25 June 2020
EMA/357513/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Veklury

International non-proprietary name: remdesivir

Procedure No. EMEA/H/C/005622/0000

Note

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

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List of abbreviations

AAS	Atomic Absorption Spectrometry
AP	Applicant's Part (or Open Part) of an ASMF
RDV	Remdesivir
RP	Restricted Part (or Closed Part) of an ASMF
API	Active Pharmaceutical Ingredient
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File
CA	Competent Authority
CFU	Colony Forming Units
CMA	Conditional Marketing Authorization
CMS	Concerned Member State
CoA	Certificate of Analysis
CQA	critical quality attribute
CRS	Chemical Reference Substance (official standard)
COVID-19	Coronavirus disease 2019
DS	Drug Substance
DSC	differential scanning calorimetry
DSM	Drug Substance Manufacturer
DP	Drug Product
DPM	Drug Product Manufacturer
DSC	Differential Scanning Calorimetry
ECMO	Extracorporeal membrane oxygenation
EDQM	European Directorate for the Quality of Medicines
GC	gas chromatography
GMP	Good Manufacturing Practice
HDPE	High Density Polyethylene
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICP	Inductively Coupled Plasma
IPC	In-Process Control
IR	Infrared (spectroscopy)

IU	International Units
LDPE	Low Density Polyethylene
LOA	Letter of Access
LOD	Limit of Detection
LOQ	Limit of Quantitation
LoQ	List of Questions
LT	Less Than
MAH	Marketing Authorisation Holder
MDD	maximum daily dose
MS	Mass Spectrometry
MV	Mechanically ventilated
ND	Not Detected
NLT	Not Less Than
NMR	Nuclear Magnetic Resonance
NMT	Not More Than
OES	Optical Emission Spectrometry
OOS	Out of Specification
PAR	proven acceptable range
PDE	Permitted Daily Exposure
PE	Polyethylene
Ph.Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
PP	Polypropylene
PVC	Polyvinylchloride
XR(P)D	X-Ray (Powder) Diffraction
QP	Qualified Person
REC	Recommendation
RH	Relative Humidity
RMS	Reference Member State
(R)RT	(Relative) Retention time
RSD	Relative Standard Deviation
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SBECD	betadex sulfobutyl ether sodium (β-cyclodextrin)

SM	Starting Material
S(m)PC	Summary of Product Characteristics
SO/SOB	Specific Obligation
TGA	Thermo-Gravimetric Analysis
UPLC	ultra performance liquid chromatography
UV	Ultraviolet (spectroscopy)
USP	U.S. Pharmacopeia

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

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Gilead Sciences Ireland UC submitted on 5 June 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Veklury, through the centralised procedure falling within the Article 3(1) and point 3 of Annex I of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 March 2020.

The applicant applied for the following indication:

Treatment of coronavirus disease 2019 (COVID 19) in adults and adolescents (aged 12 years and older with body weight at least 40 kg):

- *with pneumonia who may or may not be receiving supplemental oxygen or ventilatory support, or*
- *who are receiving supplemental oxygen or ventilatory support.*

The legal basis for this application refers to:

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

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0201/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0201/2020 is not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14-a of the above-mentioned Regulation, as it is intended for the treatment of a life-threatening disease. In addition, the above-mentioned medicinal product is intended for use in an emergency situation, in response to public health threats duly recognised by the World Health Organisation and by the Union.

In particular, the applicant stated that the submission was in response to the current global pandemic of

coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome (SARS) coronavirus (CoV)-2 infection. In December 2019, a series of pneumonia cases of unknown cause emerged in Wuhan, Hubei province, China {Huang 2020}. Sequencing analyses from respiratory tract samples of patients identified a novel CoV, which was named SARS-CoV-2 {Zhou 2020b}. Cases of the novel infectious disease caused by the SARS-CoV-2, COVID-19, rapidly increased throughout the world. As of 18 May 2020, more than 4,618,000 confirmed COVID-19 cases and 311,000 associated deaths were reported worldwide, including more than 1,890,000 cases and 167,000 deaths in the European region {World Health Organization (WHO) 2020a}.

Furthermore, it was claimed that remdesivir is a novel antiviral drug that has been evaluated for the treatment of COVID-19. Remdesivir falls within the scope of the CMA, as set out in Article 2 of the Regulation, because COVID-19 is a life-threatening disease and the World Health Organization (WHO) has declared the current SARS-CoV-2 outbreak a public health emergency of international concern and has also declared COVID-19 a pandemic {World Health Organization (WHO) 2020b} {World Health Organization (WHO) 2020c}.

Therefore, the applicant concluded that remdesivir satisfies the requirements for a CMA, as described in Article 4(1)(a) – (d) of the Regulation, through the fulfilment of an unmet medical need and the life-threatening nature of COVID-19, the ability of the applicant to be in a position to provide comprehensive clinical data, a positive risk-benefit balance, and the fact that the benefit to public health upon immediate availability of remdesivir outweighs the risks inherent in the fact that additional data are still required.

New active Substance status

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

Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Janet Koenig Co-Rapporteur: Filip Josephson

Timetable

The CHMP started the official Rolling (RR) process based on preliminary results from the NIAID-sponsored study CO-US-540-5776 (ACTT1).	30 April 2020
The applicant submitted documentation as part of a rolling review on the quality, non-clinical and clinical data to support the marketing authorization application.	1 May 2020
The Rapporteurs circulated Joint Assessment reports on	11 May 2020
The Rapporteurs circulated updated Joint Assessment reports on	14 May 2020

Extraordinary CHMP was held on and an interim Opinion on the RR was adopted by the EMEA Task Force (ETF)/CHMP (inviting the applicant to submit an application for conditional marketing authorisation) on	15 May 2020
The application was received by the EMA on	5 June 2020
The procedure started on	8 June 2020
The Rapporteurs' first Assessment Reports was circulated to all CHMP members on	12 June 2020
Updated Rapporteurs' Joint Assessment Report was circulated to all CHMP members on	16 June 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the Extraordinary PRAC meeting on	18 June 2020
Extraordinary CHMP was held on	19 June 2020
The Rapporteurs updated Joint Assessment reports were circulated to all CHMP members on	19 June 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a conditional marketing authorisation to Veklury on	25 June 2020

Additional expert consultation

During this procedure, the Committee received comments from scientific experts of Health Canada. The experts did not participate in the Committee's discussions on this application, including those leading to the scientific opinion adopted by the CHMP.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

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

On 2 April 2020, the EMA issued a Compassionate Use (CU) opinion on the use of remdesivir (updated on 11 May 2020) for the treatment of adult and paediatric patients from 12 year of age weighing at least 40 kg requiring hospitalization and supplemental oxygen (non-invasive ventilation, high-flow oxygen devices, invasive mechanical ventilation, or ECMO); due to severe COVID-19 confirmed by polymerase chain reaction (PCR) or who have known contact with a confirmed case of COVID-19, with PCR pending.

On 1 May 2020, the US FDA issued an emergency use authorization for remdesivir, allowing the distribution and use of remdesivir for the treatment of adults and children with severe COVID-19 disease defined as SpO2 ≤ 94% on room air, or requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

The Japanese Ministry of Health, Labour and Welfare also granted an emergency regulatory approval for Remdesivir. National emergency authorisations for distribution of remdesivir were issued also in UK and other countries.

According to current evidence, the COVID-19 virus is primarily transmitted between people through respiratory droplets and contact routes. Human-to-human transmission is occurring extensively. Hence, precautions to prevent human-to-human transmission are appropriate for both suspected and confirmed cases.

Although most coronavirus infections cause only mild respiratory symptoms, infection with SARS-CoV, MERS-CoV, and SARS-CoV-2 can be lethal.

Currently numerous uncertainties remain in the understanding of the spread of COVID-19 and its management. At the moment, there are no approved treatments specific for COVID-19. Evaluation and management of the disease is guided by the severity of the illness.

Well-conducted randomized trials are critical in delineating how COVID-19 should be treated. Different trials from different sponsors are in progress to assess the effects of various medications as treatment or prevention including those such as chloroquine, lopinavir/ritonavir, darunavir/ritonavir, etc. Furthermore, several studies are under way to develop an effective vaccine.

In addition, because of concerns that a hyperinflammatory state may drive many of the severe manifestations of COVID-19, several immunomodulating therapies such as glucocorticoids, convalescent plasma, and anti-cytokine therapies, are also under investigation in patients with severe disease. Some drugs, like dexamethasone, have shown promising preliminary results. However, data to inform treatment remain limited and, currently, there are no medicinal products approved in the European Union (EU) with an indication for the treatment of COVID-19[1].

2.1.2. Epidemiology

On 30 January 2020, the International Health Regulations Emergency Committee of the WHO declared the COVID-19 outbreak a Public Health Emergency of International Concern {World Health Organization (WHO, https://www.who.int/news-room/detail/27-04-2020-who-timeline---covid-19) 2020c}.

On 12 January 2020 it was announced that a novel coronavirus had been identified in samples obtained from cases and that initial analysis of virus genetic sequences suggested that this was the cause of the outbreak. This virus is referred to as SARS-CoV-2, and the associated disease as COVID-19.

Further to the WHO declaration, on 31 January 2020, Health and Human Services declared a public health emergency in the United States (US) {U. S. Department of Health & Human Services (DHHS) 2020}.

On 11 February, WHO named the syndrome caused by this novel coronavirus COVID-19 (Coronavirus Disease 2019) using its best practice guidance.

Through June 20, 2020, there have been more than 8 million confirmed cases of COVID-19 worldwide and more than 450.000 deaths.

[1] Poland has authorised a chloroquine product (Arechin) with the therapeutic indication that includes supportive treatment of SARS-Cov-2 infection. However, there is no scientific evidence on the efficacy of this chloroquine that would be comparable to the extent of evidence on remdesivir, as discussed in this report.

2.1.3. Biologic features, aetiology and pathogenesis

Coronaviruses are a group of highly diverse, enveloped, positive-sense, single-stranded RNA viruses that belong to two subfamilies, Coronavirinae and Torovirinae, in the family of Coronaviridae. These viruses were first discovered in the 1960s and can be further classified into four main genera: *Alphacoronavirus, Betacoronavirus, Gammacoronavirus*, and *Deltacoronavirus*, on the basis of their phylogenetic relationships and genomic structures.

Currently, there are seven strains of coronaviruses that are known to infect humans, including the recently identified SARS-CoV-2, human coronavirus 229E (HCoV-229E), OC43 (HCoV-OC43), NL63 (HCoV-NL63), HKU1 (HCoV-HKU1), severe acute respiratory syndrome coronavirus (SARS-CoV), and Middle East respiratory syndrome coronavirus (MERS-CoV).

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

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

2.1.4. Clinical presentation, diagnosis

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

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

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

There are few data on the clinical presentation of COVID-19 in specific populations, such as children and pregnant women. Although data are limited and mainly related to multiple small series and case reports, they generally suggest that pregnancy and childbirth do not increase the risk for acquiring SARS-CoV-2 infection and the clinical course of COVID-19 seems not be worse compared with nonpregnant women of the same age.

Clinical manifestations of COVID-19 are generally milder in children compared with adults. However, most recently, an acute presentation with a hyperinflammatory syndrome leading to multiorgan failure and shock has been described named as multisystem inflammatory syndrome temporally associated with COVID-19 in children and adolescents.

The diagnosis of COVID-19 can be established on the basis of a suggestive clinical history and the detection of SARS-CoV-2 RNA in respiratory secretions. Nucleic acid tests that detect the SARS-CoV-2 RNA genome are now widely employed to diagnose coronavirus disease 2019 (COVID-19). In addition, serological assays

measure antibody responses and determine seroconversion although they are not well suited to detect acute infections.

There are currently no approved effective antivirals or vaccines available for the treatment and prevention of COVID-19. The availability of an effective therapeutic agent with a favourable benefit/risk profile would address a serious unmet medical need for the treatment of patients with COVID-19.

2.1.5. Management

About the product

Remdesivir ("RDV", "GS-5734™") is a novel antiviral drug that has been evaluated for the treatment of COVID-19. Remdesivir is a nucleotide prodrug that is intracellularly metabolized into an analog of adenosine triphosphate that inhibits viral RNA polymerases and has broad-spectrum activity against members of the CoVs (eg, SARS-CoV-2, SARS-CoV, Middle East respiratory syndrome [MERS]-CoV), filoviruses (eg, Ebola virus, Marburg virus), and paramyxoviruses(e.g, respiratory syncytial virus, Nipah virus, Hendra virus).

In January 2020, Gilead received a request for compassionate use of RDV to treat a 35-year-old male who had tested positive for SARS-CoV-2 by real-time reverse transcriptase (rRT)-polymerase chain reaction (PCR) and whose clinical status was worsening {Holshue 2020}. Remdesivir was made available in a number of countries for single-patient compassionate use of RDV for treatment of COVID-19.

There are several ongoing or planned studies on the clinical efficacy and safety of remdesivir for the treatment of COVID-19.

The sought indication claimed by the applicant for remdesivir was:

"The treatment of coronavirus disease 2019 (COVID- 19) in adults and adolescents (aged 12 years and older with body weight at least 40 kg):

- *with pneumonia who may or may not be receiving supplemental oxygen or ventilatory support, or*
- *who are receiving supplemental oxygen or ventilatory support.* "

Type of Application and aspects on development

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above-mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive:

  According to the Applicant, a positive benefit-risk balance for remdesivir for the treatment of COVID-19 is demonstrated primarily based on evidence from the NIAID-sponsored study CO-US-540-5776 (ACTT1), an ongoing, Phase 3, randomized, double-blind, placebo-controlled, multicenter study evaluating RDV versus placebo in hospitalized patients with COVID-19. Supportive safety data are provided from four completed Phase 1 studies, two supportive ongoing Phase III studies (GS-US-540-5773, and GS-US-540-5774), and the compassionate use program.

  The Applicant states that the available data to date indicate a positive benefit-risk balance for remdesivir use in the treatment of hospitalized patients with COVID-19 for which there are no approved therapeutic agents in the EU.

- It is likely that the applicant will be able to provide comprehensive data:

The applicant states, that comprehensive clinical data will be provided from the clinical development program for RDV which includes the studies listed in **Table 1**.

Table 1*:* Overall Remdesivir Clinical Development Program

Study	Study Design	Study Status, Data Currently Available, and Timing of Final Data
Studies in Participants with COVID-19		
CO-US-540-5776 (ACTT-1) {Beigel 2020a}	Phase 3, NIAID-sponsored, randomized, double-blind, placebo-controlled, multicenter study to evaluate available investigational treatments for COVID-19, including RDV	Recruitment of ACTT-1 complete Preliminary data submitted (data cut date: 28 April 2020) Final CSR available Q3/Q4 2020
GS-US-540-5773 {Goldman 2020}	Phase 3, randomized, open-label, multicenter study in patients with severe COVID-19 conducted in 2 parts: Part A was a randomized, open-label study to evaluate the efficacy and safety of 2 RDV regimens (5 days versus 10 days) Part B is an open-label study to evaluate the safety and tolerability of RDV	Recruitment complete Interim data submitted (Day 14 analysis) Final Part A (Day 28) CSR available Q3/Q4 2020
GS-US-540-5774	Phase 3, randomized, open-label, multicenter study in patients with moderate COVID-19 conducted in 2 parts: Part A was a randomized, open-label study to evaluate the efficacy and safety of 2 RDV regimens (5 days versus 10 days) compared with SOC Part B is an open-label study to evaluate the safety and tolerability of RDV	Recruitment complete Interim data submitted (Day 11 analysis) Final Part A (Day 28) CSR available Q3/Q4 2020
CO-US-540-5758 {Wang 2020}	Phase 3, investigator-sponsored, randomized, placebo-controlled, study to evaluate the efficacy and safety of RDV in hospitalized adult patients with severe COVID-19	Study prematurely stopped (no new cases of COVID-19 at the study sites) Final data submitted in the form of a manuscript

The final clinical study report (CSR) for the NIAID-sponsored Study **CO-US-540-5776** (ACTT1) summarizing these final analyses will be available in quarter (Q) 3 and Q4 2020.

The final CSR for Part A (Day 28) of the Gilead-sponsored Study **GS-US-540-5773** summarizing the final analyses will be available in quarter (Q) Q4 2020.

The final CSR for Part A (Day 28) of the Gilead-sponsored Study **GS-US-540-5774** summarizing the final analyses will be available in quarter (Q) Q4 2020.

Final data submitted in the form of a manuscript of the IIT-study **CO-US-540-5758** is expected in Q4 2020 (subject to agreement with the sponsor).

- Unmet medical needs will be addressed:

  In the European Union (EU) there are no approved treatments for COVID-19. Treatment of severely ill patients with COVID-19 is primarily supportive. The COVID-19 pandemic has overwhelmed health care systems in several affected countries. According to the Applicant there is now substantial evidence that remdesivir will address this unmet medical need because this drug significantly shortens time to recovery, particularly in patients with severe COVID-19, and may improve COVID-19−related mortality. In addition, remdesivir has demonstrated a favourable safety profile, supporting its use in patients with COVID-19.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required:

  The Applicant considers that the overall benefit-risk balance of remdesivir in the proposed indication is positive and that with the current data, the benefits to public health of the immediate availability of this product outweigh the risks.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented in two pharmaceutical forms, as a powder for concentrate for solution for infusion, containing 100 mg remdesivir as active substance, or as concentrate for solution for infusion containing 100 mg remdesivir as active substance.

Other ingredients in the powder for concentrate for solution for infusion are betadex sulfobutyl ether sodium, hydrochloric acid (to adjust pH) and, sodium hydroxide (to adjust pH).

Other ingredients in the concentrate for solution for infusion are betadex sulfobutyl ether sodium, hydrochloric acid (to adjust pH), sodium hydroxide (to adjust pH) and water for injections.

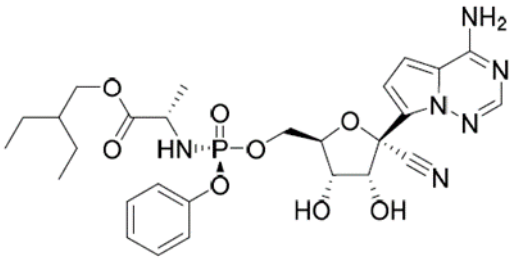
For both pharmaceutical forms, the product is available in Type I clear glass vial, an elastomeric closure, and an aluminium overseal with a flip-off cap.

2.2.2. Active Substance

General information

Remdesivir is a nucleotide prodrug RNA polymerase inhibitor developed for the treatment of emerging viruses. The chemical name of remdesivir is 2-Ethylbutyl (2S)-2-{[(S)-{[(2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f] [1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl] methoxy}-(phenoxy)phosphoryl]amino} propanoate. It corresponds to the molecular formula $C_{27}H_{35}N_6O_8P$, its relative molecular mass is 602.6 and it has the structure shown in Figure 1.

Figure 1.Structure of remdesivir.



Remdesivir is a white to off-white or yellow non-hygroscopic crystalline solid. It is soluble in ethanol and freely soluble in methanol. It is practically insoluble in water and its aqueous solubility is pH dependant and increases as the pH decreases; in water adjusted with HCl to pH 2 it is very slightly soluble. Its pKa value is 3.3 and its LogP is 3.2.

The structure of the active substance was elucidated by nuclear magnetic resonance (NMR) spectroscopy, mass spectrometry (MS), elemental analysis, infrared spectroscopy (IR), and ultraviolet spectroscopy (UV). The presented data support the proposed structure of remdesivir, but a clearer presentation of NMR data is expected (see recommendations 2.2.6). Solid state properties were confirmed using x-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC).

Remdesivir has six chiral centres and is produced as a single stereoisomer. Of the potential stereoisomeric impurities, two can be reasonably expected to be present in the final active substance. The manufacturing process for remdesivir and the control strategy for stereoisomeric impurities is described.

Remdesivir exhibits polymorphism. The manufacturing process produces either Form II or Material 2, which consists of a mixture of Form II and Form IV. Form II is the most thermodynamically stable polymorph. Important physicochemical properties of the active substance such as equilibrium solubility and stability, and the resulting finished product performance, were shown to be equivalent for Form II and Material 2.

Manufacture, characterisation and process controls

Remdesivir manufacturing process includes two synthetic steps comprising of one coupling step and one deprotection step. There is one isolated intermediate, the crude remdesivir, which leads through purification to the final remdesivir active substance. The manufacturing process has been described. The submitted information indicate that currently manufactured batches are of consistent quality that is appropriate and comparable to that of clinical development batches. However, a specific obligation (SOB) with a view to confirming that the quality of future batches will also remain appropriate and comparable to that of clinical development batches over the entire life cycle of the product is warranted in this respect. In order to ensure batch to batch consistency the applicant should expand the description of the active substance synthesis with more details regarding yields, process conditions, unambiguously specifying when each process stage is applicable, materials used and their specifications, and defining the batch size. Further, process parameter ranges should be further justified or tightened. Specifically, the process description should unambiguously reflect the production of the process validation batches and the manufacturing of future batches by clarifying when so called "optional" process steps are applied. In addition, the re-working procedures should be deleted, process conditions should be described in more detail and the applied process parameter ranges should be further justified or tightened.

Control of materials

The proposed starting materials are clearly stated, and the respective synthetic routes and specifications were presented.

However, the designation of the proposed starting materials is not fully in line with all the principles of ICH Q11. The presented remdesivir synthesis from the proposed starting materials includes one bond-forming step and one deprotection step, while only the crude active substance and final active substance are isolated. Generally, the number of steps performed under GMP are limited. In addition, several of the impurities potentially present in the proposed starting materials could affect the final active substance impurity profile.

In order to improve the impurity control strategy, lower the risk of contamination and assure comprehensive control throughout the lifecycle of the product, the MAH should, as agreed, redefine the starting materials of active substance synthesis, update all dossier documentation accordingly and implement the redefined starting materials.

The applicant agreed to redefine the starting materials to a point earlier in the synthesis and committed to do so within an acceptable timeframe. After re-definition of the starting materials the increased number of

synthetic steps conducted under GMP would mitigate risks associated with contamination and/or future changes to the synthetic route or supplier of the starting material (reference is made to ICH Q11 Q&A 5.11). The applicant agrees to submit documentation on the new starting materials in August 2020 as a variation to the MA and all affected dossier sections will be updated accordingly. The new (redefined) starting materials will be implemented in the GMP manufacturing process by June 2021. Any proposal to include additional starting material manufacturers will have to follow the applicable regulatory requirements including submission of the relevant variation(s). Considering the time required to undertake the necessary activities for the redefined starting material implementation and the emergency context of the current application, in order to ensure the supply of the medicinal product to the patients, it is deemed acceptable that the redefinition of the starting material is realised within the above timeframe and followed up as an SOB in the context of this CMA of a medicinal product to be used in an emergency situation.

The synthetic descriptions include information on used solvents and reagents. No class 1 solvents and no class 1 catalysts are used. Information on materials used in the manufacture of the active substance (e.g. solvents, reagents) was presented.

Further information on specifications for all solvents, recovered solvents (if applicable), reagents and auxiliary materials (e.g. filtration aids) used in the manufacturing process are awaited. It is expected that relevant information is moved from dossier section S.2.6 into the respective sections (S.2.3 and S.3). The synthetic scheme of the manufacturing process should be updated accordingly (see recommendation 2.2.6).

Control of critical steps

Critical process parameters and controls have been identified using a risk-based approach. In-process controls were defined. These should be supplemented with all identified critical process parameters and the specification for the isolated intermediate should be updated to include a test for assay (see recommendation 2.2.6). Process parameters have been investigated with a traditional, univariate approach and proven acceptable ranges (PARs) have been established. In the process description, parameters are defined by operating ranges. The operating ranges are however much wider than what is expected to be needed to operate the process and should be tightened.

Manufacturing process development

The manufacturing process development program summarises the differences from the current manufacturing process and the manufacturing process used for toxicology batch and clinical batch. The bond forming steps and the intermediate in the synthesis of remdesivir have not been changed. However, no information has been provided with regards to the manufacture of the starting materials during initial development work. Some solvents have been changed.

Impurities

Information on structures and the related downstream impurities was given for the specified impurities. The impurity discussion covers stereo-isomeric impurities, degradation products, residual solvents and organic volatile impurities, potentially mutagenic impurities, inorganic impurities originating from the manufacturing process and the synthesis of the (proposed) starting materials. A discussion on the carry-over of the specified impurities and downstream impurities was presented. All specified impurities can be detected downstream with the impurity method used for active substance control. However, the provided information concerning formation and control strategy for some potential impurities is incomplete.

In order to further substantiate the control strategy for the active substance the MAH should further elaborate the impurities discussion with regard to the formation of potential impurities in the proposed and redefined starting materials, the representativeness of the active substance used in the toxicological programme versus the commercial product, the contamination of the active substance by elemental impurities, and the proposed justification regarding the suitability and adequateness of the proposed

controls. Further information is requested on the fate and purge experiments as well as the suitability and adequateness of the proposed tests and acceptance criteria to further support the control strategy. A discussion on potential toxicity of La and Nd and risk of contamination of the active substance with the elements is awaited. For the material produced for toxicological studies, chromatography has been used for isolation rather than crystallisation which raises a question on the representativeness of the material.

The active substance is packaged in a double layer of polyethylene bags closed with a plastic or wire tie. The bags are held in a high-density polyethylene or fiberboard drum with a lid, or other suitable container/closure system for structural support. The specification for the primary packaging and a certificate of analysis should be provided including IR-spectra of the PE-foil. The conformity of the primary packaging to Ph. Eur. or to the EU regulation 10/2011 incl. amendments should be confirmed (see recommendation 2.2.6).

Specification

Remdesivir active substance specification includes appropriate tests for appearance (visual), identification (IR, UPLC), clarity of solution (in-house), water content (Ph. Eur.), assay (UPLC), impurities (UPLC), residual solvents and organic volatile impurities (GC) and bacterial endotoxins (Ph. Eur.).

The control strategy for remdesivir has been developed to ensure that the critical quality attributes (CQAs) of the active substance are consistently attained. The CQAs identified are appearance, identity, absence of insoluble particles, water content, assay, impurity content (including stereoisomers), residual solvent content, organic volatile impurity content, inorganic impurity content, potential mutagenic impurity content, elemental impurity content, microbial content and endotoxin content. With regards to impurities - the proposed controls are generally acceptable: a few questions are raised as discussed below.

The parameters included in the specification are acceptable. It has been sufficiently justified why "elemental impurities", "inorganic impurities", "polymorphic form", "stereochemical purity", "particle size", and "mutagenic impurities" are not included in the specification.

With regards to the proposed acceptance criteria, these have all been discussed and justified by the applicant. The limits for specified impurities are based on toxicologically qualified levels. In order to improve the control strategy for the finished substance the MAH should revise the active substance specification by including the parameter "microbial limits", by revising the proposed limits for assay, impurities, residual solvents, and water in line with batch data and/ or relevant guidelines and Ph. Eur. as applicable and confirming that the analytical method can control two unspecified impurities**.**

Analytical procedures and reference standards

The analytical procedures are all adequately described. All in house methods are sufficiently validated in line with ICH Q2 guideline. The stability indicating character of the impurity method was demonstrated by forced degradation studies. Nevertheless, as mentioned above, it should also be shown that the impurities method is also validated against two impurities stated to be controlled by the limit for unspecified impurities. Satisfactory information on the reference working standards used has been presented.

Batch analysis

Batch analysis data for 13 batches were provided in total; three lab scale batches, used for toxicology, five pilot scale batches used for clinical studies and stability and five production scale batches used for clinical studies, process validation and stability.
The batches were tested according to the specification valid at the time. The results provide a good overview of the batch history and the evolution in quality of the active substance. Overall, the results demonstrate that the active substance can be manufactured consistently and meeting the specification.

Stability

Stability data on two commercial and two pilot scale batches stored in the intended commercial packaging for up to 48 months under long term conditions 30 °C/ 75% RH and for up to 6 months under accelerated conditions 40 °C/ 75% RH, was provided according to the ICH guidelines.

Samples were tested for appearance, water content, assay, and impurity content. The results showed no trend or a loss in assay or increase in impurity content for up to 48 months. A small increase in water content was observed between the initial and three-month time points for some batches but remained consistent thereafter for up to 48 months.

A photostability study were performed on one pilot scale batch according to ICH Q1B *Photostability Testing of New Drug Substances and Products*. Appearance, assay, impurity content and water content were evaluated. According to the results remdesivir is not photolabile.

In order to evaluate conditions that may be experienced during shipping and handling, stress studies were conducted at -20 °C for one month, 50 °C /ambient humidity for two weeks, and 60 °C/ambient humidity for one week. Samples were tested for appearance, assay, impurity content, and water content. Little to no change was observed. Remdesivir is therefore considered to be stable at -20°C for a period of one month, 50 °C for two weeks and 60 °C for one week.

Considering the overall stability data, the proposed re-test period of 48 months for the active substance when stored below 30°C is acceptable but may be subject to review in relation to the pending points on batch size and impurity control as discussed previously.

2.2.3. Finished Medicinal Product

Two pharmaceutical forms have been developed; a concentrate for solution for infusion and a powder for concentrate for solution for infusion. Both have been used in clinical studies at different stages of development. Both are intended for commercialisation. Both pharmaceutical forms exhibited similar pharmacokinetic performance at total remdesivir doses of 75 mg and 150 mg. The strength of both proposed commercial formulations is 100 mg remdesivir.

It is noted that a 150 mg strength of both pharmaceutical forms has been used in some clinical studies but it is not intended for commercialisation. The only difference between 100 mg and 150 mg strengths of each form is the fill volume.

