the first confirmed negative PCR result (whichever came first).
- Oxygen usage and ventilation modality and settings. The number of days of oxygen support through discharge alive, death, or Day 10, based on the 7-point ordinal scale reported values, including days on invasive mechanical ventilation, days on high-flow oxygen devices, and days requiring low-flow supplemental oxygen was summarized. Shift in oxygen support status from baseline to Days 2 through 10, and last available assessment was also summarized.

Planned interim analysis

Prior to the final analysis, an interim analysis conducted by the data monitoring committee (DMC) was planned. Interim data reviews by the Sponsor may also be conducted. These reviews may be submitted to regulatory agencies to seek guidance regarding the overall clinical development program.

The DMC has reviewed safety, PK (if available), and efficacy data once approximately 50% of participants across the age range of 0 days to < 18 years have reached their Day 10 visit or have been discharged, whichever comes first.

Final analysis

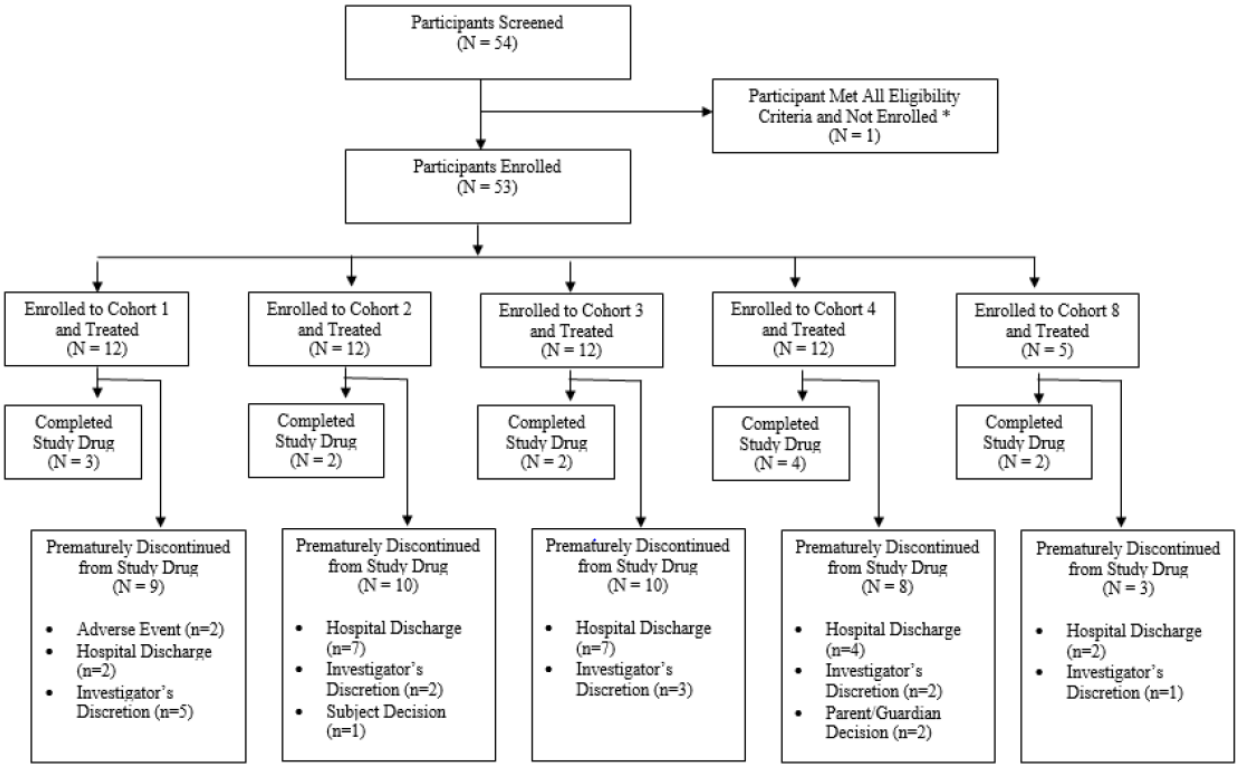
The final analysis will be performed after all participants have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

Results

Participant flow

Participants were enrolled and treated at a total of 19 study sites in Italy, Spain, the US, and the UK. Of the 54 participants screened in the study, 53 were enrolled and received at least 1 dose of study drug. One participant met all eligibility criteria but was not enrolled in the study due to investigator discretion.

A summary of study participant disposition is presented in the figure and table below.



* One participant met all eligibility criteria but was not enrolled due to investigator discretion.
Source: Figure 15.8.1

Figure 15: GS-US-540-5823: Disposition of participants (All screened participants)

Table 14: GS-US-540-5823: Disposition of participants (all screened patients)

	Cohort 1: 12 to < 18 Years and ≥ 40 kg	Cohort 2: 28 Days to < 18 Years and 20 to < 40 kg	Cohort 3: 28 days to < 18 years and 12 to < 20 kg	Cohort 4: 28 Days to < 18 Years and 3 to < 12 kg	Cohort 8: < 12 Years and ≥ 40 kg	Total
Participants screened	12	12	12	12	5	54
Participants met all eligibility criteria and not enrolled	0	0	0	0	0	1
Participants enrolled	12	12	12	12	5	53
Participants in Safety Analysis Set	12	12	12	12	5	53
Participants in Full Analysis Set	12	12	12	12	5	53
Participants completed study drug	3 (25.0%)	2 (16.7%)	2 (16.7%)	4 (33.3%)	2 (40.0%)	13 (24.5%)
Participants prematurely discontinuing study drug	9 (75.0%)	10 (83.3%)	10 (83.3%)	8 (66.7%)	3 (60.0%)	40 (75.5%)
Reasons for prematurely discontinuing study drug						
Adverse event	2 (16.7%)	0	0	0	0	2 (3.8%)
Hospital discharge	2 (16.7%)	7 (58.3%)	7 (58.3%)	4 (33.3%)	2 (40.0%)	22 (41.5%)
Investigator's discretion	5 (41.7%)	2 (16.7%)	3 (25.0%)	2 (16.7%)	1 (20.0%)	13 (24.5%)
Subject decision	0	1 (8.3%)	0	0	0	1 (1.9%)
Parent/guardian decision	0	0	0	2 (16.7%)	0	2 (3.8%)
Participants still on study up to the data cut date	0	0	1 (8.3%)	0	0	1 (1.9%)
Participants completed study	11 (91.7%)	11 (91.7%)	10 (83.3%)	9 (75.0%)	4 (80.0%)	45 (84.9%)
Participants prematurely discontinuing from study	1 (8.3%)	1 (8.3%)	1 (8.3%)	3 (25.0%)	1 (20.0%)	7 (13.2%)
Reasons for prematurely discontinuing from study						
Death	1 (8.3%)	0	0	0	1 (20.0%)	2 (3.8%)
Withdrew consent	0	1 (8.3%)	0	2 (16.7%)	0	3 (5.7%)
Lost to follow-up	0	0	1 (8.3%)	1 (8.3%)	0	2 (3.8%)

CRF = case report form; FAS = Full Analysis Set
The denominator for percentage is the number of participants in the Safety Analysis Set.
Screen failure participants were those who did not meet all eligibility criteria.
One participant met all eligibility criteria but was not enrolled due to investigator discretion.
CRF data collected up to data finalization on 29JUL2021 were included.
The FAS includes all participants who (a) were enrolled into the study and (b) received at least 1 dose of study drug.
The Safety Analysis Set includes all participants who (a) were enrolled into the study and (b) received at least 1 dose of study drug.
Source: Table 15.8.1.3

Recruitment

Participant were recruited at 19 different sites globally, including two sites in the EU, one site in the UK and 13 sites in the US. Of the 53 children, 41 were enrolled in the USA, nine in Spain, two in Italy, and one in the UK.

Cohorts 1 through 5 and 8 were enrolled in parallel. Participants in Cohorts 6 and 7 will only be enrolled once RDV exposures have been evaluated from Cohort 5 and a dose has been determined.

Conduct of the study

The table below lists the key dates relevant to the conduct of Study GS-US-540-5823.

Table 15: Study GS-US-540-5823: Key Dates

Event	Date
First participant screened	21 July 2020
First participant enrolled	22 July 2020
Last participant enrolled	05 May 2021
Last participant last visit for the primary end point	Not yet occurred
Last participant last visit for this report	24 May 2021
Database finalization	29 July 2021

Changes in the conduct of the study or planned analyses

The protocol was amended 3 times between study initiation and the time of this interim CSR, as indicated in the following table:

Table 16: Protocol and protocol amendments

Protocol/Amendment	Date
Original	29 May 2020
Amendment 1 Summary of Changes	18 June 2020
Country-Specific Protocol Amendment UK 1.1 Summary of Changes	26 June 2020
Amendment 2 Summary of Changes	22 September 2020
Country-Specific Protocol Amendment UK 2.1 Summary of Changes	25 September 2020
Amendment 3 Summary of Changes	16 February 2021
Amendment 3	16 February 2021
Country-Specific Protocol Amendment UK 3.1 Summary of Changes	22 February 2021

There were no changes of the planned analyses for this study.

Protocol Deviations:

The table below provides a categorical summary of important protocol deviations (IPDs) that were collected from screening through the 30-day follow-up visit. Protocol deviations were documented during remote monitoring visits and site follow-ups when applicable.

Table 17: Study GS-US-540-5823: Important protocol deviations

Protocol Deviation Category	Cohort 1: 12 to < 18 Years and ≥ 40 kg (N = 12)	Cohort 2: 28 Days to < 18 Years and 20 to < 40 kg (N = 12)	Cohort 3: 28 Days to < 18 Years and 12 to < 20 kg (N = 12)	Cohort 4: 28 Days to < 18 Years and 3 to < 12 kg (N = 12)	Cohort 8: < 12 Years and ≥ 40 kg (N = 5)	Total (N = 53)
Participants with at least 1 important protocol deviation	9 (75.0%)	10 (83.3%)	10 (83.3%)	10 (83.3%)	2 (40.0%)	41 (77.4%)
Missing data	7 (58.3%)	7 (58.3%)	6 (50.0%)	4 (33.3%)	0	24 (45.3%)
Off schedule procedure	4 (33.3%)	7 (58.3%)	5 (41.7%)	4 (33.3%)	1 (20.0%)	21 (39.6%)
Informed consent	2 (16.7%)	2 (16.7%)	3 (25.0%)	1 (8.3%)	1 (20.0%)	9 (17.0%)
Other	2 (16.7%)	1 (8.3%)	0	4 (33.3%)	0	7 (13.2%)
Excluded concomitant medication	1 (8.3%)	0	1 (8.3%)	0	0	2 (3.8%)
Wrong treatment or incorrect dose	0	0	2 (16.7%)	0	0	2 (3.8%)
Total number of important protocol deviations	27	21	25	20	2	95
Missing data	17	9	11	9	0	46
Off schedule procedure	5	9	7	6	1	28
Informed consent	2	2	3	1	1	9
Other	2	1	0	4	0	7
Wrong treatment or incorrect dose	0	0	3	0	0	3
Excluded concomitant medication	1	0	1	0	0	2

Participants with multiple protocol deviations were counted only once in each protocol deviation category.
For number of important protocol deviations, participants with multiple deviations were counted multiple times in each protocol deviation category.
Source: Table 15.8.2.1

Baseline data

Participant demographic and baseline characteristics are summarized in the table below.

Table 18: GS-US-540-5823: Demographic and baseline characteristics (Safety Analysis Set)

	Cohort 1: 12 to < 18 Years and ≥ 40 kg (N = 12)	Cohort 2: 28 Days to < 18 Years and 20 to < 40 kg (N = 12)	Cohort 3: 28 Days to < 18 Years and 12 to < 20 kg (N = 12)	Cohort 4: 28 Days to < 18 Years and 3 to < 12 kg (N = 12)	Cohort 8: < 12 Years and ≥ 40 kg (N = 5)	Total (N = 53)
Age (years)						
N	12	12	12	12	5	53
Mean (SD)	15.0 (1.71)	9.6 (3.63)	3.9 (1.84)	0.4 (0.29)	10.4 (1.34)	7.5 (5.79)
Median	15.0	9.0	3.5	0.5	11.0	7.0
Q1, Q3	13.5, 16.5	7.5, 12.0	2.0, 5.5	0.2, 0.7	11.0, 11.0	2.0, 12.0
Min, max	12.0, 17.0	4.0, 16.0	1.9, 7.0	0.1, 0.9	8.0, 11.0	0.1, 17.0
Sex at birth						
Male	4 (33.3%)	5 (41.7%)	7 (58.3%)	5 (41.7%)	2 (40.0%)	23 (43.4%)
Female	8 (66.7%)	7 (58.3%)	5 (41.7%)	7 (58.3%)	3 (60.0%)	30 (56.6%)
Race						
Black	5 (41.7%)	2 (18.2%)	4 (40.0%)	2 (20.0%)	1 (25.0%)	14 (29.8%)
White	7 (58.3%)	9 (81.8%)	6 (60.0%)	8 (80.0%)	3 (75.0%)	33 (70.2%)
Other	0	1	2	2	1	6
Ethnicity						
Hispanic or Latino	3 (27.3%)	7 (58.3%)	7 (58.3%)	3 (25.0%)	3 (60.0%)	23 (44.2%)
Not Hispanic or Latino	8 (72.7%)	5 (41.7%)	5 (41.7%)	9 (75.0%)	2 (40.0%)	29 (55.8%)
Not permitted	1	0	0	0	0	1

	Cohort 1: 12 to < 18 Years and ≥ 40 kg (N = 12)	Cohort 2: 28 Days to < 18 Years and 20 to < 40 kg (N = 12)	Cohort 3: 28 Days to < 18 Years and 12 to < 20 kg (N = 12)	Cohort 4: 28 Days to < 18 Years and 3 to < 12 kg (N = 12)	Cohort 8: < 12 Years and ≥ 40 kg (N = 5)	Total (N = 53)
Baseline weight (kg)						
N	12	12	12	12	5	53
Mean (SD)	89.5 (41.98)	28.1 (5.01)	15.4 (2.58)	6.2 (2.31)	69.0 (20.23)	38.0 (38.63)
Median	83.5	26.5	14.6	5.0	73.0	24.6
Q1, Q3	56.8, 106.9	25.0, 30.9	13.4, 18.2	4.4, 8.5	55.1, 80.0	12.8, 55.1
Min, max	47.3, 191.6	22.0, 39.1	12.0, 19.4	3.7, 10.1	42.9, 94.0	3.7, 191.6
Baseline height (cm)						
N	12	12	11	11	5	51
Mean (SD)	159.7 (13.19)	127.8 (14.06)	96.1 (10.89)	58.7 (10.45)	151.9 (9.25)	115.9 (39.53)
Median	162.0	129.6	94.0	59.0	150.0	117.5
Q1, Q3	151.5, 165.0	117.1, 138.1	86.0, 107.0	49.0, 70.0	144.0, 161.5	84.0, 150.0
Min, max	133.0, 187.9	101.0, 149.9	83.8, 114.0	43.5, 71.0	142.3, 161.5	43.5, 187.9
Baseline body mass index (kg/m^2)						
N	12	12	11	11	5	51
Mean (SD)	34.7 (13.38)	17.6 (4.23)	16.7 (1.67)	17.0 (3.91)	29.5 (6.42)	22.5 (10.52)
Median	33.8	17.8	16.2	16.3	28.0	18.8
Q1, Q3	21.6, 46.5	14.9, 20.2	15.6, 18.1	14.7, 20.0	27.2, 35.6	16.0, 24.8
Min, max	21.1, 55.2	11.0, 26.5	14.2, 20.1	11.4, 24.8	20.7, 36.0	11.0, 55.2
Baseline BMI-for-age percentile category						
< 5th percentile	0	3 (25.0%)	0	2 (18.2%)	0	5 (9.8%)
≥ 5th to < 95th percentile	5 (41.7%)	7 (58.3%)	8 (72.7%)	6 (54.5%)	1 (20.0%)	27 (52.9%)
≥ 95th percentile	7 (58.3%)	2 (16.7%)	3 (27.3%)	3 (27.3%)	4 (80.0%)	19 (37.3%)
Missing	0	0	1	1	0	2

BMI = body mass index; CDC = Centers for Disease Control and Prevention; max = maximum; min = minimum; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; WHO = World Health Organization
For race and ethnicity, "Not Permitted," "Missing," and "Other" were excluded from the percentage calculation.
"Not Permitted" = local regulators did not allow collection of race/ethnicity information.
BMI (kg/m^2) = weight (kg)/height (cm^2) × 10,000.
BMI percentile for children < 24 months old was computed using WHO SAS® package: www.who.int/toolkits/child-growth-standards/software.
BMI percentile for children 24 months or older was computed based on CDC: www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm
Source: Table 15.8.3.1.1

Baseline disease characteristics are summarized in the table below.

Table 19: GS-US-540-5823: Baseline disease characteristics (Safety analysis set)

	Cohort 1: 12 to < 18 Years and ≥ 40 kg (N = 12)	Cohort 2: 28 Days to < 18 Years and 20 to < 40 kg (N = 12)	Cohort 3: 28 Days to < 18 Years and 12 to < 20 kg (N = 12)	Cohort 4: 28 Days to < 18 Years and 3 to < 12 kg (N = 12)	Cohort 8: < 12 Years and ≥ 40 kg (N = 5)	Total (N = 53)
Duration of hospitalization prior to first dose of RDV (days)						
N	12	12	12	12	5	53
Mean (SD)	8 (25.1)	2 (1.1)	2 (1.4)	13 (26.3)	5 (9.2)	6 (17.6)
Median	1	1	2	2	1	1
Q1, Q3	0, 3	1, 2	1, 3	1, 7	0, 1	1, 3
Min, max	0, 88	0, 4	0, 5	1, 82	0, 21	0, 88
Duration of symptoms prior to first dose of RDV (days)						
N	12	12	12	12	5	53
Mean (SD)	21 (49.4)	5 (2.7)	5 (3.0)	5 (3.3)	7 (3.0)	9 (23.8)
Median	7	5	3	5	5	5
Q1, Q3	3, 11	3, 7	3, 7	2, 8	5, 7	3, 7
Min, max	1, 177	2, 11	1, 11	0, 9	5, 12	0, 177
ALT (U/L)						
N	11	12	11	12	5	51
Mean (SD)	38 (28.1)	31 (29.9)	35 (30.2)	23 (15.5)	25 (10.2)	31 (25.1)
Median	26	19	25	19	20	23

	Cohort 1: 12 to < 18 Years and ≥ 40 kg (N = 12)	Cohort 2: 28 Days to < 18 Years and 20 to < 40 kg (N = 12)	Cohort 3: 28 Days to < 18 Years and 12 to < 20 kg (N = 12)	Cohort 4: 28 Days to < 18 Years and 3 to < 12 kg (N = 12)	Cohort 8: < 12 Years and ≥ 40 kg (N = 5)	Total (N = 53)
Q1, Q3	19, 48	14, 37	18, 32	13, 31	20, 32	15, 33
Min, max	12, 105	8, 110	13, 113	7, 62	14, 39	7, 113
AST (U/L)						
N	11	12	11	12	5	51
Mean (SD)	65 (39.8)	39 (18.7)	49 (36.8)	52 (34.2)	33 (6.3)	49 (32.2)
Median	65	32	37	40	36	38
Q1, Q3	32, 82	26, 54	29, 68	35, 60	26, 38	29, 66
Min, max	19, 161	13, 72	22, 148	21, 148	26, 38	13, 161
Oxygen support status						
Invasive mechanical ventilation	1 (8.3%)	3 (25.0%)	3 (25.0%)	5 (41.7%)	0	12 (22.6%)
High-flow oxygen	6 (50.0%)	4 (33.3%)	3 (25.0%)	3 (25.0%)	2 (40.0%)	18 (34.0%)
Low-flow oxygen	2 (16.7%)	3 (25.0%)	0	3 (25.0%)	2 (40.0%)	10 (18.9%)
Room air	3 (25.0%)	2 (16.7%)	6 (50.0%)	1 (8.3%)	1 (20.0%)	13 (24.5%)
COVID-19–related disease manifestations						
Circulatory	2 (16.7%)	3 (25.0%)	2 (16.7%)	4 (33.3%)	0	11 (20.8%)
Gastrointestinal	6 (50.0%)	6 (50.0%)	7 (58.3%)	4 (33.3%)	4 (80.0%)	27 (50.9%)
Neurological	5 (41.7%)	3 (25.0%)	3 (25.0%)	1 (8.3%)	0	12 (22.6%)
Respiratory	9 (75.0%)	12 (100.0%)	6 (50.0%)	12 (100.0%)	5 (100.0%)	44 (83.0%)
Systemic inflammatory response	3 (25.0%)	4 (33.3%)	5 (41.7%)	2 (16.7%)	0	14 (26.4%)
SARS-CoV-2 RNA viral load (log_{10} copies) from nasal swabs[a]						
N	5	5	4	3	1	18
Mean (SD)	5.35 (1.796)	4.87 (2.807)	3.18 (0.967)	5.41 (2.165)	6.20	4.79 (2.055)
Median	5.72	3.14	2.71	5.14	6.20	4.63
Q1, Q3	4.63, 6.44	2.67, 7.69	2.69, 3.67	3.40, 7.70	6.20, 6.20	2.71, 6.44
Min, max	2.67, 7.31	2.67, 8.17	2.67, 4.63	3.40, 7.70	6.20, 6.20	2.67, 8.17
SARS-CoV-2 RNA viral load (log_{10} copies) from nasopharyngeal swabs[a]						
N	5	3	5	7	4	24
Mean (SD)	5.93 (2.172)	5.02 (2.133)	5.67 (2.273)	5.55 (1.854)	6.12 (1.628)	5.68 (1.862)
Median	5.05	5.57	6.58	6.39	6.89	6.37
Q1, Q3	4.98, 6.35	2.67, 6.82	4.02, 6.84	3.85, 7.15	5.24, 7.01	3.93, 6.91
Min, max	3.81, 9.47	2.67, 6.82	2.67, 8.26	2.67, 7.69	3.69, 7.03	2.67, 9.47
SARS-CoV-2 RNA viral load (log_{10} copies) from endotracheal tube aspirates[a]						
N	1	3	2	3	0	9
Mean (SD)	5.36	5.07 (4.168)	6.09 (0.840)	6.68 (1.540)		5.87 (2.357)
Median	5.36	2.67	6.09	7.38		5.50

