25 April 2025
EMA/150907/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Veklury

International non-proprietary name: remdesivir

Procedure No. EMEA/H/C/005622/II/0053/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.

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

Table of contents

1. Background information on the procedure 6
1.1. Type II group of variations 6
1.2. Steps taken for the assessment of the product 7

2. Scientific discussion 7
2.1. Introduction 7
2.1.1. Problem statement 8
2.1.2. About the product 10
2.1.3. The development programme 10
2.1.4. General comments on compliance with GCP 10
2.2. Non-clinical aspects 10
2.2.1. Ecotoxicity/environmental risk assessment 10
2.2.2. Conclusion on the non-clinical aspects 10
2.3. Clinical aspects 11
2.3.1. Introduction 11
2.3.2. Pharmacokinetics 11
2.3.3. Pharmacodynamics 24
2.4. Clinical efficacy 24
2.4.1. Main study: GS-US-540-5823 (CARAVAN) 24
2.4.2. Discussion on clinical efficacy 44
2.4.3. Conclusions on the clinical efficacy 47
2.5. Clinical safety 47
2.5.1. Discussion on clinical safety 52
2.5.2. Conclusions on clinical safety 53
2.5.3. PSUR cycle 53
2.6. Risk management plan 53
I.1. Additional Pharmacovigilance Activities 58
2.7. Update of the Product information 59
2.7.1. User consultation 60
2.7.2. Additional monitoring 60

3. Benefit-Risk Balance 60
3.1. Therapeutic Context 60
3.1.1. Disease or condition 60
3.1.2. Available therapies and unmet medical need 60
3.1.3. Main clinical study 61
3.2. Favourable effects 61
3.3. Uncertainties and limitations about favourable effects 63
3.4. Unfavourable effects 64
3.5. Uncertainties and limitations about unfavourable effects 64
3.6. Effects Table 65
3.7. Benefit-risk assessment and discussion 65
3.7.1. Importance of favourable and unfavourable effects 65
3.7.2. Balance of benefits and risks 66
3.8. Conclusions 67

4. Recommendations 67

List of abbreviations

%CV	percentage coefficient of variation
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC_{tau}	area under the concentration versus time curve over the dosing interval
CDC	Centres for Disease Control and Prevention
CI	confidence interval
CoV	coronavirus
COVID-19	coronavirus disease 2019
ECMO	extracorporeal membrane oxygenation
eGFR	estimated glomerular filtration rate
GMR	geometric mean ratio
ET	endotracheal tube
ICU	intensive care unit
i.e.	id est = that is
INR	international normalized ratio
IV	intravenous
m	Module
max	maximum
MERS	Middle East respiratory syndrome
NP	nasopharyngeal
OP	oropharyngeal
PCR	polymerase chain reaction
PD	pharmacodynamics
PK	pharmacokinetic(s)
PEWS	Paediatric Early Warning Score
PK	pharmacokinetic(s)
PopPK	population pharmacokinetic
Q1	first quartile
Q3	third 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
US	United States
V_c	central volume of distribution
V_p	peripheral volume of distribution

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 an application for a group of variations on 28 November 2023.

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 comprising two extensions of indication to include treatment of paediatric patients weighing at least 1.5 kg for VEKLURY, based on final results from study GS-US-540-5823; this is 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; 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 is updated in accordance. Version 8.1 of the RMP has also been submitted.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0439/2023 on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the PIP P/0439/2023 was completed. The PDCO issued an opinion on compliance for the PIP.

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.

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 was:

Rapporteur: Janet Koenig

Timetable	Actual dates
Submission date	28 November 2023
Start of procedure	23 December 2023
CHMP Rapporteur Assessment Report	20 February 2024
PRAC Rapporteur Assessment Report	23 February 2024
PRAC members comments	28 February 2024
Updated PRAC Rapporteur Assessment Report	29 February 2024
PRAC Outcome	7 March 2024
CHMP members comments	11 March 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	15 March 2024
Request for supplementary information (RSI)	21 March 2024
CHMP Rapporteur Assessment Report	21 November 2024
Updated PRAC Rapporteur Assessment Report	25 November 2024
PRAC Outcome	28 November 2024
CHMP members comments	2 December 2024
Updated CHMP Rapporteur Assessment Report	6 December 2024
2nd Request for supplementary information (RSI)	12 December 2024
CHMP Rapporteur Assessment Report	25 March 2025
PRAC Rapporteur Assessment Report	27 March 2025
PRAC members comments	02 April 2025
Updated PRAC Rapporteur Assessment Report	3 April 2025
PRAC Outcome	10 April 2025
CHMP members comments	14 April 2025
Updated CHMP Rapporteur Assessment Report	16 April 2025
Opinion	25 April 2025

2. Scientific discussion

2.1. Introduction

Remdesivir (RDV, GS-5734) is a single diastereomer, monophosphoramidate prodrug of a nucleoside analogue that is intracellularly metabolised into an analogue of adenosine triphosphate that inhibits viral RNA polymerases.

Interim data from the Phase 2/3 Study GS-US-540-5823 (Cohorts 1 to 4, and Cohort 8), evaluated the safety, tolerability, pharmacokinetics (PK), and efficacy of RDV for paediatric participants at least 28 days of age and older weighing at least 3 kg. The data from Cohorts 1 to 4, and Cohort 8 together with data from 3 Phase 3 studies (GS-US-540-5773, GS-US-540-5774, and CO-US-540-5776 [National Institute of Allergy and Infectious Diseases–sponsored Adaptive COVID-19 Treatment Trial-1; NIAID ACTT-1]) in adults and adolescents hospitalised with COVID-19 infection, as well as from Study GS-US-540-9012 in non-hospitalised adults and adolescents, supported the use of RDV for the treatment of COVID-19.

Veklury, which contains the active substance remdesivir, showed a clinically meaningful effect on time to recovery in adult and adolescent COVID-19 patients with pneumonia requiring supplemental oxygen, while being well tolerated with mild side effects. Veklury was also effective in preventing hospitalisation in adult and adolescent patients who did not need supplemental oxygen and who were at high-risk of developing severe COVID-19. Veklury was shown to be absorbed, modified and removed from the body in a similar way in children, as it is in adults; side effects observed in children were also shown to be comparable to those seen in adults.

Based on the above interim data, Veklury was approved in the European Union on 3 July 2020. At the time of submission of this application, it was indicated for the treatment of coronavirus disease 2019 (COVID-19) in

- adults and paediatric patients (at least 4 weeks of age and weighing at least 3 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment)
- adults and paediatric patients (weighing at least 40 kg) who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.

2.1.1. Problem statement

Disease or condition

COVID-19 in adult and paediatric populations.

Epidemiology

As of 28 June 2023, approximately 16.8 million children aged 0 to 17 years in the US had tested positive for COVID-19 since the onset of the pandemic. Although children with COVID-19 frequently have mild or moderate symptoms, COVID-19 can result in severe disease. Children < 1 year old and children with underlying disease are at a higher risk of developing COVID-19–related pneumonia. The cumulative incidence of COVID-19–associated hospitalizations in children aged < 18 years from 1 March 2020 to
17 June 2023 was 202 per 100,000 at Coronavirus Disease 2019-Associated Hospitalization Surveillance Network sites in the US. In total, 14,370 children with COVID-19 were hospitalized from 1 March 2020 to 17 June 2023. Between 01 March 2020 and 30 April 2023, 24.1% (3171/13,140 patients) of children aged 0 to 17 years were admitted to an intensive care unit (ICU), 6.7% (871/13,140 patients) required mechanical ventilation, and 0.6% (77/13,153 patients) died in the hospital.

In Europe, the proportion of weekly reports of cases of COVID-19 infection in children was stable for the period from 17 July 2023 to 23 July 2023. Overall hospital admission rates were also stable over

the same period. These findings are consistent with the availability of vaccines for adults and children. 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 children to severe respiratory disease. 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. Prematurity has been identified as a risk factor for severe disease in children under 2 years old.

Clinical presentation and diagnosis

People with COVID-19 may be asymptomatic or may commonly experience one or more symptoms, including fever, cough, shortness of breath or difficulty breathing, fatigue, myalgia, headache, loss of taste or smell, sore throat, nausea or vomiting, diarrhoea. Children have similar clinical manifestations of COVID-19 to adults, although typically with milder and less frequent symptoms, and significantly lower rates of severe disease and death. The clinical findings overlap with those of multiple other clinical syndromes (e.g. pneumonia, bronchiolitis, gastroenteritis and common febrile illnesses) with fever or chills and cough being the most common reported symptoms. Infants may have difficulty feeding and fever without an obvious source. As in adults, children with underlying medical conditions are at risk for severe disease, and chronic pulmonary disease (including asthma), obesity, neurological and developmental conditions, cardiovascular disease and immunosuppression conditions are the most frequently reported risk factors. Severe disease in children is associated with: elevated inflammatory markers (e.g. CRP, procalcitonin, interleukin 6, ferritin, D-dimer) at admission or during hospitalization; dyspnoea, tachypnoea, and/or hypoxia at admission; and gastrointestinal symptoms (WHO; Clinical management of COVID-19, Guideline 18 August 2023). Nucleic acid amplification tests are the reference method for detection of current SARS-CoV-2 infection (WHO, Diagnostic testing for SARS-CoV-2 infection, 2022).

Management

In the EU, vaccines against SARS-CoV-2 infection are approved, as well as antiviral treatment in adult and paediatric patients.

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

Claimed therapeutic indication

With this application, the MAH initially proposed to extend the indication to include the treatment of COVID-19 in paediatric patients from birth weighing at least 1.5 kg, based on the PK, efficacy, and safety data from the final analysis of the Phase 2/3 Study GS-US-540-5823. In practice, the MAH initial proposal for the extended indications was:

Veklury is indicated for the treatment of coronavirus disease 2019 (COVID-19) in **adults and paediatric patients (weighing at least 1.5 kg)**:

- ~~adults and paediatric patients (at least 4 weeks of age and weighing at least 3 kg)~~ with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment)
- ~~adults and paediatric patients (weighing at least 40 kg)~~ who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19

2.1.2. About the product

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; e.g., 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

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, Gilead Sciences International Ltd. submitted to the European Medicines Agency on 29 May 2023 an application for modification of the agreed paediatric investigation plan with a deferral as set out in the European Medicines Agency's decision P/0201/2020 issued on 19 May 2020, the decision P/0060/2021 issued on 5 February 2021, the decision P/0338/2021 issued on 9 August 2021 and the decision P/0221/2022 issued on 24 June 2022. This application for modification was accepted (EMEA-002826-PIP01-20-M04). The modification related to the key binding element for evaluable participants in cohort 5 of the GS-US-540-5823 study. As only three participants in cohort 5 were treated (one consent was withdrawn before the first dose) and therefore evaluable for PK and safety, the number of evaluable participants in cohort 5 was revised from four to three.

2.1.4. General comments on compliance with GCP

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

2.2. Non-clinical aspects

No new non-clinical data were submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

No new ecotoxicity data were provided, as the extended indication would not lead to a significant increase in environmental exposure through the use of remdesivir or the environmentally relevant API GS-441524, which was considered acceptable by the CHMP.

2.2.2. Conclusion on the non-clinical aspects

Remdesivir or the environmentally relevant API GS-441524 are not expected to pose a risk to the environment as a result of the extended indication.

Veklury should be used according to the precautions stated in the SmPC in order to minimise any potential risks to the environment.

2.3. Clinical aspects

2.3.1. Introduction

The proposals for extending the indications of Veklury are based on final results from study GS-US-540-5823 (the 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 which constituted the basis of the initial MAA) and a PopPK model to evaluate the PK of remdesivir and its metabolites (GS-704277 and GS-441524).

GCP

The Clinical trial GS-US-540-5823 was 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.

2.3.2. Pharmacokinetics

Absorption, Distribution, Elimination

No new information was submitted by the MAH. The disposition properties (i.e., absorption, distribution, metabolism, and elimination) of RDV and its metabolites (GS-704277 and GS-441524) have been previously characterized in adults and nonclinical studies. The underlying disposition pathways in paediatric participants are consistent with those in adults.

Effect of Intrinsic Factors

Population pharmacokinetic (PopPK) analyses were used to examine the effect of intrinsic factors of interest (e.g., body weight, age, renal function, hepatic function, demographic factors, and disease severity/status) on the PK of RDV and its metabolites in paediatric participants from birth to less than 18 years of age and weighing at least 1.5 kg in Study GS-US-540-5823.

Effect of Extrinsic Factors

No new information was submitted by the MAH. Drug-drug interaction recommendations for RDV based upon clinical results in adults may be extrapolated to the paediatric population.

Pharmacokinetics of SBECD

Plasma exposures of the excipient sulfobutylether β-cyclodextrin sodium (SBECD) following IV RDV administration in paediatric participants from birth to less than 18 years of age were comparable to those in adult participants with normal renal function. SBECD PK data in paediatric participants less than 2 years of age were very limited but appeared consistent with those in paediatric participants at least 2 years of age.

Pharmacokinetics of RDV and its Metabolites

The PK of RDV and its metabolites following IV RDV administered at a 200-mg loading dose followed by 100-mg daily maintenance doses (Cohorts 1 and 8), 5-mg/kg loading dose followed by 2.5-mg/kg daily maintenance doses (Cohorts 2 to 5), or 2.5-mg/kg loading dose followed by 1.25-mg/kg daily maintenance doses (Cohorts 6 and 7) in paediatric participants with COVID-19 are summarized in Table 1.

Evaluation of the PK of RDV and its metabolites (GS-704277 and GS-441524) was conducted using a PopPK model (CTRA-2023-1076 RDV PopPK). Higher exposures (AUC_{tau}) of metabolites GS-704277 and GS-441524, but not RDV, were observed in Cohorts 5 to 7 compared with older paediatric cohorts; however, interpretation is limited due to the small sample size.

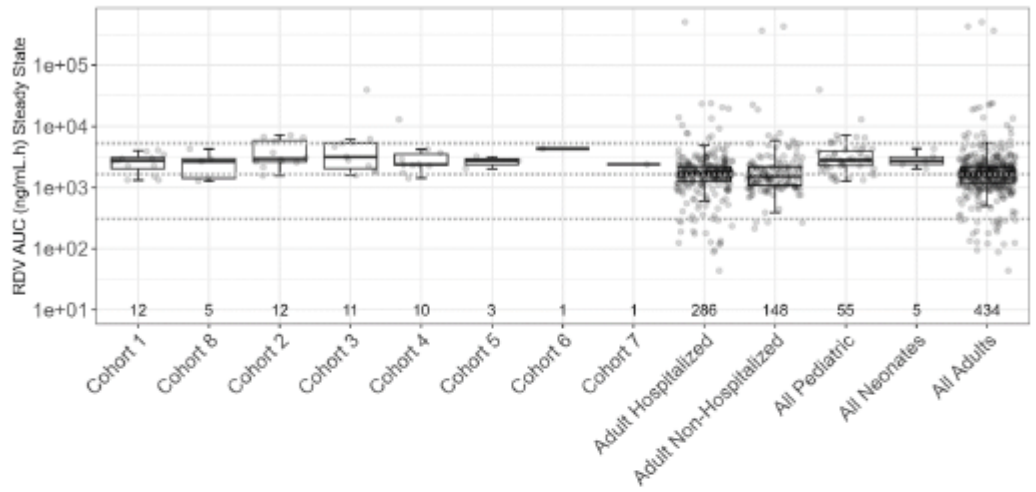
Given the limited data in Cohorts 5 to 7 in Study GS-US-540-5823, simulations of virtual populations were performed to characterize the range of PK exposures in paediatric participants of the age and weight ranges associated with these cohorts.

There was an overall trend toward increased AUC_{tau}, C_{max}, and C_{tau} (GS-441524 only) in Cohorts 5 to 7 at the RDV doses administered when compared to adults with COVID-19 in Phase 3 studies; however, interpretation is limited given the small sample size (n = 5) in Study GS-US-540-5823 (Figure 1 for RDV, Figure 2 for GS-704277 and Figure 3 for GS-441524).

Table 1 GS-US-540-5823: Mean (%CV) Population PK Model-Predicted, Steady-State Exposures for RDV, GS-704277, and GS-441524 in Paediatric Patients With COVID-19

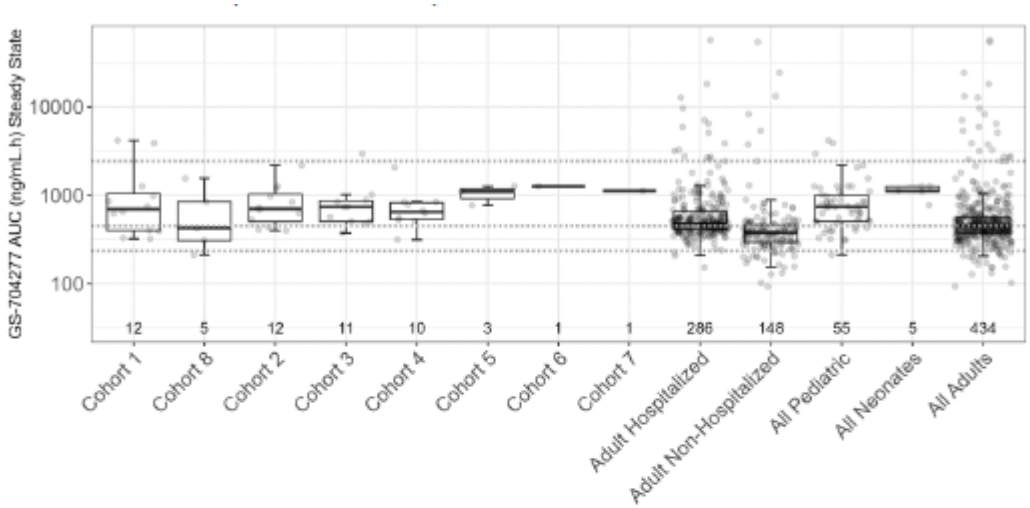
Analyte/ PK Parameter	Cohort 1: Age 12 to < 18 Years and Weight ≥ 40 kg N = 12	Cohort 2: Age 28 Days to < 18 Years and Weight 20 to < 40 kg N = 12	Cohort 3: Age 28 Days to < 18 Years and Weight 12 to < 20 kg N = 11	Cohort 4: Age 28 Days to < 18 Years and Weight 3 to < 12 kg N = 10	Cohort 5: Age 14 to < 28 Days, GA > 37 Weeks, and Weight ≥ 2.5 kg N = 3	Cohort 6: Age < 14 Days, GA > 37 Weeks, and Birth Weight ≥ 2.5 kg N = 1	Cohort 7: Age < 56 Days, GA ≤ 37 Weeks, and Birth Weight ≥ 1.5 kg N = 1	Cohort 8: Age < 12 Years and Weight ≥ 40 kg N = 5	Total N = 55
RDV									
C_{max} (ng/mL)	4108.7 (33.2)	6003.5 (31.3)	5980.1 (38.2)	5192.9 (39.8)	4829.0 (19.8)	7143.8	4395.9	4235.7 (42.3)	5204.7 (37.2)
AUC_{tau} (h•ng/mL)	2630.1 (35.1)	3937.9 (50.3)	6752.1 (161.6)	3625.7 (92.7)	2650.3 (22.2)	4320.7	2390.2	2519.6 (49.0)	3938.3 (132.8)
GS-704277									
C_{max} (ng/mL)	360.6 (57.7)	469.0 (51.1)	484.8 (50.3)	407.8 (32.5)	466.0 (23.8)	547.7	642.0	297.9 (53.8)	426.2 (47.9)
AUC_{tau} (h•ng/mL)	1222.9 (110.2)	860.3 (59.6)	876.0 (82.2)	776.0 (62.5)	1049.0 (24.2)	1264.1	1126.5	671.4 (82.4)	932.6 (84.4)
GS-441524									
C_{max} (ng/mL)	276.4 (118.4)	210.5 (57.5)	186.5 (55.3)	209.8 (23.7)	371.8 (40.6)	246.5	363.0	230.4 (110.7)	234.0 (80.3)
AUC_{tau} (h•ng/mL)	5486.2 (138.5)	3016.1 (80.4)	2751.8 (67.9)	2969.1 (31.7)	6899.3 (56.7)	3726.1	7005.4	4336.8 (131.3)	3910.9 (110.2)
C_{tau} (ng/mL)	146.7 (125.9)	83.3 (89.9)	81.9 (77.3)	86.0 (42.6)	193.4 (46.7)	119.7	196.2	117.1 (122.3)	109.1 (100.9)