2.2.3.1. Concentrate for Solution for Infusion

Description of the product and pharmaceutical development

The finished product is a sterile, preservative-free, clear, colourless to yellow concentrate for solution for infusion with a concentration of 5 mg/ml and a total content of 100 mg of remdesivir. The applicant refers to it as 'Remdesivir (GS-5734TM) injection' throughout the dossier. Instead, the EDQM standard term 'concentrate for solution for infusion' should be used throughout the dossier (see recommendation 2.2.6). The product is filled in a single use, Type I clear glass vial, sealed with an elastomeric closure and an aluminium overseal with a flip-off cap. Each vial contains 6% overfill in order to allow withdrawal of the nominal volume (20 ml) and the complete 100 mg remdesivir dose. Remdesivir concentrate for solution for infusion is to be diluted to 250ml with 9mg/ml (0.9%) sodium chloride solution prior to intravenous administration. The qualitative and quantitative composition of the finished product was presented. The

composition per ml finished product solution and the amounts of ingredients without overfill should be presented (see recommendation 2.2.6).

Formulation development

Remdesivir exhibited poor oral bioavailability in preclinical models and formulation development focused on parenteral routes of administration. Because remdesivir is poorly soluble in water, solubilising excipients and pH adjusting excipients were used to achieve clinically relevant concentrations of the medicine.

Characteristics of the active substance potentially relevant for the proposed dosage form have been discussed. Different polymorphic forms (Material II and Form II) have been used at different stages of clinical trials. Form II has been used in later clinical development and primary stability studies and is the designated commercial form. Nevertheless, since active substance is dissolved in WFI in the course of finished product manufacture the polymorphic form of the active substance is not a relevant quality attribute. Due to the extremely low aqueous solubility of remdesivir the substituted β-cyclodextrin betadex sulfobutyl ether sodium (SBECD) was selected as solubiliser for the active substance. SBECD was selected over various surfactants tested at various levels but contrary to SBECD they did not sufficiently improve the active substance solubility in order to achieve clinically relevant drug concentrations. Remdesivir is susceptible to hydrolytic degradation under acidic and basic conditions. Relevant oxidative and/or photolytic degradation has only been observed at pH 7.0, but not for the specified pH range.

Several formulation parameters were evaluated for their influence on remdesivir solubility and solution-state chemical stability, including solvent composition, acid/base agents and ionic strength, and surfactant type and content. Additionally, prototype remdesivir solutions were screened for physical and chemical compatibility with intravenous infusion fluids. The data generated in these screening studies, as well as pharmacokinetic and safety results obtained in non-clinical animal trials, led to the first 5 mg/mL concentrate for solution for infusion formulation developed to support Phase 1 clinical studies. This solution formulation contained betadex sulfobutyl ether sodium as a solubiliser and the pH was adjusted to provide sufficient remdesivir solubility. Sterilisation was performed via sterile filtration. The product was stored refrigerated (2 to 8 °C) or frozen (-25 to -10 °C) during clinical development to minimise hydrolysis of the active substance. A tabulated summary of clinical development batches was presented. Clinical and commercial formulation are identical.

Only known excipients of compendial quality are used. Compliance of betadex sulfobutyl ether sodium with Ph.Eur. (2804) should be confirmed together with the requested excipient and finished product specification update as detailed below in "Product specification". The filled amount of SBECD should be justified taking into account the content of its genotoxic impurity 1,4-butane sultone as part of the requested process description update as detailed below in "Manufacture of the product". However, considering that the excipients included in the finished product are used at ranges typically found in parenteral dosage forms and the emergency context of the present application it is acceptable to follow-up this issue as a SOB in the context of the CMA. No novel excipients are used. No excipients of human or animal origin are used. Compatibility of the active substance and excipients is inferred from stability data presented and discussed below in this report.

SBECD (cyclodextrin) and sodium appear in the Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' as excipients with known effect. SBECD is the main source of sodium. Amounts derived from sodium hydroxide, used for pH adjustment are negligible. Calculation of amounts of excipients have been performed assuming a maximum daily dose (MDD) of 200 mg. Additionally, calculation of sodium content has been performed applying the molecular mass of SBECD as referenced in the respective USP monograph. The relevant information on both excipients have been included in the product information in line with the above guideline.

Manufacturing process development

Detailed information on manufacturing development history is presented. The initial remdesivir concentrate formulation and manufacturing process were developed at a development site and later transferred with scale-up to a different site to initiate manufacture of clinical supplies. Comparative information on the manufacturing processes at all sites that have manufactured remdesivir concentrate batches are presented. This includes equipment, process parameters and in-process control results as well as development test results of representative batches. The presented comparative data show that the manufacturing processes are actually similar irrespective of the manufacturing site and stage of development.

Critical quality attributes (CQAs) have been identified and tabulated summaries were presented.
The impact of hold time on sterility of remdesivir injection solution for infusion was evaluated in relevant study. However, since holding times have to be justified on a site-specific basis, they are still required to be supported by the process validation reports and media fill results to confirm that the outcome of the presented development studies apply to the proposed manufacturing sites.
It has been demonstrated that terminal sterilisation is not feasible because the active substance is not stable when exposed to steam sterilisation conditions resulting in significant degradation (> 5%) of remdesivir. Therefore, it is sterile filtered under aseptic conditions as opposed to terminally sterilized. The selected sterilisation method is sufficiently justified in line with the relevant decision trees depicted in the guideline on sterilisation of the medicinal product, active substance, excipient and primary container EMA/CHMP/CVMP/QWP/850374/2015. Bioburden is controlled prior to filtration. Finished product is tested for sterility and bacterial endotoxins according to Ph. Eur.

An adsorption study of remdesivir onto different filters and vial materials informed the selection of the filters and containers used in manufacture and the selection of the primary packaging material.

Compatibility

Remdesivir concentrate is administered after dilution into intravenous infusion fluid as per SmPC 6.6. In-use stability studies to support physical and chemical compatibility with infusion fluids are discussed below in this report in "Stability".

A compatibility test to evaluate the potential for extractable substances was performed on representative infusion components at conditions intended to simulate product infusion. The remdesivir concentration is the same for reconstituted remdesivir powder and undiluted remdesivir concentrate. The study was performed with the concentrate, however, the results are relevant to the powder formulation as well because the two formulations contain the same components, and the 5 mg/ml solution formulation represents the worst-case for potential of SBECD to impact levels of extractable substances in the infusion fluids. The maximum daily volume of administration was used to calculate estimated daily exposures for the detected extractable substances. The applied threshold is in in line with ICH M7 principles. The results showed that found amounts of extractables are toxicologically negligible.

Container closure system

The container closure system for Veklury 100 mg concentrate for solution for infusion consists of a Type 1 clear glass vial, an elastomeric closure, and an aluminium seal with a flip-off cap. Technical drawings for all parts of the immediate packaging were provided. Detailed descriptions and respective specifications are included (parameters appearance and dimensions). Primary packaging materials comply with respective Ph. Eur. requirements (i.e. Ph. Eur. 3.2.1 and Ph. Eur. 3.2.9). A development study has been performed regarding leachables from stoppers used in the initial clinical studies. Results show only minor, toxicologically negligible leaching. An additional study to test for leachables will be performed on finished product manufactured using the proposed commercial process and packaged in the to-be-marketed container closure system. Considering the performed development study and the compendial quality of primary packaging materials, it is acceptable that the intended leachables study for commercial stoppers is

not included in the MAA Dossier. Overall, the choice of the container closure is therefore regarded as justified. However, the dossier should be updated to include the manufacturer of the elastomeric closures and Certificates of Analyses for each immediate packaging component (see recommendation 2.2.6).

Manufacture of the product and process controls

The proposed manufacturer is clearly stated. The manufacturing process of Veklury concentrate for solution for infusion consists of the following main steps: compounding of components, mixing, pH adjustment (with HCL and/or NaOH), bioburden reduction filtration, sterile filtration, vial filling, capping and product inspection. A manufacturing process flow chart and narrative description were provided. There are no isolated intermediates. However, the process description should be expanded with further details by clearly defining the batch size in line with process validation studies. Any change in batch size outside of the proposed range of the batch sizes should be applied for by submission of a variation.

The submitted information indicate that currently manufactured batches are of consistent a quality that is appropriate and comparable to that of clinical development batches. However, a SOB as discussed below, with a view to confirming that the quality of future batches will also remain appropriate and comparable to that of clinical development batches over the entire life cycle of the product is warranted in this respect. In order to ensure batch to batch consistency of the Concentrate for Solution for Infusion the MAH should expand the description of the manufacture of the finished product with more details by providing the actual process validation report, by justifying the level of betadex sulfobutyl ether sodium, by clearly defining the batch size in line with process validation studies and per manufacturing site, by defining process parameters and acceptance criteria, by introducing additional in-process controls and by providing additional batch data . More specifically the process description should further specify the conditions of sterilisation for filters, glass vials, rubber stoppers and flip-off seals, and in addition clearly state the type of filters (sterilising and non-sterilising). Operating parameters and in-process controls are indicated but in addition a test for container closure integrity should be included as in-process control and filter integrity test acceptance criteria should be given. Holding times should be included in the process description too.

Critical manufacturing steps should be referenced, and their control should be described. In addition, the grade of environment for the preparation of solutions as well as for the filling of the final material into bulk containers have been performed should be confirmed and the bioburden level before prefiltration should be given (see recommendation 2.2.6). The presented batch formula is in line with the composition stated above. Batch quantity is given based on the theoretical amount of bulk solution. The theoretical number of filled vials should be included in the batch formula for each described batch size (see recommendation 2.2.6).

Process validation

Due to the aseptic processing step, the manufacturing process is regarded to be a non-standard process according to Annex II of the process validation guideline. Accordingly, process validation data for production scale batches should be presented in addition to the provided in-process control- and release data for 4 production scale batches and 3 slightly smaller batches. These batches are representative for production scale batches manufactured by the proposed manufacturer. The submitted data indicate that the process is suitable to consistently manufacture finished product of specified quality. Moreover, the presented data show that the quality of product manufactured at the proposed commercial site and the initial clinical development manufacturing site is similar. Nevertheless, an actual process validation report is missing and should be submitted; especially information on sampling is relevant to confirm the appropriateness of the presented data. Additionally, it is noticed that IPC and batch release results are reported for a number of consecutive batches, but not for all for all batches referenced in the dossier. The reason for not reporting all the batch data should be stated and justified.

Appropriate filter validation data were also presented. However, actual filters used in routine production are still to be confirmed and the filter integrity test acceptance criteria should be clarified as mentioned above.

As discussed above, the choice of the sterile filtration/aseptic processing is considered acceptable and sufficiently justified in line with the relevant guideline. Media fill studies have also been conducted. In order to confirm the appropriateness of the aseptic processing of sterile bulk product for Concentrate for Solution for Infusion the MAH should submit the media fill results. Specifically results for three complete runs should be presented, simulating the whole manufacturing process from mixing of bulk solution to sealing of vials including routine and worst-case interventions. The actual holding times of each step in the study and he maximum processing time should be also be included in the process description as discussed above.

Product specification

The finished product release and shelf life specifications include appropriate tests for appearance (visual), identification (UPLC, UV), assay (UPLC), degradation products content (UPLC), pH(Ph. Eur.), sterility (Ph. Eur.), bacterial endotoxins (Ph. Eur.), particulate matter (Ph. Eur.) and volume in container (Ph. Eur.).

The finished product specification includes all parameters relevant for the dosage form. The proposed limits are justified but should be revised or further justified in line with batch and stability data.

In order to improve the control strategy for the Concentrate for Solution for Infusion product the MAH should revise the excipient and finished product specifications by revising the limits for assay, impurities and endotoxins in line with batch and stability data, relevant Ph. Eur. requirements and guidelines, as applicable. Specifically, the limit for assay during shelf-life should be tightened unless otherwise justified**.** Regarding the impurities, no product-specific impurities are known, therefore characterisation of impurities in the finished product is in-line with assessment regarding active substance. The specified limits for impurities are either qualified by toxicological studies or the limit (for one impurity) was set considering it is an (active) metabolite. However, the proposed impurity limits should also take into account batch and stability data and be revised accordingly. In addition, the limit for unspecified degradation products should be lowered to NMT 0.2%. to be in line with the ICH Q3B guideline's identification threshold (0.2%)**.** The proposed endotoxin limit is acceptable when the product is used in adults, but since it is stated in the SmPC that the product is intended for adults and adolescents 12 years of age and older it should be further tightened to an acceptable endotoxin level for adolescent weighing 40 kg**.**

A risk assessment for potential elemental impurities was conducted in accordance with ICH Q3D. Results show that content is well below the maximum allowable concentration based on the permitted daily exposure established for parenteral route of administration and thus no control of any elemental impurities is warranted.

A risk evaluation regarding potential presence of nitrosamines has been provided and is regarded as acceptable.

Analytical methods are adequately described, and validation data were provided for the in-house non-compendial methods according to ICH Q2 guideline. Satisfactory information regarding the reference standards used in the routine analysis of finished product has been presented.

Batch analysis

Batch analysis data was provided for three commercial scale batches from the commercial manufacturer. Batch data from the development sites were also provided as supportive data. All provided batch results comply with respective specification limits and therefore indicate consistent manufacture of the finished product.

Stability of the product

Stability data for three commercial scale batches from the development site and one commercial scale batch from the proposed commercial site have been provided. Samples have been stored in the proposed packaging for up to 12 months under long term conditions 2°C – 8°C and for six months under accelerated conditions (25°C / 60% RH) according to current ICH guidelines.

As pointed out above, the manufacturing processes from different manufacturing sites and the formulations of clinical and commercial batches are regarded as similar. Moreover, batch release data for product manufactured by the proposed manufacturer are similar to release data from historical development batches. It is expected that performance of the product will also be comparable during shelf-life. It is thus acceptable that the stability data presented are considered representative for the finished product manufactured by the proposed manufacturer. Confirmation was given that stability studies have already been initiated with product batches manufactured by the proposed manufacturer.

Samples were stored in inverted and upright position and were tested for appearance, pH, assay, degradation products and particulate matter. Sterility and bacterial endotoxin testing were performed initial and 12 months of storage at long term and 6 months at accelerated conditions. The methods used are validated and shown to be stability indicating.

The results for all quality attributes evaluated met the specification acceptance limit at each scheduled time point for up to 12 months at long term conditions. No differences are observed between the data for vials stored in the upright and inverted orientation.

At accelerated conditions over the six-month study, a significant decrease in remdesivir assay and increase in degradation product content is observed after the three-month time-point. No changes are observed in appearance, pH, or particulate matter for up to six months when the vials are stored in the upright or inverted orientations. Bacterial endotoxins and sterility were tested at initial and 6-month time points and complied with the specification. The data show that the finished product can be stored at 25 °C/60% RH for short periods of time such as may occur during shipping.

Photostability studies are adequately conducted and show that the proposed finished product is photostable.

Photostability was tested according to ICH Q1B on a pilot batch. Samples were tested for appearance, pH, assay, degradation product content, and particulate matter. No significant changes were observed in the results for appearance, pH, assay, degradation product content and particulate matter. The results confirm that the finished product is not photolabile.

Freeze-thaw studies were also conducted in line with the provided study protocol. Samples were analysed for appearance, pH, assay, degradation product content, and particulate matter and results show that the physicochemical properties of finished product remain unaffected by repeated freezing and thawing.

<u>In-use stability</u>

An in-use stability was performed as per the SmPC reconstitution instruction in section 6.6. The study was performed on the 150 mg strength (not intended for commercialisation) but this is considered acceptable since the 100 and 150 mg only differ in the filled volume in the vial. The diluted product was evaluated for appearance, pH, assay, and degradation product content. The results met the predefined criteria in the protocol and are deemed acceptable. The proposed in-use shelf life (SmPC 6.3) is supported. Confirmation was also provided that an in-use stability study will also be performed with product at the end of its shelf-life.

The proposed shelf-life is based on real time data as trends like decrease in assay and increase in impurity levels have been observed. Furthermore, according to Appendix A of ICH Q1E no extrapolation is feasible

when a product is intended to be stored in a refrigerator and significant change occur at accelerated condition within 3 months.

Thus, a shelf-life of 12 months with a storage restriction "store at 2-8°C" is acceptable based on provided data.

Adventitious agents

No excipients of human or animal origin are used.

2.2.3.2. Powder for Concentrate for Solution for Infusion

Description of the product and pharmaceutical development

The finished product is a sterile, preservative-free, white to off-white to yellow powder for concentrate for solution for infusion containing 100 mg remdesivir. The applicant refers to it as 'Remdesivir for injection' in the MA dossier. The EDQM standard term 'powder for concentrate for solution for infusion' should be used throughout the dossier (see recommendation 2.2.6). The finished product is filled in a single use, Type I clear glass vial, sealed with an elastomeric closure and an aluminium overseal with a flip-off cap. Each vial contains 5% overfill in order to allow withdrawal of the nominal volume after reconstitution (20ml). Remdesivir powder for concentrate for solution is to be reconstituted with 19 mL of sterile water for injection and immediately afterwards to be diluted to 250ml or 100ml with 9mg/ml (0.9%) sodium chloride solution prior to intravenous administration. Dilution to 100ml should be reserved for patients with severe fluid restriction, e.g. ARDS or renal failure. Following reconstitution, each vial contains a 5 mg/ml remdesivir solution. The qualitative and quantitative composition of the finished product is presented. The composition per vial and the amounts of ingredients without overfill should be presented (see recommendation 2.2.6).

Formulation development

The lyophilised formulation (powder for concentrate for solution for infusion) was developed from the concentrate for solution for infusion described above, during Phase 1 and Phase 2 clinical trials to enable room temperature storage. Most of the development studies are applicable or can be extrapolated to the powder product. This lyophilised formulation exhibited acceptable chemical stability. Through additional formulation screening studies, the concentration of SBECD in the formulation was adjusted to facilitate the additional (compared with the concentrate formulation) lyophilisation step. This adjustment, followed by adjustment to the final target pH, resulted in a shorter lyophilisation cycle and produced a stable product. Clinical and commercial formulation are identical. The first clinical batch of the lyophilised formulation was manufactured using remdesivir Material 2. All subsequent clinical lots of lyophilised product were manufactured using remdesivir Form II. However, as discussed previously the initial crystal form of the active substance has no relevance since substance is dissolved in WFI in the course of the finished product manufacturing.

Only known excipients of compendial quality are used. Compliance of SBECD with Ph. Eur. (2804) should be confirmed together with the requested excipient and finished product specification update as detailed below in "Product specification". The excipients included in the finished product are used at ranges typically found in parenteral dosage forms. However, the filled amount of SBECD should be justified taking into account the content of its genotoxic impurity 1,4-butane sultone as part of the requested process description update as detailed below in "Manufacture of the product". No novel excipients are used. No excipients of human or animal origin are used. Compatibility of the active substance and excipients is inferred from stability data presented and discussed below in this report.

Manufacturing process development

Detailed information on manufacturing development history is presented. The formulation and manufacturing process were additionally transferred to the proposed manufacturing sites to increase manufacturing capacity and support commercialization. Comparative information on the manufacturing processes at all sites that have manufactured remdesivir powder batches are presented. This includes equipment, process parameters and in-process control results as well as development test results of representative batches. The presented comparative data show that the manufacturing processes are actually similar irrespective of the manufacturing site and stage of development. It is noted that LSNE is not proposed as commercial manufacturer.

Critical quality attributes (CQAs) have been identified and tabulated summaries were presented.

The preparation of the bulk fill solution for the lyophilised product follows an analogous procedure to that used for the concentrate product except for the final filling and lyophilisation steps. The active substance is dissolved in sterile water for injection with SBECD, and the pH is adjusted using HCl and/or NaOH as necessary. The bulk solution is next passed through a bioburden reduction filter, then sterile-filtered and aseptically filled to the target fill weight. The vials are partially stoppered with fluoropolymer laminated rubber stoppers and lyophilized, then stoppered and capped with an aluminium overseal and flip-top cap. However, the impact of freezing rate and annealing time during the lyophilisation process on quality attributes and manufacturing efficiency should be discussed as detailed below in "Manufacture of the product".

The product is sterile filtered under aseptic conditions as opposed to terminally sterilised. It has been demonstrated that terminal sterilisation is not feasible because the active substance is not stable when exposed to steam sterilisation conditions resulting in significant degradation (> 5%) of remdesivir. It has also been demonstrated that terminal sterilisation (by ionising radiation) is not feasible for the powder for solution for infusion because the product is not stable when exposed to 25 and 36 kGy ionising radiation. Based on the studies presented, the selected sterilisation method is considered sufficiently justified in line with the relevant decision trees depicted in the guideline guideline on sterilisation of the medicinal product, active substance, excipient and primary container EMA/CHMP/CVMP/QWP/850374/2015. Bioburden is controlled prior to filtration.

Compatibility

The respective study on the concentrate formulation is applicable to the powder formulation too as discussed above.

Remdesivir powder concentrate for solution for infusion is administered after reconstitution with sterile water and subsequent dilution into intravenous infusion fluid as per SmPC 6.6. In-use stability studies to support physical and chemical compatibility with infusion fluids are discussed below in this report in "Stability".

Container closure system

The container closure system for Veklury 100 mg powder for concentrate for solution for infusion consists of a Type 1 clear glass vial, an elastomeric closure, and an aluminium seal with a flip-off cap. Technical drawing for all parts of the immediate packaging were provided. Detailed descriptions and respective specifications are included (parameters appearance and dimensions). Primary packaging materials comply with respective Ph.Eur. requirements (i.e. Ph.Eur. 3.2.1 and Ph.Eur. 3.2.9). It is stated that the glass vial may include a hydrophobic coating to aid with the lyophilization process. The qualitative composition of the hydrophobic coating should be stated and unambiguously laid down in respective dossier section. The dossier should also be updated to include the manufacturer of the elastomeric closures and Certificates of Analyses for each immediate packaging component (see recommendation 2.2.6).

The applicant states that a study to test for leachables in the finished product from the container closure will be conducted using various screening analytical methods. This is acceptable considering the dosage form (solid; reconstituted product has short contact time at moderate temperature, i.e. room temperature) and compendial quality of primary packaging materials. Overall, the choice of the container closure is therefore regarded as justified.

Manufacture of the product and process controls

The two proposed manufacturers are clearly stated. The manufacturing process of Veklury powder for concentrate for solution for infusion consists of the following main steps: compounding of components, pH adjustment (with HCL and/or NaOH), bioburden reduction filtration, sterile filtration, vial filling, lyophilisation, capping and product inspection. A manufacturing process flow chart and a narrative description were provided. There are no isolated intermediates. The manufacturing processes at both proposed sites are similar. The submitted information indicate that currently manufactured batches are of consistent a quality that is appropriate and comparable to that of clinical development batches. However, a SOB as discussed below, with a view to confirming that the quality of future batches will also remain appropriate and comparable to that of clinical development batches over the entire life cycle of the product is warranted in this respect. In order to ensure batch to batch consistency of the Powder for Concentrate for Solution for Infusion the MAH should expand description of the manufacture of the finished product with more details, by providing the actual process validation report, by justifying the level of betadex sulfobutyl ether sodium, by clearly defining the batch size in line with process validation studies and per manufacturing site, by defining process parameters and acceptance criteria and by introducing additional in-process controls**.**

Regarding the batch size, any change in batch size outside of the proposed range of the batch sizes should be applied for by submission of a variation. The process description should further specify the mixer speed, the conditions of sterilisation for filters, glass vials, rubber stoppers and flip-off seals, and in addition, clearly state the type of filters (sterilising and non-sterilising). Operating parameters and in-process controls are indicated but a test for container closure integrity should be included as in-process control and filter integrity test acceptance criteria should be given. Holding times should be included in the process description too. Moreover, the equipment working capacity should be indicated for the lyophilisation step. With regard to the lyophilisation step, the impact of freezing rate and annealing time on quality attributes and manufacturing efficiency should be discussed and the equipment working capacity should be indicated for the lyophilisation step.

Critical manufacturing steps should be referenced, and their control should be described. In addition, the grade of environment for the preparation of solutions as well as for the filling of the final material into bulk containers have been performed should be confirmed and the bioburden level before prefiltration should be given (see recommendation 2.2.6). The presented batch formula is in line with the composition stated above. Batch quantity is given based on the theoretical amount of bulk solution. The theoretical number of filled vials should be included in the batch formula for each described batch size (see recommendation 2.2.6).

Process validation

Due to the aseptic processing step as well as the lyophilisation, the manufacturing process is regarded to be a non-standard process according to Annex II of the process validation guideline. Accordingly, process validation data for production scale batches should be presented for both proposed manufacturers. In-process control and release data for 4 production scale batches manufactured by one of the proposed manufacturing sites and 8 production scale batches manufactured by the second proposed manufacturing site are presented. Data indicates that the processes run at both proposed sites are suitable to consistently

manufacture finished product of specified quality. Moreover, the presented data show that the quality of product manufactured at the two proposed commercial sites, as well as the initial clinical material from the development manufacturing site, is similar. Nevertheless, an actual process validation report is missing and should be submitted also as mentioned above; especially information on sampling is relevant to confirm the appropriateness of the presented data**.**

Appropriate filter validation data were also presented. However, actual filters used in routine production are still to be confirmed and the filter integrity test acceptance criteria should be clarified also as mentioned above. As discussed previously the choice of the sterile filtration/aseptic processing is considered acceptable.

In order to confirm the appropriateness of the aseptic processing of sterile bulk product for Concentrate for Solution for Infusion the MAH should submit the media fill results. Specifically results for three complete runs from each of the manufacturing site should be presented, simulating the whole manufacturing process from mixing of bulk solution to sealing of vials including routine and worst- case interventions. The actual holding times of each step in the study and the maximum processing time should be also be included in the process description as discussed above.

Product specification

The finished product release and shelf life specifications include appropriate tests for appearance (visual), identification (UPLC, UV), reconstitution (time, visual), water content (Ph. Eur.), assay (UPLC), degradation products content (UPLC), pH of solution (Ph. Eur.), uniformity of dosage units (Ph. Eur.), sterility (Ph. Eur.), bacterial endotoxins (Ph. Eur.) and particulate matter (Ph. Eur.).

The finished product specification includes all parameters relevant for the dosage form. The proposed limits have been justified but should be revised or further justified in line with batch and stability data. In order to improve the control strategy for the Powder for Concentrate for Solution for Infusion product the MAH should revise the excipient and finished product specifications by revising the limits for assay, impurities and water content in line with batch and stability data, relevant Ph. Eur. requirements and guidelines, as applicable. Specifically, the limit for assay during shelf-life and for water content and should be tightened unless otherwise justified Regarding the impurities, no product-specific impurities are known, therefore characterization of impurities in the finished product is in-line with assessment regarding active substance. The specified limits for impurities are either qualified by toxicological studies or the limit (for one impurity) was set considering it is an (active) metabolite. However, the proposed impurity limits should also take into account batch- and stability data and be revised accordingly. In addition, the limit for unspecified degradation products should be lowered to NMT 0.2% to be in line with the ICH Q3B guideline’s identification threshold (0.2%)

A risk assessment for potential elemental impurities in was conducted in accordance with ICH Q3D. Results show that content is well below the maximum allowable concentration based on the permitted daily exposure established for parenteral route of administration and thus no control of any elemental impurities is warranted.

A risk evaluation regarding potential presence of nitrosamines has been provided and is regarded as acceptable.

Analytical methods are adequately described, and validation data were provided for the in-house non-compendial methods according to ICH Q2 guideline. Satisfactory information regarding the reference standards used in the routine analysis of finished product has been presented.

Batch analysis

Batch analysis data was provided for eight commercial scale batches from the first commercial manufacturer and from four commercial scale batches from the second. The provided data comply with respective specification limits but should results should be reported for all parameters included in the specification (e.g. data on reconstitution time is missing) for completeness of information. In addition, and for the same reason, the actual numerical results should be reported instead of "traces" should be reported for the unspecified impurity. Overall the results indicate consistent manufacture of the finished product.

Stability of the product

Stability data for three commercial scale batches from the development site and one commercial scale batch from one of the proposed commercial sites have been provided. Samples have been stored in the proposed packaging for up to 12 months under long term conditions 30 °C/75% RH and for six months under accelerated conditions (40 °C/75% RH) according to current ICH guidelines. Confirmation was given that the containers used in the stability studies are the same as those proposed for routine storage.

The stability parameters tested were appearance, reconstitution, pH, water content, assay, degradation product content and particulate matter. All methods used are well validated and shown to be stability indicating. No significant changes were observed in any of the monitored parameters under any storage conditions compared to the initial values. Accelerated storage showed no increase in degradation impurities nor decrease in assay. Therefore, the shelf-life is applicable without any storage restriction.

Supportive data for one pilot and one commercial scale batch of the 150 mg strength (by the development and by one of the proposed sites respectively) for up to 36 months under long-term conditions were also submitted.

From the provided data it can be shown that there is no change in assay and no increase in degradation products. All results comply with respective acceptance limits. Only one of the supportive batches showed an out of specification (OOS) result regarding assay after 6 months of long-term storage. However, this batch also showed an assay at the lower limit of specification limit even at T=0. During storage, decrease of assay is comparable to the other batch data provided.

The submitted supportive stability results for 150 mg development strength demonstrate that the product is stable at any tested storage condition over the complete evaluated period of time (36 months long-term / 6 months accelerated conditions). Long-term stability results for the proposed 100 mg strength, which are available for up to 12 months storage, are in line with that finding. The stability profile of product batches at accelerated storage conditions is similar irrespective of the manufacturing site and/or fill volume (100 mg vs 150 mg). The supportive stability data presented for product batches of 150 mg strength are considered to be representative for the 100 mg strength because the composition of both strengths is qualitatively and quantitatively identical, the batch release data demonstrate that the product quality is similar irrespective of the manufacturing site and/or fill volume and the vial of the 150 mg represents a worst case scenario in terms of head space volume.

No photostability studies have been conducted with the powder presentation, but reference is made to studies on the concentrate presentation. This is acceptable taking into account that the concentrate presentation is less stable than the powder presentation. Based on the data from the concentrate presentation the finished product is photostable.

In-use stability studies have been extrapolated to the powder from the concentrate presentation. This is acceptable taking into account that, after reconstitution, the concentration of remdesivir in solution is the same as the concentrate (5 mg/ml). Moreover, the same instructions for dilution, administration and storage are applied to both formulations. However, it is noted that according to SmPC section 6.6 the dilution regimen for the powder for concentrate for solution for infusion after reconstitution (dilution with 0.9%

saline solution) is different; the concentrate is diluted to 250 ml whereas the reconstituted powder solution may be diluted to 100 or 250 ml.