	Cohort 1: 12 to < 18 Years and ≥ 40 kg (N = 12)	Cohort 2: 28 Days to < 18 Years and 20 to < 40 kg (N = 12)	Cohort 3: 28 Days to < 18 Years and 12 to < 20 kg (N = 12)	Cohort 4: 28 Days to < 18 Years and 3 to < 12 kg (N = 12)	Cohort 8: < 12 Years and ≥ 40 kg (N = 5)	Total (N = 53)
Q1, Q3	5.36, 5.36	2.67, 9.88	5.50, 6.68	4.91, 7.74		4.91, 7.38
Min, max	5.36, 5.36	2.67, 9.88	5.50, 6.68	4.91, 7.74		2.67, 9.88
ECG interpretation						
Normal	6 (60.0%)	4 (36.4%)	6 (54.5%)	6 (54.5%)	4 (100.0%)	26 (55.3%)
Abnormal	4 (40.0%)	7 (63.6%)	5 (45.5%)	5 (45.5%)	0	21 (44.7%)
Clinically significant	0	1 (9.1%)	0	2 (18.2%)	0	3 (6.4%)
Not clinically significant	4 (40.0%)	6 (54.5%)	5 (45.5%)	3 (27.3%)	0	18 (38.3%)
Missing/unknown	2	1	1	1	1	6
Creatinine (mg/dL)						
N	11	12	11	12	5	51
Mean (SD)	0.8 (0.35)	0.5 (0.39)	0.3 (0.16)	0.3 (0.11)	0.5 (0.11)	0.5 (0.33)
Median	0.7	0.4	0.2	0.3	0.5	0.4
Q1, Q3	0.5, 0.9	0.3, 0.6	0.2, 0.4	0.2, 0.3	0.4, 0.6	0.3, 0.6
Min, max	0.5, 1.7	0.3, 1.7	0.1, 0.7	0.1, 0.5	0.4, 0.7	0.1, 1.7
eGFR using Bedside IDMS-traceable Schwartz formula (mL/min/1.73 m^2)						
N	11	12	8	0	5	36
Mean (SD)	94.9 (30.70)	131.7 (56.88)	150.7 (57.72)		120.7 (22.47)	123.2 (49.60)
Median	92.3	121.6	148.1		130.8	119.1
Q1, Q3	78.5, 117.7	88.6, 182.3	120.1, 173.5		97.9, 135.2	87.2, 148.1
Min, max	36.7, 144.1	35.0, 229.3	62.2, 259.9		95.3, 144.1	35.0, 259.9

ALT = alanine aminotransferase; AST = aspartate aminotransferase; COVID-19 = coronavirus disease 2019; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; IDMS = isotope dilution mass spectrometry; max = maximum; min = minimum; Q1 = first quartile; Q3 = third quartile; RDV = remdesivir (GS-5734™); SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SD = standard deviation

a Per mL of transport medium.

Baseline was the last available value recorded on or prior to dosing.

A participant may have fit more than 1 COVID-19–related disease manifestation; therefore, percentages may add to more than 100%.

eGFR was calculated using Bedside IDMS-traceable Schwartz formula (mL/min/1.73 m^2) for children aged 1 to < 18 years.

Source: Table 15.8.3.2.1

With the exception of one participant in Cohort 3, medical history was reported in all participants. The most frequently reported medical history terms overall were pyrexia (30 participants, 56.6%), cough (15 participants, 28.3%), and diarrhoea and gastroesophageal reflux disease (each 12 participants, 22.6%).

Numbers analysed

The analysis sets used for data evaluation are shown in the table below.

The Full Analysis Set (FAS) included all participants who were enrolled in the study and received at least 1 dose of study drug. This was the primary analysis set for efficacy analyses.

Table 20: Study GS-US-540-5823: Analysis sets (All enrolled analysis set)

Analysis Set, n	Cohort 1: 12 to < 18 years and ≥ 40 kg	Cohort 2: 28 days to < 18 years and 20 to < 40 kg	Cohort 3: 28 days to < 18 years and 12 to < 20 kg	Cohort 4: 28 days to < 18 years and 3 to < 12 kg	Cohort 8: < 12 years and ≥ 40 kg	Total
All Enrolled Analysis Set	12	12	12	12	5	53
Full Analysis Set	12 (100.0%)	12 (100.0%)	12 (100.0%)	12 (100.0%)	5 (100.0%)	53 (100.0%)
Safety Analysis Set	12 (100.0%)	12 (100.0%)	12 (100.0%)	12 (100.0%)	5 (100.0%)	53 (100.0%)
RDV PK Analysis Set	12 (100.0%)	12 (100.0%)	11 (91.7%)	10 (83.3%)	5 (100.0%)	50 (94.3%)
Metabolites PK Analysis Set	12 (100.0%)	12 (100.0%)	11 (91.7%)	10 (83.3%)	5 (100.0%)	50 (94.3%)

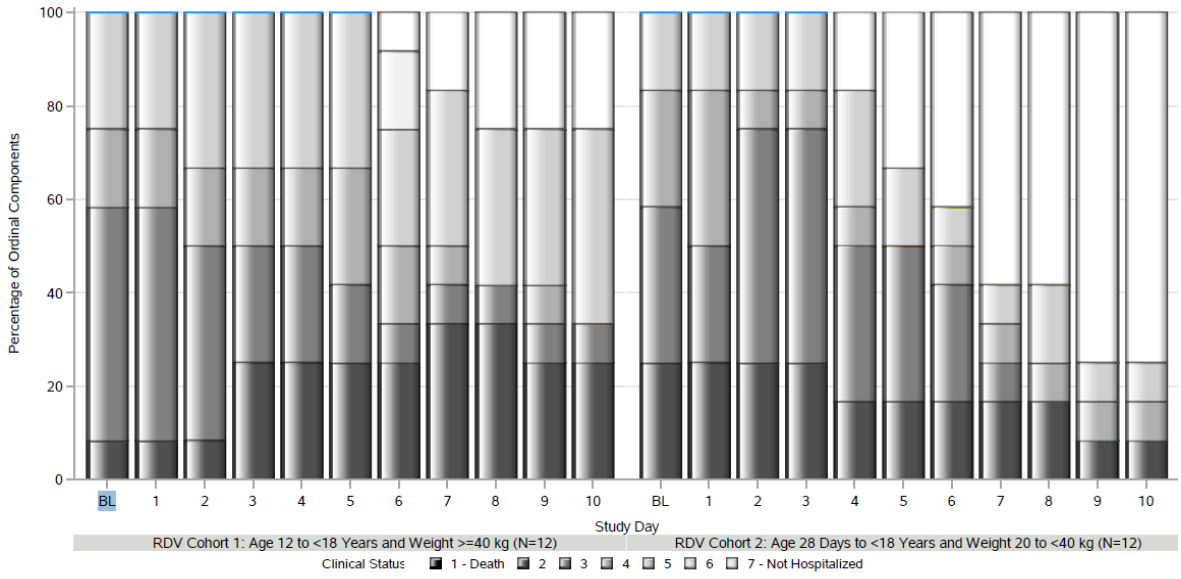
PK = pharmacokinetic(s); RDV = remdesivir (GS-5734™)
The Full Analysis Set includes all participants who (a) were enrolled into the study and (b) received at least 1 dose of study drug.
The Safety Analysis Set includes all participants who (a) were enrolled into the study and (b) received at least 1 dose of study drug.
The RDV PK Analysis Set includes all participants who were enrolled and received at least 1 dose of RDV and for whom PK concentrations of RDV were available.
The Metabolites PK Analysis Set includes all participants who were enrolled and received at least 1 dose of RDV and for whom PK concentrations of metabolite(s) (analytes) were available.
The denominator for percentage is the number of enrolled participants.
Source: Table 15.8.3.5

Outcomes and estimation

Secondary endpoints:

Clinical improvement based on the 7-Point ordinal scale

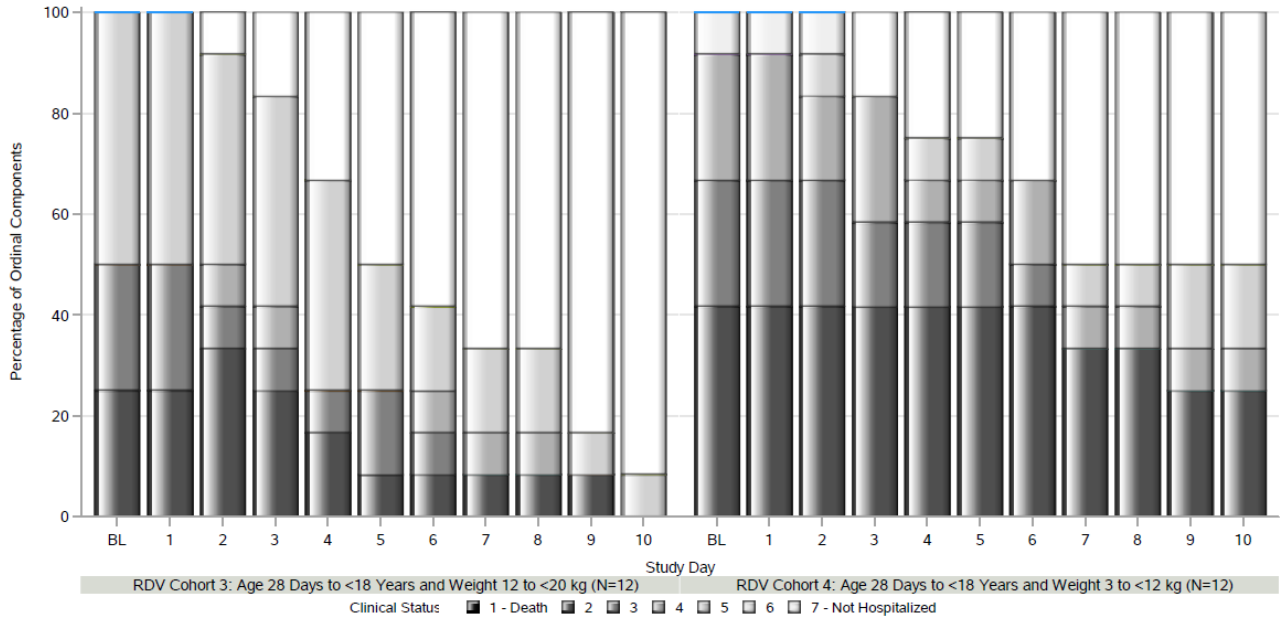
Clinical status on the 7-point ordinal scale (with an increasing score indicating improvement) by visit and cohort below is presented below.



Baseline was the last available value recorded on or prior to dosing for RDV.
7-Ordinal Scales: 1 = Death; 2 = Hospitalized, on invasive mechanical ventilation or ECMO; 3 = Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4 = Hospitalized, requiring low flow supplemental oxygen; 5 = Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise); 6 = Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care (other than per protocol RDV administration); 7 = Not hospitalized.
Last Available Assessment was derived from death, hospital discharge, and the ordinal scale as follows: 1 for all days on or after the death date; 7 for all days on or after discharged alive date; ordinal scale using the last available postbaseline record for missing assessment.

Data Extracted: CRF Data, Lab Data: 29JUL2021, PK Concentration Data: 02JUN2021
Source: .../interim1/version2/prog/g-clinstat.sas v9.4 Output file: g-clinstat.pdf 30AUG2021: 9:41

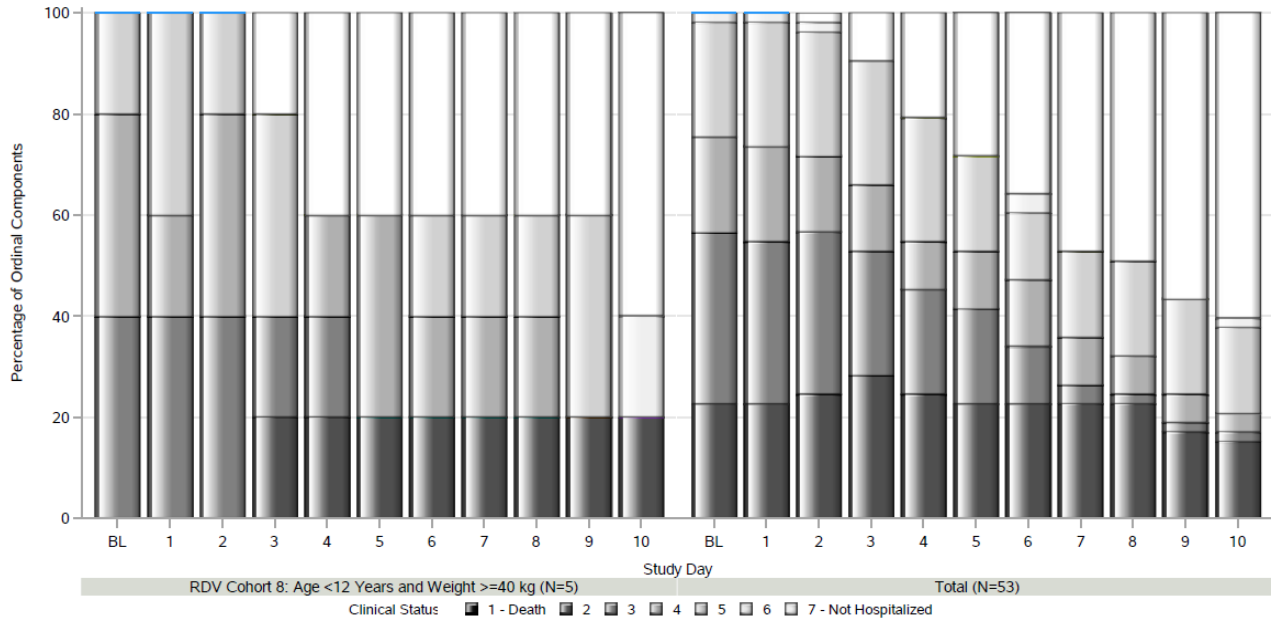
Figure 16: Clinical status (7-Point Ordinal Scale) by visit (Cohort 1 and 2)



Baseline was the last available value recorded on or prior to dosing for RDV.
7-Ordinal Scales: 1 = Death; 2 = Hospitalized, on invasive mechanical ventilation or ECMO; 3 = Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4 = Hospitalized, requiring low flow supplemental oxygen; 5 = Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise); 6 = Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care (other than per protocol RDV administration); 7 = Not hospitalized.
Last Available Assessment was derived from death, hospital discharge, and the ordinal scale as follows: 1 for all days on or after the death date; 7 for all days on or after discharged alive date; ordinal scale using the last available postbaseline record for missing assessment.

Data Extracted: CRF Data, Lab Data: 29JUL2021, PK Concentration Data: 02JUN2021
Source: .../interim1/version2/prog/g-clinstat.sas v9.4 Output file: g-clinstat.pdf 30AUG2021: 9:41

Figure 17: Clinical status (7-Point Ordinal Scale) by visit (Cohort 3 and 4)



Baseline was the last available value recorded on or prior to dosing for RDV.
7-Ordinal Scales: 1 = Death; 2 = Hospitalized, on invasive mechanical ventilation or ECMO; 3 = Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4 = Hospitalized, requiring low flow supplemental oxygen; 5 = Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise); 6 = Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care (other than per protocol RDV administration); 7 = Not hospitalized.
Last Available Assessment was derived from death, hospital discharge, and the ordinal scale as follows: 1 for all days on or after the death date; 7 for all days on or after discharged alive date; ordinal scale using the last available postbaseline record for missing assessment.

Data Extracted: CRF Data, Lab Data: 29JUL2021, PK Concentration Data: 02JUN2021
Source: .../interim1/version2/prog/g-clinstat.sas v9.4 Output file: g-clinstat.pdf 30AUG2021: 9:41

Figure 18: Clinical status (7-Point Ordinal Scale) by visit (Cohort 8 and all Cohorts)

Change from baseline in clinical status

The median (Q1, Q3) change from baseline in clinical status on Day 5 for total participants was 0.9 (0.0, 2.0) points. For each cohort, the median (Q1, Q3) changes were as follows:

- Cohort 1: 0.1 (0, 0.5) points
- Cohort 2: 1.2 (0, 3.0) points
- Cohort 3: 2.0 (0, 2.0) points
- Cohort 4: 0.8 (0, 1.0) points
- Cohort 8: 1.0 (0, 2.0) points

The median (Q1, Q3) change from baseline in clinical status on Day 10 for total participants was 2.0 (1.0, 4.0) points. For each cohort, the median (Q1, Q3) changes were as follows:

- Cohort 1: 0.5 (0, 2.0) points
- Cohort 2: 3.0 (2.0, 4.0) points
- Cohort 3: 2.5 (2.0, 4.0) points
- Cohort 4: 3.0 (0, 3.5) points
- Cohort 8: 2.0 (2.0, 3.0) points

The median (Q1, Q3) change from baseline at the time of the last assessment for total participants was 2.7 (2.0, 4.0) points and was similar across cohorts.

- Cohort 1: 2.5 (0.5, 4.0) points
- Cohort 2: 3.0 (2.5, 4.0) points
- Cohort 3: 3.0 (2.0, 4.5) points
- Cohort 4: 3.0 (0, 3.5) points
- Cohort 8: 2.0 (2.0, 3.0) points

Participants with ≥ 2-Point improvement in clinical status

Among the participants with an ordinal score of ≤ 5 points at baseline, the proportion who had a ≥ 2-point improvement in clinical status on Day 5 was 31.0% (16/52 participants; 95% CI: 18.7%-45.1%) The proportions for each cohort were as follows:

- Cohort 1: 0% (0/12 participants; 95% CI: 0.0%-26.5%)
- Cohort 2: 41.7% (5/12 participants; 95% CI: 15.2%-72.3%)
- Cohort 3: 50.3% (7/12 participants; 95% CI: 27.7%-84.8%)
- Cohort 4: 18.2% (2/11 participants; 95% CI: 2.3%-51.8%)
- Cohort 8: 40.0% (2/5 participants; 95% CI: 5.3%-85.3%)

Among the participants with an ordinal score of ≤ 5 points at baseline, the proportion who had a ≥ 2-point improvement in clinical status on Day 10 was 75.0% (39/52 participants; 95% CI: 61.1%-86.0%) The proportions for each cohort were as follows:

- Cohort 1: 41.7% (5/12 participants; 95% CI: 15.2%-72.3%)
- Cohort 2: 91.7% (11/12 participants; 95% CI: 61.5%-99.8%)
- Cohort 3: 100.0% (12/12 participants; 95% CI: 73.5%-100.0%)
- Cohort 4: 63.6% (7/11 participants; 95% CI: 30.8%-89.1%)
- Cohort 8: 80.0% (4/5 participants; 95% CI: 28.4%-99.5%)

Among the participants with an ordinal score of ≤ 5 points at baseline, the proportion who had a ≥ 2-point improvement in clinical status on last available assessment was 84.6% (44/52 participants; 95% CI: 71.9%-93.1%) The proportions for each cohort were as follows:

- Cohort 1: 75.0% (9/12 participants; 95% CI: 42.8%-94.5%)
- Cohort 2: 91.7% (11/12 participants; 95% CI: 61.5%-99.8%)
- Cohort 3: 100.0% (12/12 participants; 95% CI: 73.5%-100.0%)
- Cohort 4: 72.7% (8/11 participants; 95% CI: 39.0%-94.0%)
- Cohort 8: 80.0% (4/5 participants; 95% CI: 28.4%-99.5%)

The median (Q1, Q3) time to ≥ 2-point improvement for participants with an ordinal score of ≤ 5 points at baseline was 7 (5, 10) days. The median (Q1, Q3) time for each cohort were as follows:

- Cohort 1: 11 (6, 24) days
- Cohort 2: 6 (4, 8) days
- Cohort 3: 5 (3, 7) days
- Cohort 4: 7 (6, 17) days
- Cohort 8: 9 (4, 10) days

Participants with ≥ 1-Point improvement in clinical status

The proportion of total participants who had a ≥ 1-point improvement in clinical status on Day 10 was 77.4% (41/53 participants; 95% CI: 63.8%-87.7%). The proportions for each cohort were as follow:

- Cohort 1: 50.0% (6/12 participants; 95% CI: 21.1%-78.9%)
- Cohort 2: 91.7% (11/12 participants; 95% CI: 61.5%-99.8%)
- Cohort 3: 100.0% (12/12 participants; 95% CI: 73.5%-100.0%)
- Cohort 4: 66.7% (8/12 participants; 95% CI: 34.9%-90.1%)
- Cohort 8: 80.0% (4/5 participants; 95% CI: 28.4%-99.5%)

The proportion of total participants who had a ≥ 1-point improvement was 84.9% (45/53 participants; 95% CI: 72.4%-93.3%) at the time of the last assessment.