%CV = percentage coefficient of variation; GA = gestational age; PK = pharmacokinetic(s); RDV = remdesivir.
The GS-US-540-5823 RDV PK Analysis Set includes all enrolled participants who received at least 1 dose of RDV and had at least 1 nonmissing PK concentration datum reported by the PK laboratory for RDV.
The GS-US-540-5823 Metabolites PK Analysis Set includes all enrolled participants who received at least 1 dose of RDV and had at least 1 nonmissing PK concentration datum reported by the PK laboratory for each respective analyte.
The PK parameters from Study GS-US-540-5823 were simulated using population PK modeling with 30 minutes of duration for RDV infusions.
Cohorts 1 and 8 received RDV 200 mg on first day (loading dose) followed by 100 mg daily for up to 10 days (steady state). Cohorts 2 to 5 received RDV 5 mg/kg on first day (loading dose) followed by 2.5 mg/kg daily for up to 10 days (steady state). Cohorts 6 and 7 received RDV 2.5 mg/kg on first day (loading dose) followed by 1.25 mg/kg daily for up to 10 days.
Source: GS-US-540-5823 Final CSR, Tables 1.1.1, 1.1.2, and 1.1.3



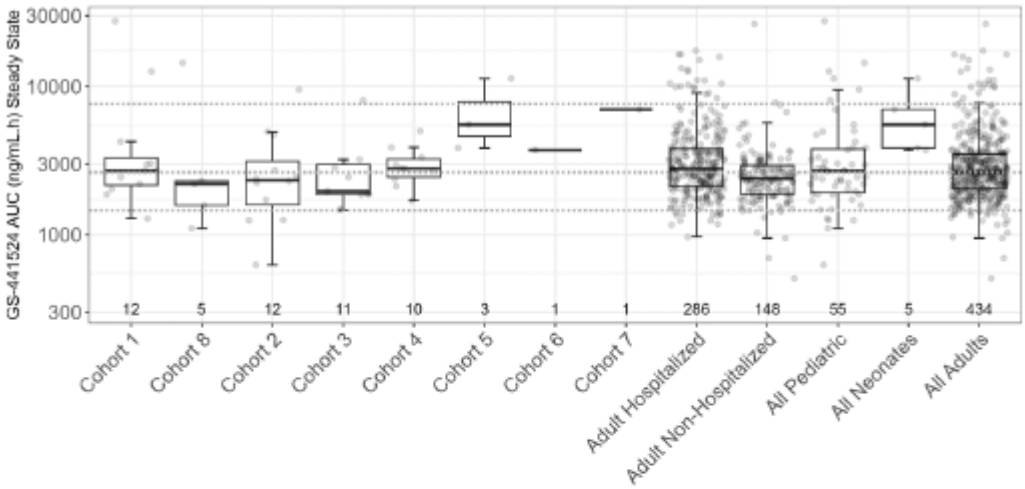
COVID-19 = coronavirus disease 2019; GA = gestational age; PopPK = population pharmacokinetic; RDV = remdesivir
The lower, middle, and upper bars of the boxplot represent the 25th, 50th, and 75th percentiles, respectively. The upper and lower whiskers represent 1.5 × the interquartile range. Circles are individual observed values.
The dotted lines represent the 5th, 50th, and 95th percentiles in Phase 3 adults (hospitalized, CO-US-540-5844; nonhospitalized, GS-US-540-9012).
All exposures in pediatric and adult participants were estimated using the final PopPK model.
In Study GS-US-540-5823, Cohort 1 (age 12 to < 18 years, weight ≥ 40 kg) and Cohort 8 (age < 12 years, weight ≥ 40 kg) received RDV 200 mg on the first day (loading dose) followed by 100 mg daily for up to 10 days; Cohorts 2 to 4 (age 28 days to < 18 years, weight 3 to < 40 kg) received RDV 5 mg/kg on the first day (loading dose) followed by 2.5 mg/kg daily for up to 10 days (steady state); Cohort 5 (age 14 to < 28 days, GA > 37 weeks, weight ≥ 2.5 kg) received RDV 5 mg/kg on first day (loading dose) followed by 2.5 mg/kg daily for up to 10 days (steady state); Cohort 6 (age 0 to < 14 days, GA > 37 weeks, weight ≥ 2.5 kg) received RDV 2.5 mg/kg on first day (loading dose) followed by 1.25 mg/kg daily for up to 10 days (steady state); and Cohort 7 (0 to < 56 days, GA ≤ 37 weeks, weight ≥ 1.5 kg) received RDV 2.5 mg/kg on first day (loading dose) followed by 1.25 mg/kg daily for up to 10 days (steady state).
Adults from 2 Phase 3 studies (hospitalized, CO-US-540-5844; nonhospitalized, GS-US-540-9012) received RDV 200 mg on the first day (loading dose) followed by 100 mg daily (steady state).
Source: CTRA-2023-1076 RDV PopPK, Figure 34

Figure 1 Boxplots of Steady-State RDV AUC_{tau} in Paediatric Participants Hospitalised With COVID-19 (GS-US-540-5823) and Phase 3 Adult Participants Hospitalised (CO-US-540-5844) and Nonhospitalised (GS-US-540-9012) With COVID-19



COVID-19 = coronavirus disease 2019; GA = gestational age; PopPK = population pharmacokinetic; RDV = remdesivir
The lower, middle, and upper bars of the boxplot represent the 25th, 50th, and 75th percentiles, respectively. The upper and lower whiskers represent 1.5 × the interquartile range. Circles are individual observed values.
The dotted lines represent the 5th, 50th, and 95th percentiles in Phase 3 adults (hospitalized, CO-US-540-5844; nonhospitalized, GS-US-540-9012).
All exposures in pediatric and adult participants were estimated using the final PopPK model.
In Study GS-US-540-5823, Cohort 1 (age 12 to < 18 years, weight ≥ 40 kg) and Cohort 8 (age < 12 years, weight ≥ 40 kg) received RDV 200 mg on the first day (loading dose) followed by 100 mg daily for up to 10 days; Cohorts 2 to 4 (age 28 days to < 18 years, weight 3 to < 40 kg) received RDV 5 mg/kg on the first day (loading dose) followed by 2.5 mg/kg daily for up to 10 days (steady state); Cohort 5 (age 14 to < 28 days, GA > 37 weeks, weight ≥ 2.5 kg) received RDV 5 mg/kg on first day (loading dose) followed by 2.5 mg/kg daily for up to 10 days (steady state); Cohort 6 (age 0 to < 14 days, GA > 37 weeks, weight ≥ 2.5 kg) received RDV 2.5 mg/kg on first day (loading dose) followed by 1.25 mg/kg daily for up to 10 days (steady state); and Cohort 7 (0 to < 56 days, GA ≤ 37 weeks, weight ≥ 1.5 kg) received RDV 2.5 mg/kg on first day (loading dose) followed by 1.25 mg/kg daily for up to 10 days (steady state).
Adults from 2 Phase 3 studies (hospitalized, CO-US-540-5844; nonhospitalized, GS-US-540-9012) received RDV 200 mg on the first day (loading dose) followed by 100 mg daily (steady state).
Source: CTRA-2023-1076 RDV PopPK, Figure 36

Figure 2 Boxplots of Steady-State GS-704277 AUC_{tau} in Paediatric Participants Hospitalised With COVID-19 (GS-US-540-5823) and Phase 3 Adult Participants Hospitalised (CO-US-540-5844) and Nonhospitalised (GS-US-540-9012) With COVID-19



COVID-19 = coronavirus disease 2019; GA = gestational age; PopPK = population pharmacokinetic; RDV = remdesivir
The lower, middle, and upper bars of the boxplot represent the 25th, 50th, and 75th percentiles, respectively. The upper and lower whiskers represent 1.5 × the interquartile range. Circles are individual observed values.
The dotted lines represent the 5th, 50th, and 95th percentiles in Phase 3 adults (hospitalized, CO-US-540-5844; nonhospitalized, GS-US-540-9012).
All exposures in pediatric and adult participants were estimated using the final PopPK model.
In Study GS-US-540-5823, Cohort 1 (age 12 to < 18 years, weight ≥ 40 kg) and Cohort 8 (age < 12 years, weight ≥ 40 kg) received RDV 200 mg on the first day (loading dose) followed by 100 mg daily for up to 10 days; Cohorts 2 to 4 (age 28 days to < 18 years, weight 3 to < 40 kg) received RDV 5 mg/kg on the first day (loading dose) followed by 2.5 mg/kg daily for up to 10 days (steady state); Cohort 5 (age 14 to < 28 days, GA > 37 weeks, weight ≥ 2.5 kg) received RDV 5 mg/kg on first day (loading dose) followed by 2.5 mg/kg daily for up to 10 days (steady state); Cohort 6 (age 0 to < 14 days, GA > 37 weeks, weight ≥ 2.5 kg) received RDV 2.5 mg/kg on first day (loading dose) followed by 1.25 mg/kg daily for up to 10 days (steady state); and Cohort 7 (0 to < 56 days, GA ≤ 37 weeks, weight ≥ 1.5 kg) received RDV 2.5 mg/kg on first day (loading dose) followed by 1.25 mg/kg daily for up to 10 days (steady state).
Adults from 2 Phase 3 studies (hospitalized, CO-US-540-5844; nonhospitalized, GS-US-540-9012) received RDV 200 mg on the first day (loading dose) followed by 100 mg daily (steady state).
Source: CTRA-2023-1076 RDV PopPK, Figure 38

Figure 3 Boxplots of Steady-State GS-441524 AUC_{tau} in Paediatric Participants Hospitalised With COVID-19 and Phase 3 Adult Participants Hospitalised (CO-US-540-5844) and Nonhospitalised (GS-US-540-9012) With COVID-19

Hospitalisation was identified as a statistically significant covariate for clearance of GS-704277, but not for RDV or GS-441524, in adults (hospitalized, Study CO-US-540-5844; nonhospitalised, Study GS-US-540-9012) and in paediatric participants from birth to less than 18 years of age. As all paediatric participants in Study GS-US-540-5823 were hospitalised, the impact of hospitalisation cannot be directly evaluated for paediatric participants. Thus, the effect of hospitalisation in paediatric participants was assumed to be the same as adults and evaluated using virtual populations for each paediatric cohort (600 virtual individuals per group, which was deemed to be a suitably large sample size). Virtual populations used for simulations were created based on age and weight distributions from paediatric growth charts ([WHO] growth chart for full-term neonates in Cohorts 4 to 6 {World Health Organization 2023}; Fenton growth chart for preterm neonates in Cohort 7 {Fenton 2023}) according to age, gestational age, and weight specifications as per the study protocol. Geometric mean ratio (GMR) values for RDV and GS-441524 exposures in hospitalised versus nonhospitalised paediatric participants were 0.859 to 1.20 for all virtual paediatric cohorts, including neonates (Table 2). The lack of a difference in PK by hospitalisation status is consistent with the lack of a hospitalisation covariate for RDV and GS-441524 in the PopPK model for paediatric participants.

Table 2 Geometric Mean Ratio and 90% CI of Steady-State Exposures for RDV, GS-7024777, and GS-441524 Between Nonhospitalised and Hospitalised Populations of Virtual Paediatric Participants With COVID-19

Analyte PK Parameter	GMR (90% CI) of Hospitalized (Test) Versus Nonhospitalized (Reference)							
	Virtual Cohort 1 (200/100 mg) N = 600	Virtual Cohort 2 (5/2.5 mg/kg) N = 600	Virtual Cohort 3 (5/2.5 mg/kg) N = 600	Virtual Cohort 4-upper (5/2.5 mg/kg) N = 600	Virtual Cohort 4-lower (5/2.5 mg/kg) N = 600	Virtual Cohort 5 (5/2.5 mg/kg) N = 600	Virtual Cohort 6 (2.5/1.25 mg/kg) N = 600	Virtual Cohort 7 (2.5/1.25 mg/kg) N = 600
RDV								
C_{max}	1.08 (0.954, 1.23)	0.975 (0.859, 1.11)	1.03 (0.907, 1.17)	0.924 (0.819, 1.04)	0.915 (0.809, 1.04)	0.979 (0.866, 1.11)	1.08 (0.956, 1.21)	0.950 (0.842, 1.07)
AUC_{tau}	1.20 (1.02, 1.40)	0.959 (0.826, 1.11)	1.04 (0.892, 1.20)	0.892 (0.762, 1.04)	0.930 (0.793, 1.09)	0.957 (0.817, 1.12)	1.15 (0.985, 1.35)	0.968 (0.830, 1.13)
GS-704277								
C_{max}	1.28 (1.13, 1.45)	1.23 (1.10, 1.39)	1.21 (1.07, 1.37)	1.33 (1.18, 1.51)	1.16 (1.03, 1.31)	1.17 (1.03, 1.32)	1.25 (1.11, 1.41)	1.11 (0.988, 1.25)
AUC_{tau}	1.56 (1.36, 1.77)	1.58 (1.38, 1.80)	1.43 (1.26, 1.64)	1.48 (1.30, 1.69)	1.58 (1.39, 1.79)	1.39 (1.21, 1.59)	1.50 (1.31, 1.72)	1.45 (1.26, 1.67)
GS-441524								
C_{max}	0.983 (0.910, 1.06)	0.891 (0.830, 0.957)	0.956 (0.886, 1.03)	1.00 (0.931, 1.08)	0.913 (0.852, 0.979)	0.915 (0.847, 0.988)	0.947 (0.880, 1.02)	0.859 (0.797, 0.927)
AUC_{tau}	1.03 (0.948, 1.11)	0.955 (0.884, 1.03)	0.983 (0.909, 1.06)	1.02 (0.943, 1.10)	0.983 (0.910, 1.06)	0.927 (0.856, 1.00)	0.972 (0.901, 1.05)	0.916 (0.847, 0.992)
C_{last}	1.07 (0.974, 1.18)	1.01 (0.912, 1.12)	0.987 (0.889, 1.10)	1.00 (0.889, 1.13)	0.981 (0.884, 1.09)	0.878 (0.798, 0.966)	0.934 (0.854, 1.02)	0.931 (0.843, 1.03)

CI = confidence interval; COVID-19 = coronavirus disease 2019; GA = gestational age; GMR = geometric mean ratio; PK = pharmacokinetic(s); RDV = remdesivir
The RDV doses are per protocol for each virtual pediatric cohort.
Virtual Cohort 1 (age 12 to < 18 years, weight ≥ 40 kg) received RDV 200 mg on first day (loading dose) followed by 100 mg daily for 5 days (steady state).
Virtual Cohort 2 (age 2 to < 18 years, weight 20 to < 40 kg) received RDV 5 mg/kg on first day (loading dose) followed by 2.5 mg/kg daily for 5 days (steady state).
Virtual Cohort 3 (age 2 to < 18 years, weight 12 to < 20 kg) received RDV 5 mg/kg on first day (loading dose) followed by 2.5 mg/kg daily for 5 days (steady state).
Virtual Cohort 4 (age 2 to < 18 years) was further stratified by weight (upper, 7 to < 12 kg; lower, 3 to < 7 kg) and received RDV 5 mg/kg on first day (loading dose) followed by 2.5 mg/kg daily for 5 days (steady state).
Virtual Cohort 5 (age 14 to < 28 days, GA > 37 weeks, weight ≥ 2.5 kg) received RDV 5 mg/kg on first day (loading dose) followed by 2.5 mg/kg daily for 5 days (steady state).
Virtual Cohort 6 (age 0 to < 14 days, GA > 37 weeks, weight ≥ 2.5 kg) received RDV 2.5 mg/kg on first day (loading dose) followed by 1.25 mg/kg daily for 5 days (steady state).
Virtual Cohort 7 (age 0 to < 56 days, GA ≤ 37 weeks, weight ≥ 1.5 kg) received RDV 2.5 mg/kg on first day (loading dose) followed by 1.25 mg/kg daily for 5 days (steady state).
Source: CTRA-2023-1076 RDV PopPK, Table 14 and Table 15

Population PK models

The previously developed PopPK model was a sequential model based on 2-compartment models for RDV and GS-704277 and a 3-compartment model for GS-441524 with first-order elimination. Adjustment to the paediatric data from Study GS-US-540-5823 was made by inclusion of allometric body weight scaling using fixed allometric exponents: 0.75 for clearance (CL)-related parameters and 1.0 for volume of distribution (V)-related parameters. Given the inclusion of paediatric subjects, a maturation function was incorporated for the CL of RDV and GS-704277 (based on the equation used in Simcyp PBPK software):

$$CL_i = TVCL \cdot \left(\frac{WT}{70}\right)^{0.75} \cdot \left(\frac{1 - 0.205}{0.542^{0.977} + age^{0.977}}\right) \cdot age^{0.977} + 0.205$$

Unlike RDV and GS-704277, the major route of elimination for GS-441524 is glomerular filtration; thus, a different renal-specific maturation function was considered:

$$CL_i = TVCL \cdot \left(\frac{WT}{70}\right)^{0.75} \cdot \frac{(age \cdot 52 + 40)^{3.38}}{47.7^{3.38} + (age \cdot 52 + 40)^{3.38}}$$

Introduction of these changes allowed for the removal of baseline bilirubin as a significant covariate in the GS-441524 model. No additional covariates were found to significantly impact RDV or GS-441524, but the previous analysis identified baseline ferritin to have a significant impact on GS-704277 in the paediatric population, and this covariate was retained in the model. A covariate search was conducted on the GS-441524 model to verify that including a maturation function did not introduce additional significant covariates. For the adult population, age >60 years was kept as a categorical covariate on GS-441524 and GS-704277 as in the previous model. Hospitalized subjects with COVID-19, adult and paediatric, had a lower CL (31.8% decrease) of GS-704277. Given the lack of data for nonhospitalised paediatric subjects with COVID-19, it was assumed that the effect of hospitalisation was the same between adult and paediatric subjects. Within the paediatric population, baseline ferritin was found to impact the CL (15.1% decrease) of GS-704277. The final model implemented an M6 method for handling BLQ samples.