In order to further substantiate the recommendations for reconstitution and storage of the Powder for Concentrate for Solution for Infusion product the MAH should submit in-use stability data for reconstituted Powder for Concentrate for Solution for Infusion diluted to 100ml with 0.9% saline solution. Moreover, a justification for the different dilution regimens for Powder for Concentrate for Solution for Infusion (dilute to 100ml or 250ml) and Concentrate for Solution for Infusion (dilute to 250ml) should be provided. The potential for handling errors should be considered**.** Specifically, the rationale for the different dilution regimens for remdesivir powder for concentrate for solution for infusion and remdesivir concentrate for solution for infusion should be provided and the risk of handling errors should be addressed. Considering the current differentiated reconstitution instructions in the respective SmPCs section 6.6 and the fact that the product is intended for hospital use only, it is acceptable that this information is submitted post approval in the context of a SOB of the CMA. Furthermore, as the presented in-use stability data do not cover this alternative dilution regimen for the powder formulation, further data should be provided to support the proposed in-use conditions as stated in SmPC section 6.3.

Based on the data for the concentrate reconstituted, diluted solution for infusion may be stored up to 4 hours at room temperature (20-25°C) or 24 hours at refrigerated temperature (2-8°C). The reconstituted product should be diluted immediately.

In conclusion, based on the totality of data presented, the proposed shelf-life of 3 years as stated in SmPC 6.3 is accepted for the 100 mg powder for concentrate for solution for infusion.

Adventitious agents

No excipients of human or animal origin are used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The applicant has applied for conditional marketing authorisation (CMA). In the context of the current public health emergency situation due to COVID-19 pandemic and the development history of the proposed medicinal products, the submitted quality documentation is considered sufficient for CMA approval.

Active substance

Remdesivir is an active substance that is not subject of an official compendium. Remdesivir is a chemically synthesised molecule, described in a two-step GMP manufacturing process. Information on development, manufacture and control of the active substance has been presented in the dossier. The submitted information indicate that currently manufactured batches are actually of a quality that is appropriate and comparable to that of clinical development batches. A number of issues have been identified in relation to the active substance that should be followed-up post approval as Specific Obligations **(SOBs)** in the context of the CMA. These relate to the synthetic process starting materials and process description. The purpose of these SOBs is to provide more detail in the dossier in order to confirm that a comprehensive control strategy is, and will be, in place throughout the future lifecycle of the product. The proposed control strategy presents no major deficiencies but should be further substantiated with regard to the formation of potential impurities in the proposed and redefined starting materials and the suitability and adequateness of the proposed controls should be further justified. The control strategy should also be improved with regard to certain active substance specification parameters and limits that should be revised in line with the presented batch analysis and stability data. The analytical procedures applied during development and proposed for quality control are all adequately described and validated as appropriate. The primary packaging of the active substance has been described and the proposed retest period of 48 months if stored below 30°C is

acceptable. Additionally, recommendations are made on how to further improve the quality documentation (see 2.2.6). The applicant has committed to pursue these issues, listed in List 1, as they have been discussed above in this report and detailed in the *Appendix* of this report within an agreed timeframe.

Finished product

Two pharmaceutical forms have been developed; a concentrate for solution for infusion 100 mg (5 mg/ml) and a powder for concentrate for solution for infusion 100 mg (5mg/ml after reconstitution). Pharmaceutical development of both pharmaceutical forms was presented in detail. Clinical and commercial formulations and manufacturing processes are similar. Excipients are of compendial grade and common for these type of dosage forms. Information on manufacturers, batch formula and manufacturing process is given. The manufacturing processes for the finished product (both pharmaceutical forms) are non-standard. The submitted information indicate that currently manufactured product batches are actually of a quality that is appropriate and comparable to that of clinical development batches. A number of issues have been identified related to the finished product that should be followed-up post approval as Specific Obligations **(SOBs)** in the context of the CMA. These relate to the manufacturing process description, process validation, aspects of the control strategy and for the powder form only, in-use stability information. The purpose of these SOBs is to provide more detail in the dossier in order to confirm that a comprehensive control strategy is, and will be, in place throughout the entire future lifecycle of the product. Satisfactory batch analysis results of the process validation batches have been provided but should be complemented by the full validation reports. The selected sterilisation processes are sufficiently justified. Additional details regarding sterile filtration and aseptic processing are required. The submitted production scale IPC and batch release data indicate that the processes run at the proposed finished product manufacturing sites are suitable to consistently manufacture finished product of specified quality. The proposed control strategy presents no major deficiencies but should be improved to be considered comprehensive. The product specifications contain all relevant parameters however, proposed limits should be further adjusted in line with batch analysis and stability data, and process validation results. A risk assessment regarding potential nitrosamine impurities has been provided and is regarded as acceptable. The container closure systems are acceptable. The presented stability data justify the proposed shelf-lives, but additional information is required to fully justify the in-use stability of the powder for concentrate for solution for infusion. The above issues should be followed-up post approval as Specific Obligations in the context of the CMA in order to ensure batch to batch consistency and thereby confirm the efficacy and safety of the medicinal product over its future lifecycle. Additionally, recommendations are made how to further improve the quality documentation (see 2.2.6). The applicant has committed to pursue these issues, listed in List 1, as they have been discussed above in this report and detailed in the *Appendix* of this report within an agreed timeframe.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this medicinal product, submitted in the emergency context of the current (COVID-19) pandemic, is considered to be consistent and acceptable in the context of a CMA.

Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in an acceptable way. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that from a quality perspective the product should have a satisfactory and uniform clinical performance.

The submitted information indicate that currently manufactured product batches are actually of a quality that is appropriate and comparable to that of clinical development batches. However, to ensure that the quality of future batches will also remain appropriate and comparable to that of clinical development batches over the life cycle of the medicinal product these issues are expected to be addressed though fulfilment of specific obligations, within the defined due dates. The identified issues discussed in this report and listed in

List 1 are compatible with the granting of a CMA.

The CHMP has identified the following specific obligations to address the identified quality developments issues that may have a potential impact on the safe and effective use of the medicinal product, and which therefore are needed to achieve comprehensive pharmaceutical (quality) data and controls for the product. In the *Appendix* of this report the specific points that need to be addressed in order to fulfil the imposed specific obligations are detailed.

List 1. The issues identified in quality documentation that require specific obligations.

1. In order to improve the impurity control strategy, lower the risk of contamination and assure comprehensive control throughout the lifecycle of the product, the MAH should, as agreed, re-define the starting materials of active substance synthesis, update all dossier documentation accordingly and implement the re-defined starting materials. The corresponding variation application must be submitted no later than by August 2020.
2. In order to ensure batch to batch consistency the MAH should expand description of the active substance synthesis with more details regarding yields, process conditions, unambiguously specifying when each process stage is applicable, materials used and their specifications, and defining the batch size. Further, process parameter ranges should be further justified or tightened.
3. In order to further substantiate the control strategy for the active substance the MAH should further elaborate the impurities discussion with regard to the formation of potential impurities in the current and redefined starting materials, the representativeness of the active substance used in the toxicological programme versus the commercial product, the contamination of the active substance by elemental impurities, and the proposed justification regarding the suitability and adequateness of the proposed controls.
4. In order to improve the control strategy for the active substance the MAH should revise the active substance specification by including the parameter "microbial limits", by revising the proposed limits for assay, impurities, residual solvents, and water in line with batch data and/ or relevant guidelines and Ph. Eur. as applicable, and confirm that the analytical method can control unspecified impurities GS-832698 and GS-832699.
5. In order to ensure batch to batch consistency of the Powder for Concentrate for Solution for Infusion the MAH should expand the description of the manufacture of the finished product with more details, by providing the actual process validation report, by justifying the level of betadex sulfobutyl ether sodium, by clearly defining the batch size in line with process validation studies and per manufacturing site, by defining process parameters and acceptance criteria and by introducing additional in-process controls.
6. In order to confirm the appropriateness of aseptic processing of sterile bulk product for the Powder for Concentrate for Solution for Infusion the MAH should submit the media fill results.
7. In order to improve the control strategy for the Powder for Concentrate for Solution for Infusion product the MAH should revise the excipient and finished product specifications by revising the limits for assay, impurities and water content in line with batch and stability data, relevant Ph. Eur. requirements and guidelines, as applicable.
8. In order to further substantiate the recommendations for reconstitution and storage of the Powder for Concentrate for Solution for Infusion product the MAH should submit in-use stability data for reconstituted Powder for Concentrate for Solution for Infusion diluted to 100ml with 0.9% saline solution. Moreover, a justification for the different dilution regimens for Powder for Concentrate for

Solution for Infusion (dilute to 100ml or 250ml) and Concentrate for Solution for Infusion (dilute to 250ml) should be provided. The potential for handling errors should be considered.

9. In order to ensure batch to batch consistency of the Concentrate for Solution for Infusion the MAH should expand the description of the manufacture of the finished product with more details by providing the actual process validation report, by justifying the level of betadex sulfobutyl ether sodium, by clearly defining the batch size in line with process validation studies and per manufacturing site, by defining process parameters and acceptance criteria, by introducing additional in-process controls and by providing additional batch data.
10. In order to confirm the appropriateness of aseptic processing of sterile bulk product for Concentrate for Solution for Infusion the MAH should submit the media fill results.
11. In order to improve the control strategy for the Concentrate for Solution for Infusion product the MAH should revise the excipient and finished product specifications by revising the limits for assay, impurities and endotoxins in line with batch and stability data, relevant Ph. Eur. requirements and guidelines, as applicable.

2.2.6. Recommendations for future quality development

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

1. In order to improve the quality documentation, the dossier sections related to the active substance are recommended to be updated as following:

    a. The critical step leading to the Intermediate should also be included in the given in-process summary table.

    b. For lifecycle purposes, the synthetic scheme of the remdesivir process presented in S.2.2 should be updated with materials used during work-up. Further, it should be clearly shown in the synthetic scheme that the precursor of the isolated intermediate is not isolated by using square brackets.

    c. Relevant information should be shifted into the respective sections (S.2.3 and S.3) from section S.2.6. Updated dossier sections should be submitted.

    d. The specification for GS-5734 Intermediate should be completed with a test for assay. Adequate limit should be set. The used method should be described.

    e. The 1H-NMR spectrum for remdesivir should be presented with actual integrals. Further, peak-dense regions in both the 1H- and 13C-NMR spectra should be magnified. Section S.3.1 of the dossier should be updated accordingly.

    f. For the primary packaging a specification and a certificate of analysis should be provided including IR-spectra of the PE-foil.

    g. The conformity of the primary packaging to Ph. Eur. or to the EU regulation 10/2011 incl. amendments should be provided.

2. In order to improve the quality documentation, the dossier sections related to Remdesivir powder for concentrate for solution for infusion are recommended to be updated as following:

    a. The finished product is a powder for concentrate for solution for infusion. Yet, the applicant refers to it as 'Remdesivir for injection' in the MA dossier. The EDQM standard term 'powder for

concentrate for solution for infusion' should be used throughout the dossier.

b. Table 1 in P.1 should also depict the amounts of ingredients without overfill.

c. The theoretical number of filled vials should be included in the batch formula for each described batch size.

d. Confirmation is required in the dossier at which grade of environment the preparation of solutions that are to be filtered as well as the filling of the final material into bulk containers have been performed.

e. Bioburden level before pre-filtration is missing. The bioburden level before pre-filtration should be given

f. Provided batch data should show results for all parameters included in the specification (e.g. data on reconstitution time is missing).

g. In the batch analysis data provided the unspecified impurity has been reported as trace. The actual figures obtained should be given.

h. The manufacturer of the elastomeric closures should be stated.

i. Certificates of Analyses for each immediate packaging component should be provided.

j. It is stated in the footnote of the specification of the vial, that the glass vial may include a hydrophobic coating to aid with the lyophilization process. The qualitative composition of the hydrophobic coating should be stated and unambiguously laid down in respective dossier section.

3. In order to improve the quality documentation, the dossier sections related to Remdesivir concentrate for solution for infusion are recommended to be updated as following:

a. The finished product is a concentrate for solution for infusion. Yet, the applicant refers to it as 'Remdesivir (GS-5734TM) injection'. The EDQM standard term 'concentrate for solution for infusion' should be used throughout the dossier.

b. The composition should also be stated per ml Remdesivir concentrate for solution for infusion.

c. Table 1.P.1 should also depict the amounts of ingredients without overfill.

d. The theoretical number of filled vials should be included in the batch formula for each described batch size.

e. Bioburden level before pre-filtration is missing. The bioburden level before prefiltration should be given.

f. Critical manufacturing steps should be referenced, and their control described in P.3.4.

g. Confirmation is required in the dossier at which grade of environment the preparation of solutions that are to be filtered as well as the filling of the final material into bulk containers have been performed.

h. The manufacturer of the elastomeric closures should be stated.

i. Certificates of Analyses for each immediate packaging component should be provided.

2.3. Non-clinical aspects

Remdesivir (RDV, GS-5734) is a single diastereomer mono-phosphoramidate prodrug of the nucleoside analog GS-441524 that is intracellularly metabolized into an active analog of adenosine triphosphate (GS-443902) that inhibits viral RNA polymerases and has antiviral activity against members of the filoviruses (eg, EBOV, MARV), coronaviruses (eg, SARS-CoV, MERS-CoV, SARS-CoV-2), and paramyxoviruses (eg, respiratory syncytial virus [RSV], Nipah virus [NiV], and Hendra virus).

The non-clinical package for remdesivir includes in vitro data and in vivo efficacy data for various coronaviruses, including SARS-CoV-2, and a PK bridge to human exposure. Nonclinical in vivo studies were in general performed with a formulation of remdesivir in 12% (w/v) sulfobutylether B-cyclodextrin sodium (SBECD) in sterile water for injection, pH 3.5 +/-0.1, which is representative of the clinical formulations.

2.3.1. Introduction

2.3.2. Pharmacology

Primary pharmacodynamic studies

The primary pharmacodynamics of RDV is discussed in the clinical section (pharmacodynamics).

Secondary pharmacodynamic studies

Within cells remdesivir is stepwise converted by hydrolase and phosphoramidase cleavage to the nucleoside analog monophosphate (GS-719700) and GS-441524-monophosphate. Further phosphorylation by nucleotide kinases results in formation of the triphosphate GS-443902.

RDV and the (phosphorylated active metabolite) GS-441524 were broadly profiled in a suite of in vitro toxicity assays. GS-441524 was devoid of any effects at high concentrations, with the exception of effects on the proliferation of various hematopoietic stem cells, with CC_{50} values ranging from 9.6 to 13.9 µM. However, these concentrations are still > 10-fold above the systemic levels of GS-441524 reached following a 200-mg IV infusion of RDV. Both RDV and the nucleoside analog GS-441524 exhibit good margins in most in vitro toxicity assays.

A relatively narrow exposure margin of < 3 (i.e., ratio of in vitro CC_{50} and clinical free C_{max} of RDV) was observed for the cytotoxic effects of RDV in primary human hepatocytes after a prolonged incubation for 5 days. In addition, in a separate experiment, mitochondrial toxicity and/or cellular toxicity was detected when human hepatocytes were treated for 3 days with RDV (0.1 to 30 µM). Results of a mechanistic study performed in a 2D hepatocyte model measuring different cytotoxic endpoints indicate, that RDV appears to be more toxic to human than rat and monkey primary hepatocytes after 14 days exposure with IC_{50} values even below 1 µM. Major metabolites GS-704277 and GS-441524 displayed a reduced toxicity (IC_{50} values between 10 – 100 µM) as compared to RDV. In a further study conducted in a 3D hepatocyte model, these findings could not completely be resembled. No striking differences in toxicities on hepatocytes were observed between RDV and its metabolites, depending on time and concentration indications of hepatocyte toxicities were apparent for all compounds while in H&E tissue sections only subtle changes were observed. These findings might explain why hepatic findings in animals are sparse as compared to humans but do not allow to draw a final conclusion on the impact of each compound (RDV and/or metabolite) on observed human liver findings (see discussion on non-clinical aspects below).

No significant inhibition of any enzyme or receptor was evident in a limited secondary pharmacology screen at a single concentration of 10 µM for both the diastereomeric mixture GS 466547 and the nucleoside analog GS-441524. The concentration of 10 µM is considered as appropriate, it is about 10 and 20 times the free clinical Cmax of the diastereomeric mixture GS 466547 and the nucleoside analog GS-441524, respectively.

Usually several hundred receptors, enzymes and ion channels are investigated. However, together with the broad studies on cytotoxicity, the secondary pharmacology testing program is considered sufficient.

Safety pharmacology programme

RDV did show only a weak inhibition in vitro of the hERG channel, IC_{20} and IC_{50} values for the inhibitory effect were 7.5 µM and 28.9 µM, respectively; at least 6-fold and 26-fold, respectively, above the estimated free drug concentration (1.1 µM) at Cmax of the currently proposed 200-mg maximum clinical dose. According to Redfern et al., drugs are very unlikely to be tosadogenic when there is a 30-fold margin between Cmax and hERG IC_{50}.

IV administration of RDV to male cynomolgus monkeys at dose levels up to 10 mg/kg had no effect on any of the cardiovascular parameters tested. The NOEL for cardiovascular effects in male monkeys was 10 mg/kg RDV, the highest dose level tested. The exposures measured in the study itself were very low, resulting in very low animal:human exposures of 0.01 for RDV and 1.3 for GS-441524.In male monkeys administered 10 mg/kg in the 2 week repeat-dose toxicity study exposures to RDV and GS-441524 at the NOEL were approximately 1180 and 381 ng/mL, respectively, based on the Day 1 Cmax which corresponds to animal:human ratios of 0.2 for RDV and 2.5 for GS-441524. Due to the low exposure, the cardiotoxic potential for RDV cannot be assessed by the in vivo study.

RDV had no effect on tidal volume or minute volume; however, respiration rates were transiently increased in animals administered ≥ 20 mg/kg and returned to control levels by 24 hours postdose. The NOEL for respiratory effects in male rats was 5 mg/kg. GS-441524 exposure at the NOEL was approximately 315 ng/mL, based on the Day 1 Cmax in male rats administered 5 mg/kg in the 2 week repeat-dose toxicity study which corresponds to an animal:human ratio of 2.

RDV had no effect on neurological function. The NOEL for male rats was 50 mg/kg. GS-441524 exposure at the NOEL was approximately 2750 ng/mL, based on the Day 1 Cmax in male rats administered 50 mg/kg in the 2 week repeat-dose toxicity study (TX-399-2003), which corresponds to an animal:human exposure ratio of 18.

Pharmacodynamic drug interactions

Pharmacodynamic drug interactions studies have not been conducted. Some recommendations have been issued to further address this issue in future development studies. In addition, some recommendations have been introduced in the SmPC as a guidance. considering the potential risks. This section will be updated when new data become available. (see 2.4.4 and 2.4.5)

2.3.3. Pharmacokinetics

The prodrug remdesivir (GS-5734) distributes into cells, where it is subsequently metabolized to form the pharmacologically active nucleoside triphosphate metabolite, GS-443902.

<u>In vitro metabolism and stability</u>

Within cells remdesivir is stepwise converted by hydrolase and phosphoramidase cleavage to the nucleoside analog monophosphate (GS-719700) and GS-441524-monophosphate. Further phosphorylation by

nucleotide kinases results in formation of the triphosphate GS-443902. Dephosphorylation of nucleotide metabolites results in conversion to the major circulating metabolite GS-441524, which is not readily re-phosphorylated.

Formation of the pharmacologically active triphosphate, GS-443902, was observed in a number of human lung cell types in vitro including normal human bronchial epithelial (NHBE) and Calu-3 as well as in PBMC, macrophages, monocytes, and human microvascular endothelial cells (HMVEC). Once formed, GS-443902 has a half-life in excess of 15 h in the various cell types mentioned, following incubation with remdesivir in vitro.

Consistent with the presence of high esterase activity in plasma in many rodent species, remdesivir was unstable in rat plasma (t1/2 ≤ 0.9 min). Remdesivir was substantially more stable in non-rodent species with t1/2 ranging from 68.5 min in human to 630 min in dog.

[^{14}C]Remdesivir was metabolized by mouse, rat, monkey, and human hepatocytes, primarily via hydrolysis. The rate of biotransformation in mouse and rat was faster relative to monkey and human at both 1 and 10 μM concentrations. The remaining unchanged [^{14}C]remdesivir accounted for <10% of the total radioactivity in samples across all the species at 120 minutes. In all four species, most of the [^{14}C]remdesivir-derived radioactivity was associated with three major metabolites; GS-704277, GS-441524, and GS-441524-monophosphate generated via hydrolysis. GS-704277 was the predominant component.

In vivo metabolism

Following IV administration of 10 mg/kg [^{14}C]remdesivir to intact and bile duct-cannulated Sprague Dawley rats, most of the radioactivity in plasma, bile, and urine was associated with the nucleoside analog GS 441524. No unchanged remdesivir was detected in any of these matrices. The other major systemic metabolite, GS-704277, was also an abundant component in plasma and bile, contributing approximately 19% and 20.3% of the total radioactivity exposure through 36 and 24 hours, respectively.

Following IV administration of 10 mg/kg [^{14}C]remdesivir to monkeys, the nucleoside analog GS-441524 was the only circulating component in the AUC-pooled plasma sample and accounted for 100% of the total radioactivity exposure through 96 hours. However, profiles of individual plasma samples showed radioactive peaks associated with remdesivir, GS-704277, GS-441524 and GS-441524-glucuronide.

Following IV administration of 10 mg/kg [^{14}C]remdesivir to rabbits, unchanged remdesivir contributed <1% of the total radioactivity through 96 hours in plasma. GS-441524 was the major circulating metabolite in plasma and accounted for approximately 45% and desamino-hydroxy-GS-441524 contributed approximately 25% of the total radioactivity exposure through 96 hours, while profiles of individual plasma samples also showed peaks associated with GS-704277

Plasma pharmacokinetics

Plasma pharmacokinetics for remdesivir, GS-441524 and GS704277 were studied following single-dose IV administration in the rat, cynomolgus monkey, rhesus monkey and African green monkeys.

The clearance of remdesivir exceeded liver blood flow in all species. In the rat remdesivir and GS-704277 achieved maximal concentrations in plasma during the infusion and exhibited short terminal elimination half-lives of 0.05 and 0.25 h, respectively. The nucleoside analog, GS-441524, achieved maximal concentration in plasma of 7.82 μM and persisted with a terminal half-life of 6.2 h. In cynomolgus monkeys remdesivir and GS-704277 achieved maximal concentrations in plasma during the infusion and exhibited short terminal elimination half-lives of 0.29 and 0.84 h, respectively. The nucleoside analog, GS-441524, achieved maximal concentration in plasma of 1.15 μM and persisted with a terminal half-life of around 7.2 h. Also, in the rhesus monkey remdesivir was rapidly eliminated followed by the sequential appearance of GS-704277 and GS-441524. The plasma profiles of remdesivir, GS-704277, and GS-441524, following 10 mg/kg remdesivir

were consistent with those seen in cynomolgus monkeys. Plasma exposures to all metabolites showed roughly dose-proportional increases between 3 and 10 mg/kg following IV bolus administration.

Intracellular (PBMC) pharmacokinetics of GS-443902

Since all target cells relevant for SARS-CoV-2 infection are not fully understood and may not be easily monitored for drug levels, peripheral blood mononuclear cells (PBMC) were initially used as a surrogate to assess intracellular activation following remdesivir administration.

The intracellular (PBMC) pharmacokinetics of remdesivir and its metabolites following a single IV administration of 3 or 10 mg/kg remdesivir were assessed in male rhesus monkeys, Levels of GS-443902 in PBMC achieved a Cmax of 33.3 µM at 2 h and had an apparent intracellular terminal elimination t1/2 of approximately 14 h. This is in line with the t1/2 of 15 h observed in human PBMCs and other cell types following in vitro incubation with remdesivir. In human subjects at clinically relevant dosing, however, the t1/2 in PBMCs was 43 h at steady state. In the rhesus monkey PBMC exposures to all metabolites showed roughly dose-proportional increases between 3 and 10 mg/kg following IV bolus administration.

The concentration-time profile of GS-443902 in PBMC was assessed following multiple daily IV administration of remdesivir as either bolus or infusion at 5 mg/kg for 7 days in the Rhesus monkey. Formation of the pharmacologically active triphosphate, GS-443902, was observed in PBMCs, with accumulation to steady-state concentrations achieved by day 7. No marked difference in exposure of GS-443902 in PBMCs was observed between bolus or infusion administration following daily dosing for 7 days. The results of iv PK studies conducted in rats and monkeys (Cynomolgus and Rhesus) indicate that administration of remdesivir results in substantial exposure to remdesivir parent compound and subsequently formed metabolites in plasma and tissues. Both rat and monkey formed the intermediate metabolite GS-704277 and the nucleoside metabolite GS-441524. Whereas in rats remdesivir is quickly (within 0.05 h) removed, metabolism in monkeys is somewhat slower (t ½ for remdesivir is 0.3 h) and mimics more the kinetic in human (t ½ 0.89 h). GS-441524 is the predominant metabolite in plasma observed in all nonclinical studies, and no gender difference in tested animals was noted.

In the performed iv PK studies in rats and monkeys, concentrations of GS-441524 and its phosphorylated metabolites were determined in PBMC at different time points. The nucleotide metabolites are rapidly formed and accumulate in PBMC following IV administration of remdesivir. The triphosphate analog (GS-443902) was the predominant metabolite in PBMCs and showed a persistent activity at 24 h.

Distribution

Remdesivir showed moderate protein binding in the rat, cynomolgus monkey, and rhesus monkey with a free fraction ranging from 8.0% in rat to 14.2% in cynomolgus monkey. The free fraction in human was 12.1%. The metabolites GS-704277 and GS-441524 exhibited very low protein binding in plasma from all tested species. The blood/plasma concentration ratios for remdesivir were 0.71 and 0.76 for the rhesus monkey and human, respectively, and for GS-704277 1.36 and 1.19, respectively indicating some exclusion of remdesivir from the cellular fraction and some association with the cellular fraction for GS-441524.

The tissue distribution following a single intravenous dose of [14C]remdesivir at 10 mg/kg to male Sprague Dawley (SD; non-pigmented) and Long Evans (LE; pigmented) rats was determined by quantitative whole body autoradiography. [14C]Remdesivir-derived radioactivity was widely distributed to most tissues by the first collection time point (0.167 hours postdose) in both SD and LE male rats. Distribution of radioactivity was similar in both SD and LE rats. Most of the tissues reached maximum concentration (Cmax) by the first collection time point for both SD and LE rats. Low levels of radioactivity were detected in testes, suggesting [14C]remdesivir-derived radioactivity crossed the blood to testes barrier. Radioactivity was eliminated from majority of the tissues by 96 hours postdose in both SD and LE rats. No melanin binding was observed.

In SD rats, the tissues showing the highest maximum concentrations of radioactivity included kidney cortex, kidney, kidney medulla, liver, arterial wall, nonpigmented skin, cecum, urinary bladder, and esophagus. The tissues with the lowest Cmax values were brain medulla, spinal cord, brain cerebellum, brain cerebrum, and bone. Radioactivity was cleared from the majority of tissues by 96 hours postdose, with the exception of cecum, kidney, kidney cortex, kidney medulla, liver, nonpigmented skin, stomach, and urinary bladder. At 168 hours postdose, radioactivity was still quantifiable in kidney, kidney cortex, kidney medulla, liver, and nonpigmented skin.

In LE rats, the distribution of radioactivity was similar to SD rats, and the tissues showing the highest maximum concentrations of radioactivity included kidney cortex, kidney, kidney medulla, liver, cecum, urinary bladder, arterial wall, and pigmented skin. The tissues with the lowest Cmax values were brain cerebellum, brain olfactory lobe, eye lens, abdominal fat, and bone. Radioactivity was cleared from the majority of tissues by 96 hours postdose, with the exception of kidney, kidney cortex, kidney medulla, liver, and pigmented skin. At 168 hours postdose, radioactivity was still quantifiable in kidney, kidney cortex, and pigmented skin. No melanin binding was observed.

The distribution of remdesivir was also determined by liquid scintillation counting following a single IV administration of 10 mg/kg [^{14}C]remdesivir to male cynomolgus monkeys. Tissues showing the highest mean concentrations of radioactivity at 4 hours postdose, excluding GI tract, were gall bladder, kidneys, liver, prostate gland, salivary gland (mandibular), pancreas, and seminal vesicle(s). Notably, appreciable levels of radioactivity were also found in lung tissue, while some of the lowest levels were seen in bone, brain, eye and testis(es). Total radioactivity declined over 168 h; elimination of radioactivity was not complete, and radioactivity was still quantifiable in most tissues. At 168 hours, a mean of 8.26% of the administered dose was retained in the tissues, mostly in liver and muscle. Most of the radioactivity in select samples was associated with GS-441524, indicating metabolism of remdesivir. In the whole body autoradiography experiments in rats and radiolabel distribution study in monkeys the trace levels of ^{14}C-remdesivir reveal fast and widely distribution to most tissues by the first collection time point (0.167 hours). Distribution of radioactivity was similar in non-pigmented and pigmented rats, indicating no relevant melanin binding. In both species, tissues with the highest maximum concentrations of radioactivity included kidney and liver, at 168 hours postdose radioactivity was still quantifiable in kidney. Radioactivity were recovered in urine and faeces in rat and monkey, indicating renal and biliary excretion as the major routes of elimination in all studied animal species.

Excretion

The routes and extent of remdesivir excretion were determined after IV administration of 10 mg/kg [^{14}C]remdesivir to Sprague-Dawley rats, rabbits and cynomolgus.