- Cohort 1: 75.0% (9/12 participants; 95% CI: 42.0%-94.5%)
- Cohort 2: 91.7% (11/12 participants; 95% CI: 61.5%-99.8%)
- Cohort 3: 100.0% (12/12 participants; 95% CI: 73.5%-100.0%)
- Cohort 4: 75.0% (9/12 participants; 95% CI: 42.0%-94.5%)
- Cohort 8: 80.0% (4/5 participants; 95% CI: 28.4%-99.5%)

Participants with recovery

Recovery, defined as an improvement from a baseline score of 2 through 5 to a score of 6 or 7 or an improvement from a baseline score of 6 to a score of 7. Recovery was reported for 62.3% (33/53) of all participants (95% CI: 47.9%-75.2%) on Day 10. The proportions for each cohort were as follows:

- Cohort 1: 25.0% (3/12 participants; 95% CI: 5.5%-57.2%)
- Cohort 2: 75.0% (9/12 participants 95% CI: 42.8%-94.5%)
- Cohort 3: 91.7% (11/12 participants 95% CI: 61.5%-99.8%)
- Cohort 4: 50.0% (6/12 participants 95% CI: 21.1%-78.9%)
- Cohort 8: 80.0% (4/5 participants 95% CI: 28.4%-99.5%)

The proportion of all participants who recovered was to 83.0% (44/53 participants, 95% CI: 70.2%-91.9%) at the time of the last assessment. The proportions for each cohort were as follows:

- Cohort 1: 75.0% (9/12 participants; 95% CI: 42.8%-94.5%)
- Cohort 2: 83.3% (10/12 participants 95% CI: 51.6%-97.9%)
- Cohort 3: 100% (12/12 participants 95% CI: 75.5%-100%)
- Cohort 4: 75.0% (9/12 participants 95% CI: 42.0%-94.5%)
- Cohort 8: 80.0% (4/5 participants 95% CI: 28.4%-99.5%)

Time to recovery:

The median (Q1, Q3) time to recovery for all participants was 7 (5, 16) days. The median (Q1, Q3) time for each cohort were as follows:

- Cohort 1: 12 (6, 24) days
- Cohort 2: 7 (5, 9) days
- Cohort 3: 5 (4, 9) days
- Cohort 4: 7 (4, 19) days
- Cohort 8: 10 (4, 10) days

Hospitalization

The hospitalisation status and duration of hospitalisation at Day 10 and last available assessment in shown in the table below.

Table 15.9.3.1.1: Hospitalization Discharge Status and Duration of Hospitalization
Full Analysis Set

	RDV Cohort 1: Age 12 to <18 Years and Weight >=40 kg (N=12)	RDV Cohort 2: Age 28 Days to <18 Years and Weight 20 to <40 kg (N=12)	RDV Cohort 3: Age 28 Days to <18 Years and Weight 12 to <20 kg (N=12)	RDV Cohort 4: Age 28 Days to <18 Years and Weight 3 to <12 kg (N=12)	RDV Cohort 8: Age <12 Years and Weight >=40 kg (N=5)	Total (N=53)
Number of Participants Still in Hospital at Day 10	9 (75.0%)	3 (25.0%)	1 (8.3%)	6 (50.0%)	2 (40.0%)	21 (39.6%)
Number of Participants Discharged Alive by Day 10	3 (25.0%)	9 (75.0%)	11 (91.7%)	6 (50.0%)	3 (60.0%)	32 (60.4%)
Number of Participants who Died on or Prior to Day 10	0	0	0	0	0	0
Number of Participants who Transferred to Other Facility on or Prior to Day 10	0	0	0	0	0	0
Number of Participants who were Released to Palliative Care on or Prior to Day 10	0	0	0	0	0	0
Number of Participants Still in Hospital at Day 30	2 (16.7%)	2 (16.7%)	0	3 (25.0%)	0	7 (13.2%)
Number of Participants Discharged Alive by Day 30	9 (75.0%)	10 (83.3%)	12 (100.0%)	9 (75.0%)	4 (80.0%)	44 (83.0%)
Number of Participants who Died on or Prior to Day 30	1 (8.3%)	0	0	0	1 (20.0%)	2 (3.8%)
Number of Participants who Transferred to Other Facility on or Prior to Day 30	0	0	0	0	0	0

Participants who died after being discharged alive, transferred to another facility, or released to palliative care and with death date prior to the indicated day were presented in each applicable row.
Only participants who were discharged alive on or prior to Day 30 were included in the duration of hospitalization descriptive statistics.
Duration of hospitalization from Day 1 = number of days from first dose to date discharged alive.
Total duration of hospitalization = number of days from hospital admission to date discharged alive.

Duration of hospitalisation:

The median (Q1, Q3) time to discharge from the hospital for all participants was 8 (5, 17) days. The median (Q1, Q3) time for each cohort were as follows:

- Cohort 1: 12 (8, 24) days
- Cohort 2: 7 (5, 9) days
- Cohort 3: 5 (4, 9) days
- Cohort 4: 7 (4, 19) days
- Cohort 8: 10 (4, 18) days

The median (Q1, Q3) total duration of hospitalisation for all participants was 9 (6, 14) days. The median (Q1, Q3) time for each cohort were as follows:

- Cohort 1: 14 (9, 16) days
- Cohort 2: 8 (6, 10) days
- Cohort 3: 8 (5, 11) days

- Cohort 4: 8 (5, 21) days
- Cohort 8: 8 (4, 25) days

SARS-CoV-2 viral load

Confirmed negative SARS-CoV-2 PCR result

Confirmed negative SARS-CoV-2 PCR results (defined as 2 consecutive negative results or a negative result at the last available sample for participants who completed or discontinued from the study) on Day 2 through Day 10 were reported for the following:

42.1% (8/19) total participants with nasal/OP samples

- Cohort 1: 33.3% (2/6) participants
- Cohort 2: 60.0% (3/5) participants
- Cohort 3: 50.0% (2/4) participants
- Cohort 4: 33.3% (1/3) participants
- Cohort 8: 0% (0/1) participant

21.4% (6/28) total participants with NP/OP samples

- Cohort 1: 0% (0/3) participants
- Cohorts 2, 3, and 4: 28.6% (2/7) participants for each cohort
- Cohort 8: 0% (0/4) participants

22.2% (2/9) total participants with ET aspirates

- Cohorts 1, 3, and 8: 0% (0/2, 0/1, and 0/0, respectively) participants for each cohort
- Cohorts 2 and 4: 3.3% (1/3) participants for each cohort

Time to first negative SARS-CoV-2 PCR result with confirmation from nasal/OP, NP/OP samples, and ET aspirates were mostly not estimable.

Change from baseline in SARS-CoV-2 viral load

The mean (SD) baseline and change from baseline in SARS-CoV-2 viral load up to Day 10 or first negative SARS-CoV-2 PCR with confirmation for total participants were as follows:

Nasal/OP swabs

- Baseline (18/53 participants): 4.79 (2.055) log10 copies/mL
- Change from baseline at Day 10 (3/53 participants): −1.59 (1.514) log10 copies/mL
- Change from baseline at day of discharge (3/53 participants): −2.59 (1.982) log10 copies/mL

Nasopharyngeal/OP

- Baseline (23/53 participants): 5.72 (1.898) log10 copies/mL
- Change from baseline at Day 10 (5/53 participants): −1.59 (1.697) log10 copies/mL
- Change from baseline at day of discharge (8/53 participants): −0.53 (1.555) log10 copies/mL

Endotracheal tube aspirates

- Baseline (8/53 participants): 5.93 (2.511) log10 copies/mL
- Change from baseline at Day 10 (1/53 participants): −5.94 log10 copies/mL
- Change from baseline at day of discharge (0/53 participants)

Oxygen usage and ventilation modality

For participants who were discharged alive on or prior to Day 10, 32 participants required oxygen support for a median (Q1, Q3) day, as follows:

- Invasive mechanical ventilation: 3 participants (all in Cohort 3) for 3 (2, 10) days
- High-flow oxygen: 14 participants across 5 cohorts for 4 (2, 5) days
  - Cohort 1: 1/12 participants for 5 (5, 5) days
  - Cohort 2: 6/12 participants for 6 (2, 6) days
  - Cohort 3: 3/12 participants for 3 (1, 4) days
  - Cohort 4: 3/12 participants for 2 (2, 5) days
  - Cohort 8: 1/5 participants for 4 (4, 4) days
- Low-flow oxygen: 15 participants across 5 cohorts for 2 (1, 4) days
  - Cohort 1: 2/12 participants for 3 (1, 5) days
  - Cohort 2: 6/12 participants for 2 (1, 2) days
  - Cohort 3: 2/12 participants for 3 (2, 4) days
  - Cohort 4: 3/12 participants for 1 (1, 6) days
  - Cohort 8: 2/5 participants for 3 (2, 4) days

PEWS Scale

PEWS Scale: Behaviour

At baseline, the 56.5% (30/53) total participants had a PEWS behaviour score of 1, 2, or 3. By Day 10, an improvement (indicated by a decreasing score) was reported for 20 participants (of whom 10, 4, and 6 participants had decreases of 1, 2, and 3 points, respectively), while increases in the PEWS behaviour score were reported for 4 participants (1 point for 3 participants; 2 points for 1 participant. Similar results were observed at the time of last assessment.

The proportion of total participants who had a ≥ 2-point improvement in PEWS behaviour score by Day 10 was 61.1% (11/19 participants; 95% CI: 35.7%-82.7%) with a median (Q1, Q3) time to improvement of 8 (4, not applicable [NA]) days (Table 15.9.2.3.1, Table 15.9.2.4.1). The proportion of participants who had a ≥ 1-point improvement in PEWS behaviour score by Day 10 was 69.0% (20/30 participants; 95% CI: 49.2%-84.7%) with a median (Q1, Q3) time to improvement of 4 (2, 8) days.

By Day 10, recovery in PEWS behaviour, defined as a baseline score of 1 through 3 improved to a score of 0, was reported for 65.5% total participants (19/30 participants; 95% CI: 45.7%-82.1%) with a median (Q1, Q3) time to recovery of 5 (3, NA) days.

PEWS Scale: Cardiovascular

At baseline, the 37.7% (20/53) total participants had a PEWS cardiovascular score of 1, 2, or 3. By Day 10, an improvement was reported for 14 participants (of whom 8, 3, and 3 participants had decreases of 1, 2, and 3 points, respectively), while increases in the PEWS cardiovascular score were reported for 3 participants (1 point for 2 participants; 2 points for 1 participant). The same results were observed at the time of last assessment.

The proportion of total participants who had a ≥ 2-point improvement in PEWS cardiovascular score by Day 10 was 66.7% (6/10 participants; 95% CI: 29.9%-92.5%) with a median (Q1, Q3) time to improvement of 3 (3, NA) days. The proportion of participants who had a ≥ 1-point improvement in PEWS cardiovascular score by Day 10 was 73.3% (14/20 participants; 95% CI: 48.8%-90.9%) with a median (Q1, Q3) time to improvement of 3 (2, 3) days. By Day 10, recovery in PEWS cardiovascular was reported for 63.2% total participants (12/20 participants; 95% CI: 38.4%-83.7%) with a median (Q1, Q3) time to recovery of 3 (2, NA) days.

PEWS Scale: Respiratory

At baseline, the 68.0% (36/53) participants had a PEWS respiratory score of 1, 2, or 3. By Day 10, an improvement was reported for 22 participants (of whom 7, 4, and 11 participants had decreases of 1, 2, and 3 points, respectively), while increases in the PEWS behaviour score were reported for 3 participants (1 point for 2 participants; 2 points for 1 participant). The same results were observed at the time of last assessment.

The proportion of participants who had a ≥ 2-point improvement in PEWS cardiovascular score by Day 10 was 57.7% (15/27 participants; 95% CI: 36.9%-76.6%) with a median (Q1, Q3) time to improvement of 4 (3, NA) days. The proportion of participants who had a ≥ 1-point improvement in PEWS cardiovascular score by Day 10 was 65.7% (23/36 participants; 95% CI: 47.8%-80.9%) with a median (Q1, Q3) time to improvement of 4 (3, 9) days.

By Day 10, recovery in PEWS cardiovascular was reported for 62.9% participants (22/36 participants; 95% CI: 44.9%-78.5%) with a median (Q1, Q3) time to recovery of 6 (3, 10) days

PEWS Scale: Total Score

The change from baseline in PEWS total score by cohort and overall is shown in the table below.

Table 21: GS-US-540-5823: Change from baseline in PEWS Score-total score

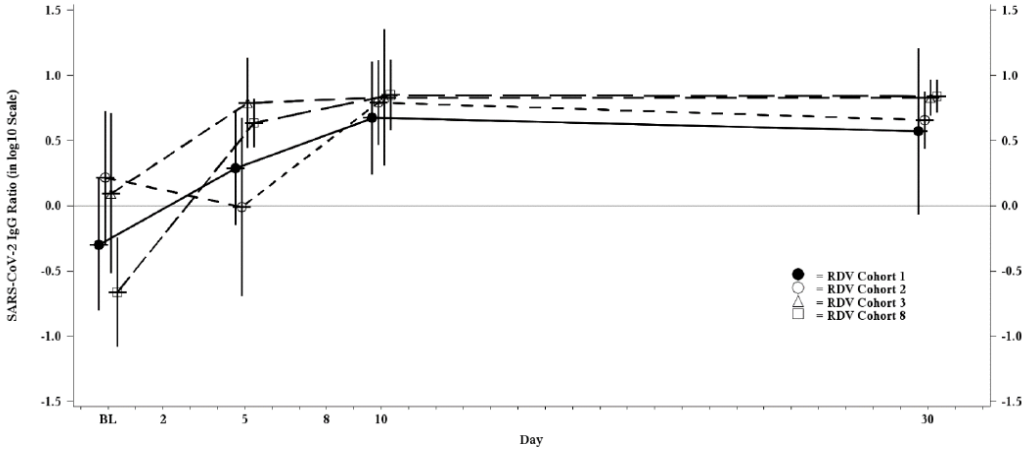
	Cohort 1: Age 12 to < 18 Years and Weight ≥ 40 kg (N = 12)	Cohort 2: Age 28 Days to < 18 Years and Weight 20 to < 40 kg (N = 12)	Cohort 3: Age 28 Days to < 18 Years and Weight 12 to < 20 kg (N = 12)	Cohort 4: Age 28 Days to < 18 Years and Weight 3 to < 12 kg (N = 12)	Cohort 8: Age < 12 Years and Weight ≥ 40 kg (N = 5)	Total (N = 53)
Change from baseline on Day 10						
N	12	12	12	11	5	52
Mean (SD)	−0.7 (1.50)	−2.4 (2.64)	−2.2 (2.69)	−2.2 (2.64)	−1.4 (4.22)	−1.8 (2.60)
Median	−0.5	−1.5	−2.0	−2.0	0.0	−1.0
Q1, Q3	−1.5, 0.0	−3.5, −0.5	−4.5, 0.0	−3.0, 0.0	−4.0, 0.0	−3.0, 0.0
Min, max	−3, 2	−9, 0	−6, 2	−8, 0	−7, 4	−9, 4
Change from baseline on last available assessment						
N	12	12	12	12	5	53
Mean (SD)	−0.7 (1.50)	−2.4 (2.64)	−2.2 (2.69)	−2.0 (2.59)	−1.4 (4.22)	−1.8 (2.59)
Median	−0.5	−1.5	−2.0	−1.5	0.0	−1.0
Q1, Q3	−1.5, 0.0	−3.5, −0.5	−4.5, 0.0	−2.5, 0.0	−4.0, 0.0	−3.0, 0.0
Min, max	−3, 2	−9, 0	−6, 2	−8, 0	−7, 4	−9, 4

max = maximum; min = minimum; PEWS = Pediatric Early Warning Score; RDV = remdesivir (GS-5734™)
Baseline was the last available value recorded on or prior to dosing for RDV. A negative change from baseline value indicates an improvement.
Total score was the sum of Behavior, Cardiovascular, and Respiratory.
Source: Table 15.9.2.2.4

Other analyses related to efficacy

Plasma SARS-CoV-2 IgG Levels

The baseline mean (SD) immunological status ratio of SARS-CoV-2 IgG for total participants with a weight of ≥ 12 kg was −0.081 (0.7085) (log10 scale), which peaked to 0.760 (0.2749) (log10 scale) on Day 10 before decreasing to 0.689 (0.4187) (log10 scale) at Day 30. The mean (SD) ratios for individual cohorts are show in the figure below.



RDV Cohort 1 (n=):	9	9	6	7
RDV Cohort 2 (n=):	9	8	3	6
RDV Cohort 3 (n=):	9	6	2	5
RDV Cohort 8 (n=):	4	3	3	2

FDA = Food and Drug Administration; Ig = immunoglobulin; ISR = immunological status ratio; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; RDV = remdesivir (GS-5473™)

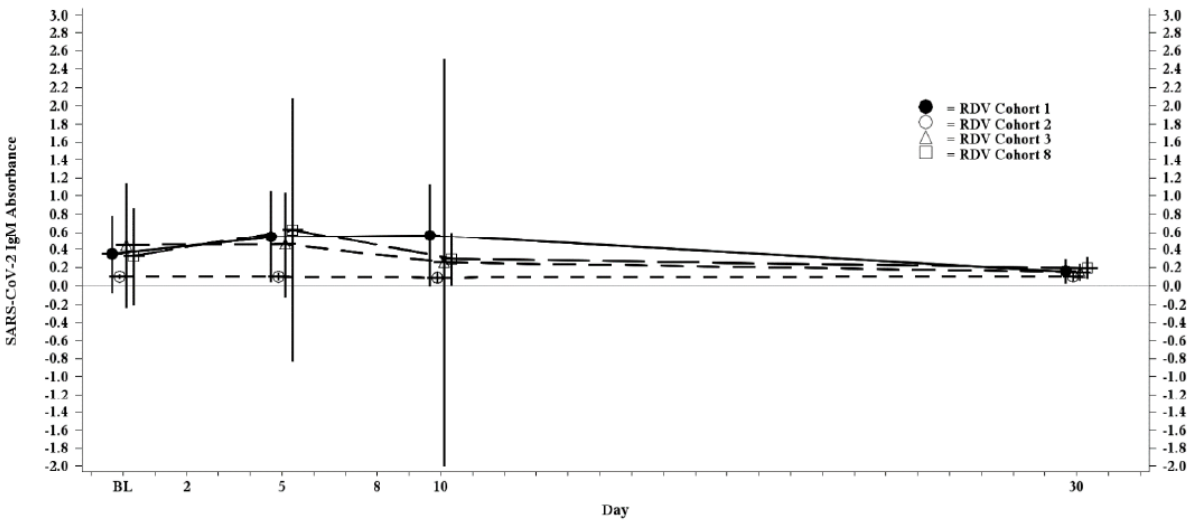
The ISR is calculated from the ratio of the optical density obtained with the test sample divided by the calculated Cut-Off Value. FDA assay inserts use ISR term.

Source: Figure 15.9.3.2.5

Figure 19: GS-US-540-5823: Mean (SD) immunological status ratio of SARS-CoV-2 IgG (in log10 scale) for participants with weights ≥ 12 kg by visit (Full Analysis Set)

Plasma SARS-CoV-2 IgM Levels

The baseline mean (SD) immunological status ratio of SARS-CoV-2 IgM for total participants with a weight of ≥ 12 kg was 0.304 (0.5695) (log10 scale), which peaked to 0.396 (0.5187) (log10 scale) on Day 5 and decreased to 0.148 (0.0854) (log10 scale) on Day 30. The mean (SD) ratios for individual cohorts are shown below.



RDV Cohort 1 (n=):	9	9	6	6
RDV Cohort 2 (n=):	9	8	3	6
RDV Cohort 3 (n=):	9	6	2	5
RDV Cohort 8 (n=):	4	3	3	4

FDA = Food and Drug Administration; Ig = immunoglobulin; ISR = immunological status ratio; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; RDV = remdesivir (GS-5473™)

The ISR is calculated from the ratio of the optical density obtained with the test sample divided by the calculated Cut-Off Value. FDA assay inserts use ISR term.

Source: Figure 15.9.3.3.5

Figure 20: GS-US-540-5823: Mean (SD) immunological status ratio of SARS-CoV-2 IgM for participants with weights ≥ 12 kg by visit (Full Analysis Set)

Viral Resistance

Baseline virology analysis

SARS-CoV-2 sequencing was attempted on baseline samples from 31 (58.5%) out of 53 participants in the full analysis set (FAS). Baseline sequencing data were obtained from 30 (56.6%) out of 53 participants in the FAS (see below).

Table 22: Baseline Sequencing Data

	Number of Participants					
	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 8	Total
FAS	12	12	12	12	5	53
Participants with no data available	5	8	6	4	0	23
Viral load < LLOQ or No SARS-CoV-2 Detected	1	5	3	1	0	10
No baseline and/or postbaseline sample	2	2	3	2	0	9
Excluded due to additional COVID-19 treatment	1	0	0	0	0	1
Excluded due to prior RDV treatment	1	0	0	0	0	1
Assay failure	0	1	0	0	0	1
Data pending	0	0	0	1	0	1
Participants with sequencing data at baseline	7	4	6	8	5	30

FAS = Full Analysis Set
Source: Appendix 3 Virology Listings, GS-US-540-5823 Interim CSR listing 16.2.7.2, listing 16.2.7.3, listing 16.2.7.4

SARS-CoV-2 variants present at baseline

Out of 30 participants with baseline sequencing data available, all had SARS-CoV-2 lineage determined.