Data

Overall, 11518 samples were used in the PopPK analysis, of which 10849 were adult PK samples and 669 were paediatric PK samples (180 from adolescents, 465 from subjects >28 days old, and 24 from subjects ≤28 days old). By gestational age, 29 samples came from preterm subjects (GA ≤37 weeks). By patient status, 4640 were samples from subjects with COVID-19 and 6878 were samples from healthy subjects (who were all adults). Neonatal cohorts were as follows (including dosing regimen applied in the study):

Table 3. Definition of Cohorts 5, 6, and 7 and Dosing Regimen Applied in Study -5823

Term neonatal subjects 0 to <28 days		
5	≥14 to <28 days of age, GA >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 for up to 10 days
6	0 to <14 days of age, GA >37 weeks, and birth weight ≥2.5 kg	IV RDV 2.5 mg/kg on Day 1 followed by IV RDV 1.25 mg/kg daily for up to 10 days
Preterm neonatal subjects 0 to <56 days		
7	0 to <56 days of age, GA ≤37 weeks, and birth weight ≥1.5 kg	IV RDV 2.5 mg/kg on Day 1 followed by IV RDV 1.25 mg/kg daily for up to 10 days

In cohort 5, three patients were evaluated, and one patient was included in each of cohorts 6 and 7.

The parameters of the final model are shown in Table 4.

Table 4. Summary of Sequential Final Model PK Parameters for RDV, GS-704277, and GS-441524

Parameter - Model	Parameter Description	Population Estimate	%RSE
θ_1 - remdesivir	CL - remdesivir (L/h)	50.4	2.56
θ_2 - remdesivir	Central volume - remdesivir (L)	7.01	0.443
θ_3 - remdesivir	Peripheral volume - remdesivir (L)	6.42	0.259
θ_4 - remdesivir	Intercompartmental clearance - remdesivir (L/h)	5.16	3.67
θ_1 - GS-704277	CL - GS-704277 (L/h)	292	5.08
θ_2 - GS-704277	Central volume - GS-704277 (L)	285	6
θ_3 - GS-704277	Peripheral volume - GS-704277 (L)	143	34.8
θ_4 - GS-704277	Intercompartmental clearance - GS-704277 (L/h)	11.3	12.5
θ_7 - GS-704277	Effect of baseline ferritin for pediatric subjects on clearance	-0.151	61
θ_8 - GS-704277	Effect of hospitalization for subjects on clearance	-0.318	19.7
θ_9 - GS-704277	Effect of age for subjects 60 years or older on central volume	-0.24	29.4
θ_1 - GS-441524	Clearance - GS-441524 (L/h)	26.2	2.99
θ_2 - GS-441524	Central volume - GS-441524 (L)	139	5.65
θ_3 - GS-441524	First peripheral volume - GS-441524 (L)	373	4.03
θ_4 - GS-441524	Intercompartmental clearance to first periph. cmt. GS-441524 (L/h)	537	4.89
θ_5 - GS-441524	Second peripheral volume - GS-441524 (L)	292	5.87

Parameter - Model	Parameter Description	Population Estimate	%RSE
θ_6 - GS-441524	Intercompartmental clearance to second periph. cmt. GS-441524 (L/h)	45.6	6.61
θ_9 - GS-441524	Effect of age for subjects 60 years or older on clearance	-0.35	10.4
ω^2_{11} - remdesivir	IIV of CL - remdesivir, Phases 1 and 2/3 (%CV)	42.8%	16.7
ω^2_{22} - remdesivir	IIV of V1 - remdesivir, Phases 1 and 2/3 (%CV)	39.6%	38.3
ω^2_{33} - remdesivir	IIV of CL - remdesivir, Phase 3 (%CV)	152%	5
ω^2_{44} - remdesivir	IIV of V1 - remdesivir, Phase 3 (%CV)	314%	61.9
ω^2_{11} - GS-704277	IIV of CL-GS-704277, Phases 1 and 2/3 (%CV)	45.4%	9.57
ω^2_{22} - GS-704277	IIV of V1 -GS-704277, Phases 1 and 2/3 (%CV)	56%	12.5
ω^2_{33} - GS-704277	IIV of CL-GS-704277, Phase 3 (%CV)	122%	13.7
ω^2_{44} - GS-704277	IIV of V1 -GS-704277, Phase 3 (%CV)	149%	11.8
ω^2_{11} - GS-441524	IIV of CL-GS-441524, Phases 1 and 2/3 (%CV)	51.5%	12
ω^2_{22} - GS-441524	IIV of V1 -GS-441524, Phases 1 and 2/3 (%CV)	90.9%	9.2
ω^2_{33} - GS-441524	IIV of Vp1-GS-441524, Phases 1 and 2/3 (%CV)	54.8%	10.1
ω^2_{44} - GS-441524	IIV of Vp2-GS-441524, Phases 1 and 2/3 (%CV)	62.4%	21.1
ω^2_{55} - GS-441524	IIV of CL-GS-441524, Phase 3 (%CV)	66.3%	8.77
ω^2_{66} - GS-441524	IIV of V1 -GS-441524, Phase 3 (%CV)	159%	11.1
ω^2_{77} - GS-441524	IIV of Vp1-GS-441524, Phase 3 (%CV)	182%	11.2
ω^2_{88} - GS-441524	IIV of Vp2-GS-441524, Phase 3 (%CV)	244%	10.2
σ_1 - remdesivir	Variance of residual error - remdesivir, Phases 1 and 2/3	0.593	10.5
σ_2 - remdesivir	Variance of residual error - remdesivir, Phase 3	1.75	0.0262
σ_1 - GS-704277	Variance of residual error - GS-704277, Phases 1 and 2/3	0.158	42.9
σ_2 - GS-704277	Variance of residual error - GS-704277, Phase 3	1.21	47.1
σ_1 - GS-441524	Variance of residual error - GS-441524, Phases 1 and 2/3	0.225	22.7
σ_2 - GS-441524	Variance of residual error - GS-441524, Phase 3	0.907	27.8
sqrt(θ_5) - remdesivir	Proportional residual error - remdesivir (%CV)	40.6%	0.142
θ_6 - remdesivir	Additive residual error - remdesivir (ng/mL)	1.8	0.428
sqrt(θ_5) - GS-704277	Proportional residual error - GS-704277 (%CV)	65%	24

Parameter - Model	Parameter Description	Population Estimate	%RSE
θ_6 - GS-704277	Additive residual error - GS-704277 (ng/mL)	1	-
sqrt(θ_7) - GS-441524	Proportional residual error - GS-441524 (%CV)	22.3%	13.1
θ_8 - GS-441524	Additive residual error - GS-441524 (ng/mL)	1	-

%CV = percentage of the coefficient of variation; %RSE = percentage of the relative standard error; θ = absolute value of the estimate; σ = variance of residual error; ω = interindividual variability; CL = clearance; IIV = interindividual variability; OFV = objective function value; periph. cmt. = peripheral compartment; PK = pharmacokinetic(s); RDV = remdesivir; V1 = central volume of distribution; Vp1 = first peripheral volume of distribution; Vp2 = second peripheral volume of distribution.

OFV – remdesivir = 25333.8809, OFV – GS-704277 = 23830.4336, and OFV – GS-441524 = 28357.3737.

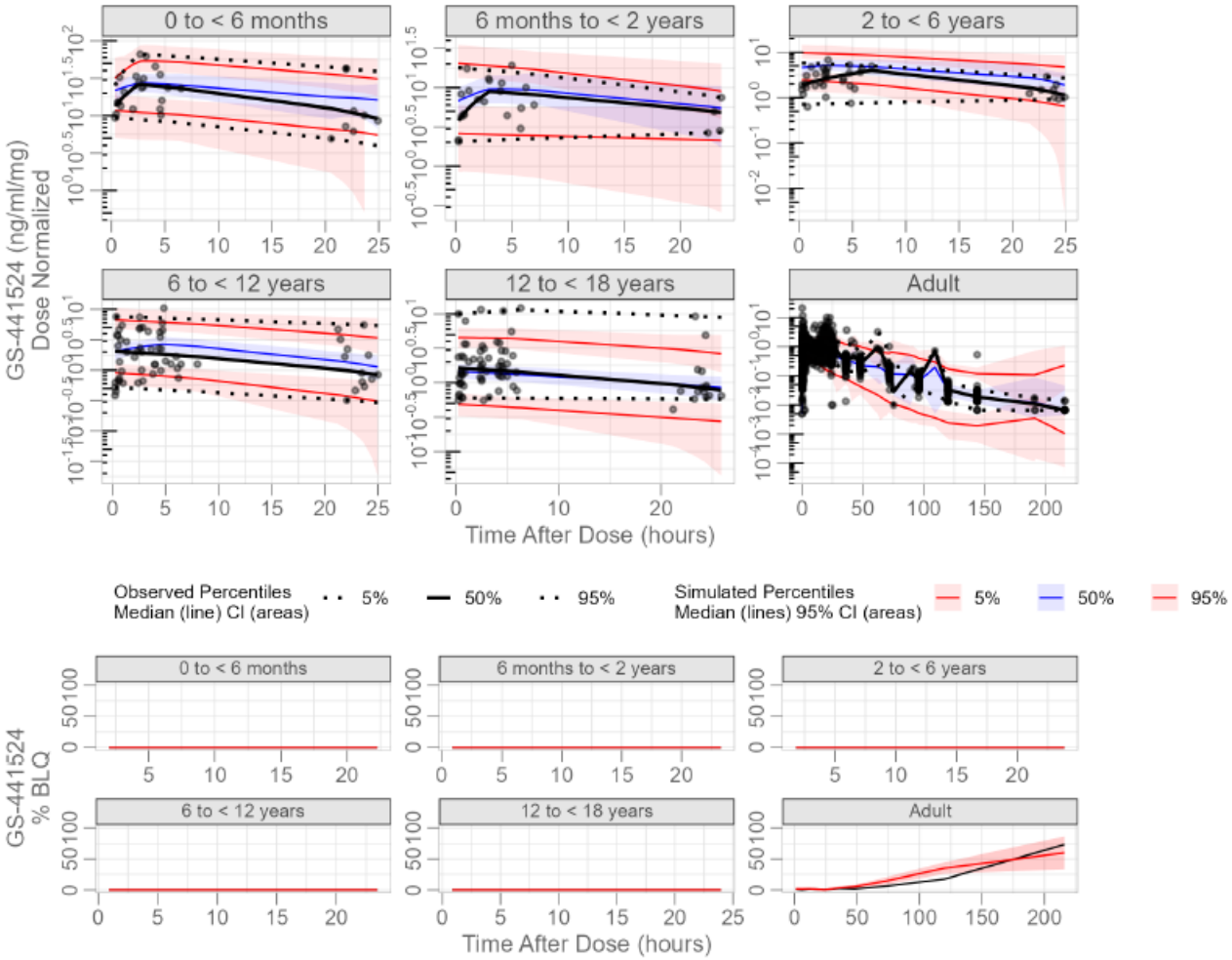
Condition number – Remdesivir = 6.891e7, Condition number – GS-704277 = 750.7, and Condition number – GS-441524 = 106.3.

Additive residual error was fixed to 1 ng/mL for the GS-704277 and GS-441524 models.

Source: RDV-Diagnostics_v2.html, M1-Diagnostics_v2.html, M2-Diagnostics_v2.html

Model evaluation

The VPCs for metabolite GS-441524 for the different age groups is shown in Figure 4 below.



BLQ = below the limit of quantitation; CI = confidence interval; VPC = visual predictive check.
Source: VPC_all_models_v5.html

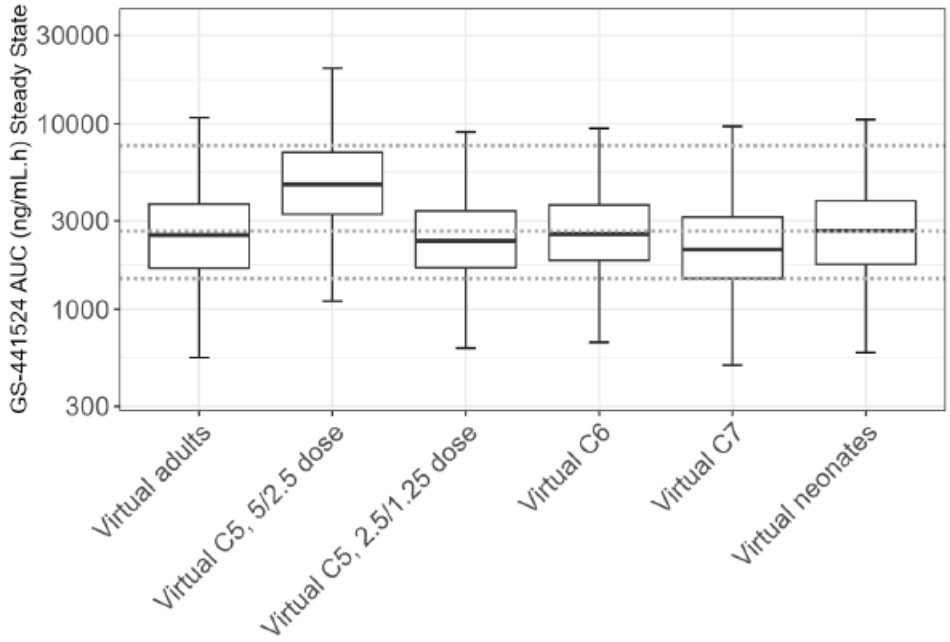
Figure 4 Dose-Normalized VPC Stratified by Age of the Final GS-441524 Model

Simulations

Simulations using the final PopPK model were performed for neonate cohorts of interest generated from relevant growth charts (Adults and Cohorts 1 to 3 and 8 from the NHANES growth chart; Cohorts 4 to 6 from the WHO growth chart; and Cohort 7 from the Fenton Preterm growth chart) following the dosing regimens per protocol. N = 600 virtual subjects were generated for each of the cohorts of interest according to the demographics specified in the enrolment criteria, with an equal distribution of males and females and an equal distribution of hospitalized and nonhospitalised subjects. Based on the initial results, additional simulations were conducted to explore dose alignment of Cohort 5 with the 2.5 mg/kg loading dose and the 1.25 mg/kg once-daily maintenance dose administered as IV infusion over 0.5 hours. The results of these simulations showed similar exposures in the virtual Cohorts 5 to 7 with the 2.5 mg/kg loading dose and the 1.25 mg/kg once-daily maintenance dose administered as IV infusion over 0.5 hours with the adult COVID-19 patient exposures. The cohorts of interest were as follows (virtual Cohorts 5 to 7 were as defined in Study GS-US-540-5823):

- Virtual Cohort 5: ≥14 days to <28 days of age, GA >37 weeks, and weight at screening ≥2.5 kg
- Virtual Cohort 6: 0 days to <14 days of age, GA >37 weeks, and birth weight ≥2.5 kg

- Virtual Cohort 7: 0 days to <56 days of age, GA ≤37 weeks, and birth weight ≥1.5 kg
- Virtual neonates: 0 days to <56 days of age, half population GA ≤37 weeks and half population GA >37 weeks, and birth weight ≥1.5 kg



AUC = area under the concentration-time curve; C = Cohort.
The lower, middle, and upper bars of the boxplot represent the 25th, 50th, and 75th percentiles, respectively. The upper and lower whiskers represent 1.5× the interquartile range.
Dotted lines represent the 5th, 50th, and 95th percentiles in Phase 3 adults (hospitalized, CO-US-540-5844; nonhospitalized, GS-US-540-9012). See Table 31 for specific exposure values.
See Table 11 for cohort age, weight, and dosing information.
Source: Simulations_v10.html

Figure 5 Boxplot of Simulated GS-441524 AUC in Virtual Neonate Cohorts and Adults

Discussion on pharmacokinetics

With this submission, the MAH provided pharmacokinetic data to support the extension of the indication to include paediatric patients from birth weighing 1.5 kg to <3 kg with pneumonia requiring supplemental oxygen and paediatric patients weighing 1.5 kg to < 40 kg not requiring supplemental oxygen but are at increased risk of progression to severe COVID-19. Evaluation of the PK data for RDV and its metabolites showed a higher exposure (AUC_{tau}) for the metabolites but not for RDV. However, the limited number of participants in cohorts 5 to 7 (n=5) limits the interpretation of these data. Therefore, virtual population simulations were performed to explore PK exposures in the paediatric participants using parameters appropriate for participants in cohorts 5 to 7. Using virtual populations of neonates and preterm neonates and infants, the overall range of steady-state exposures simulated by the PopPK model (AUC_{tau} and C_{max}; C_{tau} only for GS-445124) of RDV and its metabolites at the postulated loading and maintenance doses were within the 5^{th} and 95^{th} percentiles of exposures in hospitalised adult participants with severe COVID-19 pneumonia on supplemental oxygen and in non-hospitalised adult participants with COVID-19 at risk of disease progression and not on supplemental oxygen in Phase 3 studies. As the proposed extension of indication includes paediatric patients from birth weighing at least 1.5 kg who do not require supplemental oxygen but are at increased risk of progression to severe COVID-19, data from this paediatric patient population should be evaluated to support the extension of indication. This patient population was not included in cohorts 5 to 7 of the GS-US-540-5823 study. Therefore, an analysis of

intrinsic factors including body weight, age, renal and hepatic function, demographic factors, disease status and hospitalisation status was performed for paediatric participants from birth to 18 years of age and weighing ≥ 1.5 kg. Such an analysis has already been carried out for the interim analysis of this study. Details of the effect of intrinsic factors are discussed below.

Body weight was the most significant covariate affecting the PK of RDV and its metabolites in paediatric participants. Baseline ferritin levels (a marker of COVID-19 disease severity) had a small impact on the PK of GS-704277 within the paediatric population; however, the clinical relevance is unknown as this covariate was only identified in paediatric participants. Overall, there was no consistent trend in study GS-US-540-5823 (all cohorts) of increased or decreased exposures across body weight quartiles in paediatric participants who received a weight-based dose.

Renal function by estimated glomerular filtration rate (eGFR) was not identified as a statistically significant covariate for RDV and its metabolites in paediatric participants.

Hepatic function by baseline alanine aminotransferase (ALT) and baseline aspartate aminotransferase (AST) was not identified as a statistically significant covariate for RDV and its metabolites in paediatric participants.

Sex, race, and ethnicity were not identified as statistically significant covariates for RDV and its metabolites in paediatric participants.

Baseline oxygen support status (i.e., whether supplemental oxygen was required at the start of treatment) was not identified as a statistically significant covariate for the PK of RDV in paediatric participants from birth to less than 18 years of age (Study GS-US-540-5823). While no comparative data are available for neonates and preterm neonates and infants weighing ≥ 1.5 kg (Cohorts 5 to 7), the MAH was of the opinion that exposures of RDV and its metabolites are not expected to differ by baseline oxygenation status in this paediatric age and weight range based on the lack of PK difference demonstrated in adults and older paediatric participants.

Hospitalisation was identified as a statistically significant covariate for clearance of GS-704277, but not for RDV or GS-441524, in adults and in paediatric participants from birth to less than 18 years of age. Hospitalisation had a modest impact on the PK of GS-704277 that was not considered clinically meaningful given GS-704277 exposures are expected to be transient based on the short plasma half-life. As all paediatric participants in Study GS-US-540-5823 were hospitalised, the impact of hospitalisation cannot be directly evaluated for paediatric participants. Thus, the effect of hospitalisation in paediatric participants was assumed by the MAH to be the same as adults and evaluated using virtual populations for each paediatric cohort. The lack of a difference in PK by hospitalisation status is consistent with the lack of a hospitalisation covariate for RDV and GS-441524 in the PopPK model for paediatric participants.