In the rat means of 63.0% and 27.8% of the administered radioactivity were excreted in urine and faeces, respectively, by 168 hours postdose indicating renal and biliary excretion were the major routes of elimination. Mean overall recoveries of radioactivity after intravenous dosing to intact and bile duct-cannulated rats were 95.1 and 95.3%, respectively. In the rabbit means of 67.0 and 11.9% of the administered radioactivity were excreted in urine and faeces, respectively, by 168 hours postdose. Overall mean recovery of radioactivity after IV dosing to rabbits was 91.7%. In the cynomolgus, means of 33.6% and 25.6% of the administered radioactivity were recovered in urine and faeces, respectively, by 168 hours postdose, indicating that renal and biliary excretion were the major routes of elimination. Significant radioactivity was recovered in cage rinses, accounting for a mean of 16.9% of the dose. Overall mean recovery in monkeys was 78.8%.

Overall, the basic pharmacokinetic data obtained for remdesivir in various animal species together with the intracellular profiling and kinetics of phosphorylated metabolites, namely activation and persistence (up to 24 h) of the pharmacological active triphosphate GS-443902 in bronchoepithelial and lung tissue following IV administration in American green monkeys, support its clinical use in lung associated virus infections.

2.3.4. Toxicology

Single dose toxicity

No formal single dose toxicity studies were conducted. However, single dose PK studies in Wistar Han rat, cynomolgus monkey, and rhesus monkey were performed.

Repeat dose toxicity

Repeat-dose toxicity in rats and cynomolgus monkeys have been conducted, 2-week studies with a 4-week recovery period, and 4-week studies in both species. The 2-week GLP repeat dose studies incorporated a saline and vehicle control group. Dose levels in the 2-week GLP studies were based on single-dose IV pharmacokinetic studies in rats and cynomolgus monkeys, and target organ toxicity observed in a non-GLP repeat-dose 7-day IM study in cynomolgus monkeys.

The 2- and 4-week studies included a comprehensive battery of kidney function/injury biomarkers; the 2-week studies also included 4-week recovery periods to assess reversibility from any observed effects. In most studies, blood was collected for plasma analysis of remdesivir, the nucleoside metabolite, GS-441524, and the intermediate metabolite, GS-704277.

In addition, a 7-day non-GLP toxicity study with a 10-day recovery period in rhesus monkey was performed. An additional 7-day non-GLP study using intramuscular administration of GS-466547 (diastereomeric mixture) in cynomolgus monkeys was carried out.

In the **rat** repeated i.v. doses of RDV for 2 weeks resulted in decreases in body weight gain and food consumption, and clinical pathology and microscopic findings indicative of kidney injury and/or dysfunction in males administered ≥ 5 mg/kg/day and in females administered ≥ 20 mg/kg/day. Effects on body weight gain and food consumption, and clinical pathology and microscopic findings were mainly reversible after a 4-week recovery period. There was no NOAEL for males. The NOAEL for females was 5 mg/kg/day which corresponds to 0.6 x human AUC of GS-441524.

Also in the 4-week study in rats clinical pathology and microscopic findings indicative of kidney injury and/or dysfunction in animals administered ≥ 3 mg/kg/day, and unscheduled deaths of 2 females and decreased body weight gain and food consumption at 10 mg/kg/day were seen. Based on the nature and severity of the kidney changes the NOAEL was 3 mg/kg/day, which corresponds to 0.4-fold (males) and 0.2-fold (females) the human AUC of GS-441524.

IV administration of RDV to male **rhesus monkeys** for 7 days resulted in one high dose animal euthanized early on Day 6. The cause of morbidity was attributed to RDV-related kidney findings. These findings considered adverse at all dose levels consisted of increased mean urea nitrogen and increased mean creatinine indicating altered kidney function, with correlating histopathology findings of renal tubular atrophy and basophilia and casts. The kidney observations were considered adverse at all dose levels as there was a loss of tubules and resulting interstitial fibrosis in one recovery animal suggestive of the finding progressing to chronicity. Based on these results, a NOAEL cannot be assigned to any of the dose levels under the conditions of this study; animal:human exposure ratios were < 1 for both, RDV and GS-441524.

Whereas, IV administration of RDV to male and female **cynomolgus monkeys** for 15 days or 4 weeks at doses up to 10 mg/kg/day did not result in any adverse findings. However, these studies are of limited relevance as the doses administered are not sufficient to determine toxic effects. Exposure at the highest dose is in the range of therapeutic exposure, in both studies.

On the other hand, after daily IM administration of GS-466547 (diastereomeric mixture; 2.5, 7.5 and 15 mg/kg/day) to cynomolgus monkeys for 7 days (non-GLP), kidney changes similar to those noted in rats were observed. At 15 mg/kg/day, animals had adverse kidney changes (proximal tubular epithelial cell

degeneration/necrosis) that were visible macroscopically as pale kidney cortices and correlated with increased kidney weights in animals at ≥7.5 mg/kg/day. Clinical pathology changes in the blood and urine were compatible with renal dysfunction. The NOAEL was set at 7.5 mg/kg/day. At 7.5 mg/kg/day, the mean sex combined exposures on Day 7 were: AUC_{0-24} of 4350 ng·h/mL for GS-466547; AUC_{0-24} of 3370 ng·h/mL for GS-441524; and AUC_{0-24} of 2980 ng·h/mL for GS-704277. Thus, higher systemic exposure to metabolites were observed after IM administration which may explain the observation of kidney toxicity.

Taken together, in the IV repeat dose studies with RDV, toxicity findings were consistent with dose dependent and mainly reversible kidney injury and dysfunction at doses equal to or greater than 3 mg/kg/day in rats and 5 mg/kg/day in rhesus monkeys. There were no observable kidney changes in cynomolgus monkeys administered IV RDV at 10 mg/kg/day. Animal:Human ratios at the NOAEL were ≤ 1 in all repeated-dose toxicity studies.

The renal toxicity in the rat, cynomolgus monkey and rhesus monkey is extensive and occurs after a very short time. In the 2-week rat study the effects were mainly reversible, but it is not known whether this is the case after a longer treatment period. It is not understood why the applicant did not include a recovery phase in the 4-week studies. The good tolerability in the cynomolgus monkey is relativized by the fact that the highest dose of 10 mg/kg leads to exposures that are in the range of therapeutic exposures.

Based on cytotoxicity studies with HEK-293 cells overexpressing the human and rat variants of the organic anion transporters OAT1 and OAT3, the applicant concludes that rat nephrotoxicity is due to preferential rat OAT3-mediated uptake of the RDV metabolite GS-704277. According to the applicant, this toxicity is unlikely to occur in humans, because the HEK293 cell experiments suggest that human OAT1/3 transports GS-704277 with much less efficiency than the corresponding rat OATs. Moreover, plasma esterase activity responsible for GS-704277 formation is lower in humans as compared to rats, and therefore, GS-704277 is formed to a much lesser extent in humans. However, the presented in vitro data cannot explain the nephrotoxicity observed in rhesus monkeys. In addition, the in vitro data are not considered sufficient to exclude nephrotoxicity in human patients for the following reasons:

I. GS-704277 reaches a Cmax of 3130 ng/ml in rats after a 4-week administration of 10 mg/kg/day of RDV. This concentration, at which the animals develop clear signs of nephrotoxicity, corresponds to ~7.1 µM. This, however, is ~19-fold lower than the CC_{50} value of GS-704277 (137.4 µM) in rat OAT3-expressing HEK-293 cells. Thus, unknown factors other than OAT3-mediated transport may be responsible for rat nephrotoxicity.

II. Even if rat OAT3-mediated transport into tubular epithelial cells is the cause for rat-specific nephrotoxicity of GS-704277, certain patient subpopulations may show increased susceptibility for nephrotoxicity caused by RDV and/or metabolites for the following reasons:

- Certain OAT genetic variants (polymorphisms) may exist, which lead to a more efficient uptake of RDV metabolites into tubular epithelial cells, resulting in a higher nephrotoxicity risk.
- The extrusion of RDV metabolites from tubular epithelial cells, e.g. by multidrug resistance-associated protein (MRP)-mediated transport or other relevant transporters, has to be considered, too. Individual genetic variants of such transporters may lower extrusion of RDV metabolites and put certain patient subgroups at an increased risk of nephrotoxicity.

As the exact mechanism of the nephrotoxicity observed in preclinical studies is currently unclear, the occurrence of such adverse events in human patients cannot be fully excluded. This can only be clarified by clinical data. However, at least caution should be applied in clinical use, and constant monitoring is required, specifically with regard to potential renal adverse effects.

SBECD: The remdesivir drug product contains the excipient SBECD. According to EMA review approximately 250 mg/kg/day of SBECD (~15 g/day based on a 60 kg human) for 6 months is safe in humans older than 2

years. The RDV drug product concentrate contains 6.36 g SBECD per vial (0.105 g RDV) and the RDV drug product powder contains 3.146 g SBECD per vial (0.105 g RDV). Thus, with a daily dose of 100 mg RDV, 6360 mg or 3146 mg SBECD were administered, respectively; with a loading dose of 200 mg RDV, the twice amount. Hence, the limit of 15000 per day is not exceeded in the intended clinical use. However, the use of SBECD is contraindicated for patients with renal impairment. This is of particular importance considering the severe nephrotoxicity of RDV in rats and monkeys.

Genotoxicity

RDV and metabolite GS-441524 were negative in in vitro Ames tests. In a chromosome aberration assay in human peripheral blood lymphocytes RDV showed an equivocal response after metabolic activation and was negative without metabolic activation. In an in vivo micronucleus test performed in rats, RDV was negative up to doses of 50 mg/kg/d at GS-441524 exposures of about an order of magnitude higher than the anticipated human exposure. In conclusion, RDV and metabolite GS-441524 are not considered to be genotoxic.

Carcinogenicity

RDV is indicated for short-term use only, no carcinogenicity studies have been performed. This is agreed upon.

Reproduction and developmental toxicity

A complete program as requested by ICH M3(R2) and ICH S5 of reproductive and developmental toxicity studies was performed in rats and rabbits with intravenous injection of remdesivir.

In the fertility and early embryonic toxicity study in rats, a significant reduction in number of corpora lutea, implantation sites and viable embryos, and lower mean ovary and uterus/cervix/oviduct weights were noted at doses above 3 mg/kg/day (≈0.3x clinical exposure). No adverse effects on male reproductive performance or on spermatogenesis data were observed. Thus, the NOAEL for male and female fertility was 10 and 3 mg/kg/day, respectively. Furthermore, male and female systemic toxicity was noticed at 10 mg/kg/day in the fertility study in rats. The NOAEL was at exposures below human therapeutic exposure for the metabolites GS-441524 and GS-704277. Remdesivir did not show any adverse effects on male reproductive performance and fertility at exposures about 2-fold for GS-44125, respectively 5-fold for GS-704277, compared to human therapeutic exposures.

In the embryo-foetal development study in rats, no remdesivir-related adverse effects were observed and the NOAEL for maternal toxicity and embryo-foetal development was 20 mg/kg/day. In the embryo-foetal development study in rabbits, maternal toxicity was observed at 20 mg/kg/day, but no remdesivir-related adverse effects on embryo-foetal development were identified. Thus, the NOAEL for maternal toxicity was 10 mg/kg/day, and for embryo-foetal development 20 mg/kg/day. There were no effects of remdesivir on embryo-fetal development in rats and rabbits with NOAELs of 20 mg/kg/day in both studies. Remdesivir plasma concentrations were below the limit of quantification in rats indicating that remdesivir was rapidly cleared and extensively metabolised in this species. In rabbits, exposure to remdesivir was shown. The exposures at the NOAEL in comparison to human therapeutic exposures were about 4- to 7-times above human therapeutic exposures for the metabolites in the rat. In the rabbit, exposure levels at the NOAEL were 2-to 25-times for remdesivir and the different metabolites.

Placental transfer studies for remdesivir or its metabolites were not conducted.

In the rat pre- and post-natal development study, there were no adverse effects noted in any of the investigated parameters. Thus, the NOAELs for F_0 maternal toxicity, and F_1 developmental/neonatal, F_1 parental systemic, F_1 reproductive, and F_2 neonatal/early postnatal toxicity were all 10 mg/kg/day. Exposures at the NOAEL were about human therapeutic exposures for GS-441524 and 3-times human therapeutic exposures for GS-704277.

Remdesivir could not be detected in the blood of rat dams and pups. Dams were exposed to the metabolites GS-441524 and GS-704277 and exposure increased approximately with increasing doses of remdesivir. No accumulation was observed for the metabolites in maternal animals. Exposure to GS-441524 was shown for rat pups on PND 10, but concentrations of GS-704277 were not measurable. Altogether, Cmax levels of GS-441524 were higher in maternal rats than in pups with exposure ratios of 43- to 143-times. Milk transfer of remdesivir and/or the metabolite GS-441524 can therefore be assumed which should be considered for SmPC labelling.

Juvenile toxicity

No juvenile studies have been conducted with remdesivir. This is in agreement with the PDCO decision.

Local Tolerance

Remdesivir is intended for IV administration. Dedicated local tolerance studies with remdesivir have not been conducted; however, evaluation of local tolerance following IV administration was conducted in the repeat-dose GLP studies. In the 2-week rat study, remdesivir-related injection site observations included red discoloration of tail skin observed in males administered ≥20 mg/kg/day and females administered ≥5 mg/kg/day. In the absence of any correlating microscopic findings, these findings were not considered adverse. There were no treatment-related injection site changes observed in monkeys administered remdesivir IV up to 10 mg/kg/day for 4 weeks. Thus, no particular concerns on local tolerance have been identified. In addition, remdesivir is not a dermal or ocular irritant.

Phototoxicity

The ultraviolet-visible absorption spectrum of remdesivir exhibits absorbance maxima at 209, 246 and 274 nm. The molar extinction coefficients were 1.7 x 10^4 L $mol^{-1}cm^{-1}$ at 209 nm, 3.8 x 10^4 L $mol^{-1}cm^{-1}$ at 246 nm and 0.6 x 10^4 L $mol^{-1}cm^{-1}$ at 274 nm. Thus, no absorption above the threshold of 1000 L $mol^{-1}cm^{-1}$ within the range of natural sunlight (290 to 700 nm) is observed. In tissue distribution studies in Sprague Dawley and Long Evans rats following a single IV administration of [^{14}C]-remdesivir, high concentrations of radioactivity were observed in skin but binding to non-pigmented and pigmented skin was similar. No melanin binding was observed. Thus, remdesivir does not fulfil the criteria for further phototoxicity testing according to the ICH S10 guideline, and there are no phototoxicity concerns.

Immunotoxicity

No dedicated immunotoxicity studies have been performed with remdesivir. This is considered acceptable as no concerns were identified by standard assessments in repeat-dose toxicology studies.

Dependence

No specific studies on dependency of remdesivir were conducted. This is acceptable.

Mechanistic studies

Studies were conducted to investigate the potential of remdesivir and its major systemic metabolites, GS-441524 and GS-704277, to affect primary human and animal hepatocytes using several in vitro models. Data from these in vitro studies demonstrated that human hepatocytes are susceptible to remdesivir-mediated toxicity, likely due to the high cellular permeability and effective intracellular metabolism of the drug. GS-441524 and GS-704277 are unlikely to contribute significantly to changes in liver enzymes observed in humans treated with repeated doses of remdesivir due to their low systemic exposure and minimal effects on hepatocytes demonstrated in several independent studies.

Metabolites

The metabolite GS-441524 was tested in a non-GLP reverse mutation assay and concluded as negative. Apart from this in vitro study, no other dedicated studies were performed with remdesivir metabolites.

GS-441524 and GS-704277 are considered toxicologically qualified in the repeat-dose and reproductive toxicity studies.

Impurities

The proposed specifications of NMT 1.50% for GS-643132, and NMT 1.00% for GS-441524, GS-711463, GS-709194, GS-773151, GS-829104, GS-773085 and GS-772931A/B are considered acceptable based on toxicological qualification. In addition, the impurity GS-711463 was predicted non-mutagenic based on expert opinion.

Based on the negative results of the Ames test, GS-709200 can be considered as not-mutagenic and can be treated as class 5 impurity according to guideline ICH M7(R1).

2.3.5. Ecotoxicity/environmental risk assessment

A final conclusion on potential risk of remdesivir to the environment based on the available data cannot be drawn right now.

The applicant submitted an Environmental risk assessment with Phase I for Remdesivir, a pro-drug of the nucleoside analog GS-441524.

Initial screening $PEC_{surface\ water}$ values of 1.0 and 0.48 $\mu g \cdot L^{-1}$ for remdesivir and GS-441524, respectively, were calculated based upon the maximum daily dose (200 mg) of remdesivir. Both values exceed the EMA guideline action limit of 0.01 $\mu g \cdot L^{-1}$ therefore the $PEC_{surfacewater}$ values were refined by modifying the Fpen based on estimated potential patient population and the fixed treatment regime of the product. COVID-19 is an acute disease and hence remdesivir has a short treatment period of a maximum of 10 days. For COVID-19 reliable prevalence data is not available due to the novel nature of this disease, nor is prevalence a meaningful measurement for an acute disease. Instead the Applicant has estimated the patient population based on the latest confirmed case numbers available at time of writing. Using the modified Fpen, $PEC_{surfacewater}$ values of 0.003 and 0.0015 $\mu g \cdot L^{-1}$ were estimated and a Phase II assessment was not provided.

It is agreed that COVID-19 is an acute novel disease, with a presumable limited treatment period. Refinement based on limited treatment period can be accepted. However, a limit of 10 treatment days has not yet been identified in an SmPC. It cannot be excluded that prolonged treatment periods will be recommended in the future. It can be accepted that the treatment will be limited to one period per year per patient.

In addition, the prevalence data, or rather the number of estimated cases in the EU-population, is highly uncertain due to the availability / prioritizing of confirmatory testing and a daily increasing rate of confirmed cases. However, since the applicant considers that every confirmed case represents an individual requiring treatment with remdesivir a refined Fpen of 0.001 can be accepted at this moment.

The n-octanol/water partitioning behaviour of remdesivir was investigated using the shake-flask method. The measured log P was 3.2. The log P of GS-441524 was estimated, using the in-silico model KOWWIN, to be -1.79. No study data on the n-octanol/water partition coefficient value of remdesivir have been submitted, for GS-441524 the value is a calculated one by using a QSAR method. According to the EMA guideline on the environmental risk assessment of medicinal products for human use, the submission of data on a n-octanol/water partition coefficient value is part of a Phase I ERA to allow for a PBT screening. Hence, the log Kow should be determined experimentally. Studies performed in accordance with OECD Test Guidelines are preferred. A calculated value is generally not acceptable.

2.3.6. Discussion on non-clinical aspects

Pharmacology

The primary pharmacodynamics of RDV is discussed in the clinical section.

The secondary pharmacology testing program performed for RDV and the nucleoside analog GS-441524 is considered sufficient.

Considering the potential of RDV to affect mtDNA and induce cytotoxic liver effects slightly above therapeutically relevant drug concentrations ,the applicant was asked to include the risk of hepatoxicity to the safety concerns of the RMP and to provide relevant information on the risk of hepatotoxicity in e.g. section 4.2 and 4.8 of the SmPC document. The risk of hepatoxicity has been added to the safety concerns of the RMP to provide relevant information on the risk of hepatotoxicity in e.g. section 4.2 and 4.8 of the SmPC document (see clinical section for details).In addition, the applicant is requested to submit an integrated analysis of all available safety data from clinical trials investigating COVID-19 (CO-US-540-5776, GS-US-540-5773, GS-US-540-5774 and CO-US-540-5758) where this issue will be further evaluated.

Safety pharmacology data (cardiovascular, respiratory, CNS) do not indicate any obvious safety concerns. However, the exposure margins in the cardiovascular studies were low for both RDV (~ 0.2x) and GS-441524 (< 3x) compared to the clinical exposure at the recommended human dose.

Pharmacokinetics

The results of iv PK studies conducted in rats and monkeys (Cynomolgus and Rhesus) indicate that administration of remdesivir results in substantial exposure to remdesivir parent compound and subsequently formed metabolites in plasma and tissues. Due to the very fast (within a few minutes) disappearance of remdesivir in rats, the PK profile observed in monkeys seem to better mimic the human situation. Remdesivir (metabolite) was clearly distributed throughout the respiratory tissues, however, similar to the results from radiolabel distribution study highest levels of GS-441524 and phosphorylated metabolites were in kidney and liver.

Absorption, distribution, and metabolism studies indicate that the rat, the cynomolgus monkey, and the rabbit appear to be relevant species for the toxicological evaluation, at least based on the formation of most major metabolites. The active GS-443902 was shown to be formed intracellularly in the cynomolgus albeit possibly at a 3-4-fold lower rate than in humans. However, no studies on intracellular formation of GS-443902 was presented in the rat or the rabbit. Based on the high plasma esterase activity and the low half-life of remdesivir observed in the rat it is unclear if the active GS-443902 is formed at all in the rat. Formation in the rabbit has not been addressed. Therefore, the applicant should provide data on the intracellular formation of the active substance in the rat and the rabbit, as recommended by the CHMP. The pharmacokinetic studies were exclusively performed in male animals precluding any conclusions to be drawn on gender differences. Toxicokinetic analysis was however performed in both sexes.

In addition, the clinical mass balance study indicates presence of an unidentified major and possible human-specific metabolite M27 in plasma. Until M27 is identified, it is unclear if further non-clinical testing is warranted.

Finally, a detailed and comprehensive evaluation of potential interactions on enzymes and transporters is given in the Clinical AR (pharmacokinetic interaction studies), where several concerns are raised.

Toxicology

The non-clinical GLP safety program is in scope consistent with the ICH M3(R2) guideline for a product with a proposed dosing regimen for up to 2 weeks.

After repeated IV administration of remdesivir in GLP and non-GLP studies, signs of kidney injury (i.e. kidney tubular epithelium) and/or reduced function was evident as indicated by biomarkers at clinically relevant exposures in rats and rhesus monkeys. A similar kidney toxicity was seen in cynomolgus monkeys following IM administration of GS-466547 (racemate) but not following IV administration of remdesivir. A higher exposure of remdesivir and metabolites were observed after IM administration which may explain the presence of kidney toxicity.

The toxicity to kidney tubular epithelium was observed after short treatment durations and at or below clinically relevant exposures. While a full pathological examination was performed at study terminations at 2/4 weeks in rats and at 10 days in the rhesus non-GLP study, urine chemistry/biomarkers indicated functional disturbance and damage already after 4 days of treatment. Additionally, a death ascribed to renal toxicity was observed on Day 6 in rhesus monkeys.

The kidney toxicity is a concern for the patient population. No mechanism for the toxicity has been proposed although the Applicant speculates that the toxicity may be OAT3-dependent in rats. GS-704277, but not remdesivir or GS-441524, is an effective substrate of rat OAT3 and exhibits rat OAT3-dependent cytotoxicity. Whether a similar mechanism can explain the findings in monkeys is not clear. No further discussion on the mechanism for renal tubular damage observed in non-clinical species and the implications of these nephrotoxic effects in patients has been provided. The findings are described in SmPC section 5.3 and a warning for renal impairment is included in section 4.4. Given the limited clinical safety data, this is endorsed. Furthermore, administration of remdesivir is not recommended in patients with eGFR <30 mL/min unless the potential benefit of therapy outweighs the potential risk as the excipient betadex sulfobutyl ether sodium is renally cleared and accumulates in patients with decreased renal function, which may potentially adversely affect renal function. The risk of nephrotoxicity has been added to the safety concerns in the RMP. This if further discussed in the clinical section.

Another concern is that the exposures in the repeat-dose toxicity studies were generally low. In the rat 4-week study, the AUC exposure margins at NOAEL were 0.1/0.2-fold (males/females) for GS-441524, and 0.2/0.4-fold (males/females) for GS-704277. In the cynomolgus monkey study, the AUC exposure margins at NOAEL were 0.8-fold for remdesivir, 0.9-fold for GS-441524, and 1.8-fold for GS-704277. Thus, the repeat-dose toxicity studies cannot inform on potential risks (than kidney toxicity) that could occur in a clinical situation where exposure increases above the intended range (e.g. due to kidney or liver failure, an accidental overdose etc).

A complete reproductive and development toxicity program in rats and rabbits has been completed with no apparent findings other than adverse findings in female rats in the fertility and early embryonic development study. In this study, there were no effects on female reproductive performance (mating, fertility and conception) at any dose level. However, a significant reduction in number of corpora lutea, implantation sites and viable embryos, and lower mean ovary and uterus/cervix/oviduct weights were observed at the highest dose, 10 mg/kg/day. The Applicant is of the opinion that these adverse findings are consequences of stress/maternal toxicity. It is agreed that maternal toxicity was evident at this dose level. Lower mean body weight gains or body weight loss were noted during the pre-mating treatment period resulting in a 5.4% lower mean body weight on Day 27. At this dose level, lower mean maternal body weight gains were also noted during the gestation treatment period (GD 0-7). Food consumption was reduced accordingly. It is also agreed that the female reproductive system is sensitive to the stress associated with decreased food intake and/or decreased body weights. However, the most sensitive reproductive parameter is disturbance of the estrous cycle where no significant effect was noted. In addition, in the repeat-dose studies, there were no apparent findings (other than decreased body weights) indicating a significant stress response. Taken together, it cannot be agreed that the data are solid enough to conclude that the adverse effects in female rats are consequences of maternal stress and not human relevant as argued by the Applicant.

In the rat fertility and early embryonic development study, the AUC exposure margins at NOAEL were 1.9/0.2-fold (males/females) for GS-441524, and 4.7/0.4-fold (males/females) for GS-704277. In the embryo-foetal development studies, the AUC exposure margins at NOAEL were 1.8-fold (rabbits) for remdesivir, 3.9/4-fold (rats/rabbits) for GS-441524 and 7.4/25-fold ((rats/rabbits) for GS-704277. In the rat pre- and postnatal development study, the AUC exposure margins at NOAEL were 1-fold for GS-441524, and 2.6-fold for GS-704277.

An overall concern regarding the reproductive toxicity package is that exposures to remdesivir as well as to the two plasma metabolites GS-441524 and GS-704277 are generally low in comparison to the clinical exposure. As previously discussed (see above), it is also unknown if the active intracellular GS-443902 and the human unidentified major metabolite M27 are formed in rat and/or rabbits. Given these limitations and uncertainties, the overall conclusion is that the reproductive toxicity package is currently regarded as limited and SmPC sections 4.6 and 5.3 are updated accordingly).

The results of the 2D hepatocyte model indicate, that RDV appears to be more toxic to human than rat and monkey primary hepatocytes and that major metabolites GS-704277 and GS-441524 display a reduced toxicity as compared to RDV. The results of the 3D hepatocyte model do not completely resemble these findings. In conclusion, the data from hepatocyte (2D and 3D) models do not allow to draw a final conclusion on the impact of each compound (RDV and/or metabolite) on observed human liver findings.

A final conclusion on potential risk of remdesivir to the environment based on the available data cannot be drawn right now.

A list of recommendations has been issued to further address these points post-approval.

2.3.7. Conclusion on the non-clinical aspects

The only identified target organ of toxicity in non- clinical studies is the kidney. Kidney findings are described in SmPC section 5.3 and a warning for renal impairment is included in section 4.4.

In addition, the uncertainties in the human relevance of the reproductive toxicity package are handled by a strict SmPC labelling.

Finally, to characterise better the risk of hepatotoxicity and nephrotoxicity (in addition to the non-clinical data), both have been included in the RMP as safety concerns. Moreover, the applicant will submit an integrated analysis of all available safety data from clinical trials investigating COVID-19.

Another issue in the non-clinical dossier is the lack of data on the unknown major human metabolite observed in the clinical mass balance study (M27, see section 2.3.1). Until M27 is identified, it is unclear if this metabolite has been adequately qualified or if further non-clinical testing is warranted. From a metabolism perspective, there are also unclarities on the relevance of the animal species used in the reproductive toxicity package. Taking into account the emergency of the situation due to the pandemic, that the overall safety database available indicates a beneficial AE profile and that more data will be provided by the applicant post-approval (see list recommendations below), this point is considered acceptable at the moment pending further data.

With regards to the missing ERA studies and data, the CHMP made some recommendations to further address this issue (see above, ERA discussion and list below).

Considering the points discussed above, in the context of the obligation of the applicant to take due account of technical and scientific progress, the CHMP recommends the following points to be addressed:

a. The clinical mass balance study indicates presence of an unidentified major and possible human-specific metabolite M27 in plasma. It is expected that the applicant will address

whether this metabolite has been adequately covered in the nonclinical safety studies.

b. No studies on intracellular formation of GS-443902 was presented in the rat or the rabbit. Based on the high plasma esterase activity and the low half-life of remdesivir observed in the rat, it is unclear if the active GS-443902 is formed at all in rats. It is also unclear if the active metabolite GS-443902 is formed in rabbits. To resolve this unclarity, the applicant is asked to provide data on intracellular formation of GS-443902 in rats and rabbits.

   Additional non-clinical studies to address the identified uncertainties should be considered.

c. The applicant is asked to recalculate the Fpen, if necessary, once the length of the treatment period has been adequately established and reflected accordingly in the SmPC. In addition, the prevalence value (as calculated by the applicant as the fraction of confirmed COVID-19 cases by April 8th, 2020) should be revisited by Q2/2021, taking into account the most recent data. If indicated by the recalculated $PEC_{surfacewater}$, the ERA may need to be further updated with a Phase II assessment according to EMA guideline on environmental risk assessment (EMEA/CHMP/SWP/4447/00 corr 1*, June 2006 for both remdesivir and the active metabolite GS-441524.

d. The applicant is asked to provide suitable information on an experimentally derived n-octanol/water partition coefficient (log Kow) for GS-441524 and the full study report for remdesivir in order to assess their PBT potential. The log kow studies requested can be submitted as post-marketing measures

2.4. Clinical aspects

2.4.1. Introduction

GCP

The applicant confirmed that the NIAID-sponsored study CO-US-540-5776 and the Gilead-sponsored Phase 3 and Phase 1 studies supporting the efficacy, safety and clinical pharmacology of remdesivir were conducted under US investigational new drug applications and in accordance with recognized international scientific and ethical standards, including but not limited to the ICH Guideline for Good Clinical Practice and the original principles embodied in the Declaration of Helsinki. These standards are consistent with the requirements of the European Community Directive 2001/20/EC and the US Code of Federal Regulations, Title 21, Part 312 (21 CFR 312), as well as other local legislation.