Table 23: SARS-CoV-2 Lineages

Pango Lineage (WHO label) [a]	Number of participants, n (% out of participants with baseline sequencing data available)					
	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 8	Total
Participants with sequencing data at baseline	7	4	6	8	5	30
B.1.2	0	2 (50.0)	1 (16.7)	1 (12.5)	0	4 (13.3)
B.1.1.7 (Alpha)	0	0	0	3 (37.5)	1 (20.0)	4 (13.3)
B.1.429 (Epsilon)	0	0	2 (33.3)	1 (12.5)	0	3 (10.0)
B.1.564	1 (14.3)	1 (25.0)	0	0	0	2 (6.7)
B.1.509	1 (14.3)	1 (25.0)	0	0	0	2 (6.7)
B.1.596	0	0	2 (33.3)	0	0	2 (6.7)
Other [b]	5 (71.4)	0	1 (16.7)	3 (37.5)	4 (80.0)	13 (43.3)

a The WHO naming nomenclature as of September 22nd 2021 has been applied as applicable
b Lineages detected in 1 participant each. None were designated as variants of interest or variants of concern by CDC.
Source: Appendix 3Virology Listing 3

Baseline amino acid substitutions in nsp12 compared to SARS-CoV-2 reference sequence

Out of 30 participants with sequencing data available, P323L was the only amino acid substitution identified in ≥ 3 participants, observed in all 30 participants, consistent with currently circulating SARS-CoV-2 variants. P323L does not confer reduced susceptibility to RDV *in vitro* (PC-540-2024).

Post-baseline virology analysis

SARS-CoV-2 sequencing was attempted on postbaseline samples from 33 (62.3%) out of 53 participants in the FAS. Postbaseline sequencing data were obtained from 27 (50.9%) out of 53 participants. Sequencing failed for samples from 6 participants at postbaseline timepoints.

Table 24: Post-baseline sequencing data

	Number of Participants					
	Cohort 1	**Cohort 2**	**Cohort 3**	**Cohort 4**	**Cohort 8**	**Total**
FAS	12	12	12	12	5	53
Participants with no data available	7	9	8	6	0	30
Viral load < LLOQ or No SARS-CoV-2 Detected	1	5	3	2	0	11
No baseline and/or postbaseline sample	2	2	4	4	0	12
Excluded due to additional COVID-19 treatment	3	0	0	0	0	3
Excluded due to prior RDV treatment	1	0	0	0	0	1
Assay failure	0	2	1	0	0	3
Participants with sequencing data at baseline and postbaseline	5	3	4	6	5	23

FAS = Full Analysis Set
Source: Appendix 3 Virology Listing 8, GS-US-540-5823 Interim CSR listing 16.2.7.2, listing 16.2.7.3, listing 16.2.7.4

Post-baseline Amino Acid Substitutions Emerging in nsp12

Among the 23 participants with both baseline and post-baseline sequencing data available, amino acid substitutions in nsp12 were observed in 1 participant treated with RDV (see table below*).*

Table 25: Post-baseline amino acid substitutions emerging in nsp12

	Number of participants, n (% out of participants with sequencing data at baseline and postbaseline)					
nsp12 substitutions	**Cohort 1**	**Cohort 2**	**Cohort 3**	**Cohort 4**	**Cohort 8**	**Total**
Participants with sequencing data at baseline and postbaseline	5	3	4	6	5	23
None	4 (80.0)	3 (100)	4 (100)	6 (100)	5 (100)	22 (95.7)
Any	1 (20.0)	0	0	0	0	1 (4.3)
A656A/P [a]	1 (20.0)	0	0	0	0	1 (4.3)
G670G/V [a]	1 (20.0)	0	0	0	0	1 (4.3)

FAS = Full Analysis Set
a A656A/P and G670G/V were observed in the sample collected at Day 3 in participant 11115-21007
Source: Appendix 3Virology Listing 8, GS-US-540-5823 Interim CSR listing 16.2.7.2, listing 16.2.7.3, listing 16.2.7.4

Amino acid changes in nsp12 compared to SARS-CoV-2 reference sequence in patients with post-baseline sequencing data only

For 4 participants, post-baseline sequencing data were available without baseline sequencing data. All 4 participants had nsp12 P323L present at the post-baseline timepoint, and no additional changes amino acid changes were observed compared to the SARS-CoV-2 reference sequence. P323L does not confer reduced susceptibility to RDV *in vitro* (PC-540-2024).

Post-baseline amino acid substitutions emerging in nsp8, nsp10, nsp13 and nsp14

In total, 23 participants had both baseline and post-baseline sequencing data available (see table below).

Table 26: Postbaseline Amino Acid Substitutions Emerging in nsp8, nsp10, nsp13 and nsp14

	Number of participants, n (% out of participants with sequencing data at baseline and postbaseline)					
	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 8	Total
Participants with sequencing data at baseline and postbaseline	5	3	4	6	5	23
nsp8	None	None	None	None	None	None
nsp10	None	None	1 (25.0)	None	None	1 (4.3)
D64D/Y [a]	0	0	1 (25.0)	0	0	1 (4.3)
T101T/I [a]	0	0	1 (25.0)	0	0	1 (4.3)
nsp13	1 (20.0)	None	None	1 (16.7)	None	2 (8.7)
R248R/I [b]	1 (20.0)	0	0	0	0	1 (4.3) [c]
S259S/L	0	0	0	1 (16.7)	0	1 (4.3) [c]
V266V/F [b]	1 (20.0)	0	0	0	0	1 (4.3) [c]
nsp14	None	None	None	None	None	None

a D64D/Y and T101T/I in nsp 10 were observed in the sample collected at Day 3 in 1 participant
b R24R/I and V266V/F in nsp 13 were observed in the sample collected at Day 10 in 1 participant
c No nsp13 sequence coverage was obtained for one participant for postion 248,259 and 266
Source: appendix 3 Virology Listing 6, Appendix 3 Virology Listing 7, Appendix 3 Virology Lising 9, Appendix 3 Virology Listing 10

Ancillary analyses

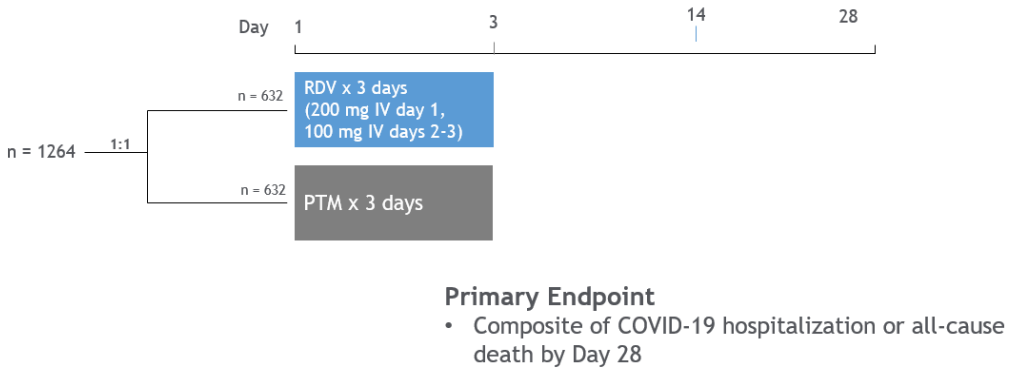
Study GS-US-540-9012 (Pinetree study)

The study design and methods of study GS-US-540-9012 were already assessed in detail in the extension of indication to adult patients who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19 (for more information please refer to procedure EMEA/H/C/005622/II/0016). Therefore, design features are only shortly summarized below.

Methods

Study GS-US-540-9012 was a Phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of treatment of early stage COVID-19 with IV-administered Remdesivir in an outpatient setting in 584 participants with confirmed COVID-19 who were at increased risk for disease progression.

The study was a multi-centre trial, conducted in 64 sites globally. The most common baseline risk factors were diabetes mellitus (62%), obesity (56%) and hypertension (48%) and were equally distributed across treatment arms. 30% of the enrolled patients were > 60 year of age. Based on available virology data, none of the patients was infected with the Delta variant. No vaccinated patients were enrolled in study 9012. Eligible participants were randomized in a 1:1 ratio to one of the two treatment groups (Figure 21). Randomization was stratified by participants who resided in a skilled nursing facility, by participant's age (< 60 vs ≥ 60 years), and by region (US vs ex-US). Participants received either study treatment with Remdesivir (RDV) or Placebo to match (PTM) for 3 days and were followed up for 28 days. Treatment with Remdesivir/placebo was given for three days. The primary efficacy endpoint was COVID-19 related hospitalisation by day 28. The analysis population included 562 patients (279 patients in the Remdesivir treatment group, and 283 patients in the placebo-arm).



Source: Information taken from the MAH's presentation on study GS-US-540-9012
Figure 21: Scheme of GS-US-540-9012 study design

Study participants

Main inclusion criteria

1. Aged ≥ 18 years (at all sites), or aged ≥ 12 and < 18 years of age weighing ≥ 40 kg (where permitted according to local law and approved nationally and by the relevant IRB or IEC)
2. Either

   At least 1 of the following pre-existing risk factors for progression to hospitalization

   - Chronic lung disease: chronic obstructive pulmonary disease, moderate-to-severe asthma, cystic fibrosis, pulmonary fibrosis
   - Hypertension: systemic or pulmonary
   - Cardiovascular or cerebrovascular disease: coronary artery disease, congenital heart disease, heart failure, cardiomyopathy, history of stroke, atrial fibrillation, hyperlipidemia
   - Diabetes mellitus: type 1, type 2, or gestational
   - Obesity (BMI ≥ 30)
   - Immunocompromised state; having a solid organ transplant, blood, or bone marrow transplant; immune deficiencies; HIV with a low CD4 cell count or not on HIV treatment; prolonged use of corticosteroids; or use of other immune weakening medicines
   - Chronic mild or moderate kidney disease
   - Chronic liver disease
   - Current cancer
   - Sickle cell disease

   OR

   Age ≥ 60 years, regardless of the presence of other pre-existing risk factors for progression
3. SARS-CoV-2 infection confirmed by molecular diagnostics (nucleic acid [e.g., PCR] or antigen testing) ≤ 4 days prior to screening
4. Presence of ≥ 1 symptom(s) consistent with COVID-19 for ≤ 7 days prior to randomization (such as fever, cough, fatigue, shortness of breath, sore throat, headache, myalgia/arthralgia)

5. Did not receive, require, or expect to require supplemental oxygen
6. Did not require hospitalization (hospitalization defined as ≥ 24 hours of acute care)

Main exclusion criteria

1. Participation in any other clinical study of an experimental treatment and prevention for COVID-19
2. Prior hospitalization for COVID-19 (hospitalization defined as ≥ 24 hours of acute care)
3. Treatment with other agents with actual or possible direct antiviral activity against SARS-CoV-2 or administration of any SARS-CoV-2 (or COVID-19) vaccine
4. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 5 × upper limit of normal (ULN) at screening or within 90 days of screening. Note: if per local practice only ALT was routinely measured, exclusion criteria were evaluated on ALT alone
5. Creatinine clearance < 30 mL/min at screening or within 90 days of screening using Cockcroft-Gault formula in participants ≥ 18 years of age or estimated glomerular filtration rate (eGFR) < 30 min/1.73m^2 at screening or within 90 days of screening using Schwartz formula in participants < 18 years of age
6. Use or planned use of exclusionary medications

Treatments

Remdesivir group:	Participants received a single dose of IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2 and 3.
Placebo group:	Participants received PTM Remdesivir on Days 1 to 3.

Duration of treatment:

The duration of treatment was up to 3 days for participants in the RDV IV for 3 days group and up to 3 days for participants in the placebo group. The last study follow-up was on Day 28.

Outcomes and estimation

Participant flow

Participants were enrolled and treated across 64 centres in the US, Denmark, Spain, and the UK.

Of the 630 participants screened, a total of 584 participants were randomized, 292 to receive RDV IV for 3 days and 292 to receive placebo for 3 days. Of these, 562 participants (279 in the RDV IV for 3 days group and 283 in the placebo group) received at least one dose of study treatment and were included in the FAS and Safety Analysis Set. Twenty-two participants met all eligibility criteria and were not randomized due to the following reasons: withdrew consent (14); outside of visit window (3); lost to follow-up (2); other (2); and investigator's discretion (1). Twenty-two randomized participants did not receive any study treatment.

As per protocol, the FAS ITT-population was the primary analysis set.

Baseline data

Demographic and baseline characteristics

Of the 8 adolescent participants, 5 were male and 3 were female. The mean (SD) age was 14 (2.3) years (range: 13 to 17 years) in the RDV IV for 3 days group and 16 (1.1) years (range: 14 to 17 years) in the placebo group. All 8 participants were White. Three of the participants were not Hispanic/Latino and 5 were Hispanic/Latino. The median (Q1, Q3) weight was 68.0 (61.0, 86.3) kg in the RDV IV for 3 days group and 72.2 (65.1, 72.2) kg in the placebo group. The median (Q1, Q3) BMI was 25.7 (21.1, 31.7) kg/m2 in the RDV IV for 3 days group and 28.7 (23.2, 29.1) kg/m2 in the placebo group.

Other Baseline Characteristics

Of the 8 adolescent participants, 6 had a risk factor of chronic lung disease, 2 had a risk factor of diabetes mellitus, and 2 had a risk factor of obesity. Median duration of symptoms prior to first dose of RDV was 2 days in the RDV IV group and 4 days in the placebo group; median duration from SARS-CoV-2 nucleic acid/antigen confirmation to first dose of study drug was 0 days in the RDV IV for 3 days group and 1 day in the placebo group. Median (Q1, Q3) baseline ALT was 20 (9, 52) U/L and 14 (13, 44) U/L in the RDV IV for 3 days and placebo group, respectively; median (Q1, Q3) baseline AST was 20 (17, 38) U/L and 20 (20, 36) U/L, respectively. Median (Q1, Q3) respiration rate was 15 (15, 16) breaths/minute and 18 (17, 18) breaths/minute, respectively. Median (Q1, Q3) nasopharyngeal SARS-CoV-2 viral load was 4.07 (3.88, 7.13) log10 copies/mL in the RDV IV for 3 days group and 7.18 (5.28, 7.49) log10 copies/mL in the placebo group.

Primary efficacy endpoint:

Composite endpoint of COVID-19-related hospitalization or all-cause death by Day 28

No adolescent participant (12 to < 18 years of age) had COVID-19-related hospitalization or all-cause death by Day 28.

Secondary efficacy endpoints:

No adolescent participant (12 to < 18 years of age) had a COVID-19–related medically attended visit (MAV) or all-cause death by Day 28. No adolescent participant in the RDV IV for 3 days group and 3 adolescent participants in the placebo group had baseline COVID-19–adapted FLU-PRO Plus questionnaire data captured prior to or on the first dosing date. None of the 3 adolescent participants in the placebo group reported alleviation (mild or absent) of baseline COVID-19 symptoms through Day 14.

One of the 8 adolescent participants was missing baseline viral load data. There was no difference between the RDV IV for 3 days group and the placebo group neither for $DAVG_7$ nor $DAVG_{14}$ in nasopharyngeal SARS-CoV-2 viral load. The RDV IV for 3 days group and the placebo group had similar changes from baseline in nasopharyngeal SARS-CoV-2 viral load at all time points. At Day 14, the mean (SD) change from baseline was −1.68 (1.155) log_{10} copies/mL in the RDV IV for 3 days group and −3.38 (1.991) log_{10} copies/mL in the placebo group. A negative nasopharyngeal SARS-CoV-2 PCR (viral load) was reported for 1 of 3 participants (33.3%) in the RDV IV for 3 days group and 1 of 4 participants (25.0%) in the placebo group at Day 14.

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

N/A

Clinical studies in special populations

N/A

Supportive studies

N/A

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Study GS-US-540-5823 (CARAVAN)

Study GS-US-540-5823 (CARAVAN) is a Phase 2/3 single arm, open-label study evaluating the safety, tolerability and pharmacokinetics of remdesivir in participants from birth to <18 years of age hospitalized with COVID-19. The primary study endpoints were the proportion of participants experiencing treatment-emergent adverse events; proportion of participants experiencing treatment-emergent graded laboratory abnormalities; and evaluation of plasma concentrations of remdesivir and metabolites, respectively. The 10 secondary endpoints related to efficacy include: assessment of clinical improvement based on scoring using the 7-point ordinal scale and PEWS score; viral load decline; change from baseline in oxygenation use; change from baseline in the use of mechanical ventilation or extracorporeal membrane oxygenation (ECMO); and time (days) to discharge from hospital. The analysis population included 53 patients, which were included in five different age Cohorts (Cohort 1: 12 patients; Cohort 2: 12 patients, Cohort 3: 12 patients, Cohort 4: 12 and Cohort 8: 5 patients).

Study GS-US-540-5823 is currently ongoing. Therefore, only an interim study report was provided. This interim clinical study report (CSR) presents data for Cohorts 1 through 4 and Cohort 8. Due to the single-arm design, no firm conclusion on efficacy is possible and the results should be interpreted with caution.

The study protocol was amended three times between study initiation and the time of this interim CSR. None of the changes is considered to have impacted the study results. A high number of important protocol deviations (IPDs) were reported during the study. Most of them were related to missing data related to primary and secondary endpoints (45%) or off-scheduled procedures (39%) through the study. According to the MAH, none of the IPDs affected the overall quality or interpretation of the data. However, no reasons or further information concerning the missing data related to the primary and secondary endpoints were provided. The MAH was asked to provide the respective information. In summary, all missing data IPDs were related to secondary efficacy endpoints (apart from the safety-related endpoint of symptom-driven physical examination at discharge for 1 participant) and data for these endpoints are available for participants on other study days. Consequently, the missing data are not considered to impact the overall interpretation of the interim Study GS-US- 540-5823 results. It is considered unfortunate that particularly a high number of viral load data are missing.

No vaccinated patients were enrolled in study 9012. The majority of the participants in the FAS were female (56.6%). Median age was 15.0 (range: 12.0 to 17.0) years in Cohort 1, 9.0 (range: 4.0 to 16.0) years in Cohort 2, 3.5 (range: 1.9 to 7.0) years in Cohort 3, 0.5 (range: 0.1 to 0.9) years in Cohort 4, and 11.0 (8.0 to 11.0) years in Cohort 8. The majority of participants were White (70.2%) and were not Hispanic/Latino (55.8%).

The median (Q1, Q3) baseline weight was 83.5 (56.8, 106.9) kg in Cohort 1, 26.5 (25.0, 30.9) kg in Cohort 2, 14.6 (13.4, 18.2) kg in Cohort 3, 5.0 (4.4, 8.5) kg in Cohort 4, and 73.0 (55.1, 80.0) kg in Cohort 8. Median BMI was 33.8 (21.6, 46.5) kg/m2 in Cohort 1, 17.8 (14.9, 20.2) kg/m2 in Cohort 2, 16.2 (15.6, 18.1) kg/m2 in Cohort 3, 16.3 (14.7, 20.0) kg/m2 in Cohort 4, and 28.0 (27.2, 35.6) kg/m2 in Cohort 8. It is of note that 53% of the patients in Cohort 1 and 80% in Cohort 8 had BMI higher than the 95th percentile for their age. Hence, all participants weighted considerably more than the 40 kg defined in the indication.

When comparing baseline disease characteristics some differences between the different cohorts were noted. The median duration of symptoms prior to the first dose was longer in Cohort 1 (7 days) than in the other cohorts (5 day, 3 days, 5 days and 5 days in Cohort 2-4 and Cohort 8, respectively). Median creatinine levels were higher and median eGFR was lower in patients of Cohort 1 compared to the other cohorts, which could have contributed to the high rate of reported renal failures observed in Cohort 1. In addition, median ALT and AST levels were higher in Cohort 1 compared to the other cohorts, suggesting that the baseline medical condition of patients in Cohort 1 may have been worse than in other cohorts. However, this does not translate into more severe COVID-19 disease, as despite the longer duration of symptoms prior to the first dose, the clinical status of patients at baseline in Cohort 1 was not worse than in the other cohorts, as only one patient had IMV or ECMO at baseline, compared to three, three, five and none in cohorts 2-4 and cohort 8, respectively. Slightly more patients in Cohort 1 received non-invasive mechanical ventilation or high-flow oxygen (N=6), compared to the other Cohorts (N=4, N=3, N=3 and N=2 in cohorts 2-4 and cohort 8, respectively). Overall, the proportion of patients with severe COVID-19 (Ordinal scale score of 2 and 3) was balanced between the Cohorts. Furthermore, the median duration of hospitalisation prior to the first dose of RDV and the characteristics of medical history were comparable between the cohorts. A question on which factors might have led to the differences in safety and efficacy data between cohort 1 (and 8) and cohorts 2-4 was posed. The MAH discussed further this issue upon request. It is agreed that the efficacy assessments are particularly challenging given the uncontrolled, open-label design of Study GS-US-540-5823 in addition to the small number of participants in each cohort. This small number of participants in each cohort is an important consideration and limits the ability to interpret reliably any apparent differences in safety as well as efficacy across the cohorts and relative to adults who received RDV in clinical trials (see also discussion in Clinical Safety).

In total, 13 of the enrolled study participants were on room air at baseline, while the others needed any kind of supportive oxygen (N=12 on IMV/ECMO, N=18 high-flow oxygen an N=10 low-flow oxygen). Considering the proposed indication in paediatric patients weighing at least 40 kg, not requiring supplemental oxygen, it is important that only four of the 53 participants (N=3 in Cohort 1 and N=1 in Cohort 1) were on room air at baseline. Hence, data is limited. Further it is notable, that 12 of the enrolled patients did receive IMV/ECMO at baseline. Considering, that the currently approved indication of remdesivir in the EU does not include the subgroup on IMV/ECMO, due to a lack of efficacy in this subgroup, it is surprising, that so many children on IMV/ECMO have received remdesivir. However, most of the participants were enrolled in the US, where there is no restriction of indication.