In conclusion, the results of the analysis of the intrinsic factors showed that the exposures of RDV and its metabolites in paediatric patients do not differ in a clinically relevant way when the baseline oxygen support or the hospitalisation status are taken into account. No other intrinsic factor was identified as a statistically significant covariate for the PK of RDV or its metabolites in paediatric participants from birth to less than 18 years of age.

The developed PopPK model based on adult and paediatric data accounted for weight based changes and included maturation functions to account for changes in the paediatric population from birth to adult age. Overall, diagnostic plots are considered acceptable and precision of parameter estimates overall was in an acceptable range. Moreover, the results of the bootstrap were found to be consistent with the final PopPK estimates for the final models.

Very limited data were available in the youngest age cohorts in the neonatal period (0-28 days term infants and 0-56 days preterm infants). The adequacy of the doses for neonates (cohorts 5, 6 and 7) was questioned. With the doses initially proposed by the popPK model and investigated in the paediatric study (GS-US-540-5823), the observed data in the neonate cohorts showed that exposure was higher than in adults and older paediatric patients, especially for the most relevant compound GS-441524. The extrapolation approach was aimed at defining doses that lead to same exposures compared to adults and older paediatric patients. Since this aim was not achieved with the doses proposed by the popPK model, the model does not yet adequately describe the PK in the neonate cohort but needed to be refined to better align with the observed data.

The need for refinement of the popPK model might especially concern the maturation of the elimination, but also other factors (e.g. total body water, body composition (adipose tissue portion), specific enzyme functions) might need to be considered. Subsequently, sensitivity analyses with respect to dose selection and VPCs were requested to be conducted for the refined model focussing on the age and weight ranges impacted by the proposed variation, also including the specific age range preterm population.

As requested, the MAH evaluated modifications to the paediatric model and presented a modified model. However, the new popPK model presented was still not considered to improve the fit to the data. In summary, the MAH provided two different popPK models in order to adequately characterise the PK of paediatric patients down to birth. Neither model was however capable to accurately characterise the clearance of the most relevant compound GS-441524. It was considered that the database was too limited to be able to develop a reliable model to characterise the PK down to birth and robust enough to allow for simulations. As none of the popPK models were considered sufficient, no dose could be recommended for paediatric patients from birth onwards to four weeks of age and below 3 kg bodyweight, as represented by cohorts 5, 6 and 7.

2.3.3. Pharmacodynamics

No trends were identified between exposures of RDV and its metabolites and the efficacy endpoints evaluated in paediatric participants from birth to less than 18 years of age in Study GS-US-540-5823. There were no significant differences in exposures of RDV and its metabolites in those with and without each of the 9 most common adverse events (AEs), although interpretation is limited due to the low incidence of these AEs in Study GS-US-540-5823.

2.4. Clinical efficacy

2.4.1. Main study: GS-US-540-5823 (CARAVAN)

Methods

Study design

Study GS-US-540-5823 is 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. The study was planned with 22 study centres in Italy, Spain, the United Kingdom, and the United States. Cohorts 5 to 7 from Study GS-US-540-5823 are included in this submission (Table 5).

Table 5. Clinical Study Providing Data for the RDV Clinical Program in the Paediatric Population

Study Number	Study Design	Participant Population		Treatment Regimens	N	Location of Summary
		Cohort	Age/Weight Group			
GS-US-540-5823[a]	A Phase 2/3 single-arm, open-label study to evaluate RDV in participants < 18 years of age with laboratory-confirmed COVID-19	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 for up to 10 days	3	**CSR:** GS-US-540-5823 Final CSR **Narrative:** m2.7.4, Section 1.2.1
		6	0 days to < 14 days of age, gestational age > 37 weeks, and birth weight ≥ 2.5 kg	IV RDV 2.5 mg/kg on Day 1 followed by IV RDV 1.25 mg/kg daily for up to 10 days	1	
		7	0 days to < 56 days of age, gestational age ≤ 37 weeks, and birth weight ≥ 1.5 kg		1	

COVID-19 = coronavirus disease 2019; CSR = clinical study report; IV = intravenous; RDV = remdesivir; N = number of participants treated

a Results from Cohorts 5 to 7 are the focus of this submission.

Main inclusion criteria:

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

- 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

Study participants

It was planned to enrol at least 4 participants in Cohort 5, and no minimum was calculated for Cohorts 6 and 7. Of the 6 participants screened; 4 participants enrolled in Cohort 5, 1 participant in Cohort 6, and 1 participant in Cohort 7. One participant in Cohort 5 enrolled but did not receive treatment due to withdrawal of consent by the parents. Another participant in Cohort 5 discontinued study drug on Day 9 at the investigator's discretion due to clinical improvement.

Treatments

In this study, dose selection of RDV to be evaluated in paediatric participants targeted similar exposures to those observed in adults. Dose selection for participants in Cohort 5 was informed by a physiologically based pharmacokinetic (PBPK) model developed to characterize the PK of RDV and the primary circulating nucleoside metabolite, GS-441524, in adults (SimCYP Version 17, Certara). For dose selection in Cohorts 6 and 7, a population pharmacokinetic (PopPK) model was used (with data from Cohorts 1 to 4 and Cohort 8 and 1 participant in Cohort 5) to predict paediatric patient exposures.

For participants in Cohort 5 (≥ 14 days to < 28 days of age, gestational age > 37 weeks, and weight at screening ≥ 2.5 kg) an RDV loading dose of 5 mg/kg followed by 2.5 mg/kg once-daily maintenance dose of RDV was selected and subsequently evaluated in the study. For participants in Cohort 6 (0 days

to < 14 days of age, gestational age > 37 weeks, and birth weight ≥ 2.5 kg) and Cohort 7 (0 days to < 56 days of age, gestational age ≤ 37 weeks, and birth weight ≥ 1.5 kg), an RDV loading dose of 2.5 mg/kg followed by 1.25 mg/kg once-daily maintenance dose of RDV was selected based on PopPK modelling and subsequently evaluated in the study. The treatment regimens are described in Table 5.

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

Objectives

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. The additional secondary endpoints are related to efficacy and safety (Table 6).

Outcomes/endpoints

The efficacy endpoints for Study GS-US-540-5823 are similar to those used in the Phase 3 studies (GS-US-540-5773, GS-US-540-5774, and CO-US-540-5776) in the original new drug application (NDA). The PEWS Scale was added as a standard scale that evaluates the risk for clinical deterioration in hospitalized paediatric patients.

Study Objectives and Endpoints:

Primary Objectives	Primary Endpoints
• To evaluate the safety and tolerability of remdesivir (RDV, Veklury®) in participants with laboratory-confirmed COVID-19 aged 0 days to < 18 years	• The proportion of participants with treatment-emergent adverse events • The proportion of participants with treatment-emergent graded laboratory abnormalities
• To evaluate the pharmacokinetics (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 Endpoints**
• 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)
• To evaluate oxygen usage and ventilation modality and settings in participants with laboratory-confirmed COVID-19 aged 0 days to < 18 years	• Change from baseline in oxygenation use • Change from baseline in the use of mechanical ventilation or extracorporeal membrane oxygenation
• To evaluate clinical improvement using the Pediatric Early Warning Score (PEWS) Scale in participants with laboratory-confirmed 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
• To 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 Endpoints**
• 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 Centers for Disease Control and Prevention: 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 CHMP acknowledged that the final study report for GS-US-540-5823 was submitted with this variation application, which focuses on data from the paediatric patient population of cohorts 5, 6 and 7. The study design was assessed during evaluation of the initial submission.

Statistical methods

This submission focuses on data from Cohorts 5 to 7 in Study GS-US-540-5823 that support an expansion of Veklury's indication to include the treatment of COVID-19 in neonates less than 28 days of age weighing at least 1.5 kg and preterm neonates and infants less than 56 days of age weighing at least 1.5 kg, as well as infants at least 28 days of age weighing between 1.5 kg to less than 3 kg.

To incorporate data from paediatric subjects enrolled in Study GS-US-540-5823 in previously developed population pharmacokinetic (PopPK) models of remdesivir (RDV) and its metabolites developed with data from studies GS-US-399-1812, GS-US-399-1954, GS-US-399-5505, GS-US-540-5823, GS-US-40-9012, and CO-US-540-5844 (REMDACTA), an updated population pharmacokinetic analysis was done.

Analysis of clinical efficacy endpoints was completed with the full analysis set.

The efficacy endpoints for Study GS-US-540-5823 include:

- Clinical improvement based on scoring using a 7-point ordinal scale (where 1 = death and 7 = not hospitalized)
- Time (days) to discharge from hospital
- 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)
- Oxygen usage and ventilation modality and settings

Clinical improvement based on scoring using the Paediatric Early Warning Score (PEWS) Scale

Results

Participant flow, Recruitment

The study was conducted at study centres in Italy, Spain, the United Kingdom, and the United States. Six participants were screened; 4 participants were enrolled in Cohort 5, 1 participant in Cohort 6, and 1 participant in Cohort 7. One participant in Cohort 5 enrolled but did not receive treatment due to withdrawal of consent by the parents.

Conduct of the study

Table 7 lists the key dates relevant to the conduct of study GS-US-540-5823:

Table 6 Study GS-US-540-5823: Key Dates

Study Start Date:	21 July 2020 (first participant screened)
Study End Date:	10 February 2023 (last participant last visit for the primary endpoint) 01 June 2023 (planned last participant last visit for this report)

Baseline data

The majority of participants in Cohorts 5 to 7 were female (60.0%; 3/5 participants) and White (80.0%; 4/5 participants).

The median (first quartile [Q1], third quartile [Q3]) age in Cohort 5 was 0.5 (0.5, 0.5) months (16 [15, 16] days), the participant in Cohort 6 was 0.4 months (12 days), and the participant in Cohort 7 was 1.0 month (30 days). The gestational age was ≥ 37 weeks for all participants in Cohort 5, 37 weeks for the participant in Cohort 6, and 32 weeks for the participant in Cohort 7. The median (Q1, Q3) baseline weight in Cohort 5 was 3.5 (2.8, 3.5) kg, the participant in Cohort 6 was 3.5 kg, and the participant in Cohort 7 was 2.2 kg.

Table 7 GS-US-540-5823: Demographic and Baseline Characteristics (Safety Analysis Set)

	Cohort 5: 14 to < 28 Days, Gest. Age > 37 Weeks, and Weight ≥ 2.5 kg (N = 3)	Cohort 6: < 14 Days, Gest. Age > 37 Weeks, and Birth Weight ≥ 2.5 kg (N = 1)	Cohort 7: < 56 Days, Gest. Age ≤ 37 Weeks, and Birth Weight ≥ 1.5 kg (N = 1)
Age (days)			
N	3	1	1
Mean (SD)	15.7 (0.58)	12	30
Median	16	12	30
Q1, Q3	15, 16	12, 12	30, 30
Min, max	15, 16	12, 12	30, 30
Sex at birth			
Male	2 (66.7%)	0	0
Female	1 (33.3%)	1 (100.0%)	1 (100.0%)
Race			
Black	0	1 (100.0%)	0
White	3 (100.0%)	0	1 (100.0%)
Ethnicity			
Not Hispanic or Latino	3 (100.0%)	1 (100.0%)	1 (100.0%)
Baseline weight (kg)			
N	3	1	1
Mean (SD)	3.3 (0.40)	3.5	2.2
Median	3.5	3.5	2.2
Q1, Q3	2.8, 3.5	3.5, 3.5	2.2, 2.2
Min, max	2.8, 3.5	3.5, 3.5	2.2, 2.2
Baseline height (cm)			
N	3	1	1
Mean (SD)	50.0 (1.73)	52.0	46.0
Median	51.0	52.0	46.0
Q1, Q3	48.0, 51.0	52.0, 52.0	46.0, 46.0
Min, max	48.0, 51.0	52.0, 52.0	46.0, 46.0
Baseline BMI (kg/m^2)			
N	3	1	1
Mean (SD)	13.0 (0.76)	12.9	10.4
Median	13.5	12.9	10.4
Q1, Q3	12.2, 13.5	12.9, 12.9	10.4, 10.4
Min, max	12.2, 13.5	12.9, 12.9	10.4, 10.4

	Cohort 5: 14 to < 28 Days, Gest. Age > 37 Weeks, and Weight ≥ 2.5 kg (N = 3)	Cohort 6: < 14 Days, Gest. Age > 37 Weeks, and Birth Weight ≥ 2.5 kg (N = 1)	Cohort 7: < 56 Days, Gest. Age ≤ 37 Weeks, and Birth Weight ≥ 1.5 kg (N = 1)
Baseline BMI-for-age percentile category			
< 5th percentile	0	0	1 (100.0%)
≥ 5th to < 95th percentile	3 (100.0%)	1 (100.0%)	0
≥ 95th percentile	0	0	0

BMI = body mass index; CSR = clinical study report; Gest. = gestational; max = maximum; min = minimum; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; WHO = World Health Organization
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
Source: GS-US-540-5823 Final CSR, Table 15.8.3.1 and Listing 16.2.3.1

The study with cohorts 5, 6 and 7 was conducted from July 2020 to June 2023 (LPLV). The CHMP acknowledged that a total of 6 patients were screened and 5 were enrolled in the study. Three participants were enrolled in cohort 5 and one each in cohorts 6 and 7. As agreed in the PIP (P/0439/2023), this number represents the minimum planned number of participants per cohort.

Numbers analysed

The analysis sets used for data evaluation are shown in the table below (cohorts 5, 6, and 7).

Table 8 Number of Participants (Analysed)

Analysis Set	Cohort 1: 12 to < 18 Years and Weight≥ 40 kg	Cohort 2: 28 Days to < 18 Years and Weight 20 to < 40 kg	Cohort 3: 28 Days to < 18 Years and Weight 12 to < 20 kg	Cohort 4: 28 Days to < 18 Years and Weight 3 to < 12 kg
All Enrolled Analysis Set	12	12	12	12
Full Analysis Set	12 (100.0%)	12 (100.0%)	12 (100.0%)	12 (100.0%)
Safety Analysis Set	12 (100.0%)	12 (100.0%)	12 (100.0%)	12 (100.0%)
RDV PK Analysis Set	12 (100.0%)	12 (100.0%)	11 (91.7%)	10 (83.3%)
Metabolites PK Analysis Set	12 (100.0%)	12 (100.0%)	11 (91.7%)	10 (83.3%)
SBECD PK Analysis Set	12 (100.0%)	12 (100.0%)	11 (91.7%)	10 (83.3%)

Analysis Set	Cohort 5: 14 to < 28 Days, Gest. Age > 37 Weeks, and Weight ≥ 2.5 kg	Cohort 6: < 14 Days, Gest. Age > 37 Weeks, and Birth Weight ≥ 2.5 kg	Cohort 7: < 56 Days, Gest. Age ≤ 37 Weeks, and Birth Weight ≥ 1.5 kg	Cohort 8: < 12 Years and Weight ≥ 40 kg	Total
All Enrolled Analysis Set	4	1	1	5	59
Full Analysis Set	3 (75.0%)	1 (100.0%)	1 (100.0%)	5 (100.0%)	58 (98.3%)
Safety Analysis Set	3 (75.0%)	1 (100.0%)	1 (100.0%)	5 (100.0%)	58 (98.3%)
RDV PK Analysis Set	3 (75.0%)	1 (100.0%)	1 (100.0%)	5 (100.0%)	55 (93.2%)
Metabolites PK Analysis Set	3 (75.0%)	1 (100.0%)	1 (100.0%)	5 (100.0%)	55 (93.2%)
SBECD PK Analysis Set	3 (75.0%)	1 (100.0%)	1 (100.0%)	5 (100.0%)	55 (93.2%)

Gest = gestational; PK = pharmacokinetic(s); RDV = remdesivir; SBECD = sulfobutylether β-cyclodextrin sodium
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 SBECD PK Analysis Set includes all participants who are enrolled and have received at least 1 dose of RDV and for whom PK concentrations of SBECD are available.
The denominator for percentage is the number of enrolled participants.

Outcomes and estimation

Of the 6 participants screened: 4 participants enrolled in Cohort 5, 1 participant in Cohort 6, and 1 participant in Cohort 7. One participant in Cohort 5 enrolled but did not receive treatment due to withdrawal of consent by the parents. Thus, a total of five participants were treated with RDV.

The median (Q1, Q3) duration of hospitalization prior to the first dose of RDV in Cohort 5 was 5 (1, 9) days, the participant in Cohort 6 was hospitalized for 1 day, and the participant in Cohort 7 was hospitalized for 3 days. The median (Q1, Q3) duration of symptoms prior to the first dose of RDV in Cohort 5 was 6 (2, 9) days, the participant in Cohort 6 had symptoms for 2 days, and the participant in Cohort 7 had symptoms for 9 days. At baseline, the only COVID-19–related disease manifestations observed in more than 1 participant were respiratory (4/5 participants). Three of 5 participants were on invasive mechanical ventilation (IMV), and 2 of 5 participants were on high-flow oxygen.

Baseline SARS-CoV-2 RNA viral load from nasal/oropharyngeal (OP) swabs and endotracheal tube (ET) aspirates was measured for 1 participant each in Cohort 5; 5.02 log10 copies/mL and 4.63 log_{10} copies/mL, respectively. The mean (SD) SARS-CoV-2 RNA viral load from nasopharyngeal (NP)/OP swabs was 5.99 (0.183) log_{10} copies/mL in Cohort 5 (2/3 participants), 4.11 log_{10} copies/mL for the participant in Cohort 6, and 8.53 log10 copies/mL for the participant in Cohort 7. The mean (SD) SARS-CoV-2 RNA viral load from rectal/faecal swabs was 4.27 (1.107) log_{10} copies/mL in Cohort 5 (3/3 participants), and 4.62 log_{10} copies/mL for the participant in Cohort 7. There was no baseline rectal/faecal swab sample for the participant in Cohort 6.

At baseline, median (Q1, Q3) alanine aminotransferase in Cohort 5 was 20 (15, 42) U/L, 8 U/L for the participant in Cohort 6, and 9 U/L for the participant in Cohort 7. The median (Q1, Q3) aspartate aminotransferase in Cohort 5 was 69 (36, 73) U/L, 23 U/L for the participant in Cohort 6, and 23 U/L for the participant in Cohort 7. The median (Q1, Q3) creatinine in Cohort 5 was 0.4 (0.3, 0.5) mg/dL, 0.3 mg/dL for the participant in Cohort 6, and 0.3 mg/dL for the participant in Cohort 7.