CSRs for the NIAID-sponsored study CO-US-540-5776 and the Gilead-sponsored Phase 3 studies are still pending.

There is currently no information on GCP inspections of the bioanalytical site (QPS, LLC (Newark, US)), which is being requested to be submitted with the pending CSRs for the NIAID-sponsored study CO-US-540-5776 and the Gilead-sponsored Phase 3 studies.

Table 2 Tabular overview of clinical studies

Phase 1 studies*****:

Study ID/ Study period	**Study objective(s)**	**Study design**	**Subjects; Gender, Age range**	**Dosage regimen; route of administration**	**Total No. of subjects entered/completed**
GS-US-399-1812 13 Aug 2015 to 2 Nov 2016	To evaluate the safety and tolerability of a single-ascending dose of RDV To evaluate the PK of RDV and its metabolites	Single-center, blinded, randomised, placebo-controlled, first-in-human, single-ascending dose study	Healthy adult male and female subjects	Cohorts 1-6: 3 mg, 10 mg, 30 mg, 75 mg, 150 mg and 225 mg RDV/placebo, single-dose, IV over 2 h, **solution formulation** Cohorts 7-9: 75 mg and 150 mg RDV/placebo, IV over 2 h and 75 mg/placebo, IV over 30 min, **lyophilised formulation**	96 subjects enrolled 96 subjects completed
GS-US-399-1954 30-Nov-2015 to 24 Mar-2016	To evaluate the safety and tolerability of multiple doses of RDV To evaluate the PK of RDV and its metabolites	Single-center, blinded, randomised, placebo-controlled multiple-dose study	Healthy adult male and female subjects	150 mg/placebo QD, IV over 1 h for 7 or 14 days, **solution formulation**	24 subjects enrolled 22 subjects completed
GS-US-399-4231 14-Dec-2019 to 12-Feb-2019	To evaluate the PK, metabolism and excretion of a single [^{14}C]-RDV dose	Single-center, open-label, mass balance study	Healthy adult male subjects	Single dose 150 mg RDV, IV over 0.5 h	8 subjects enrolled 8 subjects completed

GS-US-399-5505 9-Sep-2019 to 23-Dec-2019	To evaluate the safety, tolerability and PK of multiple doses of RDV To evaluate the PK of RDV and its metabolites	Single-center, blinded, randomized, placebo-controlled, multiple-dose study	Healthy adult male and female subjects	200 mg RDV/placebo loading dose, followed by 100 mg RDV QD for 4 or 9 days, IV over 0.5 h, **lyophilized formulation**	36 subjects enrolled 30 subjects completed

* Up to now, four Phase 1 studies in healthy adult subjects have been conducted with two different intravenous RDV formulations contributing to the characterisation of the PK of RDV and its metabolites (GS 441524 and GS-704277, GS-443902).

Phase 2/3 studies:

Study Number	**Type of Study (PK, Efficacy, Safety)**	**Population**	**Planned sample size (N)**	**RDV Dosing Regimens; Dosage Forms; Routes of Administration;**	**Study Design and Type of Control**	**Study Status**
Protocol No. 20-0006	Phase 2/3 (per amendment), Efficacy, Safety	Adults with Laboratory Confirmed SARS CoV 2 Infection (moderate and severe)	572 1:1 rand. RDV/placebo (Enrolled 1063)	200 mg IV Day 1; Followed by 100 mg IV QD Days 2-10	Multicenter, Adaptive, Double-Blinded RCT (https://clinicaltrials.gov/ct2/show/NCT04280705)	ACTT1: Start 21 Feb2020 last patient-19th April 2020;
GS-US-540-5773	Phase 3; Efficacy, Safety, PK	Adults and adolescents with severe COVID-19	Part A (N=400) • RDV x 5 days (n=200) • RDV x 10 days (n=200) Part B to enrol total of appr. 6000 pat.	200 mg IV Day 1; Followed by 100 mg IV QD Days 2-5 or Days 2-10	Multicenter, Open-Label Study (https://clinicaltrials.gov/ct2/show/NCT04292899)	Start March 06,2020 Stop Part A April 27, 2020 Ongoing
GS-US-540-5774	Phase 3: Efficacy and Safety, PK	Adults and adolescents with moderate COVID-19	Part A (N=600) • RDV x 5 days (n=200) • RDV x 10 days (n=200) • SOC (n=200) Part B to enrol total of appr. 1000 pat. after Part A ended.	200 mg IV Day 1; Followed by 100 mg IV QD Days 2-5 or Days 2-10	Multicenter, Open-Label Study (https://clinicaltrials.gov/ct2/show/NCT04292730)	Start March 15,2020 Stop Part A ? Currently: Active, not recruiting Ongoing as
CO-US-540-5758 (China Severe)	Efficacy, Safety	Adults and adolescents with severe COVID-19	N=460 2:1 rand. RDV/placebo (enrolled 237; 158 RDV/79 Plac))	200 mg IV Day 1; Followed by 100 mg IV QD Days 2-10 Vs. Placebo	Multicenter, Double-Blinded RCT (https://clinicaltrials.gov/show/NCT04257656)	Start Feb 06,2020 Stop March 12, 2020 Terminated

2.4.2. Pharmacokinetics

Methods

RDV, GS-704277, and GS-441524 were analysed using validated LC-MS/MS methods in formic acid treated plasma, urine and semen. Several methods were available in plasma and urine, without cross-validation. A method in ammonium formate treated urine was also validated for all three analytes, due to a suspected instability of GS-704277 in formic acid treated urine.

A further method was validated for the analysis of the intracellular concentration of GS-441524 and GS-443902 in PBMCs (peripheral blood mononuclear cells).

Absorption

RDV has been developed for IV administration as it has insufficient hepatic stability for oral delivery.

- Bioavailability

Two IV formulations of RDV have been developed (ready-to use solution formulation and lyophilised formulation). The absolute bioavailability of both formulations is 100%.

The proposed clinical regimen for treatment of patients with COVID-19 is a loading dose of RDV 200 mg IV, followed by daily doses of 100 mg IV for up to 10 days. This regimen is being evaluated in the compassionate use programme and in the ongoing randomised clinical trials in patients with COVID-19.

The PK of RDV and its metabolites GS-441524, GS-704277 and GS-443902 (pharmacologically active triphosphate) after administration of the applied dosing regimen to healthy subjects was examined in study GS-US-399-5505.

In this study, RDV was readily detectable in plasma and reached peak concentrations at the end of infusion. The rapid disappearance of RDV (median t1/2 ~ 1 h) was followed by transient exposure to the intermediate metabolite GS-704277 (median t1/2 ~ 1.25 h) and more persistent plasma exposure to the nucleoside metabolite GS-441524 (median t1/2 ~ 27 h) and the PBMC-associated pharmacologically active metabolite GS-443902 (median t1/2 ~ 43 h).

Peak plasma concentrations of GS-704277 and GS-441524 were observed 0.75 h and 1.5 to 2 h after start of the infusion, respectively. AUC and C_{max} of the active triphosphate GS-443902 increased from 157 h*µmol and 9.8 µmol, respectively at Day 1 to 240 h*µmol and 14.6 µmol, respectively, after multiple dosing of 100 mg RDV.

Table 3: ***PK parameter of RDV and its metabolites following single-dose administration of RDV 200 mg on Day 1 and multiple-dose administration of RDV 100 mg on Day 2-10 in healthy subjects (study GS-US-399-5505)***

PK Parameter[a]	Single Dose RDV 200 mg Day 1 (N = 28)	Multiple Dose RDV 100 mg Day 5 and Day 10 Combined (N = 28)[b]
RDV		
AUC (h•ng/mL)	2860 (18.6)	1590 (16.6)[c]
C_{max} (ng/mL)	4380 (23.5)	2230 (19.2)
T_{max} (h)	0.67 (0.25, 0.68)	0.68 (0.25, 0.75)
$t_{1/2}$ (h)	0.90 (0.80, 1.03)	0.96 (0.86, 1.08)[c]
GS-441524		
AUC (h•ng/mL)	2190 (19.1)	2230 (18.4)
C_{max} (ng/mL)	143 (21.5)	145 (19.3)
T_{max} (h)	2.00 (1.50, 4.00)	1.51 (1.50, 2.00)
C_{24} (ng/mL)	64.8 (20.8)	69.2 (18.2)
$t_{1/2}$ (h)	—	27.4 (25.3, 30.3)
GS-704277		
AUC (h•ng/mL)	698 (25.9)	462 (31.4)
C_{max} (ng/mL)	370 (29.3)	246 (33.9)
T_{max} (h)	0.75 (0.67, 0.75)	0.75 (0.75, 0.78)
$t_{1/2}$ (h)	1.27 (1.14, 1.45)	1.23 (1.15, 1.38)
GS-443902		
AUC (h•µmol)	157 (32.9)[c]	240 (25.4)
C_{max} (µmol)	9.80 (46.6)	14.6 (40.6)
T_{max} (h)	6.00 (1.00, 12.02)	6.00 (1.00, 12.00)
C_{24} (µmol)	6.90 (45.8)	10.2 (49.5)[c]
$t_{1/2}$ (h)	—	43.4 (38.7, 48.9)[d]

CV = coefficient of variation; N = number of participants in a population; PK = pharmacokinetic; RDV = remdesivir (GS-5734™)

$AUC_{0\text{-}24}$ presented for Day 1 and AUC_{tau} presented for Day 5 and Day 10; C_{24} presented for Day 1 and C_{tau} presented for Day 5 and Day 10

a All PK parameters are reported as mean (%CV) except for T_{max} and $t_{1/2}$, which are reported as median (Q1, Q3); PK parameters are reported to 3 significant figures

b N = 26 (number of participants who completed study drug)

c N = 25

d N = 20

Source: GS-US-399-5505 CSR, Tables 15.10.1.1.6.1 to 15.10.1.1.6.4

- Bioequivalence

The pharmacokinetics of single doses of 75 mg and 150 mg of both RDV formulations (liquid and lyophilised) infused over 2 h were evaluated in healthy subjects in study GS-US-399-1812.

This study was not powered for formal bioequivalence testing between formulations. However, results show that plasma exposures of RDV and its metabolites GS-441524 and GS-704277 were similar between both formulations and dose proportional.

- Influence of food

RDV was developed for intravenous administration and thus, the food effect was not evaluated.

Distribution

After administration of multiple 100 mg doses, the mean volume of distribution of RDV was approximately 93L confirming RDV distribution to tissues as observed in preclinical studies.

RDV has moderate protein binding with a free fraction of 12.1% ± 0.7% in human plasma when tested at a final concentration of 2 µM *in vitro*. Protein binding for the metabolites GS-704277 and GS-441524 was about 1 and 2%, respectively.

The mean whole blood/plasma concentration ratio was of 0.76 ± 0.07 for RDV, while GS-441524 showed some association with the cellular fraction with a ratio of 1.19 ± 0.12. The mean blood cell/plasma concentration ratio was of 0.42 ± 0.17 for RDV, while GS-441524 had a ratio of 1.46 ± 0.29.

After a single IV dose of [^{14}C]-RDV in healthy male participants, the blood-to-plasma ratio of [^{14}C]-radioactivity was 0.68 at 15 minutes from start of infusion and increased over time reaching a ratio of 1.0 at 5 hours (GS-US-399-4231).

Elimination

RDV is extensively metabolised and then primarily eliminated in urine as the nucleoside metabolite GS-441524.

Based on the mass balance study (GS-US-399-4231), the mean CL of RDV was 1,171 mL/min and the mean renal CL was 128.5 mL /min, indicating that most of its elimination was via the nonrenal route of elimination.

Most of the dose recovered in the urine was as GS-441524 (48.6%) confirming that CLr was a major pathway for elimination of this metabolite. The observed CLr was 151 mL/min for GS-441524 and 164.5 mL/min for GS-704277.

After a single 30-minute infusion of [^{14}C]-RDV in healthy participants, the median terminal half-lives of RDV, GS-704277, and GS-441524 were approximately 1, approximately 1.3, and 27 h, respectively.

- *Mass balance*

Study GS-US-399-4231 was a mass-balance study where RDV was administered as a single, IV dose of radiolabeled [^{14}C]-RDV in 8 healthy male volunteers. Participants received a single dose of RDV 150 mg containing a mixture of both unlabeled and radiolabeled [^{14}C]- RDV via IV infusion over 0.5 hour (in the fasted state). Blood samples, urine and faeces were collected up to at least 168 h post-dose.

The cumulative mean (%CV) recovery of [^{14}C] radioactivity in urine plus faeces was 92.3% (1.83%), with 74.2% (5.833%) recovered from urine and 18.1% (22.837%) recovered from faeces. The majority of the radioactive dose recovery (84.5 %) in the combined matrices was achieved within 96 h post-dose. Mean recovery of unchanged prodrug in urine was low (10.3% of dose) and no unchanged prodrug was recovered in faeces.

- *Metabolism*

In the mass-balance study, most of the identified radioactivity in plasma (approximately 44.2%) was attributed to [^{14}C]-M15 (GS-441524); 14.2% was attributed to [^{14}C]-RDV and 10.6% to an unknown metabolite (M27), that could not be identified due to short retention time and coelution with other matrix components. The previously characterized intermediate metabolite, GS-704277, was not observed. Additional analysis is ongoing using accelerator mass spectrometry to further inform on the circulating species of RDV.

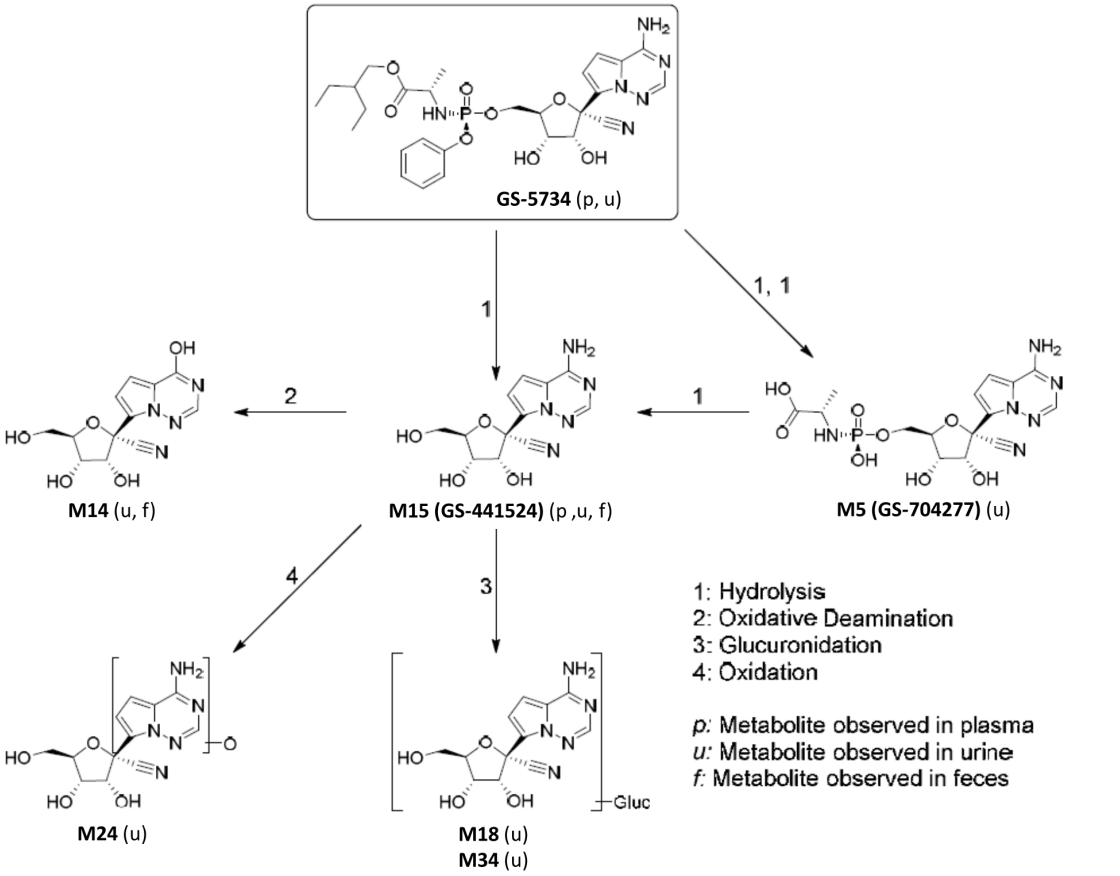
The predominant species detected in urine were GS-441524 (49%), followed by RDV (10%), GS-704277 (2.9%) and 6 other metabolites, accounting for 6% of the total radioactive dose (each less than 2%). In faeces the main metabolite was [^{14}C]- M14 (desamino-hydroxy- GS-441524 metabolite) (12%), with 0.46%

of dose recovered as [^{14}C]- M15 (GS-441524) and the remaining unidentified species accounting for a total of 0.84%.

Remdesivir is a diastereomerically pure substance. No data was provided on inter-conversion.

The proposed biotransformation pathway of RDV based on study GS-US-399-4231 is shown in the figure below:

Figure 2 Proposed intracellular metabolic pathway of RDV (GS-5734) in humans based on study GS-US-399-4231



Dose proportionality and time dependencies

Dose proportionality was shown between 3 mg and 225 mg, bracketing the doses proposed for therapy in adult COVID-19 patients.

Consistent with the short half-life, RDV did not accumulate upon daily dosing. The nucleoside analog metabolite GS-441524 reached steady-state at Day 4 and the intermediate metabolite GS-704277 at Day 1 after daily dosing of 150 mg RDV.

Intra- and inter-individual variability

No information on intra- and interindividual variability has been provided.

Pharmacokinetics in target population

Pharmacokinetic data of RDV in adult and paediatric patients with COVID-19 are not available. The applicant states that the PK of RDV in healthy adult participants is expected to be generalisable to SARS-CoV-2 infected patients with normal renal or hepatic function.

Special populations

The influence of *renal impairment* on RDV PK has not been studied yet.

The influence of *hepatic impairment* on RDV PK has not been studied yet. A substantial proportion of patients with acute Ebola virus disease who received treatment with RDV under the PALM and MEURI protocols had moderate to severe liver and renal abnormalities at presentation. No renal or hepatic abnormalities were attributed to RDV.

The effect of *gender, race* or *weight* on the PK of RDV has not been examined.

No PK data in *elderly* is available.

The PK of RDV in *pediatric patients* have not been evaluated. The safety and efficacy of adolescent patients (12 years and older) weighing ≥ 40 kg are being evaluated in the ongoing Studies GS-US-540-5773 and GS-US-540-5774. The proposed posology in adolescent patients ≥ 40 kg is the same as in adults and was based on predictions form the developed PBPK model. The disposition of RDV and metabolites is expected to be similar in adults and adolescents; thus, the PK in adult patients is expected to be generalizable to adolescents.

PBPK modelling

A PBPK model was developed to characterize the PK of RDV and the inactive primary circulating nucleoside metabolite, GS-441524, in adults. The model was verified based on its ability to describe the mean and variability of the adult exposures using data from the RDV Phase 1 program (GS-US-399-1812). The adult PBPK model was subsequently used to simulate steady-state paediatric (age range 0–18 yrs) exposures (AUC_{tau}), accounting for age-dependent changes in organ volume/size (liver and kidney), esterase expression, plasma protein binding, and organ blood flow.

Objective

The objective of RDV and GS-441524 PBPK model development was to allow prediction of paediatric exposures (AUC_{tau}) from adult data by incorporating the relevant physiologic and mechanistic information.

PBPK model development

Model development was based on the adult Phase 1 exposure data in healthy volunteers administered single doses of 75 mg RDV IV over 0.5 hr (lyophilized formulation) (GS-US-399-1812). The model was developed to estimate the exposure (AUC_{tau}) of RDV and its metabolite, GS-441524.

The observed, calculated or assumed model parameters that were incorporated and the physicochemical properties and information on the PK of each compound included in the model are described in Table 4 .

Table 4 Physiochemical and Pharmacokinetic Parameters used for development of the RDV parent and GS-441524 metabolite PBPK model in adult healthy volunteers.

	RDV	GS-441524	References
Dose used for adult PBPK model development	75 mg IV over 0.5 hr, lyophilized formulation	—	GS-US-399-1812
MW	602.6	291.3	Calculated from Structure (MarvinSketch v.16)
LogP	2.01	-1.88	
pKa	10.23 (acid) 4.86 (base)	4.86 (base)	
B/P Ratio	0.70	0.55	Assumed[a]
$f_{u,p}$	0.12	0.95	Observed (AD-399-2013) /QSAR Calculated[b]
Minimal PBPK Model K_p Scalar (Method 2)	2.1	17.6	Model Estimated from In Vivo Data (GS-US-399-1812)
CES1 S9 CL_{int} (µL/min/mg)[a]	325	—	
HEP CL_{int} (µL/min/10^6 cells)	—	0.575	
CL_r (L/hr)	5.71	9.85	Observed (GS-US-399-1812)

MW = molecular weight; LogP = water:octanol partition ration; pKa = acid dissociation constant; B/P = blood to plasma; $f_{u,p}$ = fraction unbound in plasma; K_p = plasma:tissue partition ratio; CES1 = carboxylesterase 1; S9 = subcellular liver fraction 9; CL_{int} = intrinsic clearance; HEP = hepatocyte; CL_r = renal clearance

a Assumptions made: 1) B/P ratios were assumed based on similar physicochemical properties to other nucleosides and nucleoside prodrugs (e.g. tenofovir and tenofovir alafenamide) and, 2) CES1 mediates this biotransformation and the same CES1 clearance of RDV was set as the formation clearance of GS-441524

b Calculated using GS-441524 physicochemical properties and the quantitative structure-activity relationship (QSAR) prediction module in SimCYP v.17

PBPK model evaluation

The default SimCYP Normal Healthy Volunteers population model was used for adult exposure predictions. Ten trials of N=9 subjects per trial were simulated to match the observed Phase 1 data (GS-US-399-1812). The observed and predicted AUC_{inf} of RDV and GS-441524 are depicted in Figure 3 and Figure 4, respectively. The developed PBPK model for RDV and GS-441524 adequately reproduces exposure mean and variability observed in the Phase 1 adult healthy volunteer population.

Figure 3 Observed GS-US-399-1812 and predicted RDV AUC inf after I.V administration of a single dose of 75mg RDV over 0.5hs (Lyophilized Formulation) to adult healthy volunteers

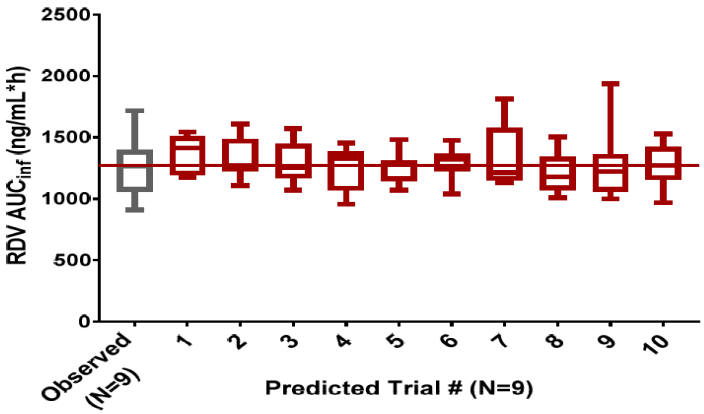


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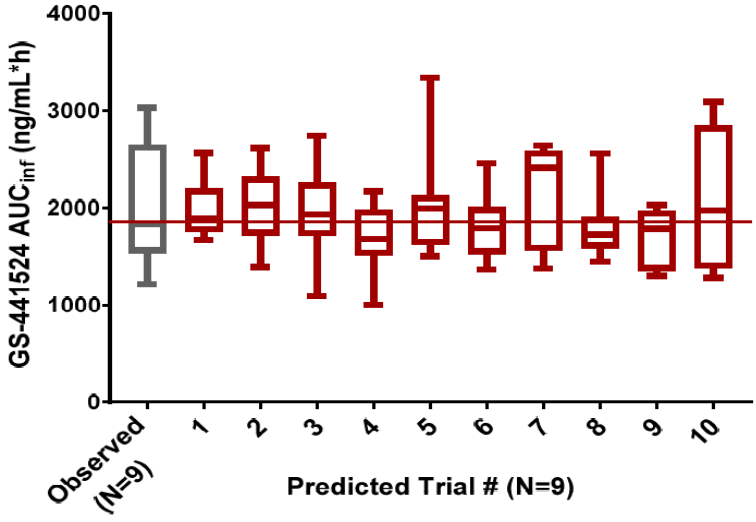
Figure 4 Observed GS-US-399-1812 and predicted GS-441524 AUC inf after I.V administration of a single dose of 75mg RDV over 0.5hs (Lyophilized Formulation) to adult healthy volunteers.



Exposure prediction in paediatric patients

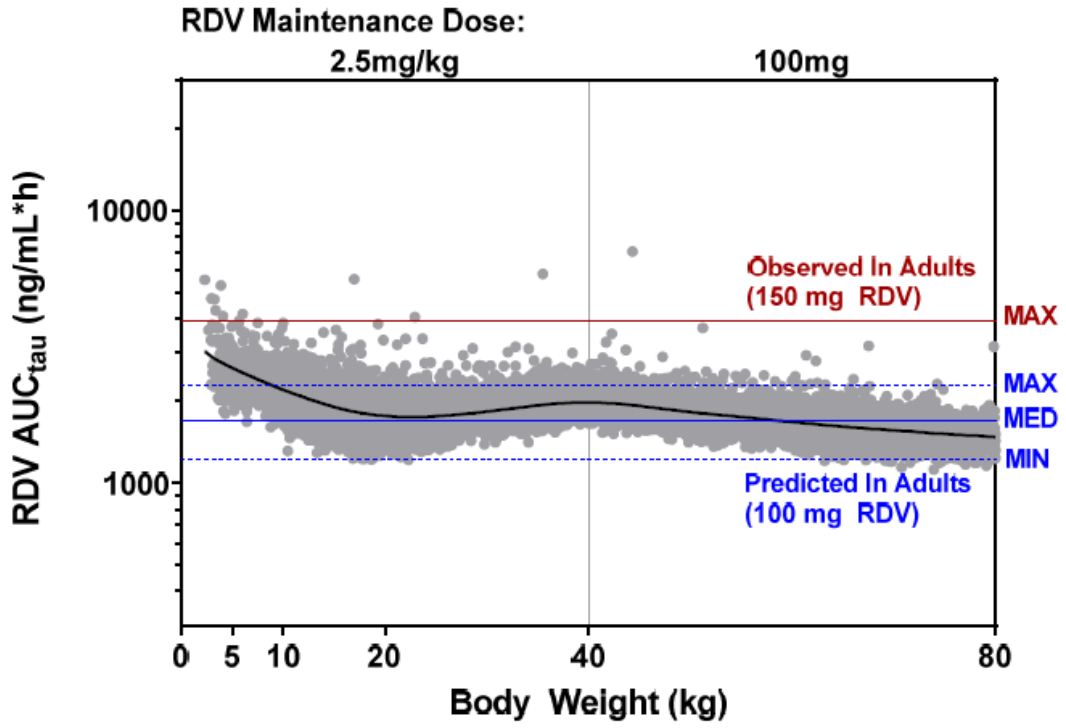
The adult PBPK model was applied to predict paediatric RDV and GS-441524 steady-state exposure after multiple daily IV administration of a therapeutic maintenance dose using the Paediatric Population Model in SimCYP and accounting for age-dependent changes in organ volume/size, enzyme expression, plasma protein binding, blood cell distribution, and organ blood flow. For these simulations, N=12000 subjects (0 to 18 years of age) were simulated.

For subjects weighing ≥ 40 kg, the adult dosage regimen was considered appropriate and as such, a loading dose of 200 mg RDV IV infused over 0.5 hr on Day 1, followed by daily 100 mg doses of RDV IV infused over 0.5 hr for 9 days was simulated. For subjects weighing ≥2.5 to < 40 kg, a weight-based regimen consisting of a loading dose of 5 mg/kg RDV IV infused over 0.5 hr on Day 1, then daily 2.5 mg/kg RDV IV infused over 0.5 hr for 9 days was simulated. Model-predicted systemic steady-state exposures ($AUC_{tau)}$ of RDV and GS-441524 are presented in

Figure 5 and

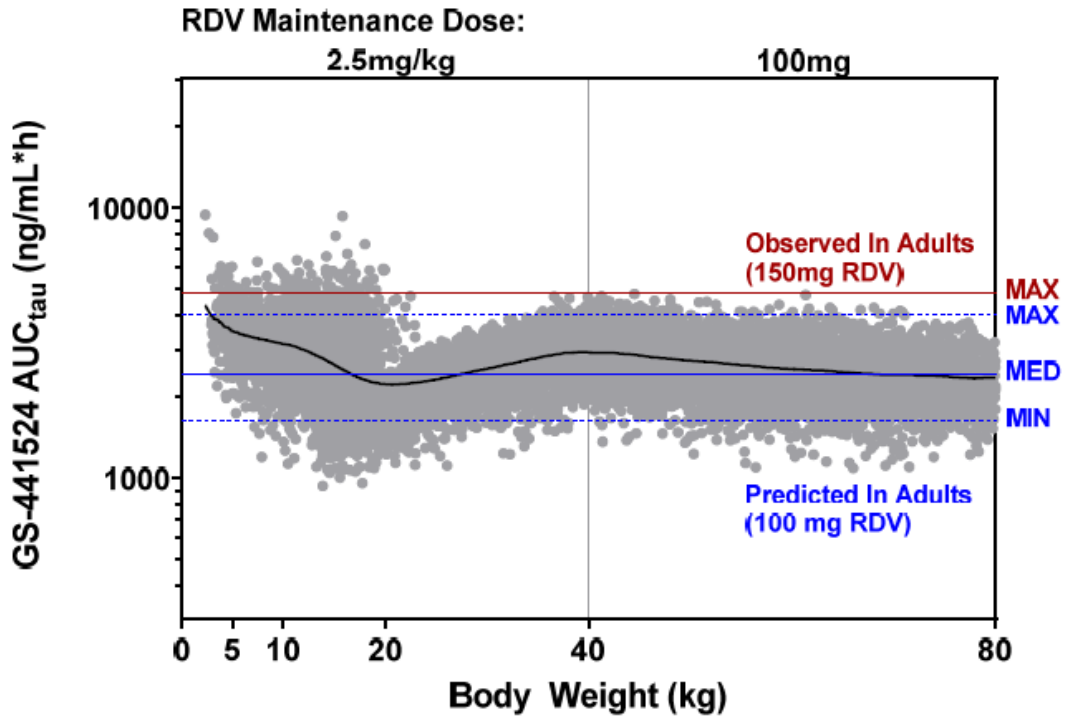
Figure 6 respectively.