Study GS-US-540-9012 (Pinetree)

Study GS-US-540-9012 (Pinetree) was a Phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate treatment with IV-administered Remdesivir in an outpatient setting in 584 participants with confirmed COVID-19 who were at increased risk for disease progression. The most common baseline risk factors were diabetes mellitus (62%), obesity (56%) and hypertension (48%) and were equally distributed across treatment arms. 30% of the enrolled patients were > 60 year of age. Based on available virology data, none of the patients was infected with the Delta variant.

Treatment with Remdesivir/placebo was given for three days. The primary efficacy endpoint was COVID-19 related hospitalisation by day 28. The analysis population included 562 patients (279 patients in the Remdesivir treatment group, and 283 patients in the placebo-arm).

However, only eight adolescents were enrolled in the study of whom three received remdesivir treatment.

Efficacy data and additional analyses

Study GS-US-540-5823

Initially, the provided paediatric dose justification was not considered sufficient. The dose selection for children was based on simulations from the PBPK model of 2020, including limited adult data and plasma concentrations (without paediatric data). The PBPK model was not updated with the new studies (-5823 and -9012), instead exposure in children and adolescents were evaluated with the popPK model. Based on the clinical data, the predictions of the old PBPK model are not reflective of the measured concentrations in paediatric patients, as plasma concentrations and exposures determined in paediatric patients revealed higher values than expected compared to adults. However, the interpretation of this data was difficult due to small sample size and high variability in phase 3 data. In addition, data from the popPK model indicate that exposure (C_{max} and AUC) were two-fold higher in paediatric patients compared to adults questioning the dosing strategy or the aimed target exposure in paediatric patients. Hence, the conclusion, that exposures of both RDV and GS-441524 in adolescents and children were maintained at or below that which was previously observed to be well tolerated in adult healthy volunteers was not agreed with the information submitted firstly (please refer to Clinical pharmacology for further information). Therefore, the MAH was asked to justify the two-fold higher exposure seen in paediatric patients above 4 weeks of age and weighing at least 3.5 kg especially in terms of safety, SBECD exposure and efficacy**.** The MAH provided the requested data. They compared the PK data from Cohorts 1-4 and 8 from study GS-US-540-5823 with the PK data of adult COVID-19 outpatients (study GS-US-540-9012). Remdesivir AUC and C_{max} were increased up to 129% (Cohort 3). The increase was lowest (33-45%) in Cohorts 1 and 4 (children and adolescence ≥ 40 kg). Similarly, the exposure of metabolite GS-704277 increased up to 124%. AUC of the intracellularly formed metabolite GS-441524 is mostly comparable between cohorts and only moderately increased compared to adult data. C_{max} and C_{tau} were up to 41% (Cohort 4) and 60% (Cohort 1) increased, respectively.

Regarding exposure to the excipient SBECD, it was not higher in paediatric patients compared to preliminary data on adult patients with mild to moderate renal impairment. Moreover, no trends were identified in SBECD exposures across paediatric age and paediatric weight bands.

The MAH further stated that no trends were identified between PK exposures of either RDV or its metabolites, and the most common AEs reported in study GS-US-540-5823. Furthermore, patients with an AE of AKI had only moderately increased PK exposures (AUC, C_{max}) of GS-441524 (70% to 100%) and SBECD (12% to 60%). Therefore, from safety view it is agreed that RDV was well tolerated during clinical studies in paediatric patients and the safety data reported during study GS-US-540-5823 are comparable to the studies in adults. Overall, no safety signal was identified based on the data provided.

Due to the single-arm design of the study 5823, the lack of a control arm and as only descriptive efficacy data have been presented, no firm conclusion on efficacy in the intended paediatric indication is possible. Hence, interpretation of efficacy data should be done with caution.

The definition of recovery in the 5823 study was defined as an improvement from a baseline ordinal score of 2 (IMV/ECMO) through 5 (hospitalised, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise) to a score of 6 (hospitalised, not requiring supplemental oxygen - no longer requires ongoing medical care (other than per protocol RDV administration) or 7 (not hospitalised) or an improvement from a baseline score of 6 to a score of 7. Hence, the study-definition of recovery was very bright and should be interpreted with caution. It is of note that a 7-point ordinal scale instead of the frequently used 11-point ordinal scale was used. The condensation of NIVM and high flow oxygen and IMV and ECMO somewhat limit the impact of improvements in clinical status and recovery.

Results of the overall population may be too optimistic, due to the fact, that patients in Cohort 3 were not as sick at baseline, as half of the patients had an ordinal score of 5 (on room air, no longer requiring ongoing medical care (other than per protocol RDV administration) at baseline. Consequently, participants in cohort 3 recovered faster than patients in the other Cohorts. Hence, interpretation should also be done based on cohorts to get a better picture on remdesivir's treatment efficacy. One patient in cohort 4 already met the term recovery (baseline ordinal scale of 6) at baseline. Only 13 participants (24.5%) received 10 doses of remdesivir. Considering that the majority of patients have only received remdesivir for 5 days (36%, N= 19) or less than five days (N=17), efficacy outcomes at D5 are also considered important.

It has been noted that efficacy outcomes in the different cohorts at D5, D10 and last available assessment vary between the cohorts, especially between Cohort 1 and the other cohorts. By Day 5, 28% of the enrolled patients were recovered. Most of them in Cohort 3 (6 patients) and Cohort 2 (4 patients). Notably, none of the patients in Cohort 1 was recovered. Twelve patients were still on IMV/ECMO, and 10 patients were receiving non-invasive ventilation or high-flow oxygen. By day 10, 60% (N=32) of the enrolled participants met the definition of recovery. However, the effect was again mainly driven by cohort 3 (11 patients) and cohort 2 (9 patients) and only 25% of the patients in cohort 1 recovered by day 10. At day 10, 20 patients were still in hospital, most of them were enrolled in Cohort 1 (N=9) and Cohort 4 (N=6), while only one participant in cohort 3 and cohort 8 and three in cohort 2 were still in hospital. Of these, eight required IMV/ECMO, three in cohort 1 and cohort 4 and one each in cohort 2 and cohort 8. At the last available assessment, 83% of the enrolled participants met the study defined criteria of recovery. In terms of cohorts, all patients in Cohort 3, and 10 of the 12 patients in Cohort 2 and 4 and 5 patients in Cohort 8 recovered. Recovery rates were lower in Cohort 1 (9/12) and Cohort 4 (9/12). In addition, six patients were still in hospital, four receiving IMV/ECMO (one in Cohort 1 and three in Cohort 4) and one was still in hospital not requiring supplemental oxygen but requiring ongoing medical care (COVID-19 related or otherwise) (Cohort 2).

In total, three patients died during the study, all of them after day 10. Two patients in Cohort 1 and one patient in Cohort 8.

The proportion of patients with an improvement in clinical status of at least 2 points, was lower in Cohort 1 and Cohort 4. By day 5 none of the patients in Cohort 1 showed a clinical improvement. Notably, in total eight out of 53 patients did not have had an improvement in clinical status of at least 2 points at the last assessment available. In line with the findings above, the median (Q1, Q3) time to $\geq$ 2-point improvement for participants with an ordinal score of $\leq$ 5 points at baseline was longer in the two cohorts receiving the adult dosing regimen and not the weight-based approach, i.e., Cohort 1 (11 days (6, 24)) and Cohort 8 (9 days (4, 10). The median (Q1, Q3) time to $\geq$ 2-point improvement for participants with an ordinal score of $\leq$ 5 points at baseline was shortest for cohort 3 (5 days).

Recovery, defined as an improvement from a baseline score of 2 through 5 to a score of 6 or 7 or an improvement from a baseline score of 6 to a score of 7. Recovery was reported for 62.3% (33/53) of all participants (95% CI: 47.9%-75.2%) on Day 10. The proportion of participants that recovered by

D5 was lower in Cohort 1 (3/12 participants) compared to the other cohorts. At the time of last available assessment, 9/12 patients in Cohort 1 and Cohort 4 recovered, while all patients in Cohort 3 have recovered. In total, nine patients did not have recovered at the time of last available assessment. Time to recovery was longer in paediatric patients receiving the adult dosing regimen (Cohort 1: 12 days; Cohort 8: 10 days, compared to Cohort 2 and 4: 7 days and Cohort 3: 5 days). These findings raised the question on the necessity of alternative dosing/posology also in this patient population that would provide similar exposures compared to adults.

In general, the overall time to recovery was shorter (7 days) than that seen in adults, which may be reflective of the generally observed less severe disease and disease progression in paediatric patients. However, as a control arm is missing, these results are difficult to interpret, and no firm conclusion is possible.

In line with the other findings the duration of hospitalisation was significantly longer in paediatric patients receiving the adult dosing regimen (Cohort 1: 12 days; Cohort 8: 10 days) compared to those receiving the weight-based dosing (Cohort 2 and 4: 7 days and Cohort 3: 5 days). Considering the complementary information provided during the assessment for the most relevant compound, paediatric exposure was comparable to adult exposure in an acceptable range. Therefore, the posology proposed by the MAH is overall considered agreeable.

PEWS total score for the total population was 0 for 22.6% (12/53) participants; 1, 2, or 3 for 37.7% (20/53) participants; 4, 5, or 6 for 24.5% (13/53) participants; and 7, 8, or 9 for 15.1% (8/53) participants. By Day 10, no improvement was reported for 32.1% (17/53) participants and increases in the PEWS total score were reported for 7.6% (4/53) participants. It is of note that median PEWS score reductions were lowest in Cohort 1 (-0.5) and Cohort 8 (0.0) receiving the adult dosing regimen.

PEWS score data for behaviour, respiratory and cardiovascular were also provided. By Day 10, recovery in PEWS behaviour, defined as a baseline score of 1 through 3 improved to a score of 0, was reported for 65.5% total participants (19/30 participants; 95% CI: 45.7%-82.1%), for PEWS respiratory recovery was reported for 62.9% participants (22/36 participants; 95% CI: 44.9%-78.5%) and for PEWS cardiovascular recovery was reported for 63.2% total participants (12/20 participants; 95% CI: 38.4%-83.7%). Notably, for all tested PEWS scores the rate of patients with no improvement at D10 and last available assessment was higher in cohort 1 compared to the other cohorts.

Confirmed negative SARS-CoV-2 PCR results (defined as 2 consecutive negative results or a negative result at the last available sample for participants who completed or discontinued from the study) on Day 2 through Day 10 were seen in 42.1% (8/19) total participants with nasal/OP samples, 21.4% (6/28) total participants with NP/OP samples and 22.2% (2/9) total participants with ET aspirates. However, different sampling techniques to evaluate viral load were used for the study participants, namely nasal swabs, NP swaps and endotracheal (ET) aspirates. In addition, the use of the different sampling techniques was not balanced between and within Cohorts. Inconsistencies in viral load at baseline from different sampling techniques were noted between the different cohorts, as well as between the same cohort. Hence, comparability of viral load results between and within cohorts could have been severely impacted by the different sampling techniques used. It is impossible, to elucidate if the differences observed in viral load are due to the age/weight-characteristics, the baseline disease status or due to the different sampling techniques used. Furthermore, time to first negative SARS-CoV-2 PCR result with confirmation from nasal/OP, NP/OP samples, and ET aspirates were mostly not estimable. Taken together, results of the viral load data cannot be considered to draw any firm and meaningful conclusion on the antiviral effect of remdesivir in paediatric patients. Furthermore, due to the lack of a control arm it is not possible to conclude on an antiviral effect of remdesivir.

The most common viral lineages detected in paediatric participants in study 5823 were B.1.2, B.1.1.7 (Alpha) and B.1.429 (Epsilon). None of the participants was infected with the Delta or Omicron variant, hence no clinical data on remdesivir's efficacy in paediatric patients infected with those variants is available.

Two substitutions emerged during remdesivir treatment and were present in combination in 1 participant: A656P and G670V. Based on analysis of prior cryo-EM structures of the SARS-CoV-2 polymerase complex {Chen 2020}, A656P and G670V have no direct interaction with the RNA or the incoming nucleotide. Neither of these substitutions have been previously associated with resistance to RDV.

No amino acid substitutions were observed in nsp8 or nsp14. Amino acid substitutions in nsp10 were observed in 1 (4.3%) out of 23 participants and amino acid substitutions in nsp13 were observed in 2 (8.7%) out of 23 participants. None of the substitutions were observed in more than one participant each. The clinical relevance of the identified mutations in nsp 10 and nsp 13 remain currently unclear.

Study GS-US-540-9012

Only eight adolescent participants were enrolled in study GS-US-540-9012, hence the efficacy dataset in adolescent patients weighing more than 40 kg who do not require supplemental oxygen and having at least one risk factor for progressing to severe disease is considered extremely limited, as only this subset is considered supportive for the proposed paediatric outpatient indication. Overall, only three adolescent patients received remdesivir in study 9012, of whom only one was female. All eight participants were included and completed the study.

Furthermore, it is notable that the median weight in adolescents treated in study 9012 were significantly above 40 kg (RDV: 68.0 (61.0, 86.3) kg, Placebo: 72.2 (65.1, 72.2) kg). Patients treated with remdesivir weighted at least 68 kg. Hence, no efficacy data on patients weighing less than 68 kg is available.

Of the eight adolescent patients, six had a risk factor of chronic lung disease, two had a risk factor of diabetes mellitus, and two had a risk factor of obesity. No discussion was provided by the MAH, if risk factors for progressing to severe COVID-19 are similar between adolescents, children and adults. However, current scientific and clinical knowledge indicate that risk factors are similar between adults, adolescents and children, hence this issue is not further pursued.

It is of note that the median duration of symptoms prior to first dose was shorter in the RDV group (2 days) compared to the placebo group (4 days). In addition, median (Q1, Q3) nasopharyngeal SARS-CoV-2 viral load was lower in the RDV group (4.07 (3.88, 7.13) log10 copies/mL) compared to the placebo group (7.18 (5.28, 7.49) log10 copies/mL). The eight adolescents were infected with B.1.2.

Concerning the primary efficacy endpoint, none of the enrolled adolescent participant (12 to < 18 years of age) had COVID-19-related hospitalization or all-cause death by Day 28, neither in the remdesivir group, nor in the placebo group.

However, no information on the secondary efficacy outcomes were provided by the MAH. The MAH was asked to provide the respective information on all relevant secondary and exploratory efficacy endpoints, i.e., data on alleviation of symptoms, MVA attendance visits, virology analyses including information on variants and the virology endpoints (i.e., viral load decay) of the study. In these data, overall, no difference on viral load between the RDV group and the placebo group were detected.

Additional expert consultation

Not applicable.

2.4.4. Conclusions on the clinical efficacy

Efficacy outcomes in the different Cohorts at D5, D10 and last available assessment in study GS-US-540-5823 vary between the cohorts, especially between Cohort 1 and the other cohorts. However, as a control arm is missing, these results are difficult to interpret as well as efficacy.

Although the results of the PK/PD analyses, showed that there was a significant difference in PK-exposure in patients with an AE of acute kidney injury, which was seen in more patients in Cohort 1 than in other cohorts (please refer to the Clinical safety section and PK/PD section for more information), the MAH provided complementary data after request that supported the dosing proposed (see discussion and conclusion of Clinical Pharmacology).

From a safety point of view, RDV was well tolerated during clinical studies in paediatric patients and the safety data reported during study GS-US-540-5823 were comparable to the studies in adults.

2.5. Clinical safety

Introduction

In support of this application for extension of indications, the Applicant presented safety data from the following clinical studies (see also **Error! Reference source not found.**):

- **Study GS-US-540-5823**: Cohorts 1 through 4 and Cohort 8 that support the current indication for adolescents ≥ 12 years and weighing ≥ 40 kg and an expansion of the current indication to include infants and children ≥ 28 days weighing ≥ 3 kg with COVID-19.
- **Study GS-US-540-9012**: Adolescent participants, which support an expansion of the indication for adolescents ≥ 12 years and weighing ≥ 40 kg with COVID-19 and at least 1 of the protocol-defined pre-existing risk-factors for progression to hospitalization.

For Study GS-US-540-5823 an interim CSR has been provided. The CSR of Study GS-US-540-9012 has already been submitted for the EoI variation EMEA/H/C/005622/II/0016. The Summary of Clinical Safety includes safety data from paediatric Study GS-US-540-582 and from adolescent patients from study GS-US-540-9012.

Patient exposure

Study GS-US-540-5823

In the table below the exposure to study drug in Study GS-US-540-5823 is shown.

Table 27: GS-US-540-5823: Exposure to study drug (Safety Analysis Set)

	Cohort 1: 12 to < 18 Years and ≥ 40 kg (N = 12)	Cohort 2: 28 Days to < 18 Years and 20 to < 40 kg (N = 12)	Cohort 3: 28 Days to < 18 Years and 12 to < 20 kg (N = 12)	Cohort 4: 28 Days to < 18 Years and 3 to < 12 kg (N = 12)	Cohort 8: < 12 Years and ≥ 40 kg (N = 5)	Total (N = 53)
Number of doses received						
N	12	12	12	12	5	53
Mean (SD)	7 (2.4)	6 (2.3)	5 (2.5)	6 (3.5)	6 (3.6)	6 (2.8)
Median	5	5	5	5	5	5
Q1, Q3	5, 9	4, 7	4, 5	3, 10	3, 10	4, 8
Min, max	3, 10	3, 10	2, 10	1, 10	3, 10	1, 10
Number of doses received						
1 dose	0	0	0	1 (8.3%)	0	1 (1.9%)
2 doses	0	0	1 (8.3%)	2 (16.7%)	0	3 (5.7%)
3 doses	1 (8.3%)	1 (8.3%)	2 (16.7%)	1 (8.3%)	2 (40.0%)	7 (13.2%)
4 doses	0	3 (25.0%)	2 (16.7%)	1 (8.3%)	0	6 (11.3%)
5 doses	6 (50.0%)	4 (33.3%)	5 (41.7%)	3 (25.0%)	1 (20.0%)	19 (35.8%)
6 doses	0	1 (8.3%)	0	0	0	1 (1.9%)
7 doses	1 (8.3%)	0	0	0	0	1 (1.9%)
8 doses	1 (8.3%)	1 (8.3%)	0	0	0	2 (3.8%)
9 doses	0	0	0	0	0	0
10 doses	3 (25.0%)	2 (16.7%)	2 (16.7%)	4 (33.3%)	2 (40.0%)	13 (24.5%)

max = maximum; min = minimum; Q1 = first quartile; Q3 = third quartile; SD = standard deviation
Source: GS-US-540-5823 Interim CSR, Table 15.8.4.1.1

Study GS-US-540-9012

All 8 adolescent participants received the planned 3 doses of the study drug; 3 adolescent participants received 3 doses of RDV and 5 adolescent participants received 3 doses of placebo (GS-US-540-9012 Final CSR, Listing 16.2.5.1).

Adverse events

Study GS-US-540-5823

Summary of Adverse Events

A total of 38 participants (71.7%) had at least 1 AE during the study (Cohort 1: 11 participants, 91.7%; Cohort 2: 7 participants, 58.3%; Cohort 3: 9 participants, 75.0%; Cohort 4: 7 participants, 58.3%; Cohort 8: 4 participants, 80.0%) (see table below). The overall majority of AEs were Grade 1 or 2 in severity and considered not related to study drug.

A total of 15 participants (28.3%) had a Grade 3 or higher AE (Cohort 1: 6 participants, 50.0%; Cohort 2: 2 participants, 16.7%; Cohort 3: 1 participant, 8.3%; Cohort 4: 4 participants, 33.3%; Cohort 8: 2 participants, 40.0%). Grade 3 or higher AEs were considered related to study drug in 3 participants (5.7%), all in Cohort 1 (25.0%).

Serious AEs were reported in 11 participants (20.8%) overall (Cohort 1: 5 participants, 41.7%; Cohort 2: 2 participants, 16.7%; Cohort 3: 0 participants; Cohort 4: 3 participants, 25.0%; Cohort 8: 1 participant, 20.0%). None of the serious adverse events (SAEs) were considered related to study drug.

Adverse events leading to premature study drug discontinuation were reported in 2 participants (3.8%), both in Cohort 1 (16.7%).

There were 3 (5.7%) treatment-emergent deaths during the study (1 participant each in Cohorts 1 [8.3%], 2 [8.3%], and 8 [20.0%]) and 1 non-treatment-emergent death (1 participant died 32 days after last dose of RDV) (Table 5; GS-US-540-5823 Interim CSR, Listing 16.2.6.7).

Table 28: GS-US-540-5823: Overall summary of Adverse Events

	Cohort 1: 12 to < 18 Years and ≥ 40 kg (N = 12)	Cohort 2: 28 Days to < 18 Years and 20 to < 40 kg (N = 12)	Cohort 3: 28 Days to < 18 Years and 12 to < 20 kg (N = 12)	Cohort 4: 28 Days to < 18 Years and 3 to < 12 kg (N = 12)	Cohort 8: < 12 Years and ≥ 40 kg (N = 5)	Total (N = 53)
AE	11 (91.7%)	7 (58.3%)	9 (75.0%)	7 (58.3%)	4 (80.0%)	38 (71.7%)
Grade 3 or higher AE	6 (50.0%)	2 (16.7%)	1 (8.3%)	4 (33.3%)	2 (40.0%)	15 (28.3%)
Study drug-related AE	4 (33.3%)	1 (8.3%)	0	1 (8.3%)	2 (40.0%)	8 (15.1%)
Study drug-related Grade 3 or higher AE	3 (25.0%)	0	0	0	0	3 (5.7%)
SAE	5 (41.7%)	2 (16.7%)	0	3 (25.0%)	1 (20.0%)	11 (20.8%)
Study drug-related SAE	0	0	0	0	0	0
AE leading to premature study drug discontinuation	2 (16.7%)	0	0	0	0	2 (3.8%)
Treatment-emergent death	1 (8.3%)	1 (8.3%)	0	0	1 (20.0%)	3 (5.7%)

AE = adverse event; DAIDS = Division of AIDS; MedDRA = Medical Dictionary for Regulatory Activities
Adverse events were coded using MedDRA Version 24.0.
Severity grades were defined by the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1, July 2017.
Treatment-emergent death refers to deaths that occurred between the first dose date and the last dose date plus 30 days (inclusive).
One participant died 32 days after the last dose date and is not counted as a treatment-emergent death.
Source: GS-US-540-5823 Interim CSR, Table 15.11.1.1.1

Common Adverse Events

In the table below, AEs reported in at least two patients in any cohort of Study GS-US-540-5823 are presented.