Table 9 GS-US-540-5823: Baseline Disease Characteristics (Safety Analysis Set)

	Cohort 5: 14 to < 28 Days, Gest. Age > 37 Weeks, and Weight ≥ 2.5 kg (N = 3)	Cohort 6: < 14 Days, Gest. Age > 37 Weeks, and Birth Weight ≥ 2.5 kg (N = 1)	Cohort 7: < 56 Days, Gest. Age ≤ 37 Weeks, and Birth Weight ≥ 1.5 kg (N = 1)
Duration of hospitalization prior to first dose of RDV (days)			
N	3	1	1
Mean (SD)	5 (4.0)	1	3
Median	5	1	3
Q1, Q3	1, 9	1, 1	3, 3
Min, max	1, 9	1, 1	3, 3
Duration of symptoms prior to first dose of RDV (days)			
N	3	1	1
Mean (SD)	6 (3.5)	2	9
Median	6	2	9
Q1, Q3	2, 9	2, 2	9, 9
Min, max	2, 9	2, 2	9, 9
ALT (U/L)			
N	3	1	1
Mean (SD)	26 (14.4)	8	9
Median	20	8	9
Q1, Q3	15, 42	8, 8	9, 9
Min, max	15, 42	8, 8	9, 9
AST (U/L)			
N	3	1	1
Mean (SD)	59 (20.3)	23	23
Median	69	23	23
Q1, Q3	36, 73	23, 23	23, 23
Min, max	36, 73	23, 23	23, 23
Oxygen support status			
Invasive mechanical ventilation	2 (66.7%)	0	1 (100.0%)
High-flow oxygen	1 (33.3%)	1 (100.0%)	0
Low-flow oxygen	0	0	0
Room air	0	0	0
COVID-19–related disease manifestations			
Circulatory	0	1 (100.0%)	0
Gastrointestinal	1 (33.3%)	0	0
Neurological	1 (33.3%)	0	0
Respiratory	2 (66.7%)	1 (100.0%)	1 (100.0%)

	Cohort 5: 14 to < 28 Days, Gest. Age > 37 Weeks, and Weight ≥ 2.5 kg (N = 3)	Cohort 6: < 14 Days, Gest. Age > 37 Weeks, and Birth Weight ≥ 2.5 kg (N = 1)	Cohort 7: < 56 Days, Gest. Age ≤ 37 Weeks, and Birth Weight ≥ 1.5 kg (N = 1)
Systemic inflammatory response	0	0	1 (100.0%)
SARS-CoV-2 RNA viral load (log_{10} copies) from nasal/OP swabs[a]			
N	1	0	0
Mean (SD)	5.02	—	—
Median	5.02	—	—
Q1, Q3	5.02, 5.02	—	—
Min, max	5.02, 5.02	—	—
SARS-CoV-2 RNA viral load (log_{10} copies) from NP/OP swabs[a]			
N	2	1	1
Mean (SD)	5.99 (0.183)	4.11	8.53
Median	5.99	4.11	8.53
Q1, Q3	5.86, 6.12	4.11, 4.11	8.53, 8.53
Min, max	5.86, 6.12	4.11, 4.11	8.53, 8.53
SARS-CoV-2 RNA viral load (log_{10} copies) from endotracheal tube aspirates[a]			
N	1	0	0
Mean (SD)	4.63	—	—
Median	4.63	—	—
Q1, Q3	4.63, 4.63	—	—
Min, max	4.63, 4.63	—	—
SARS-CoV-2 RNA viral load (log_{10} copies) from rectal/fecal swabs[a]			
N	3	0	1
Mean (SD)	4.27 (1.107)	—	4.62
Median	4.22	—	4.62
Q1, Q3	3.19, 5.40	—	4.62, 4.62
Min, max	3.19, 5.40	—	4.62, 4.62
ECG interpretation			
Normal	3 (100.0%)	0	1 (100.0%)
Abnormal	0	1 (100.0%)	0
Clinically significant	0	0	0
Not clinically significant	0	1 (100.0%)	0
Missing/unknown	0	0	0
Creatinine (mg/dL)			
N	3	1	1
Mean (SD)	0.4 (0.13)	0.3	0.3
Median	0.4	0.3	0.3

	Cohort 5: 14 to < 28 Days, Gest. Age > 37 Weeks, and Weight ≥ 2.5 kg (N = 3)	Cohort 6: < 14 Days, Gest. Age > 37 Weeks, and Birth Weight ≥ 2.5 kg (N = 1)	Cohort 7: < 56 Days, Gest. Age ≤ 37 Weeks, and Birth Weight ≥ 1.5 kg (N = 1)
Q1, Q3	0.3, 0.5	0.3, 0.3	0.3, 0.3
Min, max	0.3, 0.5	0.3, 0.3	0.3, 0.3
eGFR using Bedside IDMS-traceable Schwartz formula (mL/min/1.73 m^2)			
N	0	0	0
Mean (SD)	—	—	—
Median	—	—	—
Q1, Q3	—	—	—
Min, max	—	—	—

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CSR = clinical study report; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; Gest. = gestational; IDMS = isotope dilution mass spectrometry; max = maximum; min = minimum; NP = nasopharyngeal; OP = oropharyngeal; Q1 = first quartile; Q3 = third quartile; RDV = remdesivir; 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: GS-US-540-5823 Final CSR, Table 15.8.3.2

The CHMP acknowledged that a total of five participants were treated with RDV, three in cohort 5 and one each in cohorts 6 and 7. The median length of hospital stay prior to the first dose of RDV was 5 days in cohort 5 and 1 and 3 days in cohorts 6 and 7, respectively. Baseline SARS-CoV-2 RNA viral load was measured for all five participants using different sampling techniques, including nasopharyngeal/oropharyngeal, nasal/oropharyngeal and rectal/faecal swabs. The disease manifestations associated with COVID-19 were reported as respiratory in two of the five participants. Two other participants had a gastrointestinal or neurological manifestation. At baseline, three of the five participants were on invasive mechanical ventilation and two were on high flow oxygen support.

Clinical Improvement Based on the 7-Point Ordinal Scale

All 5 participants had a baseline ordinal scale score of 2 (hospitalized, on IMV or extracorporeal membrane oxygenation [ECMO]) or 3 (hospitalized, on noninvasive ventilation or high-flow oxygen devices). The baseline ordinal scale scores in Cohort 5 were 2 (66.7%; 2/3 participants) and 3 (33.3%; 1/3 participants). The participant in Cohort 6 had a score of 3, and the participant in Cohort 7 had a score of 2. By Day 10, the ordinal scale score for 1 participant in Cohort 5, with a baseline score of 3 (on high-flow oxygen), had increased to 7 (not hospitalized), and there was no change in ordinal scale score for any other participant in Cohort 5. At the time of the last assessment, the participant in Cohort 6 and the participant in Cohort 7 were also not hospitalized (ordinal scale scores of 7).
On Day 10, the median (Q1, Q3) changes from baseline in clinical status were as follows:

- Cohort 5: 0 (0.0, 4.0) points
- Cohort 6: 2.0 points
- Cohort 7: 2.0 points

At the time of the last assessment there was no change in clinical status from Day 10 for Cohort 5. The change from baseline at the time of the last assessment for the participant in Cohort 6 increased to 4.0 points, and for the participant in Cohort 7 increased to 5.0 points.

Three participants (1 each in Cohorts 5 to 7) had a ≥ 2-point improvement in clinical status on Day 10. There was no change in the proportion of participants who had a ≥ 2-point improvement at the time of the last assessment. The times to a ≥ 2-point improvement for these 3 participants with an ordinal scale score of ≤ 5 points at baseline were as follows:

- Cohort 5: 8 days
- Cohort 6: 10 days
- Cohort 7: 10 days

Three of the 5 participants (1 each in Cohorts 5 to 7) had a ≥ 1-point improvement in clinical status on Day 10. There was no change in the proportion of participants who had a ≥ 1-point improvement at the time of the last assessment. The times to a ≥ 1-point improvement for these 3 participants were as follows:

- Cohort 5: 8 days
- Cohort 6: 6 days
- Cohort 7: 6 days

In total, 1 of the 3 participants in Cohort 5 and neither of the participants in Cohorts 6 and 7 had recovered by Day 10 (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). At the last assessment, the participants in Cohorts 6 and 7 had also fully recovered. In Cohort 5, there was no change in the proportion of participants who had recovered. Among the 3 participants who had recovered by the time of the last assessment, the times to recovery for each cohort were as follows:

- Cohort 5: 9 days
- Cohort 6: 13 days
- Cohort 7: 19 days

Hospitalisation

In total, 3 participants (1 each in Cohorts 5 to 7) were discharged alive by Day 30. The remaining 2 participants in Cohort 5 were still hospitalised at Day 30. The durations of hospitalisation from Day 1 for the 3 participants who were discharged were as follows:

- Cohort 5: 9 days
- Cohort 6: 13 days
- Cohort 7: 19 days

The CHMP considered that, due to the single-arm design, the efficacy data presented are only descriptive and do not allow a firm conclusion on efficacy in the intended paediatric indication. In addition, the total number of five participants in cohorts 5, 6 and 7 is rather small and the interpretation of individual data points and the efficacy data in general should be considered with caution.

All participants had a baseline ordinal scale score of 2 or 3. Recovery was defined as an improvement from a baseline score of 2 through 5 to a score of 6 or 7 or an improvement from baseline score of 6 to a score of 7. For one participant in cohort 5, the score increased from 3 to 7. For all other participants in this cohort, no improvement was observed during the study. By Day 10, none of the participants in cohorts 6 or 7 had improved to a score of 6 or 7. However, both participants in cohort 6 or 7 improved to a score of 7 at the time of the final assessment. The time to recovery was 13 days for the participant

in cohort 6 and 19 days for the participant in cohort 7. The two participants from cohort 5 without improvement in the ordinal scale until the final assessment were still hospitalised at Day 30.

The efficacy outcome varied widely, from no improvement in the ordinal scale score for two participants to full recovery for the remaining three participants. It should be noted that the two participants in cohort 5 were hospitalised for 9 days/5 days with symptoms present for 9 days/6 days prior to starting treatment with the first dose of RDV. The third participant in cohort 5 started RDV treatment earlier and was hospitalised for 1 day with symptoms present for 2 days. This participant made a full recovery compared to the other two cohort 5 participants. Participants in cohorts 6 and 7 were hospitalised for 1 and 3 days, with symptoms present for 2 and 9 days respectively. As the cohort 6 participant could be treated with high flow oxygen, the cohort 7 participant required IMV. Both participants made a full recovery, taking 13 days for the participant in cohort 6 compared to 19 days for the participant in cohort 7.

SARS-CoV-2 Viral Load

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 assessed by nasal/OP samples, NP/OP samples, ET aspirates, and rectal/faecal swabs. However, it should be noted that not all planned samples were collected.

Of the participants with a given type of sample collected, the proportion of participants with confirmed negative SARS-CoV-2 PCR results on Day 2 through Day 10 were reported as follows for each sample type:

- Nasal/OP samples:
  - Cohort 5 (1/1 participant): 100%
- NP/OP samples:
  - Cohort 5 (0/2 participants): 0%
  - Cohort 6 (0/1 participant): 0%
  - Cohort 7 (0/1 participant): 0%
- ET aspirates:
  - Cohort 5 (0/2 participants): 0%
- Rectal/fecal swabs:
  - Cohort 5 to 7: (5/5 participants): 100%
  -

The median (Q1, Q3) times to negative SARS-CoV-2 PCR test result were as follows:

- Nasal/OP samples:
  - Cohort 5 (1/1 participant): 10 days
- Rectal/fecal swabs:
  - Cohort 5 (3/3 participants): 3 days (3, 5)
  - Cohort 6 (1/1 participant): 3 days
  - Cohort 7 (1/1 participant): 10 days

The SARS-CoV-2 RNA viral load (log_{10} copies/mL) from nasal/OP, NP/OP, ET aspirates, and rectal/fecal swabs at baseline, change at Day 10, and change at discharge through the first negative PCR result with confirmation are presented in Table 10.

Similar results were reported for the mean (SD) change from baseline in SARS-CoV-2 viral load up to Day 10, and change at discharge without the first negative PCR result with confirmation.

Table 10 GS-US-540-5823: SARS-CoV-2 RNA Viral Load (Log_{10} Copies per mL) and Change From Baseline up to Day 10 or First Negative PCR Result With Confirmation (Full Analysis Set)

	Cohort 5: 14 to < 28 Days, Gest. Age > 37 Weeks, and Weight≥ 2.5 kg (N = 3)	Cohort 6: < 14 Days, Gest. Age > 37 Weeks, and Birth Weight ≥ 2.5 kg (N = 1)	Cohort 7: < 56 Days, Gest. Age ≤ 37 Weeks, and Birth Weight ≥ 1.5 kg (N = 1)
Nasal/Oropharyngeal Samples			
Baseline/Day 1			
N	1	0	0
Mean (SD)	5.02	—	—
Median	5.02	—	—
Q1, Q3	5.02, 5.02	—	—
Min, max	5.02, 5.02	—	—
Change at Day 10			
N	1	0	0
Mean (SD)	−2.36	—	—
Median	−2.36	—	—
Q1, Q3	−2.36, −2.36	—	—
Min, max	−2.36, −2.36	—	—
Change at Day of Discharge			
N	0	0	0
Mean (SD)	—	—	—
Median	—	—	—
Q1, Q3	—	—	—
Min, max	—	—	—
Nasopharyngeal/Oropharyngeal Samples			
Baseline/Day 1			
N	2	1	1
Mean (SD)	5.99 (0.183)	4.11	8.53
Median	5.99	4.11	8.53
Q1, Q3	5.86, 6.12	4.11, 4.11	8.53, 8.53
Min, max	5.86, 6.12	4.11, 4.11	8.53, 8.53
Change at Day 10			
N	2	1	1

	Cohort 5: 14 to < 28 Days, Gest. Age > 37 Weeks, and Weight≥ 2.5 kg (N = 3)	Cohort 6: < 14 Days, Gest. Age > 37 Weeks, and Birth Weight ≥ 2.5 kg (N = 1)	Cohort 7: < 56 Days, Gest. Age ≤ 37 Weeks, and Birth Weight ≥ 1.5 kg (N = 1)
Mean (SD)	−3.28 (0.183)	0.28	−4.26
Median	−3.28	0.28	−4.26
Q1, Q3	−3.41, −3.15	0.28, 0.28	−4.26, −4.26
Min, max	−3.41, −3.15	0.28, 0.28	−4.26, −4.26
Change at Day of Discharge			
N	0	0	0
Mean (SD)	—	—	—
Median	—	—	—
Q1, Q3	—	—	—
Min, max	—	—	—
Endotracheal Tube Aspirates			
Baseline/Day 1			
N	1	0	0
Mean (SD)	4.63	—	—
Median	4.63	—	—
Q1, Q3	4.63, 4.63	—	—
Min, max	4.63, 4.63	—	—
Change at Day 10			
N	1	0	0
Mean (SD)	−1.92	—	—
Median	−1.92	—	—
Q1, Q3	−1.92, −1.92	—	—
Min, max	−1.92, −1.92	—	—
Change at Day of Discharge			
N	0	0	0
Mean (SD)	—	—	—
Median	—	—	—
Q1, Q3	—	—	—
Min, max	—	—	—
Rectal or Fecal Swabs			
Baseline/Day 1			
N	3	0	1

	Cohort 5: 14 to < 28 Days, Gest. Age > 37 Weeks, and Weight≥ 2.5 kg (N = 3)	Cohort 6: < 14 Days, Gest. Age > 37 Weeks, and Birth Weight ≥ 2.5 kg (N = 1)	Cohort 7: < 56 Days, Gest. Age ≤ 37 Weeks, and Birth Weight ≥ 1.5 kg (N = 1)
Mean (SD)	4.27 (1.107)	—	4.62
Median	4.22	—	4.62
Q1, Q3	3.19, 5.40	—	4.62, 4.62
Min, max	3.19, 5.40	—	4.62, 4.62
Change at Day 10			
N	0	0	1
Mean (SD)	—	—	−2.43
Median	—	—	−2.43
Q1, Q3	—	—	−2.43, −2.43
Min, max	—	—	−2.43, −2.43
Change at Day of Discharge			
N	0	0	0
Mean (SD)	—	—	—
Median	—	—	—
Q1, Q3	—	—	—
Min, max	—	—	—

CSR = clinical study report; Gest. = gestational; LOD = limit of detection; LLOQ = lower limit of quantitation; max = maximum; min = minimum; PCR = polymerase chain reaction; Q1 = first quartile; Q3 = third quartile; RDV = remdesivir; SD = standard deviation
Baseline was the last available value recorded on or prior to dosing.
Change from baseline in SARS-CoV-2 viral load up to Day 10 or up to the first negative PCR result with confirmation (whichever comes first).
For nasal/oropharyngeal, nasopharyngeal/ oropharyngeal, and endotracheal aspirates: LLOQ = 1018 copies/mL; LOD = 925 copies/mL. Records with "< 1018cp/mL SARSCoV2 detected" were imputed as 509 copies/mL; "No SARS-CoV-2 detected" were imputed as 462.5 copies/mL.
For rectal/fecal swabs: LLOQ = 488 copies/mL; LOD = 306 copies/mL. Records with "< 488cp/mL SARSCoV2 detected" were imputed as 244 copies/mL; "No SARS-CoV-2 detected" were imputed as 153 copies/mL.
Viral load data after participants taking chloroquine, hydroxychloroquine, bamlanivimab, casirivimab/imdevimab, molnupiravir, lopinavir-ritonavir, and ribavirin during the study were excluded from the summaries.
Source: GS-US-540-5823 Final CSR, Table 15.9.4.1.1, Table 15.9.4.2.1, Table 15.9.4.3.1, and Table 15.9.4.4.1

The CHMP noted that the reduction in viral load for study participants was shown by SARS-CoV-2 PCR results from Day 2 to Day 10. As noted by the MAH, not all planned samples were collected. According to the study protocol, nasal and oropharyngeal samples (combined, if unable to collect nasopharyngeal and oropharyngeal sample) and rectal or faecal swabs should have been collected on days 3, 5, 7 and 10 or at discharge if earlier. Endotracheal tube aspirates should have been collected on the same days in case the participant was intubated. It is not clear from the information provided why not all planned procedures were carried out and why the swab collection technique for SARS-CoV-2 RT-qPCR testing was not consistent on Day 1, 3, 5, 7 and 10. The comparability of viral load results between and within cohorts may have been greatly affected by the different sampling techniques used. However, the PCR data showed a clear reduction in viral load. As only a single arm was tested, it is difficult to interpret the efficacy of RDV on viral load reduction.

Oxygen Usage and Ventilation Modality

In Cohort 5, 1 of the 3 participants was on high-flow oxygen from baseline to Day 7. Following an improvement in their condition, this participant was switched to room air on Day 8, prior to discharge from hospital on Day 9. The other 2 participants in Cohort 5 were on IMV from baseline until the last available assessment and were still hospitalized at Day 30.

The participant in Cohort 6 was on high-flow oxygen from baseline to Day 5. As the participant's condition improved, they were switched to low-flow oxygen from Day 6 to Day 9 and then to room air on Day 10. The participant was discharged from hospital on Day 13.

The participant in Cohort 7 was on IMV from baseline to Day 5. As the participant's condition improved, they were switched to high-flow oxygen from Day 6 to Day 9 and then to low-flow oxygen on Day 10. The participant was discharged from hospital on Day 19.

The CHMP noted that two of the five participants remained on invasive mechanical ventilation (IMV) without any improvement until the final assessment on Day 30, both from cohort 5. A third participant (cohort 7) started the study on IMV and was able to switch to low-flow oxygen on Day 10. Two participants, one from cohort 5 and one from cohort 6, started on high-flow oxygen and improved enough to be taken off supplemental oxygen on Days 8 and 10, respectively.

For both participants in cohort 5 without improvement, additionally, the ordinal scale score did not show recovery as defined in the study protocol.

PEWS Scale

Clinical scoring using the PEWS Improvement Scale was performed at screening and daily for the duration of RDV dosing in Study GS-US-540-5823. The PEWS scale is comprised of 3 subscales (behaviour, cardiovascular, and respiratory) each with a score of 0 to 3 to give a total score of 0 to 9. An improvement in the participant's condition is measured as a reduction in PEWS score.