Figure 5 Predicted RDV AUC tau in Paediatric subjects following I.V administration of daily over RDV 0.5hr (Lyophilized Formulation)



The simulated RDV dosage regimen for pediatric subjects, ≥ 40 kg, was a single RDV 200 mg loading dose on Day 1 followed by 9 once daily 100 mg maintenance doses.
The simulated RDV dosage regimen for pediatric subjects, < 40 kg, was a single RDV 5 mg/kg loading dose on Day 1 followed by 9 once daily 2.5 mg/kg maintenance doses.
The adult observed and predicted exposures are from the RDV Phase 1 program in healthy volunteers (GS-US-399-1812 and GS-US-399-1954).
Red line: maximum (MAX) observed AUC_{tau} after 14 daily doses of 150 mg RDV IV over 1 hr, solution formulation (red, GS-US-399-1954, Section 15.1, Table 4.1).
Blue lines: minimum (MIN), median (MED) and maximum (MAX) observed AUC_{tau} predicted from after a single daily dose of 75 mg RDV IV over 0.5 hr, lyophilized formulation (blue, GS-US-399-1812, Section 15.1, Table 4.1.1). Predicted AUC_{tau} values were determined for after 100 mg RDV maintenance dose based on observed AUC_{inf}*(100mg/75mg).
Gray dots: AUC_{tau} values predicted across the weight range based on the RDV and GS-441524 PBPK model.
Black line: LOWESS smoother line of predicted AUC_{tau} across the weight range.

Figure 6 GS-441524 AUC tau in Paediatric subjects following I.V administration of daily over RDV 0.5hr (Lyophilized Formulation)



The simulated RDV dosage regimen for pediatric subjects, ≥ 40 kg, was a single RDV 200 mg loading dose on Day 1 followed by 9 once daily 100 mg maintenance doses.
The simulated RDV dosage regimen for pediatric subjects, < 40 kg, was a single RDV 5 mg/kg loading dose on Day 1 followed by 9 once daily 2.5 mg/kg maintenance doses.
The adult observed and predicted exposures are from the RDV Phase 1 program in healthy volunteers (GS-US-399-1812 and GS-US-399-1954).
Red line: maximum (MAX) observed AUC_{tau} after 14 daily doses of 150 mg RDV IV over 1 hr, solution formulation (red, GS-US-399-1954, Section 15.1, Table 4.1).
Blue lines: minimum (MIN), median (MED) and maximum (MAX) observed AUC_{tau} predicted from after a single daily dose of 75 mg RDV IV over 0.5 hr, lyophilized formulation (blue, GS-US-399-1812, Section 15.1, Table 4.1.1). Predicted AUC_{tau} values were determined for after 100 mg RDV maintenance dose based on observed AUC_{inf}*(100mg/75mg).
Gray dots: AUC_{tau} values predicted across the weight range based on the RDV and GS-441524 PBPK model.
Black line: LOWESS smoother line of predicted AUC_{tau} across the weight range.

Pharmacokinetic interaction studies

Only *in vitro* data are available for interactions of RDV and its metabolites with other medicinal products.

The calculated cut-off values (according to EMA DDI guideline) used in the interpretation of *in vitro* data to predict potential interactions *in vivo* are listed below:

Table 5 Cut-off values used in the interpretation of in vitro data to predict potential interactions in vivo

Substance	Fraction unbound (%)	D1		D5	
		Cmax [µM]	50x Cmax,u [µM]	Cmax [µM]	50x Cmax,u [µM]
RDV = GS-5734	12.1	7.3	44.0	3.7	22.4
GS-441524	100	Same as D5		0.50	24.9
GS-704277	100	0.74	37	0.49	24.6
Data from study GS-US-399-5505 RDV D1 4378 ng/ml, D5 2229 ng/ml					

Enzymes

Substrate

- The enzymes responsible for the hydrolytic metabolism of RDV are unknown.
- RDV is a substrate of CYP2C8, 2D6, and 3A4 *in vitro*.

Perpetrator

- Using the day 1 cutoff, RDV is an inhibitor of CYP2B6 (Ki: 39.5 µM) , 2C8 (Ki: 24.1 µM), 2C9 (Ki: 43.1 µM), 2D6 (Ki: 39.3 µM), and 3A4 (Ki: 0.98 µM) *in vitro*
- Using the steady-state cutoff, *in vitro* inhibition was observed for CYP3A4
- RDV inhibited UGT 1A1 (IC_{50} 1.5 µM), 1A3 (IC_{50} 3.8 µM), 1A4 (IC_{50} 5.9 µM), 1A9 (IC_{50} 36.1 µM), and 2B7 (IC_{50} 16.2 µM), but not 1A6 *in vitro*. None of the potential UGT interactions was found clinically relevant, according to the mechanistic static model.
- GS-441524 and GS-704277 did not inhibit any of UGT 1A1, 1A3, 1A4, 1A6, 1A9 or 2B7 *in vitro*
- GS-441524 and GS-704277 are not inhibitors of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A4 *in vitro*
- RDV is not an inhibitor of CYP1A2 or CYP2C19 at clinically relevant concentrations *in vitro*
- RDV is an inducer of CYP1A2 and possibly 3A4 *in vitro*
- GS-704277 is an inducer of CYP1A2, 2B6 and 3A4 *in vitro*
- GS-441524 is not an inducer of CYP1A2, 2B6 or 3A4 *in vitro*
- Information on CYP inhibition is missing for major metabolite M27 and any further major metabolite
- Information on time-dependant inhibition by RDV is missing

Transporters

Substrate

- RDV is a substrate of PgP and OATP1B1, but not of BCRP and OATP1B3 *in vitro*
- Information is missing on whether RDV is a substrate of OAT1, OAT3 or OCT2

Perpetrator

- RDV is an inhibitor of OATP1B1 (IC_{50}: 2.8 µM), OATP1B3 (IC_{50}: 2.1 µM), BSEP (IC_{50}: 22 µM), and MRP4 (IC_{50}: 5.1 µM) *in vitro*
- RDV is not an inhibitor of PgP, BCRP, MRP2, MRP3 or NTCP *in vitro*
- Information is missing on whether RDV is an inhibitor of OAT1, OAT3 or OCT2

The ability of RDV to inhibit CYP enzymes and transporters, as well as its inducing capacity, has been only tested *in vitro* and *in-silico.*

An *in vivo* DDI study with rifampin is planned**.**

Due to the likelihood of co-administration of RDV and dexamethasone in severe COVID-19, the potential for this interaction was specifically addressed. Members of the Department of Pharmacology at the University of Liverpool hosting the well-recognized website: https://covid19-druginteractions.org/ concluded the following: "Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Remdesivir is a prodrug predominantly metabolised by hydrolase, with some involvement (in vitro) of CYPs 2C8, 2D6 and 3A4, and is transported by P-gp. Dexamethasone is a moderate inducer of CYP3A4 and P-gp. Induction is dose-dependent and occurs after multiple doses. Dexamethasone is unlikely to have a clinically significant effect on remdesivir as remdesivir has a moderate-high hepatic extraction ratio, and is used for a short duration in the treatment of COVID-19. Dexamethasone is a substrate of CYP3A4 and although remdesivir inhibits CYP3A4, due to remdesivir's rapid clearance after i.v administration, remdesivir is unlikely to have a significant effect on dexamethasone exposure." This evaluation is supported.

2.4.3. Pharmacodynamics

Mechanism of action

Remdesivir is intracellularly metabolized to form the pharmacologically active nucleoside triphosphate metabolite (RDV-TP, GS-443902). Biochemical studies demonstrated that RDV-TP acts as an analog of ATP and competes with the natural ATP substrate to selectively inhibit viral RNA-dependent RNA polymerases (RdRp). The primary mechanism of inhibition is incorporation of RDV-TP into nascent RNA chains by RdRp, causing delayed RNA chain termination during the process of viral replication. The coronavirus RdRp of SARS-CoV-2, SARS-CoV, and MERS-CoV were shown to incorporate RDV-TP more efficiently than ATP (based on steady-state kinetic parameters for single nucleotide incorporation) with selectivity values of 0.26, 0.32, and 0.35, respectively, when compared with ATP. Incorporation of RDV-TP for Coronavirus RdRp was also more efficiently than for other viral RdRp such as those from EBOV or RSV. In contrast to classic chain-terminators, inhibition is not seen immediately following the incorporated RDV-TP. For all three coronavirus RdRp complexes, a specific delayed RNA termination at position i+3 was observed. The structural reasons for the precise termination event remain to be elucidated.

Primary and Secondary pharmacology

In vitro antiviral activity

The in vitro activity of RDV in human airways epithelial (HAE) cells and other cell lines, as well as its selectivity, are described in the table below.

Table 6 In vitro activity of RDV against SARS-CoV-2 in HAE, Vero, and Huh 7 Cells

Virus	Cell Type	EC_{50} (µM)	CC_{50} (µM)	Selectivity Index (CC_{50}/EC_{50})
SARS-CoV-2 clinical isolate	HAE	0.0099	> 10	> 1000
	Vero	0.137 after 24 hours 0.750 after 48 hours	> 100	> 730 > 133
SARS/SARS-CoV-2 nsp12 nLUC	Huh7	0.0035	> 10	> 1000

CC_{50} = 50% cytotoxic concentration; EC_{50} = 50% effective concentration
Source: m2.6.3, Section 2.1, PC-540-2003, PC-540-2001, PC-540-2002, {Brown 2019, Sheahan 2017}

Effect of protein binding on antiviral activity has not been investigated.

Effect of other antiviral agents on the activity of RDV has not been investigated.

In vitro activity against other viruses

The in vitro antiviral activity of RDV on other viruses aside from SARS-CoV-2 has been analysed in several studies. RDV demonstrated potent antiviral activity for several Ebola viruses and strains (EC_{50}s ranging from 0.07 to 0.24 µM), Marburg virus (EC_{50} 0.061 µM), Junin virus (EC_{50} 0.47 µM), Lassa virus (1.65 µM), MERS (0.52 µM), respiratory syncytial virus A2 (EC_{50} 0.017 µM), HCV 1b (EC_{50} 0.097 µm), HCV 2a (EC_{50} 0.084 µM). It was found to be only weakly active for human rhinovirus serotype-10 (EC_{50} 2.5 µM). It was not active against Chikungunya virus and Venezuelan equine encephalitis virus (EC_{50} >20 µM) as well as HIV-1 (EC_{50} >50 µM) and HBV (EC_{50} similar to CC_{50}).

Viral drug resistance

The *in vitro* development of resistance to RDV in CoVs has been assessed by cell culture passaging of Murine Hepatitis Virus (MHV), a related animal CoV, in the presence of the RDV nucleoside analogue GS-441524. After 23 passages, two mutations were selected: F476L and V553L, which reside within the predicted fingers domain of the conserved right-hand structure of the RdRp. Further studies are considered necessary to better characterise the resistance profile of RDV *in vitro*, i.e. primary HAE cells infected with SARS-CoV2 and in SARS-CoV2 clinical isolates.

Introduction of the MHV resistance mutations into the corresponding residues of SARS-CoV polymerase (F480L and V557L) resulted in the same *in vitro* susceptibility changes (6-fold reduced susceptibility to RDV), suggesting that the conserved residues across divergent CoVs reflect conserved functions impaired by RDV, potentially implying common pathways to resistance across CoVs.

Pc-540-2006: Genetic Conservation of RNA-Dependent-RNA Polymerase of SARS-CoV-2 in Patient Isolates

The rapid spread of SARS-CoV-2 in the human population worldwide may result in viral diversification from the original common ancestor. These circulating clinical isolates could possibly include Amino acid substitutions positions that were previously shown to be associated with reduced susceptibility to RDV *in vitro* (SARS-CoV-2 positions F480 and V557) or other nsp12 amino acid residues that are predicted to be in close proximity to the binding site of RDV.

SARS-CoV-2 full genome sequences of 1993 clinical isolates from 52 countries collected between December 2019 and March 2020, were downloaded from public databases and compared to the references strain Wuhan-Hu-1 viral isolate (NC_ 045512).

Sequence alignments demonstrate that nsp12 of SARS-CoV-2 reference strain (Wuhan-Hu-1 viral isolate, NC_ 045512) exhibits 96% sequence identity with SARS-CoV, 71% with MERS-CoV, and 66% with MHV. The nsp12 amino acid substitutions in MHV nsp12 F476 and V553 associated with reduced susceptibility to RDV were identified to correspond to F480 and V557 SARS-CoV-2 nsp12, respectively and are conserved across all coronaviruses. Among n=1993 SARS-CoV-2 clinical isolates from December 2019 to March 2020 obtained from 52 countries, no amino acid substitutions were detected at the nsp12 residues F480 and V557 that are associated with reduced susceptibility to RDV *in vitro.* This observation suggests a low probability of pre-existence resistance to RDV among circulating clinical isolates of SARS-CoV-2.

Residues located in close proximity to the binding site of RDV were identified from a model of an elongating SARS-CoV-2 RdRp complex as previously described (PC-540-2005). This model was used to identify amino acids in nsp12 that directly interact with the metal ions or RDV-TP or may contribute to the inhibitor's delayed chain termination. No amino acid substitutions were observed at any of the identified residues in nsp12 that directly interact with the metal ions or RDV-TP or may contribute to the inhibitor's delayed chain termination. Furthermore, a larger set of residues were also considered that are located within 5Å and 10Å from the active site and residues that are located within 7Å of the primer RNA C1' positions. One substitution (A547V) within 10 Å of the active site was identified in one sequence of the 1993 clinical isolates investigated.

Other amino acid substitutions within nsp12 and the overall genetic drift across full genome sequences at the nucleotide level were evaluated. Amino acid substitutions in nsp12 were observed at other residues in 874/1993 (44%) clinical isolates. The most prevalent nsp12 substitution was P323L, which was observed in 812/1993 (41%) clinical isolates from 37 of 52 countries. All other variants were observed in less than 1% of clinical isolates each.

In addition, the number of nucleotide changes relative to the reference strain Wuhan-Hu-1 viral isolate (NC_ 045512) across the full genome for each clinical isolate was calculated. There were on average eight nucleotide changes from the reference for 1993 SARS-CoV-2 clinical isolates from December 2019 to March 2020.

In vivo activity (animal models)

Rhesus macaque model of SARS-CoV-2 disease

A rhesus macaque model was recently established by Munster et al., 2020 as a potential model of SARS-CoV-2 infection. Eight rhesus macaques (4 males, 4 females) were inoculated with a total dose of $2.6x10^6$ $TCID_{50}$ of SARS-CoV-2 via a combination of intratracheal (1.6×10^6 $TCID_{50}$), intranasal (4×10^5 $TCID_{50}$), ocular (2×10^5 $TCID_{50}$), and oral (4×10^5 $TCID_{50}$) routes. The animals were observed twice daily for clinical signs of disease using a standardized scoring sheet, as described previously {Brining 2010}. The predetermined endpoint for this experiment was 3 days post inoculation (dpi) for one group of 4 animals, and 21 dpi for the remaining 4 animals. Clinical exams were performed on 0, 1, 3, 5, 7, 10, 12, 14, 17 and 21 dpi on anaesthetized animals. On exam days, clinical parameters such as bodyweight, body temperature and respiration rate, nasal, throat, urogenital and rectal swabs, and blood were collected as well as ventro-dorsal and lateral chest radiographs.

Rhesus macaques became infected one day post inoculation (dpi) with disease lasting 8-16 days. On day one post inoculation (dpi), all animals showed changes in respiratory pattern and piloerection, as reflected in their clinical scores. Rhesus macaques became infected one day post inoculation (dpi) with disease lasting 8-16 days. On day one post inoculation (dpi), all animals showed changes in respiratory pattern and

piloerection, as reflected in their clinical scores. Weight loss was observed in all animals; body temperatures spiked on 1 dpi but returned to normal levels thereafter. Under anesthesia, the animals did not show increased respiration; however, all animals showed irregular respiration patterns. Radiographs showed pulmonary infiltrates in all animals starting on 1 dpi with mild pulmonary infiltration primarily in the lower lung lobes. By 3 dpi, progression of mild pulmonary infiltration was noted into other lung lobes although still primarily in the caudal lung lobes.

Serum was analyzed for changes in cytokine and chemokine levels at different time points after inoculation. Statistically significant changes were only observed on 1 dpi, with increases in IL1ra, IL6, IL10, IL15, MCP-1, MIP-1b, and on 3 dpi a small but statistically significant decrease in TGFα was observed. Although changes occurred in the levels of some of these cytokines later after inoculation, these mostly occurred in single animals and were thus not statistically significant.

Virus shedding was highest from the nose; virus could be isolated from swabs collected on 1 and 3 dpi, but not thereafter. Viral loads were high in throat swabs immediately after inoculation but were less consistent than nose swabs thereafter; in one animal throat swabs were positive on 1 and 10 dpi but not on any of the sampling dates in between. One animal showed prolonged shedding of viral RNA in rectal swabs from 7-17 dpi; infectious virus could not be isolated from these swabs. Urogenital swabs remained negative in all animals throughout the study. On 1, 3 and 5 dpi bronchoalveolar lavages (BAL) were performed on the 4 animals in the group euthanized on 21 dpi as a measure of virus replication in the lower respiratory tract. High viral loads were detected in BAL fluid in all animals on all three time points; infectious virus could only be isolated in BAL fluid collected on 1 and 3 dpi. No viral RNA could be detected in blood throughout the study or urine collected at 3 and 21 dpi.

On 3 dpi, varying degrees of gross lung lesions were observed in all animals. By 21 dpi, gross lesions were still visible in the lungs of two of four animals. Additionally, all animals had an increased lung weight:body weight ratio, indicative of pulmonary edema.

Serum was analyzed for the development of IgG against SARS-CoV spike in ELISA. By 10 dpi, all four animals had seroconverted to SARS-CoV-2 spike. At 21 dpi ELISA titers ranged between 1600 – 3200 for all four animals. Neutralizing responses also started to appear at 10 dpi and ranged from 10 – 60 at 21 dpi.

Pc-540-2004: Topline report: Evaluation of the Efficacy of Remdesivir against SARS-CoV-2 in a Rhesus Macaque Model

The purpose of this study was to characterize the *in vivo* antiviral activity of remdesivir against SARS-CoV-2 in the rhesus macaque model described above. A topline report with preliminary results was provided. Additional analyses are in progress and a full manuscript describing the complete study results will follow this topline report.

Twelve rhesus macaques were randomly assigned to two groups (N=6 [3M/3F] per group). All animals were inoculated as described previously with a total dose of 2.6×10^6 $TCID_{50}$/ml dilution SARS-CoV-2 via intranasal (4×10^5 $TCID_{50}$), oral (4×10^5 $TCID_{50}$), ocular (2×10^5 $TCID_{50}$), and intratracheal (1.6×10^6 $TCID_{50}$) routes.

Treatments were as follows:

Table 7 Design of remdesivir efficacy study against SARS-CoV-2 in rhesus macaques

Group No.	Group Description	No. of Animals (N)	Treatment Timing and Duration
1	Remdesivir	N = 6 (3M/3F)	12h post inoculation: 10 mg/kg remdesivir Days 1-6 dpi: 5 mg/kg remdesivir
2	Vehicle	N = 6 (3M/3F)	12h post inoculation: 2 mL/kg vehicle solution Days 1-6 dpi: 1 mL/kg vehicle solution

The animals were observed twice daily for clinical signs of disease, using a standardized scoring sheet as described previously {Brining 2010}.

The predetermined endpoint for this experiment was 7 dpi. Clinical examinations were performed daily (1, 2, 3, 4, 5, 6, and 7 dpi) and body weight, respiration rate, nose swabs, throat swabs and rectal swabs were collected on anesthetized animals.

Bronchoalveolar lavage (BAL) was collected on dpi 1, 3, and 7. Dorsal−ventral and lateral chest radiographs was collected on dpi 1, 3, 5, and 7.

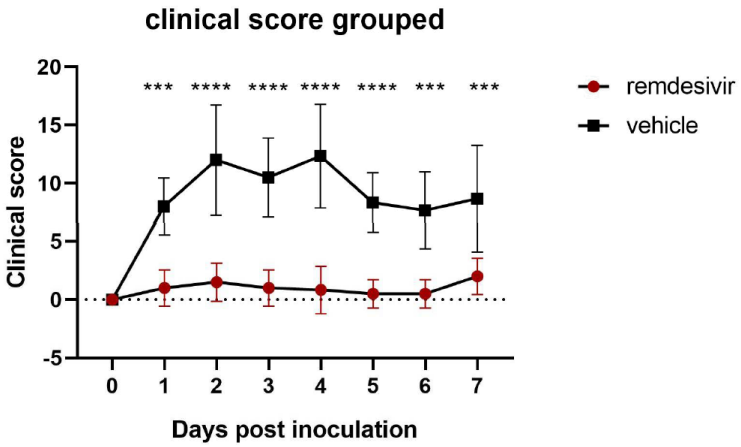
After euthanasia at 7 dpi, necropsies were performed. The percentage of gross lung lesions was scored by a board-certified veterinary pathologist blinded to the group assignment of the animals.

Results:

The preliminary results of the study demonstrated that remdesivir reduced the clinical disease signs in SARS-CoV-2-infected rhesus macaques. The model was non-lethal. After inoculation with SARS-CoV-2 on day 0, all animals were closely observed for signs of disease, and clinical scores were assigned according to a previously determined scoring sheet. All vehicle-treated animals displayed signs of disease, such as increased respiration and shortness of breath after inoculation, starting as early as 1 dpi. The clinical scores were assessed in blinded fashion and were statistically significantly lower in remdesivir-treated animals than in vehicle-treated control animals at 1 to 7 dpi (

Figure 7)

Figure 7 Clinical signs in rhesus macaques inoculated with SARS-CoV-2 and treated with remdesivir or vehicle



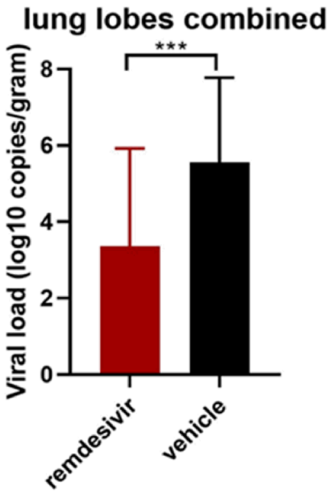
Values represent averages from 6 animals per group. Asterisks indicate statistically significant differences in a two-way ANOVA with Dunnett's multiple comparisons. ***P < 0.001; ****P < 0.0001.

Upon necropsy at 7 dpi, the area of each lung lobe affected by gross lesions was estimated by a board-certified veterinary pathologist. The Majority of animal treated with remdesivir had no pathological findings, only one of six animals had <20% of area affected by gross lesions in the upper and lower parts of the right lung lobe. In contrast, gross lung lesions were present in several lung lobes of all the vehicle-treated control animals. The total area of the lungs affected by gross lesions was statistically significantly smaller in the remdesivir-treated animals than in vehicle-treated control animals. At 3 to 7 dpi, there were statistically significantly fewer infiltrates in the lungs of animals treated with remdesivir as compared to vehicle-treated control animals.

At 7 dpi, all animals were euthanized, and respiratory tissues were collected for quantitative analysis of the levels of viral RNA by qRT-PCR. Compared to vehicle-treated control animals, remdesivir treatment resulted in significantly lower levels of SARS-CoV-2 replication in the lungs, with the average lung viral RNA 2.2 logs lower in the combined lung lobes (

Figure 8).

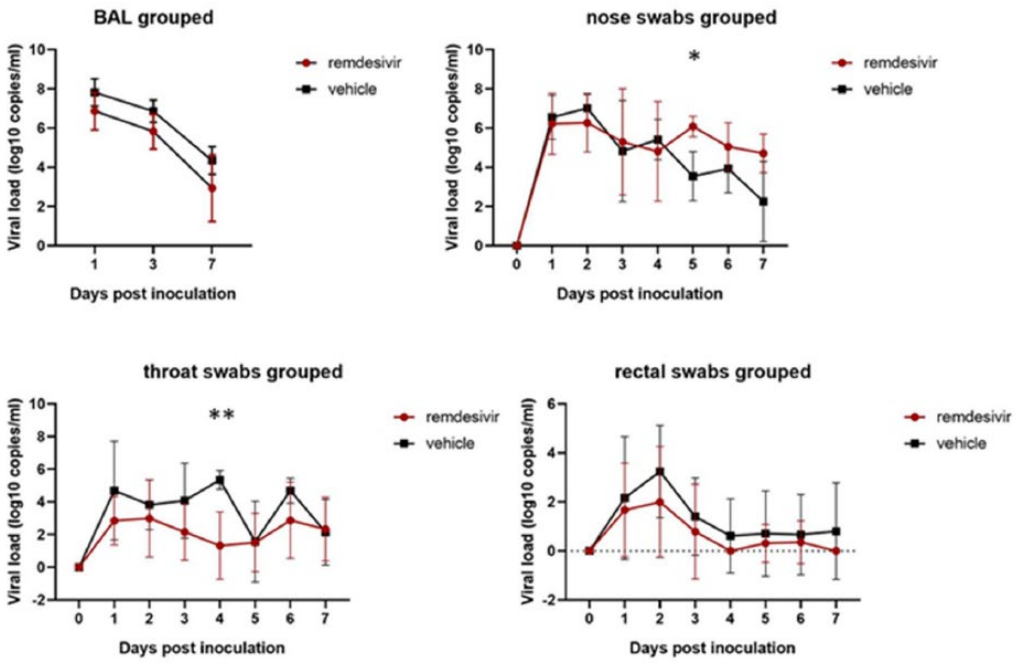
Figure 8 Viral loads in respiratory tract tissues of rhesus macaques inoculated with SARS-CoV-2 and treated with remdesivir or vehicle



At necropsy, one sample per lung lobe was collected per animal (6 samples per animal) and viral load was determined. Averages and SDs per group are indicated. Asterisks indicate statistically significant differences in a two-way ANOVA with Dunnett's multiple comparisons. ***P < 0.001.

Remdesivir-treated animals had only significantly lower viral loads as measured by viral RNA copies in throat swabs on 4 dpi compared to vehicle-treated control animals). No difference was observed in bronchoalveolar lavage, nose swabs and rectal swabs, except for the nose swabs at 5 dpi where viral load was lower in vehicle control compared to remdesivir-treated animals.

Figure 9 Viral loads in swabs from rhesus macaques inoculated with SARS-CoV-2 and treated with remdesivir or vehicle



Values represent averages from 6 animals per group. Asterisks indicate statistically significant differences in a two-way ANOVA with Dunnett's multiple comparisons. *P < 0.05; **P < 0.01. BAL, Bronchoalveolar lavage.

Infectious virus was isolated from bronchoalveolar lavage (BAL) fluid at 1 and 3 dpi. In BAL collected on 1 dpi, the viral titer was significantly lower in remdesivir-treated animals compared to vehicle-treated control animals. At 3 dpi infectious virus was no longer detected in BAL from remdesivir-treated animals but could still be isolated from the vehicle-treated animals.

There is also evidence of activity in mice and macaque models of SARS-Cov and MERS-Cov (please see below), providing supportive evidence based on similar viral susceptibility and similar pathogenesis.

Pc-399-2038: A blinded, randomized, vehicle-controlled evaluation of the efficacy of intravenous GS-5734 against middle east respiratory syndrome Corona Virus (MERS-CoV) in Rhesus Monkeys

The objective of this study was to characterize the efficacy of GS-5734 in a non-human primate (rhesus macaque) MERS-Co V disease model. The prophylactic efficacy of GS- 5734 administered as intravenous slow bolus once daily for seven days beginning one day before virus exposure was tested.

Each group received vehicle or 10 mg/kg GS-5734 via a daily bolus i.v. injection.

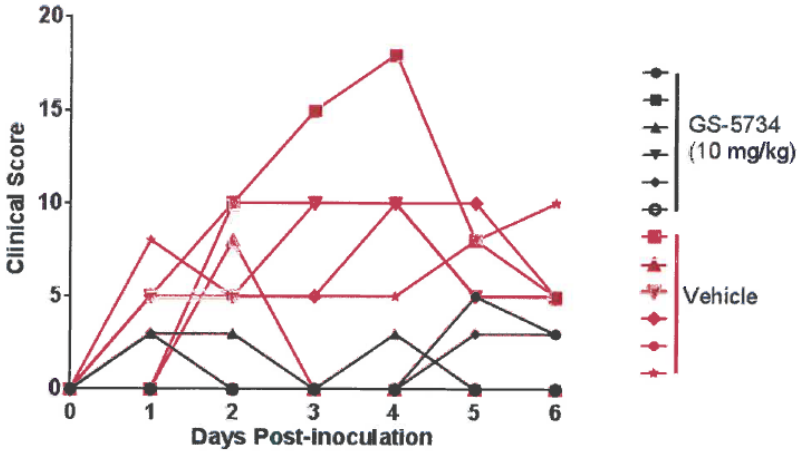
At DO, all animals were challenged with a target dose of 7 x 10^6 tissue culture infectious dose 50 (TCIDso) of MERS-CoV through a combination of intratracheal (4 mL), intranasal (0.5 mL each nostril), oral (1 mL) and ocular (1 mL) with MERS-CoV (1x106 TCID5o/mL).