Table 29: GS-US-540-5823: Adverse events reported in at least two participants in any Cohort (Safety Analysis Set)

	Cohort 1: 12 to < 18 Years and ≥ 40 kg (N = 12)	Cohort 2: 28 Days to < 18 Years and 20 to < 40 kg (N = 12)	Cohort 3: 28 Days to < 18 Years and 12 to < 20 kg (N = 12)	Cohort 4: 28 Days to < 18 Years and 3 to < 12 kg (N = 12)	Cohort 8: < 12 Years and ≥ 40 kg (N = 5)	Total (N = 53)
Number of participants experiencing any AE	11 (91.7%)	7 (58.3%)	9 (75.0%)	7 (58.3%)	4 (80.0%)	38 (71.7%)
Number of participants experiencing any AE by PT						
Constipation	3 (25.0%)	1 (8.3%)	1 (8.3%)	1 (8.3%)	3 (60.0%)	9 (17.0%)
Acute kidney injury	4 (33.3%)	0	0	1 (8.3%)	1 (20.0%)	6 (11.3%)
Hyperglycaemia	1 (8.3%)	1 (8.3%)	1 (8.3%)	2 (16.7%)	0	5 (9.4%)
Pyrexia	1 (8.3%)	2 (16.7%)	1 (8.3%)	1 (8.3%)	0	5 (9.4%)
Alanine aminotransferase increased	2 (16.7%)	0	0	1 (8.3%)	1 (20.0%)	4 (7.5%)
Hypertension	2 (16.7%)	1 (8.3%)	0	0	1 (20.0%)	4 (7.5%)
Hypomagnesaemia	0	1 (8.3%)	0	1 (8.3%)	2 (40.0%)	4 (7.5%)
Agitation	0	1 (8.3%)	2 (16.7%)	0	0	3 (5.7%)
Bradycardia	0	2 (16.7%)	0	1 (8.3%)	0	3 (5.7%)
Infusion-site extravasation	0	2 (16.7%)	0	0	0	2 (3.8%)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term
Adverse events were coded using MedDRA Version 24.0.
Preferred terms were presented by descending order of the total frequencies.
Multiple AEs were counted only once per participant per PT.
Source: GS-US-540-5823 Interim CSR, Table 15.11.1.4.1

Adverse Events by Severity

Overall, 15 participants (28.3%) experienced Grade 3 or higher AEs during the study. Grade 3 or higher AEs were reported in 6 participants (50%) in Cohort 1, 2 participants (16.7%) in Cohort 2, 1 participant (8.3%) in Cohort 3, 4 participants (33.3%) in Cohort 4, and 2 participants (40.0%) in Cohort 8 (GS-US-540-5823 Interim CSR, Table 15.11.2.1.1).

Grade 3 or higher AEs were considered related to study drug in three participants (5.7%), all in Cohort 1 (GS-US-540-5823 Interim CSR, Table 15.11.2.3.1). Study drug-related Grade 3 or higher AEs of ALT increased were reported in two participants (16.7%), both in Cohort 1 and both of whom had ALT elevations at baseline. None of the Grade 3 or higher AEs related to study drug were SAEs.

Grade 4 hyperbilirubinemia, Grade 3 ALT increased, and Grade 3 AST increased, all of which were related to study drug and which resulted in premature discontinuation of study drug, occurred in one participant who eventually died as a result of multiorgan failure. One participant, who had elevated ALT and AST at baseline, experienced a Grade 3 study drug-related AE of ALT increased that resulted in premature discontinuation of study drug (GS-US-540-5823 Interim CSR, Listing 16.2.6.2).

Related Adverse Events

Overall, 8 participants (15.1%) experienced an AE considered related to study drug during the study (GS-US-540-5823 Interim CSR, Table 15.11.2.2.2). Study drug-related AEs were reported in 4 participants (33.3%) in Cohort 1, one participant (8.3%) in Cohort 2, no participants in Cohort 3, one

participant (8.3%) in Cohort 4, and 2 participants (40.0%) in Cohort 8. No study drug-related SAEs were reported during the study (GS-US-540-5823 Interim CSR, Table 15.11.2.5.1).

Individual study drug-related AEs reported in more than one participant were ALT increased (3 participants [5.7%] overall, 2 in Cohort 1 [16.7%] and 1 in Cohort 4 [8.3%]) and AST increased (2 participants [3.8%] overall, 1 in Cohort 1 [8.3%] and 1 in Cohort 4 [8.3%]). In Cohort 1, study drug-related Grade 3 ALT increased in 1 participant and study drug-related Grade 3 ALT increased and Grade 3 AST increased in 1 participant resulted in discontinuation of study drug (Section 2.1.5; GS-US-540-5823 Interim CSR, Listing 16.2.6.6). One participant in Cohort 4 had Grade 2 ALT increased and Grade 1 AST increased considered related to study drug (GS-US-540-5823 Interim CSR, Listing 16.2.6.2).

Study GS-US-540-9012

No adolescent participant in the RDV group experienced any AE during the study (GS-US-540-9012 Final CSR, Table 15.11.2.12).

One adolescent participant in the placebo group experienced a Grade 1 AE of fatigue that was considered not related to the study drug or study procedure (GS-US-540-9012 Final CSR, Table 15.11.2.1.5 and Listing 16.2.7.1).

Serious adverse event/deaths/other significant events

Study GS-US-540-5823

Serious Adverse Events

Serious AEs were reported in a total of 11 participants (20.8%), including 5 participants (41.7%) in Cohort 1, 2 participants (16.7%) in Cohort 2, no participants in Cohort 3, 3 participants (25.0%) in Cohort 4, and 1 participant (20.0%) in Cohort 8. None of the SAEs reported during the study were considered related to study drug (GS-US-540-5823 Interim CSR, Table 15.11.2.5.1), see table below.

Table 30: GS-US-540-5823: Serious adverse events (Safety Analysis Set)

	Cohort 1: 12 to < 18 Years and ≥ 40 kg (N = 12)	Cohort 2: 28 Days to < 18 Years and 20 to < 40 kg (N = 12)	Cohort 3: 28 Days to < 18 Years and 12 to < 20 kg (N = 12)	Cohort 4: 28 Days to < 18 Years and 3 to < 12 kg (N = 12)	Cohort 8: < 12 Years and ≥ 40 kg (N = 5)	Total (N = 53)
Number of participants experiencing any SAE	5 (41.7%)	2 (16.7%)	0	3 (25.0%)	1 (20.0%)	11 (20.8%)
Number of participants experiencing any SAE by PT						
Cardiorespiratory arrest	0	1 (8.3%)	0	1 (8.3%)	0	2 (3.8%)
Multiple organ dysfunction syndrome	1 (8.3%)	0	0	0	1 (20.0%)	2 (3.8%)
Pyrexia	1 (8.3%)	0	0	1 (8.3%)	0	2 (3.8%)
Respiratory distress	1 (8.3%)	0	0	0	1 (20.0%)	2 (3.8%)
Septic shock	1 (8.3%)	0	0	1 (8.3%)	0	2 (3.8%)
Thrombosis	1 (8.3%)	0	0	1 (8.3%)	0	2 (3.8%)
Acute kidney injury	1 (8.3%)	0	0	0	0	1 (1.9%)
Cardiac failure	0	0	0	0	1 (20.0%)	1 (1.9%)
Cardiogenic shock	0	1 (8.3%)	0	0	0	1 (1.9%)
Cellulitis	0	1 (8.3%)	0	0	0	1 (1.9%)
Empyema	1 (8.3%)	0	0	0	0	1 (1.9%)
Enterococcal bacteraemia	0	0	0	1 (8.3%)	0	1 (1.9%)
Gastrointestinal necrosis	0	0	0	0	1 (20.0%)	1 (1.9%)
Haemodynamic instability	0	0	0	0	1 (20.0%)	1 (1.9%)
Hyperkalaemia	0	0	0	1 (8.3%)	0	1 (1.9%)
Hypocalcaemia	0	0	0	1 (8.3%)	0	1 (1.9%)
Hypotension	0	1 (8.3%)	0	0	0	1 (1.9%)
Negative pressure pulmonary oedema	1 (8.3%)	0	0	0	0	1 (1.9%)
Pneumoperitoneum	0	0	0	0	1 (20.0%)	1 (1.9%)
Pulmonary haemorrhage	1 (8.3%)	0	0	0	0	1 (1.9%)
Respiratory failure	0	1 (8.3%)	0	0	0	1 (1.9%)
Supraventricular tachycardia	0	0	0	1 (8.3%)	0	1 (1.9%)
Vomiting	1 (8.3%)	0	0	0	0	1 (1.9%)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SAE = serious adverse event
Adverse events were coded using MedDRA Version 24.0.
Preferred terms were presented by descending order of the total frequencies.
Multiple AEs were counted only once per participant per PT.
Source: GS-US-540-5823 Interim CSR, Table 15.11.2.4.2

Deaths

Three treatment-emergent deaths occurred during the study (GS-US-540-5823 Interim CSR, Listing 16.2.6.7), all in participants with complex medical histories. The cause of death for one participant (Cohort 1) was reported as multisystem organ failure (Day 14); this participant, with pre-existing elevated transaminases and hyperbilirubinemia (GS-US-540-5823 Interim CSR, Listing 16.2.4.1), had

an SAE of multiple organ dysfunction syndrome and prematurely discontinued study drug due to AEs of ALT increased, AST increased, blood sodium increased, and hyperbilirubinemia (GS-US-540-5823 Interim CSR, Listing 16.2.6.4 and Listing 16.2.6.6; Section 3.1.4). The cause of death for one participant (Cohort 2), who had SAEs of hypotension, cardiorespiratory arrest, and respiratory failure, was reported as respiratory failure secondary to removal from life support (Day 35). For a third participant (Cohort 8), who had SAEs of pneumoperitoneum, fatal respiratory distress, haemodynamic instability, gastrointestinal necrosis, cardiac failure, and multiple organ dysfunction syndrome, the cause of death was reported as respiratory, cardiac, and kidney failure as well as acute blood loss (Day 18).

One non-treatment-emergent death that occurred 32 days after the last dose of RDV was also reported (GS-US-540-5823 Interim CSR, Table 15.11.1.1.1). The participant, who had been in Cohort 1 and had SAEs during the study of septic shock as well as pulmonary haemorrhage that was considered fatal, died as a result of hypoxemic and hypercarbic respiratory failure secondary to SARS-CoV-2 acute respiratory distress syndrome and cytomegalovirus pneumonitis in the setting of systemic lupus erythematosus and lupus nephritis.

Study GS-US-540-9012

No SAEs were reported during study GS-US-540-9012.

Laboratory findings

Study GS-US-540-5823

There were no clinically relevant changes over time in median values for haematology parameters in any cohort (GS-US-540-5823 Interim CSR, Tables 15.11.3.1.1 to 15.11.3.1.4). Median values were generally within the relevant reference ranges (GS-US-540-5823 Interim CSR, Listing 16.2.8.10).

Median values for clinical chemistry parameters were generally within reference ranges (GS-US-540-5823 Interim CSR, Tables 15.11.3.2.1 to 15.11.3.2.8; Listing 16.2.8.10).

In general, median ALT increased during RDV dosing and returned to baseline levels by Day 30. The changes were considered a result of participants' underlying medical conditions and severity of COVID-19 disease and were not clinically significant. No trends were noted in median AST values during the study.

There was no apparent trend in median changes from baseline in total bilirubin values for participants ≥ 14 days old (GS-US-540-5823 Interim CSR, Table 11.3.2.4 and Figure 11.5.6).

Median serum creatinine values generally remained stable during the study, with no clinically significant changes from baseline.

No trends were noted in coagulation parameters (prothrombin time, activated partial thromboplastin time [aPTT], prothrombin/international normalized ratio [INR]) (GS-US-540-5823 Interim CSR, Tables 15.11.3.3.1 to 15.11.3.3.3). Prothrombin time was elevated at baseline in all cohorts, and aPTT was elevated at baseline except in Cohort 4; both generally remained high throughout RDV dosing (GS-US-540-5823 Interim CSR, Listings 16.2.4.2 and 16.2.8.11). Concomitant use of enoxaparin or enoxaparin sodium and of heparin was reported for 21 (39.6%) and 10 (18.9%) of participants in Cohorts 1 through 4 and Cohort 8, respectively (GS-US-540-5823 Interim CSR, Table 15.8.5.1.1 and Table 15.8.5.1.2).

In the table below Grade 3 or 4 laboratory abnormalities reported during Study GS-US-540-5823 are shown.

Table 31: GS-US-540-5823: Grade 3 or 4 laboratory abnormalities (Safety Analysis Set)

	Cohort 1: 12 to < 18 Years and ≥ 40 kg (N = 12)	Cohort 2: 28 Days to < 18 Years and 20 to < 40 kg (N = 12)	Cohort 3: 28 Days to < 18 Years and 12 to < 20 kg (N = 12)	Cohort 4: 28 Days to < 18 Years and 3 to < 12 kg (N = 12)	Cohort 8: < 12 Years and ≥ 40 kg (N = 5)	Total (N = 53)
Maximum treatment-emergent toxicity grade						
Grade 3	6 (50.0%)	0	3 (25.0%)	4 (36.4%)	2 (40.0%)	15 (28.8%)
Grade 4	3 (25.0%)	2 (16.7%)	1 (8.3%)	0	1 (20.0%)	7 (13.5%)
Grade 3 or 4	9 (75.0%)	2 (16.7%)	4 (33.3%)	4 (36.4%)	3 (60.0%)	22 (42.3%)
Hematology						
Hemoglobin (decreased)	12	12	12	10	5	51
Grade 3	4 (33.3%)	1 (8.3%)	0	2 (20.0%)	1 (20.0%)	8 (15.7%)
Grade 4	0	0	0	0	1 (20.0%)	1 (2.0%)
Lymphocytes (decreased)	12	11	5	0	5	33
Grade 3	0	0	0	0	0	0
Grade 4	1 (8.3%)	0	0	0	1 (20.0%)	2 (6.1%)
Neutrophils (decreased)	12	12	12	10	5	51
Grade 4	0	0	1 (8.3%)	0	0	1 (2.0%)
Platelets (decreased)	12	12	12	10	5	51
Grade 3	1 (8.3%)	0	0	0	0	1 (2.0%)
WBC (decreased)	12	12	12	10	5	51
Grade 3	1 (8.3%)	0	0	0	1 (20.0%)	2 (3.9%)
Chemistry						
ALT (increased)	12	12	12	10	5	51
Grade 3	1 (8.3%)	0	0	1 (10.0%)	0	2 (3.9%)
AST (increased)	12	12	12	11	5	52
Grade 3	1 (8.3%)	0	0	0	0	1 (1.9%)
Creatinine (increased)	12	12	12	11	5	52
Grade 3	1 (8.3%)	0	1 (8.3%)	1 (9.1%)	1 (20.0%)	4 (7.7%)
Grade 4	1 (8.3%)	0	0	0	0	1 (1.9%)
eGFR, Bedside Schwartz (decreased)	12	12	11	0	5	40
Grade 3	1 (8.3%)	0	4 (36.4%)	0	1 (20.0%)	6 (15.0%)
Grade 4	1 (8.3%)	0	0	0	0	1 (2.5%)
Serum glucose (hyperglycemia)	12	12	12	11	5	52
Grade 3	1 (8.3%)	0	1 (8.3%)	0	0	2 (3.8%)
Direct bilirubin (increased)	7	7	4	3	2	23
Grade 3	1 (14.3%)	1 (14.3%)	0	0	0	2 (8.7%)
Albumin (decreased)	12	12	11	10	5	50
Grade 3	0	0	0	1 (10.0%)	0	1 (2.0%)
Alkaline phosphatase (increased)	12	12	11	10	5	50
Grade 4	0	1 (8.3%)	0	0	0	1 (2.0%)

	Cohort 1: 12 to < 18 Years and ≥ 40 kg (N = 12)	Cohort 2: 28 Days to < 18 Years and 20 to < 40 kg (N = 12)	Cohort 3: 28 Days to < 18 Years and 12 to < 20 kg (N = 12)	Cohort 4: 28 Days to < 18 Years and 3 to < 12 kg (N = 12)	Cohort 8: < 12 Years and ≥ 40 kg (N = 5)	Total (N = 53)
Serum potassium (hypokalemia)	12	12	12	11	5	52
Grade 3	0	1 (8.3%)	0	0	1 (20.0%)	2 (3.8%)
Serum sodium (hypernatremia)	12	12	12	11	5	52
Grade 4	1 (8.3%)	0	0	0	0	1 (1.9%)
Coagulation						
Prothrombin time (increased)	12	12	10	8	4	46
Grade 3	1 (8.3%)	1 (8.3%)	0	1 (12.5%)	0	3 (6.5%)
aPPT (increased)	11	11	9	9	5	45
Grade 3	1 (9.1%)	1 (9.1%)	0	0	0	2 (4.4%)
Grade 4	0	1 (9.1%)	0	0	0	1 (2.2%)
Prothrombin/INR (increased)	12	12	10	9	5	48
Grade 3	0	1 (8.3%)	0	0	0	1 (2.1%)
Urinalysis						
Urine glucose (glycosuria)	11	11	11	9	4	46
Grade 3	1 (9.1%)	0	0	1 (11.1%)	0	2 (4.3%)
Urine protein (proteinuria)	8	9	10	7	2	36
Grade 3	1 (12.5%)	0	0	0	1 (50.0%)	2 (5.6%)

ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; DAIDS = Division of AIDS; eGFR = estimated glomerular filtration rate; IDMS = isotope dilution mass spectrometry; INR = international normalized ratio; WBC = white blood cell
The denominator for percentage is the number of participants in the Safety Analysis Set with at least 1 postbaseline value for the test under evaluation, specified in each laboratory test row.
Participants were counted once for the maximum postbaseline severity for each laboratory test under evaluation.
Severity grades are defined by the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1, July 2017.
eGFR was calculated using Bedside IDMS-traceable Schwartz formula (mL/min/1.73 m²) for children 1 to < 18 years old.
Source: GS-US-540-5823 Interim CSR, Table 15.11.4.1.2

Study GS-US-540-9012

No clinically relevant findings were observed in haematology, chemistry, or coagulation parameters in the adolescent participants (GS-US-540-9012 Final CSR, Listings 16.2.8.1 through 16.2.8.8).

No adolescent participant experienced Grade 3 or higher laboratory abnormality (GS-US-540-9012 Final CSR, Listings 16.2.8.11).

Safety in special populations

No intrinsic and extrinsic factors were assessed for participants ≥ 28 days to < 18 years old for the interim analysis of Study GS-US-540-5823 or the final analysis of Study GS-US-540-9012; therefore, no new findings relevant to intrinsic and extrinsic factors are submitted with this update to the initial application.

Safety related to drug-drug interactions and other interactions

No clinical drug-drug interaction studies have been completed with RDV.

Discontinuation due to adverse events

Study GS-US-540-5823

Two participants (3.8%) prematurely discontinued study drug due to AEs, both in Cohort 1 (16.7%) (GS-US-540-5823 Interim CSR, Table 15.11.2.5.3). One participant prematurely discontinued study drug after 5 doses of RDV because of AEs of Grade 3 ALT increased, Grade 3 AST increased, Grade 4 blood sodium increased, and Grade 4 hyperbilirubinemia; this participant had elevated transaminases

and hyperbilirubinemia at study entry and died on Day 14 as a result of multisystem organ failure (Section 2.1.3 and Section 3.1.4; GS-US-540-5823 Interim CSR, Listing 16.2.6.6). With the exception of blood sodium increased, the events were considered related to study drug. One participant, who had elevated ALT and AST at baseline, prematurely discontinued study drug after 3 doses of RDV because of Grade 3 ALT increased, which was considered related to study drug (Sections 2.1.2.2 and 2.1.2.3; GS-US-540-5823 Interim CSR, Listing 16.2.8.3). None of the AEs that resulted in premature study drug discontinuation were reported as SAEs.

Study GS-US-540-9012

None of the three adolescent patients treated during Study GS-US-540-9012 discontinued treatment due to AEs.

Post marketing experience

No post marketing safety data were submitted.

2.5.1. Discussion on clinical safety

Overall, 53 paediatric patients (with laboratory confirmed COVID-19, hospitalised and requiring medical care for COVID-19) received up to 10 doses of IV RDV during open-label Study GS-US-540-5823. Furthermore, three adolescent patients were treated with 3 doses of IV RDV in an outpatient setting (confirmed COVID-19 who were at increased risk for disease progression) during the randomized, double-blind, placebo-controlled Study GS-US-540-9012.