Behaviour:

The PEWS behaviour scores at baseline in Cohort 5 were 3 (66.7%; 2/3 participants), and 1 (33.3%; 1/3 participants). The participant in Cohort 6 had a score of 2 and the participant in Cohort 7 had a score of 3. By Day 10, 4 participants had improvements in PEWS behaviour score: 2 participants in Cohort 5 (with baseline scores of 3 and 1, respectively) had decreases of 1 point, the participant in Cohort 6 had a decrease of 2 points, and the participant in Cohort 7 had a decrease of 2 points. The same results were observed at the time of last assessment.

Cardiovascular:

The PEWS cardiovascular scores at baseline in Cohort 5 were 1 (66.7%; 2/3 participants), and 0 (33.3%; 1/3 participants). The participant in Cohort 6 had a score of 2, and the participant in Cohort 7 had a score of 0. By Day 10, 2 participants had improvements in PEWS cardiovascular score: 1 participant in Cohort 5 had a decrease of 1 point, and the participant in Cohort 6 had a decrease of 2 points. The same results were observed at the time of last assessment.

Respiratory:

The PEWS respiratory scores at baseline in Cohort 5 were 1 (33.3%; 1/3 participants), and 3 (66.7%; 2/3 participants). The participant in Cohort 6 had a baseline score of 2, and the participant in Cohort 7 had a baseline score of 3. By Day 10, 3 participants had improvements in PEWS respiratory score: the participant in Cohort 5 with a baseline score of 1 decreased by 1 point, the participant in Cohort 6 had

a decrease of 2 points, and the participant in Cohort 7 had a decrease of 3 points. The same results were observed at the time of last assessment.

Total Score:

The PEWS total scores (maximum score of 9) at baseline in Cohort 5 were 2 (33.3%; 1/3 participants) and 7 (66.7%; 2/3 participants). The participant in Cohort 6 had a baseline score of 6, and the participant in Cohort 7 had a baseline score of 6. By Day 10, all 5 participants had improvements in PEWS total score: in Cohort 5 there was a 2-point decrease in 1 participant, and a 1-point decrease in 2 participants. The participant in Cohort 6 had a decrease of 6 points, and the participant in Cohort 7 had a decrease of 5 points. The same results were observed at the time of last assessment.

Table 11. GS-US-540-5823: Change From Baseline in PEWS Score-Total Score (Full Analysis Set)

	Cohort 5: 14 to < 28 Days, Gest. Age > 37 Weeks, and Weight ≥ 2.5 kg (N = 3)	**Cohort 6: < 14 Days, Gest. Age > 37 Weeks, and Birth Weight ≥ 2.5 kg (N = 1)**	**Cohort 7: < 56 Days, Gest. Age ≤ 37 Weeks, and Birth Weight ≥ 1.5 kg (N = 1)**
Change from baseline on Day 10			
N	3	1	1
Mean (SD)	−1.3 (0.58)	−6.0	−5.0
Median	−1.0	−6.0	−5.0
Q1, Q3	−2.0, −1.0	−6.0, −6.0	−5.0, −5.0
Min, max	−2, −1	−6, −6	−5, −5
Change from baseline on last available assessment			
N	3	1	1
Mean (SD)	−1.3 (0.58)	−6.0	−5.0
Median	−1.0	−6.0	−5.0
Q1, Q3	−2.0, −1.0	−6.0, −6.0	−5.0, −5.0
Min, max	−2, −1	−6, −6	−5, −5

CSR = clinical study report; Gest. = gestational; max = maximum; min = minimum; PEWS = Pediatric Early Warning Score; Q1 = first quartile; Q3 = third quartile; RDV = remdesivir; SD = standard deviation
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: GS-US-540-5823 Final CSR, Table 15.9.2.2.4

The CHMP noted that all participants improved their PEWS score by at least one point by Day 10. In particular, the two participants from cohorts 6 and 7 improved significantly by 6 and 5 points respectively. For the two cohort 5 participants who remained in ordinal score 2 for the whole study, the PEWS score improved by one point.

SARS-CoV-2 variants

At baseline, the amino acid substitutions nsp12 P227L, nsp12 P323L, and nsp13 P77L were observed in the SARS-CoV-2 RNA from participants in Cohorts 5 to 7. The EC_{50} fold changes of nsp12 P227L and

nsp13 P77L were 1.11- and 0.53-fold, respectively, indicating similar susceptibility to RDV as the wild-type reference sequence.

At postbaseline, 1 of 4 participants with sequencing data at both baseline and postbaseline available had emergent substitutions in nsp12. The nsp12 V166V/L amino acid substitution emerged at Day 10 as a mixture with wild type in 1 participant who was treated with RDV for 5 days. This participant experienced an ordinal scale ≥ 2-point improvement at Day 10 and was released from the hospital on Day 13. The EC_{50} fold change was 1.85 for the nsp12 V166L substitution using the subgenomic replicon system, indicating similar susceptibility to RDV as the wild-type reference sequence.

The CHMP noted that, in one participant, an emergent substitution was identified postbaseline. The nsp12 V166V/L amino acid substitution was shown to have a similar susceptibility to RDV as the wild-type reference sequence.

2.4.2. Discussion on clinical efficacy

Study GS-US-540-5823 is 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. In cohorts 5 to 7, clinical efficacy was only assessed in participants who were hospitalised. This should be noted as the proposed indication extension includes paediatric patients (1.5 kg to <40 kg body weight) who do not require supplemental oxygen and who are at increased risk of progression to severe COVID-19 and are thus typically not hospitalised. The study was planned with 22 study centres in Italy, Spain, the United Kingdom, and the United States. Cohorts 5 to 7 from Study GS-US-540-5823 are included in this submission. 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. The additional secondary endpoints are related to efficacy and safety (Table 6).

In this study, dose selection of RDV to be evaluated in paediatric participants targeted similar exposures to those observed in adults. Dose selection for participants in Cohort 5 was informed by a physiologically based pharmacokinetic (PBPK) model developed to characterize the PK of RDV and the primary circulating nucleoside metabolite, GS-441524, in adults (SimCYP Version 17, Certara). For dose selection in Cohorts 6 and 7, a population pharmacokinetic (PopPK) model was used (with data from Cohorts 1 to 4 and Cohort 8 and 1 participant in Cohort 5) to predict paediatric patient exposures.

Of the 6 participants screened; 4 participants enrolled in Cohort 5, 1 participant in Cohort 6, and 1 participant in Cohort 7. One participant in Cohort 5 enrolled but did not receive treatment due to withdrawal of consent by the parents.

The median (Q1, Q3) duration of hospitalization prior to the first dose of RDV in Cohort 5 was 5 (1, 9) days, the participant in Cohort 6 was hospitalized for 1 day, and the participant in Cohort 7 was hospitalized for 3 days. The median (Q1, Q3) duration of symptoms prior to the first dose of RDV in Cohort 5 was 6 (2, 9) days, the participant in Cohort 6 had symptoms for 2 days, and the participant in Cohort 7 had symptoms for 9 days. At baseline, the only COVID-19–related disease manifestations observed in more than 1 participant were respiratory (4/5 participants). Three of 5 participants were on invasive mechanical ventilation (IMV), and 2 of 5 participants were on high-flow oxygen.

All participants had a baseline ordinal scale score of 2 or 3. Recovery was defined as an improvement from a baseline score of 2 through 5 to a score of 6 or 7 or an improvement from baseline score of 6 to a score of 7. For one participant in cohort 5, the score increased from 3 to 7. For all other participants in this cohort, no improvement was observed during the study. By Day 10, none of the participants in cohorts 6 or 7 had improved to a score of 6 or 7. However, both participants in cohort 6 or 7 improved

to a score of 7 at the time of the final assessment. The time to recovery was 13 days for the participant in cohort 6 and 19 days for the participant in cohort 7. The two participants from cohort 5 without improvement in the ordinal scale until the final assessment were still hospitalised at Day 30.

The reduction in viral load for study participants is shown by SARS-CoV-2 PCR results from day 2 to day 10. As noted by the MAH, not all planned samples were collected. It is not clear from the information provided why not all planned procedures were carried out and why the swab collection technique for SARS-CoV-2 RT-qPCR testing was not consistent on Day 1, 3, 5, 7 and 10. The comparability of viral load results between and within cohorts may have been greatly affected by the different sampling techniques used. However, the PCR data show a clear reduction in viral load.

Two of the five participants remained on invasive mechanical ventilation (IMV) without any improvement until the final assessment on Day 30, both from cohort 5. A third participant (cohort 7) started the study on IMV and was able to switch to low flow oxygen on Day 10. Two participants, one from cohort 5 and one from cohort 6, started on high flow oxygen and improved enough to be taken off supplemental oxygen on Days 8 and 10 respectively.

All participants improved their PEWS score by at least one point by day 10. In particular, the two participants from cohorts 6 and 7 improved significantly by 6 and 5 points respectively. For the two cohort 5 participants who remained in ordinal score 2 for the whole study, the PEWS score improved by one point.

Cohorts 5 to 7 did not collect data from paediatric participants who were not hospitalised. Comparison of the steady-state RDV AUC_{tau} of hospitalised paediatric participants with non-hospitalised adult participants from the Phase 3 studies (Figure 1) shows an overall trend towards higher RDV levels in paediatric participants. Further elaboration of the effect of intrinsic factors such as baseline oxygen or hospitalisation status of paediatric participants did not show a statistically significant effect on the PK of RDV. Due to the limited number of paediatric participants in cohorts 5 to 7, the effect of hospitalisation was further assessed using virtual populations of paediatric study cohorts. This analysis showed no clinically significant difference in RDV C_{max} and AUC_{tau} (within the 5^{th} and 95^{th} percentile bounds of observed exposures in adults with COVID-19 in Phase 3 studies), suggesting no significant effect of hospitalisation status on efficacy (Table 2).

Efficacy data and additional analyses

Using virtual populations of neonates and preterm neonates and infants, the overall range of PopPK model-simulated steady-state exposures (AUC_{tau} and C_{max}; C_{tau} for GS-445124 only) of RDV and its metabolites at the 2.5/1.25 mg/kg loading/maintenance dose were within the 5th and 95th percentiles of exposures in hospitalized adult participants with severe COVID-19 pneumonia on supplemental oxygen and non-hospitalized adult participants with COVID-19 at risk for disease progression and not on supplemental oxygen in the Phase 3 studies CO-US-540-5844 and GS-US-540-9012, respectively.

For a virtual population of infants weighing between 1.5 kg and less than 3 kg (not evaluated in Study GS-US-540-5823), the overall range of PopPK model-simulated steady-state exposures (AUC_{tau} and C_{max}; C_{tau} for GS-445124 only) of RDV and its metabolites at the 2.5/1.25 mg/kg loading/maintenance dose were within the 5th and 95th percentiles of exposures in hospitalized adult participants with severe COVID-19 pneumonia on supplemental oxygen and non-hospitalized adult participants with COVID-19 at risk for disease progression and not on supplemental oxygen in the Phase 3 studies CO-US-540-5844 and GS-US-540-9012, respectively.

In summary, according to the MAH these data supported the proposed clinical dosing regimen of IV RDV in the paediatric populations described in Table 12.

Table 12. Proposed RDV Dosage in Paediatric Patients Weighing at Least 1.5 kg

Pediatric Patient Population	RDV Loading Dose	RDV Maintenance Dose
Neonates less than 28 days of age weighing at least 1.5 kg	2.5 mg/kg on Day 1	1.25 mg/kg once daily from Day 2 for a total treatment duration of up to 10 days
Preterm neonates and infants less than 56 days of age weighing at least 1.5 kg		
Infants at least 28 days of age weighing between 1.5 kg to less than 3 kg		

RDV = remdesivir

The CHMP noted that the proposed dosing regimen was tested in a virtual population of neonates and preterm infants, and in a virtual population of infants weighing between 1.5 and less than 3 kg. The simulated steady-state parameters of RDV and its metabolites showed exposures within the 5th and 95th percentiles of known exposures in hospitalised adult patients with severe COVID-19 pneumonia on supplemental oxygen and in non-hospitalised adult patients with COVID-19 at risk of disease progression.

In addition, the extrapolation of adult efficacy and safety data to paediatric patients is based on matching paediatric and adult systemic exposures.

With regard to the extension of the indication to paediatric patients weighing 1.5 kg to <40 kg who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19, similarity of disease as an assumption allowing extrapolation from adults needed to be presented following the "Structured guidance on the use of extrapolation" published on the EMA website. The MAH was requested to:

- Review all relevant data to identify potential differences between characteristics of adults and paediatric patients (1.5 kg to <40 kg) of different age groups;

- Exploit existing evidence in the extrapolation concept including the comparability of risk factors and the risk of progression to severe disease status in adults and paediatric patients (1.5 kg to <40 kg) of different age groups;

- Discuss the applicability of risk factors for progression to severe COVID-19 as defined in GS-US-540-9012.

The provided review of data from the MAH on the similarity of disease characteristics between paediatric and adult patients indicates that although there are physiological differences (e.g. organ maturation, liver and kidney function, body size), no significant discrepancies have been identified in the characteristics of adults and paediatric patients of different age groups with regard to disease progression and clinical outcome. The characteristics of the symptoms and their intensity can vary between paediatric and adult patients. Certain comorbidities are unique, or more common in, children, which increases their risk for severe COVID-19 (e.g. prematurity, genetic diseases, congenital heart disease). In general, the severity of the disease tends to be less in children; however, the general characteristics of the disease and many risk factors for severe COVID-19 are similar in children and adults.

It could therefore be concluded that there is sufficient similarity between the disease characteristics, risk factors and the risk of severe progression for both paediatric and adult patients. The risk factors for progression to severe disease as defined in PINETREE (GS-US-540-9012) are consistent with those identified in the literature for paediatric and adult patients.

More data would however be needed to allow for dosing recommendations in the vulnerable neonate population.

2.4.3. Conclusions on the clinical efficacy

The efficacy data should be interpreted with caution as the study was conducted as a single arm study. The efficacy data are descriptive only. Viral load assessments show a reduction from baseline to day 10. However, the sampling technique was not consistent throughout the study and may have contributed to inconsistent results. The data on oxygen consumption and ventilation modality show that three of the five participants improved significantly and were off supplemental oxygen or on low flow oxygen by day 10. Two participants showed no improvement.

There is sufficient similarity between the disease characteristics, risk factors and the risk of severe progression for paediatric and adult patients. The risk factors for progression to severe disease as defined in PINETREE (GS-US-540-9012) are consistent with those identified in the literature for paediatric and adult patients.

More data in the neonate population would however be needed to allow for dosing recommendations.

2.5. Clinical safety

Introduction

In support of this application for extension of indications, the Applicant presented safety data from the following clinical study:

- **Study GS-US-540-5823**: Safety data from the final analysis of the Phase 2/3 Study GS-US-540-5823, including neonates less than 28 days of age and preterm neonates and infants less than 56 days of age in Cohorts 5 to 7, to include the treatment of COVID-19 in paediatric patients from birth weighing at least 1.5 kg.

Safety data from Cohorts 1 to 4 and Cohort 8 in Study GS-US-540-5823 were provided in previous submissions to support Veklury's current indication for the treatment of COVID-19.

Patient exposure

Participants were to receive up to 10 doses of study drug; participants who demonstrated clinical improvement could be considered for a shorter treatment period of fewer than 10 days.

Table 13. GS-US-540-5823: Exposure to Study Drug (Safety Analysis Set)

	Cohort 5: 14 to < 28 Days, Gest. Age > 37 Weeks, and Weight ≥ 2.5 kg (N = 3)	Cohort 6: < 14 Days, Gest. Age > 37 Weeks, and Birth Weight ≥ 2.5 kg (N = 1)	Cohort 7: < 56 Days, Gest. Age ≤ 37 Weeks, and Birth Weight ≥ 1.5 kg (N = 1)
Number of doses received			
N	3	1	1
Mean (SD)	9 (1.2)	5	10
Median	10	5	10
Q1, Q3	8, 10	5, 5	10, 10
Min, max	8, 10	5, 5	10, 10
Number of doses received			
5 doses	0	1 (100.0%)	0
8 doses	1 (33.3%)	0	0
10 doses	2 (66.7%)	0	1 (100.0%)

CSR = clinical study report; Gest. = gestational; max = maximum; min = minimum; Q1 = first quartile; Q3 = third quartile; SD = standard deviation
Source: GS-US-540-5823 Final CSR, Table 15.11.1.1

The CHMP noted that three of the five participants received the maximum of 10 planned doses of RDV. In cohorts 5 and 6, one participant was stopped after eight and five doses, respectively, due to clinical improvement.

Adverse events

Common adverse events in patients treated with COVID-19 included nausea, headache and rash. In addition, increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and prolongation of prothrombin time or IRN were observed in clinical trials.

Summary of Adverse Events:

There were 3 participants who had at least 1 AE: 2 participants in Cohort 5, and the participant in Cohort 6. No AEs were reported in more than 1 participant. One participant in Cohort 5 experienced 5 Grade 4 AEs, all of which were serious adverse events (SAEs). The participant in Cohort 6 also had an SAE. The severity of AEs was graded using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Paediatric Adverse Events, Version 2.1 dated July 2017.

There were no AEs considered related to study drug, no AEs leading to premature study drug discontinuation, and no treatment-emergent deaths reported in Cohorts 5 to 7.

Table 14. GS-US-540-5823: Overall Summary of Adverse Events (Safety Analysis Set)

	Cohort 5: 14 to < 28 Days, Gest. Age > 37 Weeks, and Weight ≥ 2.5 kg (N = 3)	Cohort 6: < 14 Days, Gest. Age > 37 Weeks, and Birth Weight ≥ 2.5 kg (N = 1)	Cohort 7: < 56 Days, Gest. Age ≤ 37 Weeks, and Birth Weight ≥ 1.5 kg (N = 1)
AE	2 (66.7%)	1 (100.0%)	0
Grade 3 or higher AE	1 (33.3%)	0	0
Study drug–related AE	0	0	0
Study drug–related Grade 3 or higher AE	0	0	0
SAE	1 (33.3%)	1 (100.0%)	0
Study drug–related SAE	0	0	0
AE leading to premature study drug discontinuation	0	0	0
Treatment-emergent death	0	0	0

AE = adverse event; CSR = clinical study report; DAIDS = Division of AIDS; Gest. = gestational; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event
AEs were coded using MedDRA Version 26.0.
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).
Source: GS-US-540-5823 Final CSR, Table 15.11.2.1.1

Table 15 shows the adverse events recorded for cohorts 5 to 7 using MedDRA version 26.0.