The primary endpoint for this study was viral load in lung tissue at Day 6 post-infection. Antiviral efficacy was measured based on the level of reduction in clinical scores, radiographic lung changes, lung pathology, immunohistochemical staining and viral titers in lower and upper respiratory tract tissues in GS-5734-treated animals compared to vehicle-treated animals. Clinical scoring and pathology were conducted in a blinded fashion to reduced potential bias.

Results:

Disease signs in vehicle-treated animals were attributed to MERS-CoV infection. Time weighted average clinical scores were significantly higher (p = 0.006, Figure 10) in vehicle-treated animals compared to GS-5734-treated animals. All vehicle-treated animals showed signs of respiratory disease such as hunched posture and increased respiration rates. These signs were not apparent in GS-5734- treated animals.

Figure 10 Clinical sign scores in MERS-CoV-infected rhesus monkeys treated with vehicle or 10 mg/kg GS-5734 Clinical scoring is based upon a selected set of parameters designed to assess general health of the animals and distress due to MERS-Co V infection



All vehicle-treated animals showed evidence of lung pathology associated with MERS-CoV infection with 5 out of 6 animals showing moderate to serious interstitial infiltrates with pathology that localized to both the upper and lower lobes of the lung. In contrast, GS-5734- treated animals showed reduced lung pathology with three out of the six treated animals showing no evidence of MERS-CoV induced lung injury. The remaining animals showed evidence of mild interstitial pulmonary infiltrates localized to the lower lobes of the lung. Viral RNA was detected in all respiratory tract tissues in vehicle-treated animals.

Viral RNA in the lungs was significantly reduced in GS-5734-treated animals compared to vehicle controls.

Table 8 Lung viral RNA concentrations in MERS-CoV-infected rhesus monkeys treated with vehicle or 10 mg/kg GS-5734

	Day 6 Average Lung Viral RNA (Log_{10} $TCID_{50}$eq/g)	
	Vehicle (N = 6)	GS-5734, 10 mg/kg (N = 6)
Mean (SD)	0.26 (0.66)	3.58 (0.89)
P-value vs Vehicle group[a]	-	0.0022

[a]p-value calculated using Student's t-test

Viral RNA was quantified in nose swabs and throat swabs at Day 1, 3, 5 and 6 post-infection. Differences in the time-weighted viral load between vehicle-treated and GS-5734-treated animals were not statistically different (p> 0.05, Mann Whitney Test). However, the duration of shedding was reduced in GS-5734-treated animals (5/6 animals with negative nasal swab) compared to the vehicle controls (5/6 animals with positive nasal swab). Viral RNA was detected in one vehicle-treated animal in the urine at Day 6 post-infection and no viral RNA was detected in the blood.

Animals treated with a 10 mg/kg dose of remdesivir displayed changes in serum creatinine and Blood urea nitrogen (BUN) suggestive of altered renal function. All animals treated with GS-5734 (CoV144-149) had essentially normal pulmonary tissue with no evidence of MERS-Co V associated pathology, compared to the

vehicle-treated animals (CoV150-155), which developed some degree of pulmonary pathology associated with MERS-Co V infection. Lesions were characterized as multifocal, mild to marked, interstitial pneumonia frequently centered on terminal bronchioles. Histopathology analysis showed evidence of cortical renal tubular changes and necrosis of the renal tubular epithelial cells.

2.4.4. Discussion on clinical pharmacology

Methods

All analytical methods were adequately validated. For urine and plasma, two bioanalytical methods were validated for RDV, GS-704277 and GS-441524. Furthermore, plasma samples of study GS US 399 1954 were analysed with two different methods, QPS-60-1560 and QPS 60-15117 (switch after run 2). The reasons for this is unclear, and no information on a cross-validation was provided. Therefore, the CHMP recommended the applicant to provide clarification on these issues. As a consequence, it has been included in the list of recommendations that the applicant should address post-approval.

PBPK model analysis

The PBPK model is mainly of importance for the paediatric investigation plan regarding dose selection. The PK of RDV in paediatric patients have not been evaluated. The safety and efficacy of adolescent patients (12 years and older) weighing ≥ 40 kg are being evaluated in the ongoing Studies GS-US-540-5773 and GS-US-540-5774.

The PBPK model seem to adequately predict the AUC for RDV and GS-441524 in healthy adults receiving 75 mg/day dose. It is unclear if the model can adequately predict C_{max} and C_{min} or if the model is able to predict exposures at higher doses including the 200 mg loading dose followed by 100 mg/day dosing. Additional information is requested to further support the adequacy of the model.

The assumptions regarding physiochemical properties have been discussed by the applicant. There are uncertainties regarding those assumptions, i.e. that CES1 is the primary liver esterase involved in RDV to GS-441524 biotransformation but the assumptions are considered adequate at this time. It is agreed that the disposition of RDV and metabolites is expected to be similar in adults and adolescents. With adolescent population potentially weighing less than adults, the exposure in adolescents may be increased compared to adults.

The applicant has used a PBPK model to predict exposure (AUC) for subjects with different body weight with the proposed posology. AUC at steady state is predicted to be slightly higher in 40 kg patients compared to 70 kg patient but generally within the studied exposure range. Same posology in adolescent ≥40 kg as in adults is supported. The additional feedback regarding the PBPK and overall modelling strategy was provided by MSWP to PDCO in the PIP.

C-QT modelling analysis

The C-QT modelling analysis has generally been conducted according to guideline. The analysis indicates that RDV, GS-441524 and GS-704277 do not cause QTcF interval prolongation at the therapeutic exposure levels.

The major limitation of this analysis is that higher exposure levels have not been studied. However, further information is requested in addition to a number of other aspects that should be addressed by the Applicant post -approval for a comprehensive assessment this modelling analysis.

Absorption

Although the solution formulation and the lyophilised formulation were not formally bioequivalent in the comparison submitted, the results indicate that the two RDV formulations result in comparable plasma concentrations.

Distribution

The *in vitro* protein binding and blood distribution studies were conducted in adequate conditions, despite the use of only one test concentration. It is thus not known whether the protein binding of RDV is linear at physiological concentrations. In the absence of in vivo protein binding data, experimental data of protein binding at several physiologically relevant concentrations should be provided post-authorisation, supporting the linearity of RDV protein binding at relevant concentrations.

RDV is moderately bound to plasma proteins, while its metabolites GS-704277 and GS-441524 are not bound to plasma proteins. RDV is somewhat excluded from the cellular fraction, while GS-441524 exhibits a tendency to associate with the cellular fraction.

Elimination

A single dose mass-balance study is sufficient since there are no major dose- or time- dependencies, and the results can be extrapolated to the suggested clinical dose. The total recovery of radioactivity was 92% of the dose which is above the 90% limit recommended according to the Guideline on interactions and thus sufficient. More than 80% of the recovered radioactivity was identified which is also in agreement with the recommendations in this guideline. The radiolabel was in a stable position.

Data indicate that active renal secretion may be involved in particular for RDV but possibly also for the metabolites.

The applicant has not sufficiently discussed the involvement of hepatic metabolism in the metabolism of RDV. The applicant should provide a discussion supporting their conclusion that the impact of CYP2C8, 2D6, and 3A4 on RDV disposition is expected to be minimal since RDV metabolism is predominantly mediated by hydrolase activity. Should the low impact of CYP2C8, 2D6, and 3A4 on RDV disposition be confirmed, the corresponding SmPC warning in section 4.5 may be removed.

Data substantiating that hydrolysis is the primary route of metabolism for RDV must be provided to determine the risk of victim interactions. If an enzyme is responsible for more than 25% of the elimination, its inhibition should be studied in vivo. CES1 (carboxylesterase 1) is included in the PBPK model, but not discussed elsewhere. Information regarding how (which enzymes) and where the different metabolites are formed; the risk of clinical interaction and the possible existence of polymorphism should be explored (see list of recommendations).

In the mass balance study, there appears to be a currently unknown major metabolite M27, representing 10.6% of the drug-related exposure in plasma (and with almost the same exposure as parent drug). This is a concern, considering that this metabolite could potentially be a human-specific metabolite. Apart from this, around 30% of the radioactivity in plasma is unknown. It is somewhat surprising that the intermediate metabolite (GS-704277) was not observed, considering that this metabolite has been measured in plasma using LC-MS/MS. The applicant states that additional analysis is ongoing using accelerator mass spectrometry to further inform on the circulating species of RDV. The applicant should submit data from additional analysis of the circulating species of RDV from the human mass balance study in order to clarify the identity of the currently unknown major metabolite M27 and to clarify if any other major metabolites are present in plasma. Data on CYP inhibition by the major metabolite M27 is also required, as well as for potential additional major metabolites, according to requirements in the Guideline on interactions.

Finally, the applicant should provide data to support that inter-conversion to the other diastereomer does not occur in vivo. These aspects are included in the list of recommendations.

- *Pharmacokinetics of metabolites*

The main metabolite GS-441524 as well as the intermediate metabolite GS-704277 has been characterized in plasma. Peripheral blood mononuclear cell PK parameters of the active triphosphate metabolite GS-443902 has also been assessed. Plasma RDV exposure as well as intracellular trough concentration of the active triphosphate metabolite GS-443902 in PBMCs (compared to data in rhesus monkey) is used to justify the suggested clinical dose.

Dose proportionality and time dependencies

The results of study GS-US-399-1812 indicate dose-proportionality for RDV and the metabolites GS-441524 and GS-704277 (although the 90% CI for the slope for AUC_{inf} for GS-441524 does not cover 1) in the dose range 3 to 225 mg (single dose). Dose-proportionality following multiple-dose administration has not been assessed.

As expected, considering the half-life (around 1 hour), no accumulation was observed for RDV following multiple dosing in study GS-US-399-1954, and the PK profile was very similar when comparing day 1 to day 7 and day 14. The metabolite GS-441524, having a longer terminal half-life of around 25 hours in this study (ranged from 13 to 31 hours in the single-dose study GS-US-399-1812), reached steady state by day 4 and the accumulation index was 1.9. AUC_{tau} is similar to AUC_{inf} following a 150 mg dose in the single dose study GS-US-399-1812 for remdesivir and GS-441524; thus, there are no indications of time-dependency. It is not clear why accumulation occurred for the intermediate metabolite GS-704277, since no accumulation would be expected considering the short half-life compared to the dosage interval. However, overall, the results do not indicate time-dependency.

In study GS-US-399-5505, the suggested clinical dose regimen for COVID-19 was used (200 mg on day 1 followed by 100 mg once daily for up to 10 days, administered as a 30 min IV infusion). Since no PK data from patients are available, this is the only study investigating the exposure following the suggested clinical dose of RDV. In absence of patient data, data from this study are relevant in order to support dose selection, to set cut-offs for in vitro interaction studies and to bridge to preclinical safety data.

Intra- and inter-individual variability

Data regarding intra- and inter-subject variability should be presented (see list of recommendations).

Pharmacokinetics in target population

The applicant is encouraged to obtain PK data in patients and to further discuss potential differences in patients compared to healthy volunteers (see list of recommendations).

Special populations

PK of parent drug and active metabolites has not been documented in special populations. Thus, any effect of organ dysfunction or demographics on the exposure of RDV and its metabolites is currently unknown.

The potential involvement of the liver in the metabolism of RDV is currently unknown, which is reflected in the SmPC (see SmPC comment). A phase 1 study in subjects with hepatic impairment (without COVID-19) is planned and has been included in the pharmacovigilance plan in the RMP.

Remdesivir is not cleared unchanged in urine to any substantial extent, but its main metabolite GS-441524 is found in urine and the metabolite levels in plasma may theoretically increase in patients with impaired renal function. A phase 1 study in subjects with severe renal impairment and on dialysis is planned and has been included in the pharmacovigilance plan in the RMP. Until data are available, the suggested wording in the SmPC is generally considered adequate from a pharmacokinetic perspective.

The effect of demographic factors (gender, race, age, weight etc.) on the PK of RDV should be investigated. It is agreed that the disposition of RDV and metabolites is expected to be similar in adults and adolescents. With adolescent population potentially weighing less than adults, the exposure in adolescents may be increased compared to adults. The applicant has used a PBPK model to predict exposure (AUC) for subjects with different body weight with the proposed posology. AUC at steady state is predicted to be slightly higher in 40 kg patients compared to 70 kg patient but generally within the studied exposure range. Same posology in adolescent as adults ≥40 kg is supported.

Pharmacokinetic interaction studies

The outstanding interaction issues are regrouped into two RECs, one on the effect of other medicinal products on remdesivir, and one on the effect of remdesivir on other medicinal products.

Missing data

Data on substantiating that hydrolysis is the primary route of metabolism for RDV must be provided to determine the risk of victim interactions. If an enzyme is responsible for more than 25% of the elimination, its inhibition should be studied *in vivo* if possible. CES1 (carboxylesterase 1) is included in the PBPK model. Information regarding how (which enzymes) and where (hepatic or non-hepatic) the different metabolites are formed; the risk of clinical interactions and the possible existence of polymorphism should be explored.

No *in vitro* CYP inhibition data have been provided for the major metabolite M27, or any other currently unidentified major metabolite. According to guideline, metabolites with an AUC both larger than one fourth of the AUC of parent drug and larger than 10% of the drug-related exposure needs to be investigated for CYP inhibition. M27 appears to represent more than 10% of the total radioactivity, thus data is required. If any further major metabolites were present in the remaining radioactivity, this would warrant further *in vitro* testing.

Time-dependent inhibition should be studied for all CYP enzymes. The IC_{50} with and without preincubation should be compared for each enzyme.

Several transporters have not been studied (inhibition) for RDV: OAT1, OAT3 and OCT2.

Perpetrator

Using the day 1 cutoff, RDV is an inhibitor of CYP2B6, 2C8, 2C9, 2D6, and 3A4 at clinically relevant concentrations. For some of these enzymes, the interactions may be only short-lived, as RDV has a short half-life. At the steady state, it is only the inhibition of CYP3A41 that is expected to result in clinically relevant interactions. Since CYP inhibition data is incomplete (TDI and major metabolite M27), no final conclusion on inhibition can be drawn at the moment. The mechanistic static model is not found applicable here, as RDV is both an inhibitor and potentially an inducer of CYP3A4 (see below) and its TDI potential is unknown. Therefore, an in vivo study with a sensitive CYP3A4 substrate (midazolam) should be performed to investigate the inhibition and the induction of CYP3A4 by RDV. The applicant may also consider implementing the aspect of the optimal delay between administration of RDV and sensitive CYP3A4 substrates in the design of the in vivo study. Appropriate warnings are included in the SmPC until this data is available.

RDV is an inhibitor of UGT 1A1, 1A3, 1A4, 1A9, and 2B7, according to the basic model with the D1 or D5 cutoff. Nevertheless, none of the potential UGT interactions was found clinically relevant, according to the mechanistic static model, where AUCR for UGT1A1 inhibition by RDV was 1.22. This is calculated using the initially determined IC50/Ki. The new in vitro experiment however results in a lower IC_{50} of 1.5 µM. The clinical relevance of this signal is nevertheless deemed low, and by extension, the signal of the other UGTs that all have a higher IC_{50}. The in vitro UGT inhibition findings should nevertheless be described in section 5.2 of the SmPC.

In vitro CYP 1A2, 2B6 and 3A4 induction has been observed by either RDV or GS-704277. Since data is missing for inhibition of CYPs by M27, it is unclear what the net effect of these potential interactions may be. This is adequately covered by a general warning in the SmPC.

The clinical relevance of induction signals by GS-704277 is considered low, as it is currently not identified as a major metabolite, and has a very short half-life in vivo. Furthermore, such data is not required by the GL.

The *in vitro* induction assays suffered from a low stability of RDV, and the relevant concentration range was not covered in the assay.

In vitro induction of CYP1A2 was observed for RDV. The applicant argued that this interaction was not clinically relevant, based on the mechanistic static model. It was however the theoretical and not the actual concentrations that were used in that calculation, which leads to an underestimation of the interaction potential due to RDV´s instability. The SmPC therefore contains a warning for the co-administration of remdesivir with substrates of CYP1A2 with a narrow therapeutic index that may be at risk of loss of efficacy.

CYP3A4 induction data by RDV is inconclusive, due to both the instability issue, and the incompleteness of donor 3 data. Therefore, the applicant should include the study of CYP3A4 induction in the design of the midazolam study that is requested for CYP3A4 inhibition, unless new adequate in vitro data is provided. Awaiting these data, a warning for loss of efficacy of sensitive CYP3A4 substrates with narrow therapeutic index upon co-administration with remdesivir is included int the SmPC.

RDV is an inhibitor of OATP 1B1 and 1B3 at clinically relevant concentrations. In vivo studies with sensitive substrates are required, unless otherwise justified. Appropriate warnings are included in the SmPC until this data is available.

RDV is a weak inhibitor of BSEP at clinically relevant concentrations.

RDV is an inhibitor of MRP4 at clinically relevant concentrations. To date, no clinically relevant interactions via MRP4 inhibition are known, and sensitive substrates in vivo are not available. It is therefore agreed that no warning in section 4.5 of the SmPC is warranted. The information is however mentioned in section 5.2.

Substrate

The applicant should provide a discussion supporting their conclusion that the impact of CYP2C8, 2D6, and 3A4 on RDV disposition is expected to be minimal since RDV metabolism is predominantly mediated by hydrolase activity. This is required in order to understand the relevance of these pathways and the risk of clinically relevant interaction. Should the low impact of CYP2C8, 2D6, and 3A4 on RDV disposition be confirmed post-authorisation, the corresponding SmPC warning in section 4.5 may be removed.

RDV is a substrate of OATP1B1 and P-glycoprotein (P-gp). The applicant has not commented on the extent of hepatic metabolism of RDV. Therefore, the risk of interaction is unclear, as is the need for *in vivo* studies, particularly considering that RDV is both a substrate and an inhibitor of OATP1B1. Until this discussion is available, a corresponding warning is included in the SmPC. Should post-authorisation the hepatic metabolism of RDV be confirmed as low, then warnings for victim interactions via OATP1B1 & PgP inhibition/induction may be removed from the SmPC section 4.5 and be mentioned only in section 5.2.

Furthermore, the results of the DDI study with rifampin should be submitted as soon as they are available.

Discussion on pharmacodynamics

Biochemical studies demonstrated that the active triphosphate metabolite of RDV, GS-443902, acts as an analogue of adenosine triphosphate (ATP) and competes with the natural ATP substrate to selectively inhibit viral RNA-dependent RNA polymerases (RdRp).

Remdesivir inhibited the *in vitro* replication of SARS-CoV-2 in several cell types, with nanomolar EC_{50} and high selectivity index, indicating that it may serve as a direct acting antiviral *in vivo*. Due to the sequence

homologies of the polymerases, *in vitro* activity against SARS-Cov and MERS-Cov data are considered supportive.

An EC_{50} of 0.0099 µM by RDV was shown for a clinical isolate of SARS-CoV-2 in primary HAE cells. The applicant points out that comparable inhibition had been previously reported for SARS-CoV with an EC_{50} of 0,069 µM, using the same experimental set-up, but with HAE cells derived from a different donor. The results indicate potent inhibition of SARS-CoV-2 by RDV and are considered promising. Nonetheless, the database is rather limited. Besides, variability is anticipated for primary HAE cultures derived from individual donors. Therefore, confirmation by replicate investigations using primary HAE cells derived from another donor would add valuable data.

Another study performed in Vero cells infected with a clinical SARS-CoV-2 isolate showed inhibition by RDV with EC_{50} 0,137 µM and 0,750 µM (after 24 and 48 hours, respectively). In principle, these data re-affirm study results discussed above, however information on the study methods is limited and partly inconsistent.

Further results of an EC_{50} around 0,0035 µM in Huh7 cells infected with a recombinant infectious virus construct (containing the SARS-CoV-2 polymerase gene, nsp12, inserted into the backbone of a recombinant luciferase-expressing SARS-CoV) also add valuable information on RDV antiviral activity.

Additional studies on antiviral activity of RDV or GS-466547 against MERS and SARS virus also support the proposed mechanisms of action.

In vitro data provided and discussed above on the antiviral activity of RDV comprise analysis in HAE cells, Vero cells, and Huh7 cells. To further substantiate information already obtained, it is considered of value to analyse antiviral activity of RDV in potential SARS-CoV-2 target cells expressing the ACE2 receptor and TMPRSS2 serine protease (e.g. Calu-3 (human lung epithelial cell), CaCo2 (colorectal epithelial cells), and U251 (glioblastoma cells)).

The amount of serum protein binding on RDV has been analysed, the mean free fraction in human plasma was 12.1%. Nevertheless, the impact of serum protein binding on antiviral activity has not been addressed. The Committee has issued a recommendation to address this point.

No analyses have been performed on the influence of other antiviral agents on the activity of RDV. In case of SARS-CoV-2 patients with pre-existing HIV, HBV or HCV infection, which is treated with antivirals, effect of these antivirals on RDV should be determined. These analyses should be explored.

Among circulating clinical isolates of SARS-CoV-2, no amino acid substitutions were observed at the highly conserved nsp12 amino acid residues F480 and V557 previously shown to be associated with reduced susceptibility of coronaviruses to RDV *in vitro* or for any other residues that directly interact with the metal ions or RDV-TP or may contribute to the inhibitor's delayed chain termination. However, one substitution (A547V) was detected within 10 Å of the active site. It is important to note, that this study did not provide any information about development of resistance to RDV in patients receiving remdesivir treatment. Thus, no information about on-treatment development of resistance is available at the moment. The applicant should address this issue in the near future, to characterise the resistance profile of RDV. This is important, due to the observed increasing genetic drift of SARS-CoV-2 and the associated risk of substitutions that may be potentially associated with reduced susceptibility to RDV.

In general, three substitutions were identified, A574V, P323L and A97V. New data indicate the presence of at least three genetically and geographically distinct clusters of the SARS-CoV-2 genomes (Forster et al., PNAS, 2020). The emergent clusters have been found to be associated with signature structural changes in specific viral proteins, including a substitution P323L in RdRp (Bhowmik et al, preprint, bioRxiv). This substitution is hypothesized to rigidify the RdRp structure and potentially influence the replication of the viral RNA (Begum, 2020, preprint biorxiv). Substitution P323L, which was detected in more than 41% of the tested clinical isolates, seems to be quite frequent in clinical isolates collected in Europe, while A97V was

detected more often in the Asian-pacific region. Thus, it seems that there might be different geographic distribution of viral strains. Further discussion should be provided by the applicant regarding the different geographic distribution of viral strains during the pandemic, taking current knowledge of variants A, B and C (https://doi.org/10.1073/pnas.2004999117) **.** Furthermore, the substitutions A574V, A97V and P323L should be analysed for their susceptibility to RDV preferably in HAE cells, using different clinical isolates, i.e. variants A, B and C to evaluate the effect of this signature mutations on RDV susceptibility**.**

Mice are not suitable for evaluation of remdesivir in SARS-CoV-2 due to high levels of esterase activity that rapidly degrade the prodrug. In addition, knockout mice that do not degrade remdesivir rapidly lack expression of the human ACE2 receptor required for infection and are thus not a suitable model for SARS-CoV-2 (Zhou et al. BiorXiv 2020). Based on this, the choice of rhesus macaques as non-human primate target species for establishing a SARS-CoV-2 disease model seems to be reasonable.

The rhesus macaque model resembles a moderate COVID-19 disease, thus conclusions from this animal model might not be transferable to severe disease. The inoculation with SARS-CoV-2 induced a transient, moderate disease in rhesus macaques with signs of infection one day post inoculation (dpi) with disease lasting 8-16 days. All animals showed signs of respiratory disease, i.e. changes in respiratory pattern, as reflected in their clinical scores, detectable viral RNA in swabs from the nose and throat of all animals as well as in bronchoalveolar lavages (BAL) and pulmonary infiltrates, a hallmark of human disease. However, different levels of pulmonary involvement with regard to infiltrates on x-ray and the presence of lung lesions on 3 dpi were observed”

The duration of disease in rhesus macaques seems to be very short with differences also in incubation times, compared to the disease in humans. In addition, differences observed in pulmonary involvement, duration of viremia, serological and immunological responses might impact the validity of this animal disease model for SARS-CoV-2 in humans**.**

A topline report with preliminary results of the study that evaluated the efficacy of remdesivir against SARS-CoV-2 in a non-lethal Rhesus Macaque Model was submitted. Additional analyses are in progress and a full manuscript describing the complete study results will follow this topline report.

The NIH study in rhesus macaques is currently the most advanced animal model for COVID-19. However, as discussed above, the model is based on an initial study, evaluating a limited number of rhesus macaques (N=8) and does not seem to capture all human disease characteristics. Based on current staging approaches, the rhesus macaque model does recapitulate moderate Phase IIA, where markers of systemic infections, i.e. cytokines and chemokines, are not regularly elevated (Siddiqi, 2020).

One of the uncertainties includes the relevance of the animal models for human COVID-19, as well as the fact that RDV was administered only 12 hours after viral challenge in the animal model. Considering that in the established model, the first evaluation of clinical symptoms was done at 1 dpi, it remains unclear, if the animals already developed COVID-19 symptoms when they received RDV. This is not reflective of the currently studied use of remdesivir in COVID—19 patients, where first administration is unusual before day 4 of symptom onset. Thus, animals in this model may not be representative for the clinical status of patients that will receive RDV in clinical practice, as it rather reflects a prophylactic or post-exposure than a therapeutic approach.

The preliminary results indicate that in this model RDV only has an impact on clinical aspects (e.g., active in reducing the amount of lesions in the lung). The data on antiviral effects are equivocal. No effect of viral levels in upper respiratory tract was shown. Considering that RDV is supposed to be a direct acting antiviral, an antiviral effect would have been anticipated.

Mouse and rhesus macaque models of SARS-Cov and MERS-Cov are supportive of the hypothesis of efficacy. However, no in vivo studies have been conducted in animal models of any coronavirus infection where treatment was initiated later than one day after viral inoculation.

2.4.5. Conclusions on clinical pharmacology

The available pharmacokinetic documentation consists of studies mainly aiming at describing the general pharmacokinetic properties of RDV and its metabolites in healthy volunteers. One main issue is the presence of a currently unknown major human metabolite as it was previously discussed.

No PK data in patients is available, and the effect of intrinsic factors, including the effect of organ dysfunction and the effect of demographics on the PK of RDV has not been examined.

In vitro antiviral activity of RDV against SARS-CoV-2 has been shown in primary HAE cells (EC_{50} of 0.0099 µM).

The resistance profile of RDV to date is considered incompletely characterized *in vitro* and *in vivo.* New data indicate the presence of geographically distinct clusters of viral strains, with signature structural changes in specific viral proteins. The observed increasing genetic drift of SARS-CoV-2, evolving viral diversity and different geographic distribution of virus strains might have a substantial effect on the remdesivir efficacy, highlighting the importance to further characterise the resistance profile of RDV.

As discussed, one of the uncertainties includes the relevance of the animal models for human COVID-19, as well as the fact that RDV was administered only 12 hours after viral challenge in the animal model.

Overall, *in vitro* and preclinical *in vivo* data support the hypothesis that RDV may provide benefit in COVID-19. However, the currently available data on antiviral effects are limited. Further data on the antiviral activity *in vitro* and *in vivo* are needed to support the classification of remdesivir as a direct acting antiviral and its efficacy on circulating viral strains.

A number of issues need to be resolved post-approval (see list of RECs and addition of RI and HI study in RMP). There are no in vivo studies regarding interactions and several issues are raised regarding the in vitro interaction studies performed and the possible in vivo consequences of these findings. These requirements are not considered to preclude approval as appropriate warnings are included in the SmPC but constitute two different RECs.

In conclusion, from a pharmacology point of view, a conditional marketing authorisation application is acceptable. Certain aspects should be further studied and provided after approval by the applicant considering the discussion above and the recommendations that the Committee agreed. In addition, appropriate warnings have been included in the SmPC. Some of these warnings could be removed once more information becomes available.