During **Study GS-US-540-5823**, overall, in 38 patients (71.7%) at least 1 AE was reported. The rate of reported AEs was highest in Cohort 1 (11 patients [91.7%]) compared to the other cohorts (Cohort 2: 7 patients [58.3%]; Cohort 3: 9 patients [75.0%]; Cohort 4: 7 patients [58.3%]; Cohort 8: 4 patients [80.0%]). When comparing with clinical studies conducted in adult hospitalized patients with COVID-19, the overall rate of AEs reported during Study GS-US-540-5823 is in principle comparable to the studies in adults (GS-US-540-5773: RDV for 5 Days 70.5%, RDV for 10 Days 73.6%; GS-US-540-5774: RDV for 5 Days 50.8%, RDV for 10 Days 54.9%; CO-US-540-5776 (only Grade 3 or 4 AEs reported, where the rate in Study GS-US-540-5823 was 28.3%): 28.8%; CO-US-540-5758: 66%).

However, the high rate of AEs in Cohort 1 needs further discussion, even if only a small number of patients was included in Cohort 1 (n=12) and the relevance of the reported rate is limited. In line with this finding, more patients in Cohort 1 had a Grade 3 or higher AE (6 patients [50.0%]) compared to the other cohorts (Cohort 2: 2 patients [16.7%]; Cohort 3: 1 patients [8.3%]; Cohort 4: 4 patients [33.3%]; Cohort 8: 2 patients [40.0%]) and the only 3 patients with Grade 3 or higher AEs considered related to study drug were from Cohort 1 [25.0%]. Furthermore, more SAEs were reported in Cohort 1 (5 patients [41.7%]) compared to the other cohorts (Cohort 2: 2 patients [16.7%]; Cohort 3: 0 patients; Cohort 4: 3 patients [25.0%]; Cohort 8: 1 patient [20.0%]). However, none of the serious adverse events (SAEs) were considered related to study drug. Nevertheless, AEs leading to premature study drug discontinuation were only reported in two patients in Cohort 1 [16.7%] and none in the other cohorts. The reported rates of AEs and Grade 3 or higher AE in Cohort 8 were intermediate between those of Cohort 1 and Cohorts 2-4, however, due to the small number of patients treated in Cohort 8 (n=5), it is even more difficult to draw a conclusion here.

When comparing baseline disease characteristics, it appears that the median duration of symptoms prior to first dose of RDV was higher in Cohort 1 (7 days) than in the other cohorts (Cohort 2: 5 days; Cohort 3: 3 days; Cohort 4: 5 days; Cohort 8: 5 days) which could refer to a worse disease condition.

However, the median duration of hospitalisation prior to the first dose of RDV was comparable between cohorts. Furthermore, no differences in oxygen support status at baseline and COVID-19–related disease manifestations between cohorts could be identified. In addition, characteristics of medical history seem to be comparable between cohorts.

In Cohorts 1 and 8 a fixed dose of RDV was administered (IV RDV 200 mg on day 1 followed by IV RDV 100 mg daily for up to 10 days), whereas in Cohorts 2-4 a weight-based dosage was used (IV RDV 5 mg/kg on day 1 followed by IV RDV 2.5 mg/kg daily for up to 10 days). Therefore, the question arises to what extent differences in the PK profile could have led to differences in the safety data. When comparing PK data, AUC_{tau} and C_{max} of RDV and metabolites GS-704277 and GS-441524 in Cohorts 1 and 8 were lower than in Cohorts 2, 3 and 4. Compared to data from adults treated with RDV, AUC_{tau} and C_{max} were significantly higher in the paediatric population (RDV AUC_{tau} 200.3%, C_{max} 193.3%; GS-704277 AUC_{tau} 151.9%, C_{max} 180.4%; GS-441524 AUC_{tau} 94.9%, C_{max} 110.2%). For the discussion and conclusion of the appropriateness of the dosages in the paediatric populations, please see section PK/PD. In this regard, after evaluating the requested information the Committee agreed on the dosing proposed and on the MAH´s conclusion that no dose reduction is required, and it is supported from the PK view (see discussion and conclusion of Clinical Pharmacology).

For the safety assessment of Study GS-US-540-5823 it can be concluded that PK data from Cohorts 1 and 8 compared to Cohorts 2-4 do not explain differences in rates of reported AEs, Grade 3 or higher AEs and SAEs. Upon request, the MAH discussed which factors might have contributed to the differences in efficacy and safety data between Cohort 1 (and 8) and Cohorts 2-4 of Study GS-US-540-5823, including a potential role of SBECD exposure. Overall, some differences in terms of baseline characteristics between cohorts were identified which could suggest that participants in Cohorts 1 and 8 may have had more severe COVID-19. However, other characteristics such as presence of complex medical conditions were similar between cohorts. It is outlined that any discrepancies in efficacy assessments are confounded by the small number of participants in each cohort as well as the open-label, uncontrolled study design which is agreed. Furthermore, it is concluded that the higher percentages of participants with any AE, Grade 3 or higher AEs, and SAEs in Cohort 1 may reflect the small sample number in each cohort. According to the analysis of the MAH no association was identified with common AEs or with AKI and PK exposures of RDV and its metabolites or with SBECD concentrations. Overall, the argumentation of the MAH is agreed. No safety signal was identified during Study GS-US-540-5823 and it seems most likely that the differences observed between cohorts reflect the small sample size and study design.

In Cohorts 1 and 8 numerically more patients experienced AEs of constipation (Cohort 1: 3 patients [25%], Cohort 2: 1 patient [8.3%]; Cohort 3: 1 patient [8.3%]; Cohort 4: 2 patients [16.7%]; Cohort 8: 3 patients [60.0%]). Furthermore, AEs of acute kidney injury were more frequently reported in Cohort 1 (Cohort 1: 4 patients [33.3%], Cohort 2: 0 patients; Cohort 3: 0 patients; Cohort 4: 1 patient [8.3%]; Cohort 8: 1 patient [20.0%]). According to the interim CSR, at baseline median creatinine levels were higher and median eGFR was lower in patients of Cohort 1 compared to the other cohorts which could possibly be related to the differences in rates of acute kidney injury. However, no further information is available. Of the reported cases of acute kidney injury, one AE was considered as SAE and the remaining AEs as non-serious AEs. Case narratives were not presented for all cases of acute kidney injury in the interim CSR. For a profound assessment, the Applicant was requested to provide details of all reported cases of acute kidney injury during Study GS-US-540-5823 including causality assessments. Furthermore, a possible causal relationship to plasma concentrations of SBECD were further discussed and a comparison of plasma concentrations of SBECD between paediatric patients and adults after treatment with RDV requested. On view of the information provided as stated above and according to the analysis of the MAH no association was identified with common AEs or with AKI and PK exposures of RDV and its metabolites or with SBECD concentrations. This is

agreed. No safety signal was identified during Study GS-US-540-5823. The differences observed between cohorts are likely reflecting the small sample size and study design.

Overall, however, the AEs reported during Study GS-US-540-5823 are in accordance with the AEs reported during clinical studies conducted in adult hospitalised patients with COVID-19.

The reported rate of AEs considered related to study drug during study GS-US-540-5823 (8 patients [15.1%]) was comparable to rates in clinical studies investigated RDV in hospitalised patients. The reported adverse reactions are in general in accordance with the known safety profile of RDV.

The overall rate of reported SAEs (20.8%) was comparable to rates reported in clinical studies in adult hospitalised COVID-19 patients (Study CO-US-540-5776: 21.1%, Study CO-US-540-5758: 18%). The listed PTs were only reported as single cases. None of the SAEs reported during the study were considered related to study drug.

During Study GS-US-540-5823 three treatment-emergent deaths occurred, all in patients with complex medical histories. One patient died due to multisystem organ failure on day 14. This patient from Cohort 1 had elevated transaminases and hyperbilirubinemia at baseline, developed an SAE of multiple organ dysfunction syndrome and prematurely discontinued study drug due to AEs of ALT increased, AST increased, blood sodium increased, and hyperbilirubinemia. For the second patient from Cohort 2 the cause of death was reported as respiratory failure secondary to removal from life support (Day 35). This patient developed SAEs of hypotension, cardiorespiratory arrest, and respiratory failure. The third patient (Cohort 8) died due to respiratory, cardiac, and kidney failure as well as acute blood loss on Day 18. For this patient SAEs of pneumoperitoneum, fatal respiratory distress, haemodynamic instability, gastrointestinal necrosis, cardiac failure, and multiple organ dysfunction syndrome were reported.

Furthermore, one non-treatment-emergent death was reported. This patient from Cohort 1 died 32 days after the last dose of RDV due to hypoxemic and hypercarbic respiratory failure secondary to SARS-CoV-2 acute respiratory distress syndrome and cytomegalovirus pneumonitis in the setting of systemic lupus erythematosus and lupus nephritis.

The Grade 3 or 4 laboratory abnormalities reported during Study GS-US-540-5823 were in accordance with laboratory abnormalities documented for clinical studies in adult hospitalized COVID-19 patients.

Two patients prematurely discontinued study drug due to AEs, both in Cohort 1.

During **Study GS-US-540-9012** no adolescent patient in the RDV group experienced any AE.

2.5.2. Conclusions on clinical safety

Overall, RDV was well tolerated during clinical studies in paediatric patients. The overall rate of AEs, AEs considered related to study drug and SAEs reported during **Study GS-US-540-5823** was comparable to clinical studies which investigated RDV in adult hospitalized patients with COVID-19. No safety signal could be identified. Differences in safety data between Cohort 1 (and 8) and Cohorts 2-3 were observed and further discussed. It is concluded that the higher percentages of participants with any AE, Grade 3 or higher AEs, and SAEs in Cohort 1 may reflect the small sample number in each cohort. According to the analysis of the MAH no association was identified with common AEs or with AKI and PK exposures of RDV and its metabolites or with SBECD concentrations which is overall agreed. No safety signal was identified during Study GS-US-540-5823 and it seems most likely that the differences observed between cohorts reflect the small sample size and study design.

Exposure to the excipient SBECD was not higher in paediatric patients compared to preliminary data on adult patients with mild to moderate renal impairment. Moreover, no trends were identified in SBECD exposures across paediatric age and paediatric weight bands

The significance of the results is limited due to the small numbers of patients treated in each cohort.

In addition, safety data from the three adolescent patients from **Study GS-US-540-9012** with confirmed COVID-19 who were at increased risk for disease progression and received 3 doses of RDV in an outpatient setting, are regarded as too limited to draw any firm conclusion on the safety profile of RDV in this patient population. However, no AES were reported in the adolescents included in this study.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted/was requested to submit an updated RMP version 5.0 with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 5.0 is acceptable.

The CHMP endorsed this advice.

Safety concerns

Important Identified Risks	None
Important Potential Risks	None
Missing Information	Safety in patients with hepatic impairment
	Safety in patients with severe renal impairment
	Safety in pregnant and lactating women

Pharmacovigilance plan

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				

Activity (Status)	Summary of Objectives	Safety Concerns Addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
Remdesivir pregnancy safety report (Ongoing)	To provide information on pregnant women and birth outcomes with the use of RDV during pregnancy from postmarketing sources and the compassionate use program (IN-US-540-5755) and expanded access program (GS-US-540-5821).	Safety in pregnancy	Submission of report	Yearly, within the PSUR
GS-US-540-5912 A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study Evaluating the Efficacy and Safety of Remdesivir in Participants with Severely Reduced Kidney Function who are Hospitalized for COVID-19 (Ongoing)	To evaluate the safety and tolerability of RDV in participants with severely reduced kidney function who are hospitalized for COVID-19	Safety in patients with severe renal impairment	Submission of study report	31 Januar y 2023
GS-US-540-9014 A Phase 1 Open-Label, Adaptive, Single-Dose Study to Evaluate the Pharmacokinetics of Remdesivir and its Metabolite(s) in Subjects with Normal Hepatic Function and Hepatic Impairment (Ongoing)	To evaluate the pharmacokinetics of RDV and its metabolite(s) in subjects with hepatic impairment	Safety in patients with hepatic impairment	Submission of study report	30 June 2 023
GS-US-540-9015 A Phase 1 Open-Label, Parallel-Group, Single-Dose Study to Evaluate the Pharmacokinetics of Remdesivir and Metabolites in Participants with Normal Renal Function and Renal Impairment (Ongoing)	To evaluate the pharmacokinetics of RDV and its metabolite(s) in subjects with renal impairment	Safety in patients with severe renal impairment	Submission of study report	30 Novem ber 2022
Study of the PK and safety of RDV in pregnant women (IMPAACT 2032) (Ongoing)	To evaluate the pharmacokinetics and safety of remdesivir in pregnant individuals with coronavirus disease 2019 (COVID-19).	Safety in pregnancy	Submission of study report	31 Decem ber 2022

Risk minimisation measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important identified risk(s)		
None		
Important potential risk(s)		
None		
Missing information		

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Safety in patients with hepatic impairment	Routine risk minimization measures: SmPC section 4.2, 4.4, 4.8 and 5.2 PL section 2	Additional pharmacovigilance activities: Study GS-US-540-9014 (Phase 1 study in subjects with hepatic impairment) Submission of study report: 30 June 2023
Safety in patients with severe renal impairment	Routine risk minimization measures: SmPC section 4.2, 4.4 and 5.2 PL section 2	Additional pharmacovigilance activities: Study GS-US-540-9015 (Phase 1 study in subjects with renal impairment) Submission of study report: 30 November 2022 Study GS-US-540-5912 (Phase 3 study in patients with severely reduced kidney function who are hospitalized for COVID-19) Submission of study report: 31 January 2023
Safety in pregnant and lactating 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: Remdesivir pregnancy safety report Submission of report: Yearly within the PSUR Study of the PK and safety of RDV in pregnant women (IMPAACT 2032) Submission of study report: 31 December 2022

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 of the SmPC have been updated. The Package Leaflet as well as the instructions for healthcare professionals have been updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet.

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Veklury (remdesivir) is included in the additional monitoring list as <include reason(s) as *it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.*

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The human disease caused by SARS-CoV-2 has been designated COVID-19 and was first detected in Wuhan, China in December 2019. In most (~80%) cases, COVID-19 presents as a mild-to-moderately severe, self-limited acute respiratory illness with fever, cough, and shortness of breath. Symptoms are thought to appear 2 to 14 days after exposure. COVID-19 can be severe, resulting in pneumonia, severe acute respiratory syndrome, hypercoagulation, kidney failure, and death.

The vulnerability of children to infection with SARS-CoV-2 is expected to be equivalent to that of adults; however, similar to SARS-CoV and Middle East respiratory syndrome-CoV, SARS-CoV-2 infection appears to be less common in children {Cruz 2020, Dong 2020, Lee 2020, Zimmermann 2020}. With moderate to severe COVID-19, both populations display similar symptoms. Although COVID-19 infections usually lead to mild or moderate symptoms in children, some progress to severe disease and require hospitalization (49.7 per 100,000 cases at Coronavirus Disease 2019 Associated Hospitalization Surveillance Network sites in the US from 01 March 2020 to 14 August 2021 and 0.1%-0.2% in Europe from 04 January to 20 June 2021) {Delahoy 2021, European Centre for Disease Prevention and Control 2021}.

More than 2 years after identification of SARS-CoV-2, the pandemic continues to burden healthcare systems worldwide. New variants have also evolved, such as the alpha, delta and omicron variants, that challenge the ability to end the pandemic. As children in the US returned to schools in the fall of 2021, the number of cases of COVID-19 and of hospitalizations increased with higher numbers in school districts without a universal masking policy {Budzyn 2021, Jehn 2021}. While vaccination against COVID-19 infection is effective in preventing COVID-19, vaccines are not yet available for all children and breakthrough cases of COVID-19 can occur in those who are vaccinated.

There is no regulatory guidance on SARS-CoV-2 drug development. Concerning endpoints, an impact on mortality would be the most clinically relevant as well as scientifically persuasive outcome of a study in COVID-19. However, this may not be readily demonstrated in a study program, due to its limited size and/or limited effects of the treatment administered.

Notably, mortality is not the only clinically relevant endpoint. In analogy with developments in the influenza field, an ordinal scale for classifying patient response at a given day or as a time to recovery endpoint, was proposed by WHO, and has been used in several trials, including all four RCTs that are relevant to this application. Provided that the study is efficiently double-blinded, these are anticipated to produce unbiased effect estimates.

Anti-influenza agents have been approved based on an impact on time to recovery. Such endpoints are considered to capture clinical benefit for COVID-19 also, both in terms of the alleviation of symptoms and suffering, as well as in terms of saving public health resources.

3.1.2. Available therapies and unmet medical need

In the EU currently two vaccines against SARS-CoV-2 infection are approved for paediatric patients. Corminaty for children aged five years and older and Spikevax for children aged six years and older.

Dexamethasone can be used in the EU to treat COVID-19 in adolescents aged 12 years and older and weighing at least 40 kg after EMA's CHMP completed its review under Article 5(3). Treatment with Dexamethasone have been proven effective and safe in the treatment of severe COVID-19 of severe COVID-19 in adolescents aged 12 years and older and weighing at least 40 kg and require supplemental oxygen. Furthermore, Remdesivir is approved for the treatment of COVID-19 in adolescent patients aged 12 years and older and weighing at least 40 kg who require low-flow oxygen, high-flow oxygen or non-invasive mechanical ventilation at the start of therapy.

Currently, some monoclonal antibodies are approved for the treatment of mild and moderate COVID-19 infection in adolescent patients outside the hospital setting, Xevudy (sotrovimab) and Ronapreve (casirivimab/imdevimab). Xevudy and Ronapreve are indicated for treating COVID-19 in adults and adolescents (from 12 years of age and weighing at least 40 kilograms) who do not require supplemental oxygen and who are at increased risk of their disease becoming severe. Ronapreve can also be used for preventing COVID-19 in people aged 12 years and older weighing at least 40 kilograms. Evushed was approved for preventing COVID-19 in people aged 12 years and older weighing at least 40 kilograms.

Currently, there are no approved antiviral treatments for the treatment of COVID-19 in children and adolescents below the age of 12 or weighing less than 40 kg.

In addition, paediatric patients with COVID-19 are treated with relevant supportive care, including e.g., oxygen, mechanical ventilation and other life support, as required.

While vaccination against COVID-19 infection is effective in preventing COVID-19, vaccines are not yet available for all children and breakthrough cases of COVID-19 can occur in those who are vaccinated. There is a high medical need for an effective agent for treatment of COVID-19 for children and adolescents especially for those below 12 years of age or weighing less than 40 kg.

3.1.3. Main clinical studies

There are two studies supporting the clinical efficacy and safety of RDV for the treatment of COVID-19 in children and adolescents below 18 years of age:

Study GS-US-540-5823

The study supporting the clinical efficacy and safety of RDV for the treatment of COVID-19 in paediatric patients aged ≥ 28 days to < 18 years of age and weighing ≥ 3 kg with pneumonia requiring oxygen (low- or high-flow oxygen or other non -invasive ventilation at start of treatment) is the ongoing Phase 2/3 uncontrolled, open-label, single arm study **(GS-US-540-5823**) evaluating the safety, tolerability, PK, and efficacy of RDV in paediatric participant in 53 participants from birth to < 18 years of age.

Study GS-US-540-9012

The study supporting the clinical efficacy and safety of remdesivir in paediatric patients >12 years of age weighing at least 40 kg who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19 is the phase 3, randomized, double-blind, placebo-controlled, multicenter study (**GS-US-540-9012**) evaluating the efficacy and safety of treatment of early stage COVID-19 with IV-administered Remdesivir in an outpatient setting in 584 participants with confirmed COVID-19 who were at increased risk for disease progression.

For study GS-US-540-9012 only the subset of eight adolescents with COVID-19 were considered.

3.2. Favourable effects

Study GS-US-540-5823 (CARAVAN)

Study GS-US-540-5823 (CARAVAN) is a Phase 2/3 single arm, open-label study evaluating the safety, tolerability and pharmacokinetics of remdesivir in participants from birth to <18 years of age hospitalized with COVID-19. The primary study endpoints were the proportion of participants experiencing treatment-emergent adverse events; proportion of participants experiencing treatment-emergent graded laboratory abnormalities; and evaluation of plasma concentrations of remdesivir and metabolites, respectively. The 10 secondary endpoints related to efficacy include: change from baseline in oxygenation use; change from baseline in the use of mechanical ventilation or extracorporeal membrane oxygenation (ECMO); assessment of clinical improvement based on scoring using the 7-point ordinal scale; and time (days) to discharge from hospital. The analysis population included 53 patients, which were included in five different age Cohorts (Cohort 1: 12 patients; Cohort 2: 12 patients, Cohort 3: 12 patients, Cohort 4: 12 and Cohort 8: 5 patients).

Based on the provided data, 62.3% participants (33/53, 95% CI: 47.9%-75.2%) from the overall enrolled population recovered by Day 10 as measured by the 7-point ordinal scale for clinical status, while 83.0% of the overall participants (44/53, 95% CI: 70.2%-91.9%) have recovered at the time of the last assessment.

By Day 10, 60.4% (32/53) and by Day 30, 83.0% (44/53) of the overall enrolled population were discharged from the hospital alive.

The median (Q1, Q3) changes from baseline in clinical status reported for the overall participants on Day 10 and at the time of the last assessment were 2.0 (1.0, 4.0) points and 3.0 (2.0, 4.0) points.

Confirmed negative SARS-CoV-2 PCR results on Day 2 through Day 10 were reported for 42.1% (8/19) total participants with nasal/oropharyngeal (OP) samples, 21.4% (6/28) total participants with NP/OP samples, and 22.2% (2/9) total participants with ET aspirates.

PEWS total score for the total population was 0 for 22.6% (12/53) participants; 1, 2, or 3 for 37.7% (20/53) participants; 4, 5, or 6 for 24.5% (13/53) participants; and 7, 8, or 9 for 15.1% (8/53) participants.