Table 15. GS-US-540-5823: Adverse Events Reported in Participants in Cohorts 5 to 7 (Safety Analysis Set)

	Cohort 5: 14 to < 28 Days, Gest. Age > 37 Weeks, and Weight ≥ 2.5 kg (N = 3)	Cohort 6: < 14 Days, Gest. Age > 37 Weeks, and Birth Weight ≥ 2.5 kg (N = 1)	Cohort 7: < 56 Days, Gest. Age ≤ 37 Weeks, and Birth Weight ≥ 1.5 kg (N = 1)
Number of participants experiencing any AE	2 (66.7%)	1 (100.0%)	0
Number of participants experiencing any AE by PT			
Acidosis	1 (33.3%)	0	0
Anaemia	1 (33.3%)	0	0
Bacterial disease carrier	1 (33.3%)	0	0
Cardiopulmonary failure	1 (33.3%)	0	0
Chest wall haematoma	1 (33.3%)	0	0
Conjunctivitis	1 (33.3%)	0	0
Hypertension	1 (33.3%)	0	0
Infusion-site extravasation	1 (33.3%)	0	0
Pneumothorax	1 (33.3%)	0	0
Seizure	1 (33.3%)	0	0
Urinary tract infection	0	1 (100.0%)	0

AE = adverse event; CSR = clinical study report; Gest. = gestational; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term
AEs were coded using MedDRA Version 26.0.
PTs were presented by descending order of the total frequencies.
Multiple AEs were counted only once per participant per PT.
Treatment-emergent adverse events are (1) any AEs that begin on or after the date of first dose of study drug up to the date of last dose of study drug plus 30 days, or (2) any AEs leading to premature discontinuation of study drug.
Source: GS-US-540-5823 Final CSR, Table 15.11.2.1.4

Serious adverse events/deaths/other significant events

There was 1 participant in Cohort 5 with a medical history of respiratory failure who experienced 5 Grade 4 AEs during the study (cardiopulmonary failure [2 events], acidosis, pneumothorax, and seizure). All 5 events were SAEs. There were no Grade 3 AEs. Table 16summarises the SAEs recorded during the study.

There were no AEs considered related to study drug reported in Cohorts 5 to 7. There were no treatment-emergent deaths reported in Cohorts 5 to 7 during the study. There were no participants in Cohorts 5 to 7 who discontinued study drug prematurely due to an AE.

Table 16. GS-US-540-5823: Serious Adverse Events (Safety Analysis Set)

	Cohort 5: 14 to < 28 Days, Gest. Age > 37 Weeks, and Weight ≥ 2.5 kg (N = 3)	Cohort 6: < 14 Days, Gest. Age > 37 Weeks, and Birth Weight ≥ 2.5 kg (N = 1)	Cohort 7: < 56 Days, Gest. Age ≤ 37 Weeks, and Birth Weight ≥ 1.5 kg (N = 1)
Number of participants experiencing any SAE	1 (33.3%)	1 (100.0%)	0
Number of participants experiencing any SAE by PT			
Acidosis	1 (33.3%)	0	0
Cardiopulmonary failure	1 (33.3%)	0	0
Pneumothorax	1 (33.3%)	0	0
Seizure	1 (33.3%)	0	0
Urinary tract infection	0	1 (100.0%)	0

AE = adverse event; CSR = clinical study report; Gest. = gestational; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SAE = serious adverse event
AEs were coded using MedDRA Version 26.0.
Treatment-emergent adverse events are (1) any AEs that begin on or after the date of first dose of study drug up to the date of last dose of study drug plus 30 days, or (2) any AEs leading to premature discontinuation of study drug.
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 Final CSR, Table 15.11.4.2

The CHMP noted that two out of three participants in cohort 5 had a baseline ordinal scale score of 2 (both with oxygen support of invasive mechanical ventilation) and all were treated in an intensive care unit. From this cohort, one participant experienced 5 SAEs (cardiopulmonary failure [2 events], acidosis, pneumothorax, and seizure). Acidosis is a known adverse event that can occur during intensive care. The other recorded SAEs of cardiopulmonary failure, pneumothorax and seizure could be related to the underlying COVID-19 disease. Of note, both participants with invasive mechanical ventilation had pulmonary infiltrates at screening. The recorded SAEs were not considered by the investigators to be related to the study drug. The participant in cohort 6 experienced a urinary tract infection that was not considered to be related to the study drug. The number and type of adverse events observed in the study are not higher or significantly different from those reported in previous RDV studies in adult and adolescent patients with underlying COVID-19 disease and are consistent with the known safety profile of RDV. Overall, there were no adverse events recorded during study participation that were considered to be related to the study drug. No new safety signals were identified.

Laboratory findings

All participants had a graded laboratory abnormality. Grade 3 and 4 laboratory abnormalities only occurred in Cohort 5 (Table 17). One participant had Grade 4 increased aPTT at Day 8 which was still Grade 4 at the time of the last coagulation assessment (Day 10) and had a Grade 1 increased direct bilirubin concentration (0.5 mg/dL) at Day 10 that met criteria for Grade 3 (0.5 mg/dL) at Day 30 due to the participant reaching > 28 days of age.

One participant had Grade 3 increased creatinine at Day 2 that decreased to Grade 2 at Day 5. One participant had graded laboratory abnormalities reported due to sample collection error (haemolysis occurred) that were Grade 4 (increased aPTT, increased prothrombin time, and increased prothrombin/INR on Day 10) and Grade 3 (hyperkalaemia on Day 5). This participant also had Grade 2 hyperkalaemia at baseline/Day 1.

Table 17. GS-US-540-5823: Grade 3 or 4 Laboratory Abnormalities (Safety Analysis Set)

	Cohort 5: 14 to < 28 Days, Gest. Age > 37 Weeks, and Weight ≥ 2.5 kg (N = 3)	Cohort 6: < 14 Days, Gest. Age > 37 Weeks, and Birth Weight ≥ 2.5 kg (N = 1)	Cohort 7: < 56 Days, Gest. Age ≤ 37 Weeks, and Birth Weight ≥ 1.5 kg (N = 1)
Maximum treatment-emergent toxicity grade	3	1	1
Grade 3	1 (33.3%)	0	0
Grade 4	2 (66.7%)	0	0
Grade 3 or 4	3 (100.0%)	0	0
Chemistry			
Creatinine (increased)	3	1	1
Grade 3	1 (33.3%)	0	0
Direct bilirubin (increased)	2	1	1
Grade 3	1 (50.0%)	0	0
Serum potassium (hyperkalemia)	3	1	1
Grade 3	1 (33.3%)	0	0
Coagulation			
Prothrombin time (increased)	2	0	1
Grade 4	1 (50.0%)	0	0
aPTT (increased)	3	1	1
Grade 4	2 (66.7%)	0	0
Prothrombin/INR (increased)	3	1	1
Grade 4	1 (33.3%)	0	0

aPTT = activated partial thromboplastin time; DAIDS = Division of AIDS; Gest. = gestational; INR = international normalized ratio
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.
Source: GS-US-540-5823 Final CSR, Table 15.11.6.4.2

Overall, the CHMP considered that laboratory findings were consistent with the known safety profile in adult and adolescent patients with underlying COVID-19 disease. No new safety signals were identified.

Discontinuation due to adverse events

No participant discontinued study participation due to adverse events.

2.5.1. Discussion on clinical safety

Overall, across Cohorts 5 to 7, no new safety concerns were identified in neonates less than 28 days of age weighing at least 1.5 kg and preterm neonates and infants less than 56 days of age weighing at least 1.5 kg who were administered RDV for up to 10 days. No adverse events were considered related

to the study drug. There were no treatment-emergent deaths reported, and there were no participants who discontinued study drug prematurely due to an AE. Blood pressure, heart rate, and respiratory rate were generally stable during the study. Most participants (4 of 5 participants) received at least 1 concomitant medication other than RDV for the treatment of COVID-19, including immune modulator medication, anti-inflammatory medication, and experimental antiviral medication.

The exposure results for the patient in Cohort 7 have been addressed in the discussion of the PK data.

2.5.2. Conclusions on clinical safety

Overall, across Cohorts 5 to 7, no new safety concerns were identified in neonates less than 28 days of age weighing at least 1.5 kg and preterm neonates and infants less than 56 days of age weighing at least 1.5 kg who were administered RDV for up to 10 days. The laboratory findings are consistent with the known safety profile in adult and adolescent patients with underlying COVID-19 disease.

No new safety signals were identified, although it has to be considered that the sample size is limited.

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 initially submitted an updated RMP version (version 8.1) with this application at its start in December 2023. The RMP was updated with the final data from the Study GS-US-540-5823 which evaluated the safety, tolerability, PK and efficacy of remdesivir in participants from birth to <18 years of age with COVID-19 (results for cohorts 5-7 are parts of this submission).

The initially proposed updates to the RMP were in the context of the application originally proposing to extend the Veklury indications to paediatric population weighing at least 1.5 kg with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment) and paediatric population weighing at least 1.5 kg who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19. The following parts of the RMP were updated: Part I, Part II – Epidemiology, Clinical study exposure, Populations not studied in clinical studies, Post-authorization exposure, Part III, Part VI and annexes.

Subsequent updated versions, were submitted during the course of the assessment, up to RMP version 8.4, which reflected the final recommendations.

Notably, RMP version 8.3 included data from the drug-drug interaction studies (US-540-9013, GS-US-611-6409, GS-US-540-6587) and QT/QTc study (GS-US-540-9053). In addition, clinical exposure and pregnancy FUQs were also updated within this RMP version.

RMP version 8.4 was provided to adapt the RMP to the final CHMP recommendation whereby the extension of indication was granted only to paediatric patients at least 4 weeks of age and weighing at least 3 kg who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19). RMP Parts I and VI were adapted accordingly.

The (main) proposed RMP changes were the following (updates are summarised or shown as track changes, when relevant):

Safety concerns

Epidemiology of the indications and target population

The incidence of COVID-19 infection in neonates is lower than adult and older paediatric populations. This is possibly related to maternal antibodies that offer protection during the first few months of life {Carsetti 2020}. In the US, incidence rates ranged from 63.1 to 91.1 per 100,000 births {Wallace 2023},{Devin 2022}. Rates were similarly low in the EU, ranging from 56 to 153 per 100,000 births {Gale 2021, Goulding 2023}. Vertical transmission from mother to baby also appears to be low: under 1% to 3% of babies born to women with confirmed infection at time of birth had a neonatal infection {Hamidi 2022},{Norman 2021},{Goulding 2023},{Devin 2022}.

Specific complications among neonates with COVID-19

As with paediatric cases of COVID-19, the data from large population-based studies suggest that cases in neonates are generally mild and have an overall good prognosis {Gale 2021},{Devin 2022},{Goulding 2023}. In a US study using encounter data across all care settings, only 7.7% of neonates diagnosed with COVID-19 had severe disease {Devin 2022}. Yet, in samples of neonates either receiving in hospital ward or neonatal intensive care, the fraction with severe disease was much higher at 26 to 42% {Gale 2021},{Akin 2022}, and the proportion requiring either respiratory support or supplemental oxygen varied from 13% to 33% {Scarsi 2021}. Admission to intensive care units ranged from 4.4% to 11%. {Devin 2022},{Gale 2021},{Goulding 2023}. However, these requirements may have been necessitated by other conditions such as prematurity and may not have been caused by COVID-19 infection.

Neonates with severe COVID-19 are more likely to have been born premature and to require respiratory support, receive a higher number of medications, and have longer overall length of stay (LOS) {Devin 2022}. They also have a higher incidence of comorbidities including cardiac abnormalities which may impact disease progression {Devin 2022}.

Although the majority of COVID-19 infections are either asymptomatic or mild, there is still risk of cardiac involvement including myocarditis. In neonates testing positive for SARS-CoV-2 who received care within neonatal intensive care units (NICUs), myocarditis was the most common major complication affecting around 6% of cases {Akin 2022}.

Multi-system inflammation syndrome in children (MIS-C) appears to be a rare complication in neonates, as in with children. In a study using healthcare encounter data from over 120 US health systems, only one suspected MIS-C case out of 918 positive SARS-CoV-2 diagnoses was identified {Devin 2022}.

Neonatal death from COVID-19 is possible although very rare. In the US {Devin 2022}, {Wallace 2023},{Hamidi 2022} and EU {Goulding 2023},{Gale 2021} mortality rates (all causes) ranging from 0% to 2% were reported. Devin and colleagues noted that one infant with suspected MIS-C died out of a total of 918 positive cases, and in Gale's study of 66 neonates with confirmed COVID-19 infection, one infant died due to a cause unrelated to COVID-19.

Preterm delivery is a leading cause of neonatal morbidity {Platt 2014}. However, studies comparing outcomes between preterm infants born to mothers testing positive for SARS-CoV-2 versus those testing negative did not find any significant differences with regards to development of respiratory distress syndrome, use of mechanical ventilation, duration of hospitalization, or mortality between groups {Yasa 2023},{Ciplak 2023},{Adams 2022}. In some studies {Yasa 2023},{Adams 2022}, a limited number of preterm infants with SARS-CoV-2 positive mothers were identified which may have

impacted statistical power.

The PRAC noted that the MAH amended information regarding epidemiology of COVID-19 in neonates and provided information regarding complications in this patient population, which was acknowledged

Nonclinical part of the safety specification

Conclusions from the drug-drug interaction studies (GS-US-611-6409, GS-US-540-6587) were included, which was endorsed.

Clinical trial exposure

Table 18: Number of Participants in Gilead-Sponsored Clinical Studies and Compassionate Use Exposure

Duration of Exposure (Days)	Persons (n)	Person Days
Healthy Volunteer Participants		
GS-US-399-1812	78	78
GS-US-399-1954	16	165
GS-US-399-4231	8	8
GS-US-399-5505	29	237
Total	**131**	**488**
Hospitalized COVID-19 Participants		
IN-US-540-5755	240	2080
GS-US-540-5773	4838	35406
GS-US-540-5574	887	5261
GS-US-540-5823	58	351
GS-US-540-5912	163	747
Total	**6186**	**43,845**
COVID-19 Participants not requiring Supplemental Oxygen		
GS-US-540-9012	279	829
Total	**279**	**829**
Other Volunteer Participants without COVID-19 infection		
GS-US-540-9014	32	32
GS-US-540-9015	75	81
GS-US-540-6587	14	140
GS-US-540-9013	9	26
GS-US-540-9053	60	60
GS-US-611-6409	39	39
Total	**229**	**378**
Grand Total	**6825**	**45,540**

The PRAC noted that the MAH updated tables in RMP Part II, Module SIII. Numbers of participants of the CARAVAN study (GS-US-540_5823), DDI studies (GS-US-540-9013, GS-US-540-6409, GS-US-540-6587) and QT/QTc study (GS-US-540-9053) were included. Other tables in this RMP section were also acceptably updated.

Populations not studied in clinical trials

Table 19.Exposure of Special Populations Included or not in Clinical Development Programs and Compassionate Use Program

Type of special population	Exposure	Considered to be Missing Information
Pediatric patients	As of 04 August 2023, 77 pediatric patients were included in the compassionate use program, 21 were included in Study GS-US-540-5773 and GS-US-540-5774, 3 were included in Study GS-US-540-9012, 58 were included in GS-US-540-5823	No Rationale: The safety profile in adolescents aged 12 to < 18 years is not anticipated to differ from that in adults. Pediatric patients of at least 4 weeks of age and >3 kg are included in the indication.

Identified and potential risks

The MAH stated that no new safety concerns have been identified or reclassified since the submission of the last RMP.

The PRAC noted that no new safety concern had been identified after reviewing the safety data from 5 paediatric participants included in cohorts 5-7 of the CARAVAN study.

AEs were observed in 3 from 5 participants and SAEs in 2 of them. None of the AEs/SAEs which occurred during the study was considered related to remdesivir and no discontinuation of the study medication was issued in the study. The SAEs were Grade 2 urinary infection in the participant in cohort 6 and five Grade 4 AEs in one of the participants from cohort 5. The participant was a 15-days old boy with baseline weight of 2.8 kg who had a history of respiratory failure and was on IMV at baseline. He experienced cardiopulmonary failure on day 1. The SAEs subsided until day 4, when the participant experienced seizures which have been controlled by application of phenobarbital since day 4. His hospital stay was complicated by pneumothorax, acidosis and recurrence of cardiopulmonary failure at day 7. This led to initiation of ECMO in the patient. None of these SAEs were considered related to RDV, severe COVID-19 and invasive treatment of the patient provide alternative explanation for occurrence of these SAEs.

No new safety concern has been identified after reviewing the laboratory data from 5 paediatric participants.

No update to the RMP PART II Modules SVII and SVIII is considered necessary based on information provided within the dossier in support of this application.

Table 20.Summary of Safety Concerns

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

Considering the very limited number of neonates (n= 4) and preterm neonates/infants (n=1) included in the study and very limited data regarding pharmacokinetics of the excipient sulfobutylether β-cyclodextrin sodium, the MAH was asked to summarize and discuss safety data from this patient population in future PSURs. The MAH agreed with the proposal. The proposal to extend the Veklury´s indications to neonates (i.e. paediatric patients younger than 4 weeks of age and weighing less than 3 kg) was withdrawn by the MAH.

Pharmacovigilance plan

Monitoring of data on treatment failure due to emerging variants

As requested by Pharmacovigilance Risk Assessment Committee (PRAC), data on treatment failure due to emerging variants will be monitored regardless of COVID-19 Public Health Emergency of International Concern status, from all available data sources, including but not limited to:

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

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

Other Forms of Routine Pharmacovigilance Activities

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

I.1. Additional Pharmacovigilance Activities

Table 21.Ongoing and Planned Additional Pharmacovigilance Activities

Title	Rationale and Objectives	Design and Populations	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

Amendment of the pharmacovigilance plan was requested in PSUSA/00010840/202305, when the MAH was asked to continue monitoring of the data on treatment failure due to emerging variants of SARS-CoV-2 regardless of COVID-19 pandemic status. The RMP was updated adequately.

Risk minimisation measures

Summary Table of Pharmacovigilance and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important identified risk(s)		
None		
Important potential risk(s)		
None		
Missing information		
Safety in pregnant women	Routine risk minimization measures: SmPC section 4.6 PL section 2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Post-marketing pregnancy report form Post-marketing pregnancy outcome report form Additional pharmacovigilance activities: None

RMP Annexes

The pregnancy and pregnancy outcome FUQs were renamed and slightly reorganized.

The changes made to the Pregnancy report and Pregnancy outcome report forms were noted and acknowledged by the PRAC without additional comments, as the content of the questionnaires remains very similar.

Overall conclusion on the RMP

The PRAC considered that the risk management plan version 8.4 was acceptable.

During the course of this procedure, version 9.0 of the RMP was approved as part of another variation that concerned only the RMP (EMEA/H/C/005622/II/0062), as part of which a Cat. 3 additional pharmacovigilance activity (study CO-US-540-6127 – Covid Pregnancy Registry) was removed.

Therefore, the final RMP version endorsed by the CHMP with this procedure was the Risk Management Plan version 10, consolidating the changes approved in v8.4 with v9.0.

2.7. Update of the Product information

As a result of this group of variations, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 of the SmPC were proposed to be amended, to include the proposed new therapeutic indication, update the posology for adult and paediatric patients, add efficacy information from the GS-US-540-5823 study and to update pharmacokinetic parameters. The MAH initial proposals for the extended indications were:

Veklury is indicated for the treatment of coronavirus disease 2019 (COVID-19) in **adults and paediatric patients (weighing at least 1.5 kg)**:

- ~~adults and paediatric patients (at least 4 weeks of age and weighing at least 3 kg)~~ with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment)
- ~~adults and paediatric patients (weighing at least 40 kg)~~ who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19

The CHMP however only partly supported the initially proposed extensions. The MAH, in line with the CHMP position, withdrew the type II variation to extend the indication for use in paediatric patients weighing at least 1.5 kg with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment) and agreed to the CHMP-recommended wording of the indication.

The other proposed extension of indications "*To extend the indication for use in paediatric patients weighing at least 1.5 kg who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19*" was considered acceptable, but with the age cut-off and the weight threshold consistent with the ones previously approved for with pneumonia requiring supplemental oxygen (4 weeks of age and weighing at least 3 kg). The following extension of indication was recommended:

> Veklury is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults and paediatric patients (**at least 4 weeks of age and weighing at least 3 kg**):
>
> - with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment)
> - who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.

The MAH agreed with the CHMP recommendations, and provided product information amended accordingly.

2.7.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Veklury (remdesivir) was included in the additional monitoring list at the time of this procedure.

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 cases, COVID-19 presents as a mild-to-moderately severe, self-limited acute respiratory illness with fever, cough, and shortness of breath. Although children with COVID-19 frequently have mild or moderate symptoms, COVID-19 can result in severe disease. Children < 1 year old and children with underlying disease are at a higher risk of developing COVID-19–related pneumonia. The cumulative incidence of COVID-19–associated hospitalizations in children aged < 18 years from 01 March 2020 to 17 June 2023 was 202 per 100,000 at Coronavirus Disease 2019-Associated Hospitalization Surveillance Network sites in the US. In Europe, the proportion of weekly reports of cases of COVID-19 infection in children was stable for the period from 17 July 2023 to 23 July 2023. Overall hospital admission rates were also stable over the same period. These findings are consistent with the availability of vaccines for adults and children. 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 children to severe respiratory disease. 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. Prematurity has been identified as a risk factor for severe disease in children under 2 years old.

3.1.2. Available therapies and unmet medical need

Authorised COVID-19 treatments for children younger than 12 years of age consist only of remdesivir (Veklury), which is currently approved for children from at least 4 weeks of age and weighing at least 3 kg, with pneumonia requiring supplemental oxygen.

For adolescents aged 12 years and older and weighing at least 40 kg following treatments are available (EMA; Authorised COVID-19 treatments):

- (tixagevimab and cilgavimab); used to prevent COVID-19 in adults and adolescents and to treat COVID-19 in adults and adolescents who do not require supplemental oxygen and who are at increased risk of the disease becoming severe.
- (casirivimab and imdevimab); for treating COVID-19 in adults and adolescents who do not require supplemental oxygen and who are at increased risk of their disease becoming severe
- (sotrovimab); for treating COVID-19 in adults and adolescents who do not require supplemental oxygen and who are at increased risk of the disease becoming severe.

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.

3.1.3. Main clinical study

Study GS-US-540-5823 was a single-arm, open-label study where pharmacokinetics, efficacy and safety of remdesivir in paediatric patients from birth to < 18 years of age with COVID-19 was assessed. The study was planned with 22 study centres in Italy, Spain, the United Kingdom, and the United States.

This assessment focuses on data from Cohorts 5 to 7 of Study GS-US-540-5823 to support the proposed extension of indication.

3.2. Favourable effects

Efficacy endpoints were secondary and descriptively analysed and therefore these should be interpreted with caution.

The analysis population included 5 patients, who were included in three different age cohorts:

- Cohort 5: ≥ 14 days to < 28 days of age, gestational age > 37 weeks, and weight at screening ≥ 2.5 kg; 3 participants
- Cohort 6: 0 days to < 14 days of age, gestational age > 37 weeks, and birth weight ≥ 2.5 kg; 1 participant
- Cohort 7: 0 days to < 56 days of age, gestational age ≤ 37 weeks, and birth weight ≥ 1.5 kg; 1 participant

Based on the data provided, three of the five patients with a baseline ordinal scale score of two or three had an improvement of ≥ 2 points during study participation. Time to recovery, defined as an improvement from a baseline score of 2 to 5 to a score of 6 or 7, or an improvement from a baseline score of 6 to a score of 7, ranged from 9 days (1 participant in cohort 5) to 19 days (1 participant in cohort 7).

Confirmed negative SARS-CoV-2 PCR results on Day 2 through Day 10 were reported for all 5 participants.

Two of the 5 participants (1 each in Cohorts 5 and 6) were on high-flow oxygen from baseline to Day 7 and Day 5, respectively. Both participants were off oxygen support and breathing room air on Day 8 and Day 10 prior to being discharged from hospital on Day 9 and Day 13, respectively. The remaining 3 participants (2 in Cohort 5 and 1 in Cohort 7) were on IMV at baseline. The participant in Cohort 7 was switched to high-flow oxygen from Day 6 to Day 9 and then low-flow oxygen on Day 10. The participant was discharged from hospital on Day 19. The other 2 participants in Cohort 5 were on IMV from baseline until the last available assessment and were still hospitalized at Day 30.

The PEWS total scores at baseline in Cohort 5 were 2 (33.3%; 1/3 participants), and 7 (66.7%; 2/3 participants). The participant in Cohort 6 had a baseline score of 6, and the participant in Cohort 7 had a baseline score of 6. By Day 10, all 5 participants had reductions in PEWS total score (indicating improvement): in Cohort 5 there was a 2-point decrease in 1 participant, and a 1-point decrease in 2 participants. The participant in Cohort 6 had a decrease of 6 points, and the participant in Cohort 7 had a decrease of 5 points. The same results were observed at the time of last assessment.

The provided review of data from the MAH on the similarity of disease characteristics between paediatric and adult patients indicates that although there are physiological differences (e.g. organ maturation, liver and kidney function, body size), no significant discrepancies have been identified in the characteristics of adults and paediatric patients of different age groups with regard to disease progression and clinical outcome. The characteristics of the symptoms and their intensity can vary between paediatric and adult patients. Certain comorbidities are unique, or more common in children, which increases their risk for severe COVID-19 (e.g. prematurity, genetic diseases, congenital heart disease). Risk factors for severe disease in the later Omicron era in the adult population include e.g. older age, immunocompromised status, haematological malignancy, diabetes, kidney disorders, coronary artery disease, chronic heart failure or cardiomyopathy, obesity, and multimorbidity. For paediatric patients, risk factors include e.g. prematurity, cardiovascular disease and circulatory congenital abnormalities, diabetes, obesity and neurological disorders. As per US CDC "[…] like adults, children and teens with obesity, diabetes, asthma or chronic disease, sickle cell disease or who are immunocompromised can also be at increased risk for getting very sick from COVID-19". As discussed by the MAH, COVID-19-associated hospitalisation rates increased rapidly in accordance with increased Omicron circulation in infants and children aged 0-4 years, a group not yet eligible for vaccination, resulting in hospitalisation rates approximately five times higher than during the period of the Delta virus variant. Data provided by the MAH show that infants aged <6 months are the second largest demographic group hospitalised after the elderly aged >75 years, accounting for 44% of hospitalisations during the Omicron peak. Of those < 6 months, approximately 15% were identified as positive for COVID-19. Certain comorbidities are unique or more common to children that place them at higher risk for severe COVID-19 (e.g. prematurity, genetic diseases, congenital heart disease); however, many risk factors for severe COVID-19 are shared between children and adults. The risk factors for progression to severe COVID-19 as defined in PINETREE (GS-US-540-9012) appear to be consistent with those identified in the literature for both paediatric and adult patients.

The impact of new virus variants on the efficacy of RDV treatment in both paediatric and adult patients was discussed by the MAH. The dominant SARS-CoV-2 variant of concern as of 2022 remains Omicron, which accounts for >98.8% of variants sequenced globally (as tracked by GISAID). With regard to the efficacy of RDV against new virus variants, the MAH described that the majority of amino acid substitutions observed in SARS-CoV-2 variants occur in the envelope glycoprotein (spike), while the SARS-CoV-2 RdRp and the target of RDV are highly conserved. However, few amino acid changes in RdRp have been observed in circulating SARS-CoV-2 variants. The data presented do not indicate a lack of efficacy of RDV against these tested variants.

Pharmacokinetics

The developed PopPK model based on adult and paediatric data accounted for weight based changes and included maturation functions to account for changes in the paediatric population from birth to adult age. Overall, diagnostic plots are considered acceptable and precision of parameter estimates overall was in an acceptable range. Moreover, the results of the bootstrap were found to be consistent with the final PopPK estimates for the final models. Simulations using the final PopPK model were performed for neonate cohorts of interest generated from relevant growth charts (Adults and Cohorts 1 to 3 and 8 from the NHANES growth chart; Cohorts 4 to 6 from the WHO growth chart; and Cohort 7

from the Fenton Preterm growth chart) following the dosing regimens per protocol. The results of these simulations showed similar exposures in the virtual Cohorts 5 to 7 with the 2.5 mg/kg loading dose and the 1.25 mg/kg once-daily maintenance dose administered as IV infusion over 0.5 hours with the adult COVID-19 patient exposures.

3.3. Uncertainties and limitations about favourable effects

Due to the single-arm design of GS-US-540-5823, the lack of a control arm and the fact that only descriptive efficacy data were presented, efficacy data are of limited value. In addition, the total number of five participants in cohorts 5, 6 and 7 is rather small and the interpretation of individual data points and the efficacy data in general should be considered with caution. Overall, no firm conclusion can be drawn regarding efficacy in the intended paediatric indication.

The adequacy of the doses for neonates (cohorts 5, 6 and 7) was questioned. With the doses initially proposed by the popPK model and investigated in the paediatric study (GS-US-540-5823), the observed data in the neonate cohorts showed that exposure was higher than in adults and older paediatric patients, especially for the most relevant compound GS-441524. The extrapolation approach was aimed at defining doses that lead to same exposures compared to adults and older paediatric patients. Since this aim was not achieved with the doses proposed by the popPK model, the model does not yet adequately describe the PK in the neonate cohort but needs to be refined to better align with the observed data. It is recognized that a dose reduction to half (2.5 mg/1.25 mg) has already been proposed for the term neonates 2-4 weeks old (C5) by the company. These new doses needed to be justified with the refined model. Subsequently, for cohorts 6 and 7 new doses also needed to be defined according to the refined model.

The need for refinement of the popPK model might especially concern the maturation of the elimination, but also other factors (e.g. total body water, body composition (adipose tissue portion), specific enzyme functions) might need to be considered. Subsequently, sensitivity analyses with respect to dose selection should be conducted and VPCs conducted for the refined model focussing on the age and weight ranges impacted by the current variation also including the specific age range preterm population. Additionally, the proposed dosing for subjects above 28 days is questioned. This dosing should be discussed and justified and supported by simulations in the relevant age cohorts, i.e. simulations for subjects 29-56 days weighing 1.5-2.9 kg and simulations for subjects 29-56 days weighing 3+ kg. The dose proportionality is demonstrated between 3 to 225 mg, therefore patients weighing 1.5 kg and treated with 1.25 mg/kg, should take 1.88 mg (rounded to 2 mg) that is outside the range of dose proportionality. This implies that for doses below 3 mg, the behaviour of the exposure is unknown hampering the possibility to make predictions on the exposure. This was discussed by the MAH and the result was as follows:

The available popPK models do not adequately describe the PK in the neonate cohorts. Therefore, no dosing recommendations can be given to support exposure matching. It is considered that more data in the neonate populations would be needed to inform the model and subsequently allow for dosing recommendations in this vulnerable population. However, no new data have been provided, so that high uncertainties remain in PK, especially in clearance, for the neonatal groups, so that dosing recommendations could not be supported by the CHMP based on the existing models. Due to this lack of a reliable model to characterise PK from birth onwards, robust enough to allow simulations for the youngest patient population, the CHMP only supported a part of the initially proposed extensions of indications.

In line with the CHMP position, the MAH withdrew the type II variation application to extend the indication for Veklury to use in paediatric patients weighing at least 1.5 kg with pneumonia requiring supplemental

oxygen and agreed to the CHMP-recommended wording of the indication, thus addressing the uncertainty.

As discussed by the MAH, risk factors for progression to severe COVID-19 disease in the later Omicron era in the paediatric and adult populations are limited by the number of comparative analyses assessing risk in the context of the Omicron virus variant. The available data focus on American, Asian and Middle Eastern populations.

3.4. Unfavourable effects

In total, five paediatric participants received up to ten doses of RDV during the GS-US-540-5823 trial (cohorts 5, 6 and 7). In general, RDV was well tolerated and no adverse events were considered to be related to the study drug. No treatment-emergent deaths were reported and there were no participants who discontinued treatment prematurely due to an AE.

No new safety concerns were identified in neonates less than 28 days of age weighing at least 1.5 kg and in preterm neonates and infants less than 56 days of age weighing at least 1.5 kg.

3.5. Uncertainties and limitations about unfavourable effects

The safety data from only five participants from different cohorts were considered limited to draw conclusions on the safety profile of RDV in this patient population. Overall, the reported results are consistent with the known safety profile of RDV in adult and adolescent patients with underlying COVID-19 disease.

In the cohorts 5 to 7 only hospitalised participants were assessed. As the PK data for RDV showed no clinically significant differences between hospitalised and non-hospitalised adult participants and the data from a virtual paediatric patient population, the clinical safety of this likely healthier paediatric population should not be of concern. This is further supported by the fact that the duration of treatment for this patient population is only three days, compared to 5 to 10 days for paediatric patients with pneumonia and requirement of supplemental oxygen.

The available popPK models do not adequately describe the PK in the neonate cohorts. The available very limited data (cohort 5 n=3, cohort 6 n=1 and cohort 7 n=1) give indications of higher exposure compared to adults and older paediatric age cohorts. Since no reliable model is available, no dosing recommendations can be given for the neonate cohorts. It was considered that more data in the neonate populations would be needed to inform the model and subsequently allow for dosing recommendations in this vulnerable population. As no new data were provided, high uncertainties remained in PK for the neonatal groups, especially with regards to clearance, so dosing recommendations could not be supported based on the existing models.

The MAH agreed to summarise and discuss neonatal and preterm safety data in future PSURs.

3.6. Effects Table

Table 22. Effects Table for Veklury for the treatment of coronavirus disease 2019 in paediatric patients (data cut-off: 01 June 2023) based on CARAVAN Study (GS-US-540-5823)

Effect	Short description	Treatment		Uncertainties / Strength of evidence
General				**Unc:** Lack of a control arm **Unc**: Limited number of participants
Favourable Effects				
Paediatric patient population	Observed concentrations and model-predicted AUC	Paediatric patients aged at least 4 weeks and weighing at least 3 kg	Exposure for GS-441524 within the 5th and 95th percentiles of exposures in hospitalised adult participants with severe COVID-19 pneumonia on supplemental oxygen and in non-hospitalised adult participants with COVID-19 at risk of disease progression and not on supplemental oxygen, 50th percentile AUC comparable or slightly lower than in adult patients	
Unfavourable Effects				
Paediatric patient population	Observed concentrations and model-predicted AUC	Paediatric patients below 4 weeks of age or below 3 kg bodyweight	Exposure for GS-441524 higher compared to older paediatric and adult patients, 25th percentile AUC of neonates above 75th percentile of AUC in adult patients	**Unc:** observed concentrations indicate higher exposure compared to older patients, thus prone to safety risks **Unc:** no adequate model available to describe PK in neonates **Unc:** No model available fit for purpose to conduct simulations supporting dose recommendations for neonates

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The extrapolation of adult efficacy and safety data to paediatric patients is based on matching paediatric and adult systemic exposures.

From study GS-US-540-5823, no firm conclusion can be drawn regarding efficacy in the intended paediatric indication.

RDV was well tolerated and no new safety concerns were identified in neonates less than 28 days of age weighing at least 1.5 kg and in preterm neonates and infants less than 56 days of age weighing at least 1.5 kg.

3.7.2. Balance of benefits and risks

PK, efficacy and safety data from the final analysis of the Phase 2/3 GS-US-540-5823 study, cohorts 5 to 7, have been included in this submission to extend the indication to include treatment of COVID-19 in paediatric patients.

No new safety signals were identified and the safety data reported are consistent with the known safety profile of RDV treatment in adult and adolescent patients with underlying COVID-19 disease.

The adequacy of the doses for neonates (cohorts 5, 6 and 7) was questioned. With the doses initially proposed by the popPK model and investigated in the paediatric study (GS-US-540-5823), the observed data in the neonate cohorts showed that exposure was higher than in adults and older paediatric patients, especially for the most relevant compound GS-441524. The extrapolation approach was aimed at defining doses that lead to same exposures compared to adults and older paediatric patients. Since this aim was not achieved with the doses proposed by the popPK model, the model did not adequately describe the PK in the neonate cohort but needed to be refined to better align with the observed data.

The updated model provided in the responses did not improve the model fit to the observed data and therefore is not suitable to characterise the PK in the neonate cohorts and support dosing recommendations. The available very limited data (cohort 5 n=3, cohort 6 n=1 and cohort 7 n=1) give indications of higher exposure (especially for metabolite GS-441524, since this is most closely related to the active form of RDV) compared to adults and older paediatric age cohorts. Since no reliable model is available, no dosing recommendations can be given for the neonate cohorts. It is considered that more data in the neonate populations will be needed to inform the model and subsequently allow for dosing recommendations in this vulnerable population. However, no new data have been provided, so that high uncertainties remained in PK, especially in clearance, for the neonatal groups, so that dosing recommendations cannot be supported with the existing models.

Due to the lack of a reliable model to characterise PK from birth onwards, robust enough to allow simulations for the youngest patient population, the CHMP only supported a part of the initially proposed extensions of indications. The MAH, in line with the CHMP position, withdrew the type II variation for Veklury to extend the indication for use in paediatric patients weighing at least 1.5 kg with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment) and agreed to the CHMP-recommended wording of the indication.

The other proposed extension of indications *"To extend the indication for use in paediatric patients weighing at least 1.5 kg who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19"* was considered acceptable with the age cut-off and weight threshold consistent with the ones previously approved for with pneumonia requiring supplemental oxygen (i.e.: 4 weeks of age and weighing at least 3 kg). The MAH agreed with the CHMP recommendations, and provided product information amended accordingly.

The provided review of data from the MAH on the similarity of disease characteristics of paediatric and adult patients indicates that although there are physiological differences (e.g. organ maturation, liver and kidney function, body size), no significant discrepancies have been identified in the characteristics of adults and paediatric patients of different age groups with regard to disease progression and clinical

outcome. The characteristics of the symptoms and their intensity can vary between paediatric and adult patients. Certain comorbidities are unique, or more common, in children, which increases their risk for severe COVID-19 (e.g. prematurity, genetic diseases, congenital heart disease). In general, the severity of the disease tends to be less severe in children; however, the general characteristics of the disease and many risk factors for severe COVID-19 are similar in children and adults.

The impact of new virus variants on the efficacy of RDV treatment in both paediatric and adult patients were discussed. The data presented do not indicate a lack of efficacy of RDV against these tested variants.

3.8. Conclusions

The overall benefit-risk of Veklury for the extension of indications *"To extend the indication for use in paediatric patients at least 4 weeks of age and weighing at least 3 kg who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19*" is positive.

The following wording for the indications section is recommended for approval:

Veklury is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults and paediatric patients (**at least 4 weeks of age and weighing at least 3 kg**):

- ~~adults and paediatric patients (at least 4 weeks of age and weighing at least 3 kg)~~ with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment)

- ~~adults and paediatric patients (weighing at least 40 kg)~~ who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation 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

Extension of indication to include treatment of paediatric patients who are at least 4 weeks of age and weighing at least 3 kg who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19 for Veklury, based on final results from study GS-US-540-5823; this is 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. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 10 of the RMP is approved with this variation.

The variation 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 variation, amendments to Annexes 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/0439/2023 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.