Study GS-US-540-9012 (Pinetree)

Study GS-US-540-9012 (Pinetree) was a Phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate treatment with IV-administered Remdesivir in an outpatient setting in 584 participants with confirmed COVID-19 who were at increased risk for disease progression. The most common baseline risk factors were diabetes mellitus (62%), obesity (56%) and hypertension (48%) and were equally distributed across treatment arms. 30% of the enrolled patients were > 60 year of age. Based on available virology data, none of the patients was infected with the Delta variant. Treatment with Remdesivir/placebo was given for three days. The primary efficacy endpoint was COVID-19 related hospitalisation by day 28. The analysis population included 562 patients (279 patients in the Remdesivir treatment group, and 283 patients in the placebo-arm). Only eight adolescents were enrolled in the study of whom three received remdesivir treatment.

None of the eight enrolled adolescent participant (12 to < 18 years of age) had COVID-19-related hospitalization or all-cause death by Day 28, neither in the remdesivir group, nor in the placebo group

3.3. Uncertainties and limitations about favourable effects

GS-US-540-5823

Due to the single-arm design of the study 5823, the lack of a control arm and as only descriptive efficacy data have been presented, efficacy data from study 5823 are of limited value. No firm conclusion on efficacy in the intended paediatric indication is possible.

The exposure in C_{max} and AUC of remdesivir and its metabolites were up to 2.3-fold higher in paediatric patients compared to adult outpatients. However, no trends were identified between PK exposures of either RDV nor its metabolites and the most common AEs reported in study GS-US-540-5823. Moreover, exposure of the intracellular metabolite GS-441524 which is considered the most relevant metabolite, and which has the longest half-life is mostly comparable between cohorts and only moderately increased compared to data from adult outpatients.

Nine participants were not discharged alive by Day 30, of these seven were still hospitalized (2 in each of Cohorts 1 and 2; 3 in Cohort 4) and two had died (1 each in Cohorts 1 and 8).

By Day 10, no improvement in PEWS score was reported for 32.1% (17/53) participants; increases in the PEWS total score were reported for 7.6% (4/53) participants.

Efficacy outcomes (clinical improvement, recovery, hospital discharge, hospital duration improvement in PEWS score) in the different Cohorts at D5, D10 and last available assessment vary between the cohorts, especially between Cohort 1 and the other cohorts. The MAH provided additional analysis, however, it remains unclear, which factors might have contributed to the differences in efficacy and safety data between Cohort 1 (and 8) and Cohorts 2-4. Exposure to the excipient SBECD was not higher in paediatric patients compared to preliminary data on adult patients with mild to moderate renal impairment. Moreover, no trends were identified in SBECD exposures across paediatric age and paediatric weight bands. Overall, it is concluded that the number of patients treated in the different cohorts is too limited to draw any conclusion based on the observed differences.

Data supporting the efficacy of remdesivir in patients aged at least 4 weeks and weighing at least 3.5 kg with pneumonia who require supplemental oxygen (low-flow, high-flow or non-invasive mechanical ventilation at the start of therapy) is considered limited.

None of the participants was infected with the Delta or Omicron variant, hence no clinical data on remdesivir's efficacy in paediatric patients infected with those variants is available.

No vaccinated patients were enrolled in study 5823.

Different sampling techniques to evaluate viral load were used for the study participants, namely nasal swabs, NP swaps and endotracheal (ET) aspirates, which were not balanced between and within cohorts. Comparability of viral load results between and within cohorts could have been severely impacted by the different sampling techniques used.

GS-US-540-9012:

Only eight adolescent participants were enrolled in study GS-US-540-9012, of which only three adolescent patients received remdesivir. The efficacy dataset in adolescent patients weighing more than 40 kg and having at least one risk factor for progressing to severe disease is extremely limited.

Median weight in adolescents treated in study 9012 were significantly above 40 kg. Patients treated with remdesivir weighted at least 68 kg. No efficacy data on patients weighing less than 68 kg is available.

No vaccinated patients were enrolled in study 9012.

3.4. Unfavourable effects

Overall, 53 paediatric patients (laboratory confirmed COVID-19, hospitalized and requiring medical care for COVID-19) received up to 10 doses of RDV during open-label Study GS-US-540-5823. Furthermore, 3 adolescent patients were treated with 3 doses of RDV in an outpatient setting (confirmed COVID-19 who were at increased risk for disease progression) during the randomized, double-blind, placebo-controlled Study GS-US-540-9012. In general, RDV was well tolerated during clinical studies in paediatric patients.

During **Study GS-US-540-5823**, overall, in 38 patients (71.7%) at least 1 AE was reported. The rate of reported AEs was highest in Cohort 1 (11 patients [91.7%]) compared to the other cohorts (Cohort 2: 7 patients [58.3%]; Cohort 3: 9 patients [75.0%]; Cohort 4: 7 patients [58.3%]; Cohort 8: 4 patients [80.0%]). When comparing with clinical studies conducted in adult hospitalized patients with COVID-19, the overall rate of AEs reported during Study GS-US-540-5823 is comparable to the studies in adults.

The reported rate of AEs considered related to study drug during study GS-US-540-5823 (8 patients [15.1%]) was comparable to rates in clinical studies conducted RDV in hospitalised patients. The reported adverse reactions are in general in accordance with the known safety profile of RDV.

The overall rate of reported SAEs (20.8%) was comparable to rates reported in clinical studies in adult hospitalised COVID-19 patients (Study CO-US-540-5776: 21.1%, Study CO-US-540-5758: 18%). The listed PTs were only reported as single cases. None of the SAEs reported during the study were considered related to study drug.

During Study GS-US-540-5823 three treatment-emergent deaths occurred, all in patients with complex medical histories. No safety signal could be identified based on these cases.

Two patients prematurely discontinued study drug due to AEs, both in Cohort 1.

During Study **GS-US-540-9012** no adolescent patient in the RDV group experienced any AE

3.5. Uncertainties and limitations about unfavourable effects

During **Study GS-US-540-5823** the reported rate of AEs in Cohort 1 was higher compared to the other cohorts. In line with this finding, more patients in Cohort 1 had a Grade 3 or higher AE (6 patients [50.0%]) compared to the other cohorts (Cohort 2: 2 patients [16.7%]; Cohort 3: 1 patients [8.3%]; Cohort 4: 4 patients [33.3%]; Cohort 8: 2 patients [40.0%]) and the only 3 patients with Grade 3 or higher AEs considered related to study drug were from Cohort 1 [25.0%]. Furthermore, more SAEs were reported in Cohort 1 (5 patients [41.7%]) compared to the other cohorts (Cohort 2: 2 patients [16.7%]; Cohort 3: 0 patients; Cohort 4: 3 patients [25.0%]; Cohort 8: 1 patient [20.0%]). However, none of the serious adverse events (SAEs) were considered related to study drug. Nevertheless, AEs leading to premature study drug discontinuation were only reported in 2 patients in Cohort 1 [16.7%] and none in the other cohorts. The reported rates of AEs and Grade 3 or higher AE in Cohort 8 were intermediate between those of cohort 1 and cohorts 2-4, however, due to the very low number of patients treated in Cohort 8 (n=5), it is even more difficult to draw a conclusion here.

When comparing baseline disease characteristics, it appears that the median duration of symptoms prior to first dose of RDV was higher in Cohort 1 (7 days) than in the other cohorts (Cohort 2: 5 days; Cohort 3: 3 days; Cohort 4: 5 days; Cohort 8: 5 days) which could refer to a worse disease condition. However, the median duration of hospitalisation prior to the first dose of RDV was comparable between cohorts. Furthermore, no differences in oxygen support status at baseline and COVID-19–related disease manifestations between cohorts could be identified. In addition, characteristics of medical

history seem to be comparable between cohorts. Furthermore, PK data from Cohorts 1 and 8 compared to Cohorts 2-4 did not explain differences in rates of reported AEs, Grade 3 or higher AEs and SAEs. The MAH further analysed which factors might have contributed to the differences in safety data between Cohort 1 (and 8) and Cohorts 2-4, however, no respective factors have been identified. Overall, it is concluded that the number of patients treated in the different cohorts is too limited to draw any conclusion based on the observed differences.

In Cohorts 1 and 8 numerically more patients experienced AEs of constipation (Cohort 1: 3 patients [25%], Cohort 2: 1 patient [8.3%]; Cohort 3: 1 patient [8.3%]; Cohort 4: 2 patients [16.7%]; Cohort 8: 3 patients [60.0%]). Furthermore, AEs of acute kidney injury were more frequently reported in Cohort 1 (Cohort 1: 4 patients [33.3%], Cohort 2: 0 patients; Cohort 3: 0 patients; Cohort 4: 1 patient [8.3%]; Cohort 8: 1 patient [20.0%]). Of the reported cases of acute kidney injury, one AE was considered as SAE and the remaining AEs as non-serious AEs. As requested, details of all reported cases of acute kidney injury during Study GS-US-540-5823 including causality assessments were presented. Overall, no safety signal could be identified based on these data.

Furthermore, safety data from the 3 adolescent patients from **Study GS-US-540-9012** with confirmed COVID-19 who were at increased risk for disease progression and received 3 doses of RDV in an outpatient setting, are regarded as too limited to draw any firm conclusion on the safety profile of RDV in this patient population.

3.6. Effects Table

Table 32

Effect	Short description	Unit	RDV (up to 10 days)	Control	Uncertainties / Strength of evidence	References
Favourable Effects **Study GS-US-540-5823**						
Clinical improvement	< 2 point of improvement in clinical status on a 7-point ordinal scale at D10	% [95% CI]	Overall: 75% (39/52) [61.1, 86] Cohort 1: 41.7% (5/12) [15.2,72.3] Cohort 2: 91.7% (11/12) [61.5, 99.8] Cohort 3: 100% (12/12) [73.5, 100.0] Cohort 4: 63.6% (7/11) [30.8, 89.1] Cohort 8: 80.0% (4/5) [28.4-99.5]	-	**Unc:** Lack of a control arm **Unc:** Worse outcomes in Cohort 1 **Unc:** Overall results are driven by the better baseline clinical status in coh ort 3	(1)
Recovery	Improvement from a baseline score of 2 through 5 to a score of 6 or 7 or an improvement from a baseline score of 6 to a	% [95% CI]	Overall: 62.3% (33/53) [47.9, 75.2] Cohort 1: 25.0% (3/12) [5.5,57.2] Cohort 2:	-	**Unc:** Lack of a control arm **Unc:** Worse outcomes in Cohort 1 **Unc:** Overall results are driven by the better baseline clinical status in cohort 3	(1)

Effect	Short description	Unit	RDV (up to 10 days)	Control	Uncertainties / Strength of evidence	References
	score of 7 at D10		75.0% (9/12) [42.8, 94.5] <u>Cohort 3:</u> 91.7% (11/12) [61.5, 99.8] <u>Cohort 4:</u> 50.0% (6/12) [21.1-78.9] <u>Cohort 8:</u> 80.0% (4/5) [28.4-99.5]			
Antiviral effect	Change in viral load	c/ml		-	**Unc:** Lack of a control arm **Unc:** different sampling techniques were used (Nasal/OP, NP/OP, ET, comparability of results is not given **Unc:** Lack of *in vivo* data that demonstrate antiviral effect (POC)	(1)
Hospitalisation	Duration of hospitalisation	Median time [Q1, Q3]	<u>Overall:</u> 7 days [5, 12] <u>Cohort 1:</u> 12 days [8, 15] <u>Cohort 2:</u> 7 days [5, 9] <u>Cohort 3:</u> 7 days [4, 9] <u>Cohort 4:</u> 7 days [4, 17] <u>Cohort 8:</u> 7 days [4, 14]	-	**Unc:** Lack of a control arm **Unc:** Worse outcomes in Cohort 1 **Unc:** Overall results are driven by the better baseline clinical status in cohort 3	(1)
PEWS score	Change from baseline in PEWS score at D10	Median change (SD) [Q1, Q3]	<u>Overall:</u> -1.0 [-3.0, 0.0] <u>Cohort 1:</u> -0.5 [-1.5, 0.0] <u>Cohort 2:</u> -1.5 [-3.5, -0.5] <u>Cohort 3:</u> -2.0 [-4.5, 0.0] <u>Cohort 4:</u> -2.0 [-3.0, 0.0]	-	**Unc:** Lack of a control arm **Unc:** Worse outcomes in Cohort 1 **Unc:** Overall results are driven by the better baseline clinical status in cohort 3	(1)

Effect	Short description	Unit	RDV (up to 10 days)	Control	Uncertainties / Strength of evidence	References
			Cohort 8: 0.0 [-4.0, 0.0]			
Study GS-US-540-9012 Favourable Effects	Composite endpoint of COVID-19-related hospitalization or all-cause death by Day 28		8 adolescents included out of 562 patients included in the FAS and Safety Analysis Set (3 adolescents received RDV)		Very limited sample size	
Unfavourable Effects ***Study GS-US-540-5823***						
AEs	Reported rate	%	71.7	-	Overall rate comparable to reported rates in studies of RDV in hospitalized adults, however, appropriateness of extrapolation of the adult safety data to the paediatric population questioned. Furthermore, differences between cohorts which should be further discussed	(1)
ADRs	Reported rate	%	15.1	-	Overall rate comparable to reported rates in studies of RDV in hospitalized adults, however, appropriateness of extrapolation of the adult safety data to the paediatric population questioned. Furthermore, differences between cohorts which should be further discussed	(1)
SAEs	Reported rate	%	20.8	-	Overall rate comparable to reported rates in studies of RDV in hospitalized adults, however, appropriateness of extrapolation of the adult safety data to the paediatric population questioned. Furthermore, differences between cohorts which should be further discussed	(1)
Study GS-US-540-9012 Favourable Effects	Reported rate	%	0		No SAE were reported but only 3 adolescents received RDV.	

Abbreviations: RDV= remdesivir, NP= Nasopharyngeal, OP = oropharyngeal, ET= endotracheal tube aspirates, POC= proof of concept, AE= adverse events

Notes: (1) CARAVAN Study (GS-US-540-5823)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The high medical need for an effective agent for treatment of COVID-19 in paediatric patients is undisputed.

Provided efficacy data from **study GS-US-540-5823** showed improvements in clinical status of children ≥ 28 days and weighing ≥ 3 kg with laboratory-confirmed COVID-19, including clinical improvement based on the 7-point ordinal scale and the PEWS Scale, discharge from hospital, and oxygen usage after treatment with RDV. In particular, high rates of recovery as measured by the 7-point ordinal scale for clinical status (62.3% by Day 10; 83.0% at the time of the last assessment) and hospital discharge (60.4% by Day 10; 83.0% by Day 30) were seen.

However, due to the single-arm design of the study 5823, the lack of a control arm and as only descriptive efficacy data have been presented, efficacy data from study 5823 are of limited value. No firm conclusion on efficacy in the intended paediatric indication is possible.

Exposure of RDV and its metabolites in paediatric patients was higher compared to adult patients, however, AUC of the intracellularly formed metabolite GS-441524 was mostly comparable between cohorts and only moderately increased compared to data from adult outpatients. No trends were identified between PK exposures of either RDV or its metabolites and the reported AEs. Further optimisation of the dosing regimen to reduce the high variability in PK parameter seems difficult to achieve, given that the proposed dosing scheme already used individual weight-based dosing per kg bodyweight. Thus, the higher plasma concentrations in the paediatric population could be acceptable.

None of the participants was infected with the Delta or Omicron variant, hence it remains unclear, if the magnitude of benefit is also applicable to paediatric patients infected with the Delta and Omicron variant. However, *in vitro* data indicate that remdesivir might retain the antiviral activity against these two variants.

Confirmed negative SARS-CoV-2 PCR results (defined as 2 consecutive negative results or a negative result at the last available sample for participants who completed or discontinued from the study) on Day 2 through Day 10 were seen in 42.1% (8/19) total participants with nasal/OP samples, 21.4% (6/28) total participants with NP/OP samples and 22.2% (2/9) total participants with ET aspirates. However, different sampling techniques to evaluate viral load were used for the study participants, namely nasal swabs, NP swaps and endotracheal (ET) aspirates. In addition, the use of the different sampling techniques was not balanced between and within Cohorts. Hence, comparability of viral load results between and within cohorts could have been severely impacted by the different sampling techniques used. It is impossible to elucidate if the differences observed in viral load are due to the age/weight-characteristics, the baseline disease status or due to the different sampling techniques used. Furthermore, time to first negative SARS-CoV-2 PCR result with confirmation from nasal/OP, NP/OP samples, and ET aspirates were mostly not estimable. Taken together, results of the viral load data cannot be considered to draw any firm and meaningful conclusion on the antiviral effect of remdesivir in paediatric patients. Furthermore, due to the lack of a control arm it is not possible to conclude on an antiviral effect of remdesivir.

In addition, the provided efficacy data from study **GS-US-540-9012,** showed that none of the eight enrolled adolescent participant (12 to < 18 years of age) had COVID-19-related hospitalisation or all-cause death by Day 28, neither in the remdesivir group, nor in the placebo group, which is reassuring. However, no difference on viral load between the RDV group and the placebo group have been detected.

Overall, only eight adolescent participants with confirmed COVID-19 who were at increased risk for disease progression were enrolled in study GS-US-540-9012, of whom only three adolescent patients received remdesivir. Hence, the efficacy and safety dataset in adolescent patients weighing more than 40 kg and having at least one risk factor for progressing to severe disease is considered too limited to draw any meaningful conclusion on the efficacy and safety in this patient population. Furthermore, it has been noted that the median weight in adolescents treated in study 9012 was significantly above 40 kg. Patients treated with remdesivir weighted at least 68 kg. Hence, no efficacy data on patients weighing less than 68 kg is available.

No vaccinated paediatric patients were enrolled in study GS-US-540-5823 or -9012. Hence, it remains unclear, if the magnitude of benefit of remdesivir documented in unvaccinated patients is applicable to a population comprising vaccinated and/or naturally primed seropositive subjects.

3.7.2. Balance of benefits and risks

Remdesivir was initially given a 'conditional marketing authorisation' in the EU on 3 July 2020 for the treatment of COVID-19 in adults and adolescents from 12 years of age with pneumonia who require supplemental oxygen (oxygen via nasal cannula, non-invasive ventilation or high flow oxygen devices, IMV or ECMO). Since the first approval, the therapeutic indication was restricted to exclude patients with pneumonia who required IMV and ECMO at the start of therapy (December 2020, EMEA/H/C/005622/II/0012) and extended to include adult patients who do not require supplemental oxygen and who are at increased risk of progression to severe COVID-19 (December 2021, EMEA/H/C/005622/II/0016).

Within this procedure, the **extension of indication** to paediatric patients with pneumonia who require supplemental oxygen (low-flow, high-flow oxygen or non-invasive mechanical ventilation at the start of therapy) and to adolescent patients weighing more than 40 kg not requiring supplemental oxygen and having at least one risk factor for progressing to severe COVID-19 is evaluated.

Provided efficacy data from study GS-US-540-5823 showed improvements in clinical status of children ≥ 28 days and weighing ≥ 3 kg with laboratory-confirmed COVID-19, including clinical improvement based on the 7-point ordinal scale and the PEWS Scale, discharge from hospitalization, and oxygen usage after treatment with RDV. In particular, high rates of recovery as measured by the 7-point ordinal scale for clinical status (62.3% by Day 10; 83.0% at the time of the last assessment) and hospital discharge (60.4% by Day 10; 83.0% by Day 30) were seen.

However, due to the single-arm design of the study 5823, the lack of a control arm and as only descriptive efficacy data have been presented, efficacy data from study 5823 are of limited value. No firm conclusion on efficacy in the intended paediatric indication is possible. However, data are considered sufficient to support the proposed paediatric indications.

Overall, RDV was well tolerated during clinical studies in paediatric patients and the safety data reported during study GS-US-540-5823 are comparable to the studies in adults. Overall, no safety signal was identified based on the data provided. No factors could be identified which explain differences between cohorts and it is concluded that due to the limited number of patients in the different cohorts no further conclusion can be drawn. Furthermore, no trends have been identified between exposures of remdesivir and its metabolites or SBECD exposure and reported AEs. Further optimisation of the dosing regimen to reduce the high variability in PK parameters seems difficult to achieve, given that the proposed dosing scheme already used individual weight-based dosing per kg bodyweight.

Only 8 adolescents were included in study 9012 and thus results on efficacy and safety are very limited. However, the proposed dose has already been approved for adolescents >40 kg in need of supplemental oxygen and since the provided exposure in this age group is comparable to adults, there is no objection to extension of the outpatient indication to adolescents weighing more than 40 kg.

Hence, the **extension of indication** to paediatric patients with pneumonia who require supplemental oxygen (low-flow, high-flow oxygen or non-invasive mechanical ventilation) at the start of therapy and in adolescent patients weighing more than 40 kg not requiring supplemental oxygen and having at least one risk factor for progressing to severe COVID-19 **is supported.**

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall B/R of Veklury is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends, the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Grouped application of two Extensions of indication to include:
- treatment of 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, based on interim results from Study GS-US-540-5823; a phase 2/3 single-arm, open-label study to evaluate the safety, tolerability, pharmacokinetics, and efficacy of Remdesivir in participants from birth to <18 years of age with COVID-19;
- treatment of 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, based on data from 8 adolescent patients who were included in Study GS-US-540-9012, which was initially assessed by the CHMP as part of procedure II/16 (Extension of Indication to include treatment of adults).

As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet as well as the instructions for healthcare professionals have been updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Version 5.0 of the RMP has also been submitted.

The group of variations leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0060/2021 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.