Recommendations for future and ongoing development:

Pharmacology:

- The applicant should submit data from additional analysis of the circulating species of RDV from the human mass balance study in order to clarify the identity of the currently unknown major metabolite M27 and to clarify if any other major metabolites are present in plasma. Data on CYP inhibition by the major metabolite M27 should be also considered, as well as for potential additional major metabolites, according to requirements in the Guideline on interactions.
- The applicant should provide data to support that inter-conversion to the other diastereomer does not occur in vivo.
- The applicant is encouraged to obtain PK data in patients and to discuss potential differences in patients compared to healthy volunteers. The effect of demographic factors (gender, race, age, weight etc.) on the PK of RDV should also be investigated. Data regarding intra- and inter-subject variability should also be presented.
- Information on GCP inspections of the bioanalytical site (QPS, LLC (Newark, US)) should be provided

- Effect of other medicinal products on remdesivir:

    a. Data substantiating that hydrolysis is the primary route of metabolism for remdesivir must be provided to determine the risk of victim interactions. If an enzyme is responsible for more than 25% of the elimination, its inhibition should be studied in vivo if possible. CES1 (carboxylesterase 1) is included in the PBPK model, but not discussed elsewhere. Information regarding how (which enzymes) and where (hepatic or non-hepatic) the different metabolites are formed; the risk of clinical interactions and the possible existence of polymorphism should be explored.

    b. The applicant should provide a discussion supporting their conclusion that the impact of CYP2C8, 2D6, and 3A4 on remdesivir disposition is expected to be minimal since remdesivir metabolism is predominantly mediated by hydrolase activity. This may be particularly relevant in the case of co-administration with the CYP3A4 inducer dexamethasone. Should the low impact of CYP2C8, 2D6, and 3A4 on remdesivir disposition be confirmed, the corresponding SmPC warning in section 4.5 may be removed.

    c. Should the hepatic metabolism of remdesivir be confirmed as low, then warnings for victim interactions via OATP1B1 & PgP inhibition/induction may be removed from the SmPC section 4.5 and be mentioned only in section 5.2.

    d. In studies AD-399-2007 and AD-399-2008, the investigation of RDV as substrate of transporters was carried out using a single concentration. According to appendix 3 of the interaction GL, at least four concentrations covering 100-fold difference in concentration should be studied. No information on saturation of the transporters at the studied concentration is available. The applicant should discuss and motivate the use of a single concentration. Unless adequate justifications are provided, the studies would need to be redone under conditions following the GL

- Effect of remdesivir on other medicinal products:

    a. An in vivo study with a sensitive CYP3A4 substrate (midazolam) should be performed to investigate the inhibition of CYP3A4 by RDV. The induction of CYP3A4 by RDV should be studied in vivo as well, unless new adequate in vitro data is provided, with sufficient RDV actual concentration. The SmPC warning in section 4.5 may be removed if these studies show negative results. The applicant may also consider implementing the aspect of the optimal delay between administration of RDV and sensitive CYP3A4 substrates in the design of the in vivo study.

    b. RDV is an inhibitor of OATP 1B1 and 1B3 at clinically relevant concentrations. In vivo studies with sensitive substrates are required, unless otherwise justified.

    c. Time-dependent inhibition was investigated with at a single concentration. The difference in remaining activity between incubation with and without NADPH shows the difference between inhibitory effects by the parent and possible metabolites and is not the relevant output for the study of TDI. The IC50 with and without preincubation should be compared for each enzyme for RDV. The choice of probe substrate (CYP2D6) and control inhibitor (2C8, 2C9, 2C19, 2D6, 3A4) should be justified. For metabolites, this data is not expressly required by the GL.

    d. In vitro-studies investigating the effect of RDV as inhibitor of the following transporters should be submitted: OAT1, OAT3 and OCT2.

    e. Unless adequate justifications are provided, the following studies would need to be redone with acceptable substrates and controls:

i. CYP inhibition (AD-540-2004 and AD-540-2013): the selected enzyme marker reactions are in line with the GL, except for CYP2C9 and CYP2D6. While the choice of reaction may be acceptable, this requires justification. The same holds true for control inhibitors, where those used for CYP 1A2 and 2C19 differ from the GL.

ii. UGT inhibition: The design of study AD-540-2015 is acceptable. The choice of probe substrate and control inhibitor should be justified.

iii. Transporter assays: The applicant should justify the choice of probe substrate and positive control and their respective concentrations, where applicable. The applicant should also comment on the lack of information on non-specific binding and cell viability in the experiments involving cells for those studies where this information was missing [non-specific binding: all; cell viability: AD-399-2029, AD-399-2007, AD-399-2008].

- DDI study with rifampicin: The results of the DDI study with rifampin should be submitted as soon as they are available.

- In the absence of in vivo protein binding data, experimental data of protein binding at several physiologically relevant concentrations should be provided, supporting the linearity of RDV protein binding at relevant concentrations.

- For urine and plasma two bioanalytical methods were validated for RDV and GS-441524. The reason for this is unclear. Furthermore, plasma samples of studies GS-US-399-1954 and GS-US-399-1812 were analysed with two different methods, QPS-60-1560 and QPS 60-15117. The reason for this is unclear, and no information on a cross-validation is provided. The applicant should provide clarification on these issues and should discuss if this could have an impact on the comparability of results (e.g. in study GS-US-399-1812 between cohorts and formulations). Unless it can be motivated that no cross-validation is required, such a cross-validation should be provided.

Pharmacodynamics:

- Analysis of antiviral activity using additional cells and clinical isolates; analysis of influence of other antiviral agents on RDV activity; provision of missing data.

- Analysis of antiviral activity of RDV to clinical isolates of circulating viral strains from different geographical regions, i.e. clinical isolates with substitutions P323L, A97V and A574V.

- Genotypic and phenotypic resistance analysis of clinical isolates from patients receiving RDV treatment.

- Further information on the establishment of the Rhesus macaque models should be provided, including the study report and a discussion of the validity of the animal disease model for SARS-CoV-2 in humans

- Further data on study PC-540-2004 should be provided, including the final study report of study PC-540-2004.

- Study report of evaluating the prophylactic and therapeutic administration of RDV in a rhesus macaques model of MERS-CoV should be provided.

- The dose used to build the C-QT model is only 1.5-fold the proposed therapeutic maintenance dose (100mg) and 0.75-fold the proposed therapeutic loading dose (200mg). According to Garnett et al. 2018 higher doses leading to at least twice as high Cmax concentrations as with the therapeutic doses (https://doi.org/10.1101/2020.03.21.001628) should be investigated for appropriate C-QT analysis:

a. The Applicant should include additional data for the highest investigated doses if PK and corresponding QT data are available. And if this is not feasible the Applicant is requested to critically discuss how this concern will be addressed.

b. Some figures for the C-QT modelling are missing/were not found and should be provided.

c. A figure of observed vs predicted ΔΔQTcF should be provided.

d. C-QTc plot (ΔΔQT on y-axis, concentration on x-axis) of observed data overlaid with the model prediction (including confidence interval) should be provided.

e. The applicant should provide predictions from the C-QT model resulting from the mean concentrations observed in study 399-1954.

f. As an additional sensitivity analysis, a C-QT model that corresponds to the final model but omits altogether the RDV concentration and that of both metabolites should also be employed in order to evaluate the full treatment effect on its own avoiding post-randomisation covariates.

g. The applicant should provide bootstrap confidence intervals for the C-QT model for which the procedure includes model building, i.e. model building steps 2-4 should be performed for each bootstrap sample resulting potentially in different final models for the different bootstrap samples.

h. As sample sizes were small for the C-QT analysis, the applicant should provide reassurance that coverage probability of the derived bootstrap confidence intervals is acceptable.

i. With respect to the bootstrap resampling for the C-QT analysis it should be clarified how stratification within visits was conducted and how this could be done when taking subject identifier as the unit of resampling. An additional analysis without stratification according to visit should be presented.

j. The Applicant should provide the SAP including the software and the dataset used for the C-QT analysis (and the updated dataset including data on higher doses).

2.5. Clinical efficacy

2.5.1. Dose response studies

No dedicated dose-finding study in humans has been conducted. Selection of this dosing regimen is based on the PK bridge from animal data to human doses and efficacy using the results of *in vivo* efficacy studies conducted in SARS-CoV-2- and MERSCoV-infected rhesus monkeys, and available PK data in healthy rhesus monkeys and Phase 1 studies in healthy participants.

PK bridge between animal models and humans and relevance for dose selection

The basis for a PK bridge from animal data to human doses and efficacy is based on the results of studies conducted in healthy and MERS-infected rhesus monkeys and PK data from Phase 1 studies in healthy volunteers.

For the treatment of COVID-19, the dose has been selected to target exposures (plasma and PBMC) associated with efficacy at 10 mg/kg and 5 mg/kg, respectively, in the MERS-infected rhesus monkeys. This results in a dosing regimen (based on allometric scaling) that requires a 200 mg loading dose followed by 9 days of 100 mg once daily.

Available PK (plasma and PBMC) data illustrating comparable PK across species are described below.

The pharmacokinetics of 5 mg/kg daily dose (7 days) in rhesus monkeys (Study AD-399-2030) and a repeat doses of 100 mg (5 to 10 days) in healthy adult human volunteers (Study GS-US-399-5505), both administered as 30-min IV infusion revealed, that at these doses, similar systemic plasma exposures of RDV was achieved in both species. Additionally, the intracellular exposures of the active nucleoside triphosphate metabolite GS-443902 observed in rhesus monkey PBMCs receiving 5 mg/kg daily dose (7 days) were comparable to concentrations achieved in human PBMCS on administration of repeat doses of 100 mg RDV.

Table 9: Pharmacokinetics of RDV in Plasma and Nucleoside Triphosphate Metabolite GS-443902 (PBMCs) following Repeat RDV Doses (30-minute IV Infusion) to Healthy Rhesus Monkeys (5 mg/kg) and Healthy Humans (100mg)

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

N = number in a population; PBMC = peripheral blood mononuclear cell; RDV = remdesivir (GS-5734™); SD = standard deviation

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

b N = 25

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

In humans, RDV exhibits dose proportionality in its PK at doses from 3 mg to 225 mg (Study GS-US-399-1812). In rhesus monkeys, dose proportional increases in RDV plasma exposure were seen across 3 mg/kg and 10 mg/kg (AD-399-2002 and AD-399-2022, respectively).

A loading dose of 200 mg in humans is required to target efficacy at the 10 mg/kg loading dose in MERS infected rhesus monkeys. PK (plasma and PBMC) of a single dose of 200 mg RDV in healthy volunteers has been examined and compared to values expected (due to dose proportionality) with 10 mg/kg in rhesus monkeys based on available data at 5 mg/kg.

Table 10: Pharmacokinetics of Plasma RDV and Nucleoside Triphosphate Metabolite GS-443902 (PBMCs) following a 200 mg Single Dose of RDV to Healthy Volunteers

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

CV = coefficient of variation; N = number in a population; PBMC = peripheral blood mononuclear cell; RDV = remdesivir (GS-5734™)
Source: GS-US- 399-5505 CSR, Table 15.10.1.1.6.1 and Table 15.10.1.1.6.4

Plasma RDV exposure following a 200 mg single dose (2862.5 h*ng/mL) is similar to the expected exposure in rhesus monkeys; i.e., 2 x 1430 h*ng. Additionally, trough (C24h) PBMC concentrations of nucleoside triphosphate metabolite GS-443902 following a 200 mg dose are comparable to values seen in rhesus monkeys.

Given the emergency situation due to the SARS-CoV-2 pandemic with urgent need for causal therapies and the safety data available from studies in Ebola Virus disease, this approach was deemed acceptable.

2.5.2. Main studies

NIAID ACTT(1): A Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Adults. (Study code: CO-US-540-5776)

Methods

This study is an adaptive, randomized, double-blinded, placebo-controlled trial to evaluate the safety and efficacy of novel therapeutic agents in hospitalized adults diagnosed with COVID-19. The study is a multi-center trial that will be conducted in up to approximately 60 sites.

Subjects were randomised 1:1 to placebo or investigational product.

The study set-up is adaptive in terms of allowing the possibility of introducing new study arms.

Study participants

Adults hospitalised with laboratory-confirmed SARS-CoV-2 infection. Illness of any duration, and at least one of the following:

• Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), OR

• SpO2 ≤ 94% on room air, OR

• Requiring supplemental oxygen, OR

• Requiring mechanical ventilation.

Notable exclusion criteria are ALT/ or AST > 5 times the upper limit of normal or estimated glomerular filtration rate (eGFR) < 30 ml/min (including patients receiving hemodialysis.

Randomisation was stratified by site and by severity of illness at enrolment:

- Severe disease: requiring mechanical ventilation, requiring oxygen, a SpO2 ≤ 94% on room air, or tachypnoea (respiratory rate ≥ 24 breaths/min).
- Mild-moderate disease: SpO2 > 94% and respiratory rate < 24 breaths/min without supplemental oxygen.

Treatments

Remdesivir (from lyophilized formulation) administered as a 200 mg intravenous (IV) loading dose on Day 1, followed by a 100 mg once-daily IV maintenance dose for the duration of the hospitalization up to a 10-day total course; or a placebo.

Rules for concomitant medications

If the local standard of care per written policies or guidelines for treatment for COVID-19 or SARS-CoV-2 infection (i.e., not just an individual clinician decision) includes lopinavir/ritonavir (Kaletra), hydroxychloroquine or other agents, (e.g. those targeting the host immune response), then continuing these during the study is permitted. If there are no written policies or guidelines for local standard of care, concomitant use of any other experimental treatment or off-label use of marketed medications intended as specific treatment for COVID-19 or SARS-CoV-2 infection are prohibited. This includes medications that target the host immune response.

Outcomes/endpoints

The study started 21 Feb 2020. The initial primary endpoint was to compare subject clinical status (8-point ordinal scale) at Day 15. The ordinal scale is as follows:

8. Death;

7. Hospitalized, on invasive mechanical ventilation or ECMO;

6. Hospitalized, on non-invasive ventilation or high flow oxygen devices;

5. Hospitalized, requiring supplemental oxygen;

4. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise);

3. Hospitalized, not requiring supplemental oxygen - no longer requiring ongoing medical care;

2. Not hospitalized, limitation on activities and/or requiring home oxygen;

1. Not hospitalized, no limitations on activities

While according to the publication, the decision to change the primary endpoint was already taken on 22 March 2020, the approval by FDA occurred only late during the trial (mid-April 2020) according to clinicaltrials.gov as follows: The primary outcome is time to recovery by Day 29. Day of recovery is defined as the first day on which the subject satisfies criterion 1, 2 or 3 on the ordinal scale above.

Because the primary efficacy endpoint was a time to event endpoint, this trial was powered based on the number of patients required to achieve 400 patients meeting recovery criteria. This was planned to provide 85% power for detecting a hazard ratio of 1.35 (on a scale where values greater than 1.00 corresponded to faster recovery in the remdesivir group). The two-sided type I error rate was set at 5%.

At the same time as the change of endpoint described above, the sample size estimation was adjusted to be 572 subjects to achieve 400 subjects with a "recovered" status (per the primary objective). The primary analysis was finally based on an intention-to-treat population, including 1059 randomized subjects.

The original primary endpoint was termed a "key secondary endpoint" at this time.

Virological investigations

Oropharyngeal (OP) swabs and plasma and serum were to be collected on Day 1; and Days 3, 5, 8, and 11 (while hospitalized); and OP swabs and serum on Day 15 and 29 (if attends an in- person visit or still hospitalized) and). The protocol states that relevant assays are not developed yet, and the ability to test samples at one central lab is not clear. Therefore, while viral load/shedding is thought to be an important endpoint, considering the limitations above, it is listed as an exploratory endpoint.

OP swabs are preferred, but if these are not obtainable, nasopharyngeal (NP) swabs may be substituted.

Due to limited lack of swabs and other supplies at some sites and limitations on personal protective equipment (PPE), the inability to obtain these samples are not considered protocol deviations and should be documented in the subject's record.

Participant flow

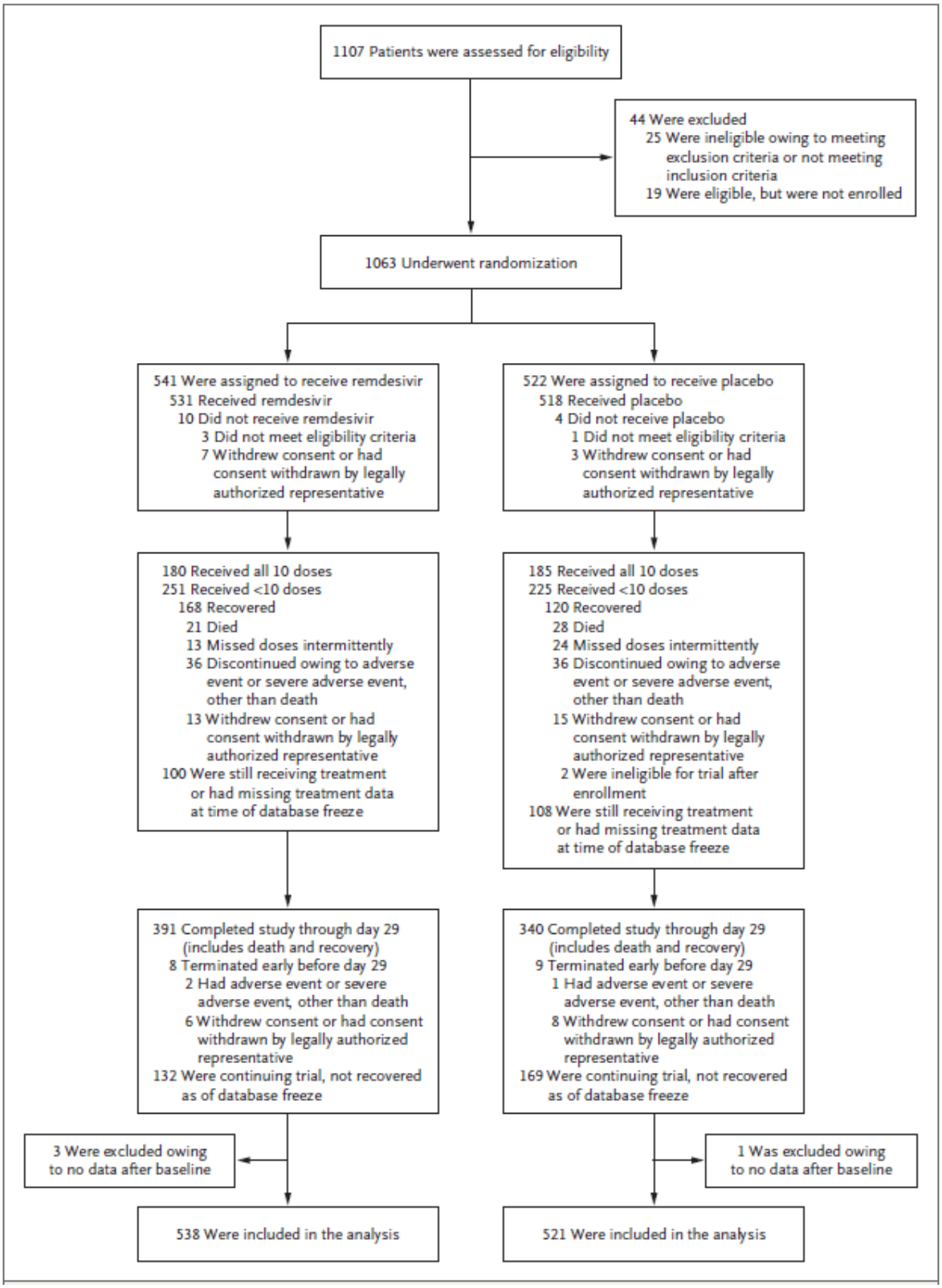


Figure 11 Enrolment and Randomization

Source: Beigel et al, NEJM ,2020

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

As of April 28, 2020, a total of 391 patients in the remdesivir group and 340 in the placebo group had completed the trial through day 29, recovered, or died. Eight patients who received remdesivir and 9 who received placebo terminated their participation in the trial before day 29. There were 132 patients in the remdesivir group and 169 in the placebo group who had not recovered and had not completed the day 29 follow-up visit.

The analysis population included 1059 patients for whom we have at least some postbaseline data available (538 in the remdesivir group and 521 in the placebo group). Four of the 1063 patients were not included in the primary analysis because no postbaseline data were available at the time of the database freeze.

Conduct of the study

Enrolment was halted on April 19, 2020 after 1063 patients had been randomized.

The statistical analysis plan pre-specified an interim analysis to be conducted by the data safety monitoring board (DSMB) after 200 of the 400 recoveries had been observed. This meeting was scheduled for April 27, 2020. However, due to rapid enrolment there had already been over 400 recoveries in the analysis set presented to the DSMB at this meeting.

Because this exceeded the originally planned final number of recoveries in the trial, no interim adjustment to significance tests or confidence intervals was applied for the DSMB analysis.

In summary, it is understood that type 1 error control has been maintained.

Baseline data

Baseline demographics were reasonable well balanced between treatment group and strata.

64% were male; Hispanics/Latinos and African/Afro-American patients made up a proportion of approximately 20% each. In total, 117 patients came from centres in the EU (24 moderate; 93 severe).

Table 11 : Baseline demographics

Characteristic	All Subjects (N=1063)	Remdesivir Subjects (N=541)	Placebo Subjects (N=522)
Age (years), mean (+/-SD)	58.9 (15.0)	58.6 (14.6)	59.2 (15.4)
18-39 years, no.(%)	119 (11.2)	59 (10.9)	60 (11.5)
40-64 years, no.(%)	559 (52.6)	295 (54.5)	264 (50.6)
65+ years, no.(%)	385 (36.2)	187 (34.6)	198 (37.9)
Male sex, no.(%)	684 (64.3)	352 (65.1)	332 (63.6)
Race			
American Indian or Alaska Native, no.(%)	7 (0.7)	4 (0.7)	3 (0.6)
Asian, no.(%)	134 (12.6)	77 (14.2)	57 (10.9)
Native Hawaiian or Other Pacific Islander, no.(%)	3 (0.3)	2 (0.4)	1 (0.2)
Black or African American, no.(%)	219 (20.6)	108 (20.0)	111 (21.3)
White, no.(%)	565 (53.2)	279 (51.6)	286 (54.8)
Multi-racial, no.(%)	3 (0.3)	2 (0.4)	1 (0.2)
Unknown, no.(%)	132 (12.4)	69 (12.8)	63 (12.1)
Ethnicity			
Not Hispanic or Latino, no.(%)	750 (70.6)	380 (70.2)	370 (70.9)
Hispanic or Latino, no.(%)	249 (23.4)	132 (24.4)	117 (22.4)
Not Reported, no.(%)	30 (2.8)	16 (3.0)	14 (2.7)
Unknown, no.(%)	34 (3.2)	13 (2.4)	21 (4.0)
Days from symptom onset to randomization (median, IQR)[a]	9 (6,12)	9 (6,12)	9 (7,13)
Disease severity			
Mild/moderate disease, no.(%) *(SpO2 > 94% and respiratory rate < 24 breaths/min without supplemental oxygen.)*	120 (11.3)	63 (11.6)	57 (10.9)
Severe disease, no.(%) *(requiring mechanical ventilation, requiring oxygen, a SpO2 ≤ 94% on room air, or respiratory rate ≥ 24 breaths/min).*	943 (88.7)	478 (88.4)	465 (89.1)
Summary of Comorbidities[b]			
None, no.(%)	193 (21.0)	91 (19.5)	102 (22.5)
One, no.(%)	248 (27.0)	131 (28.1)	117 (25.8)

Characteristic	All Subjects (N=1063)	Remdesivir Subjects (N=541)	Placebo Subjects (N=522)
2 or More, no.(%)	479 (52.1)	245 (52.5)	234 (51.7)
BMI (kg/m^2), mean(+/-SD)[c]	30.6 (7.4)	30.7 (7.4)	30.5 (7.3)
Comorbidities[b]			
Hypertension, no.(%)	460 (49.6)	231 (49.3)	229 (49.9)
Coronary artery disease, no.(%)	107 (11.6)	61 (13.0)	46 (10.0)
Congestive heart failure, no.(%)	46 (5.0)	23 (4.9)	23 (5.0)
Chronic respiratory disease (emphysema), no.(%)	70 (7.6)	33 (7.0)	37 (8.1)
Chronic oxygen requirement, no.(%)	20 (2.2)	16 (3.4)	4 (0.9)
Asthma, no.(%)	106 (11.4)	59 (12.6)	47 (10.3)
Chronic liver disease (chronic hepatitis, cirrhosis), no.(%)	18 (1.9)	9 (1.9)	9 (2.0)
Chronic kidney disease, no.(%)	54 (5.8)	32 (6.8)	22 (4.8)
Type 1 diabetes I, no.(%)	11 (1.2)	7 (1.5)	4 (0.9)
Type 2 diabetes II, no.(%)	275 (29.7)	144 (30.6)	131 (28.7)
Obesity, no.(%)	342 (37.0)	177 (37.7)	165 (36.2)
Cancer, no.(%)	71 (7.7)	39 (8.3)	32 (7.0)
Immune deficiency (acquired or innate), no.(%)	64 (6.9)	28 (6.0)	36 (7.9)
Ordinal Scale			
4. Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care (COVID-19 related or otherwise), no.(%)	127 (11.9)	67 (12.4)	60 (11.5)
5. Hospitalized, requiring supplemental oxygen, no.(%)	421 (39.6)	222 (41.0)	199 (38.1)
6. Hospitalized, on non-invasive ventilation or high flow oxygen devices, no.(%)	197 (18.5)	98 (18.1)	99 (19.0)
7. Hospitalized, on invasive mechanical ventilation or ECMO, no.(%)	272 (25.6)	125 (23.1)	147 (28.2)
Missing at Baseline, no.(%)	46 (4.3)	29 (5.4)	17 (3.3)
Region/Country			
Asia, no.(%)	52 (4.9)	26 (4.8)	26 (5.0)
Europe, no.(%)	163 (15.3)	84 (15.5)	79 (15.1)

The study recruited patients with a broad range of ages, with a median of 59 years. Males are over-represented, similar to the real-life population hospitalised with COVID-19.

80% of patients were recruited in North America; 15% in Europe and 5% in Asia.

The median patient is overweight. Nearly half of the patients have hypertension and one quarter of patients has type II diabetes, which is representative of common risk factors for severe disease.

The median duration of disease at randomisation is nine days, with a very wide full range of durations.

Outcomes and estimations

The below information is based on the publication of Beigel JH et al and two reports for the DSMB (24th and 28th April 2020).

As of April 28, 2020, a total of 391 patients in the remdesivir group and 340 in the placebo group had completed the trial through day 29, recovered, or died. Eight patients who received remdesivir and 9 who received placebo terminated their participation in the trial before day 29. There were 132 patients in the remdesivir group (24.4%) and 169 (32.4%) in the placebo group who had not recovered and had not completed the day 29 follow-up visit. The analysis population included 1059 patients for whom at least some post-baseline data available (538 in the remdesivir group and 521 in the placebo group).

In the remdesivir arm, 180/538 (33%) participants received 10 doses of remdesivir, while 202/538 (38%) participants received <10 doses of remdesivir because of recovery, death or intermittent missed doses (31%, 4% and 2%, respectively). 100 participants (19%) were still receiving remdesivir or had missing treatment data as of the database freeze on April 28, 2020.

Of those assigned to receive placebo, 185/521 (36%) participants received 10 doses of placebo, while 172/521 (33%) participants received < 10 doses because of recovery, death or intermittent missed dose (23%, 5% and 5 %, respectively). 108 (21%) participants were still receiving placebo or had missing treatment data as of the database freeze.

Primary outcome

Preliminary results suggest that the median difference in time to recovery is 4 days favouring the remdesivir group In the primary endpoint RDV was superior to placebo in the treatment of hospitalized participants with COVID-19. This benefit was also observed in the key secondary endpoint of recovery by the ordinal scale at Day 15 (see tables below).

Notably, the efficacy demonstration was confined to the severe stratum, whereas no effect could be shown in the mild-moderate stratum which only recruited approximately 120 patients.

Table 12 Outcomes overall and by baseline disease severity in the intent-to-treat population

	Overall		Mild-Moderate Disease Stratum		Severe Disease Stratum	
	Remdesivir (n=538)	Placebo (n=521)	Remdesivir (n=62)	Placebo (n=57)	Remdesivir (n=476)	Placebo (n=464)
Days to Recovery						
Number of Recoveries	334	273	52	46	282	227
Median (95% CI)	11 (9, 12)	15 (13, 19)	5 (4, 7)	5 (4, 7)	12 (10, 14)	18 (15, 21)
Recovery Rate Ratio (95% CI); p-value[a]	1.32 (1.12, 1.55); p<0.001		1.09 (0.73,1.62)		1.37 (1.15, 1.63)	
Mortality						
Hazard Ratio (95% CI)[a]	0.70 (0.47, 1.04)		0.48 (0.04, 5.27)		0.71 (0.48, 1.05)	
Number of Deaths by 14 Days	32	54	1	1	31	53
Kaplan-Meier Estimate (95% CI)	7.1% (5.0%,9.9%)	11.9% (9.2%,15.4%)	1.6% (0.2%,10.9%)	2.9% (0.4%,19.1%)	7.7% (5.4%,10.8%)	13.0% (10.0%,16.7%)
Ordinal Scale at Day 15±2 Visit[b] N (%) in each category						
Total with Day 15 Ordinal Score Data	434	410	51	45	383	365
1 - Not hospitalized, no limitations	99 (22.8)	76 (18.5)	15 (29.4)	12 (26.7)	84 (21.9)	64 (17.5)
2 - Not hospitalized, with limitations	158 (36.4)	127 (31.0)	26 (51.0)	24 (53.3)	132 (34.5)	103 (28.2)
3 - Hospitalized, no active medical problems	11 (2.5)	6 (1.5)	6 (11.8)	3 (6.7)	5 (1.3)	3 (0.8)
4 - Hospitalized, not on oxygen	23 (5.3)	20 (4.9)	1 (2.0)	1 (2.2)	22 (5.7)	19 (5.2)
5 - Hospitalized, on oxygen	34 (7.8)	40 (9.8)	1 (2.0)	4 (8.9)	33 (8.6)	36 (9.9)
6 - Hospitalized, on high flow oxygen or non-invasive mechanical ventilation	16 (3.7)	14 (3.4)	1 (2.0)	0 (0)	15 (3.9)	14 (3.8)
7 - Hospitalized, on mechanical ventilation or ECMO	60 (13.8)	72 (17.6)	0 (0)	0 (0)	60 (15.7)	72 (19.7)
8-Death	33 (7.6)	55 (13.4)	1 (2.0)	1 (2.2)	32 (8.4)	54 (14.8)
Odds Ratio; p-value[c]	1.50 (1.18, 1.91); p=0.001		1.13 (0.53, 2.41)		1.54 (1.19, 1.99)	

n = Number of subjects in analysis.
a Recovery rate ratio and hazard ratio calculated from the stratified Cox model. Recovery rate ratio and hazard ratio p-values calculated using the stratified log-rank test. Recovery rate ratios > 1 indicate benefit for remdesivir. Hazard ratios <1 indicate benefit for remdesivir.
b Ordinal Scale at Day 15 Visit is the participant's worst ordinal scale score during the previous day. In the remdesivir arm, 103 participants did not have ordinal scale scores for the day 15 visit at the time of the data freeze (11 Mild-Moderate, 92 Severe). In the placebo arm, 109 participants did not have ordinal scale scores for the day 15 visit at the time of the data freeze (12 Mild-Moderate, 97 Severe). Note, 2 subjects died 15 days post-randomization and are included in the ordinal scale but not in the 14-day mortality estimate.
c Odds ratio and odds ratio p-values calculated using a proportional odds model. Odds ratio values > 1 indicate benefit for remdesivir. P-value and confidence intervals have not been adjusted for multiple comparisons.

Figure 12 Kaplan-Meier plot of time to recovery/discharge

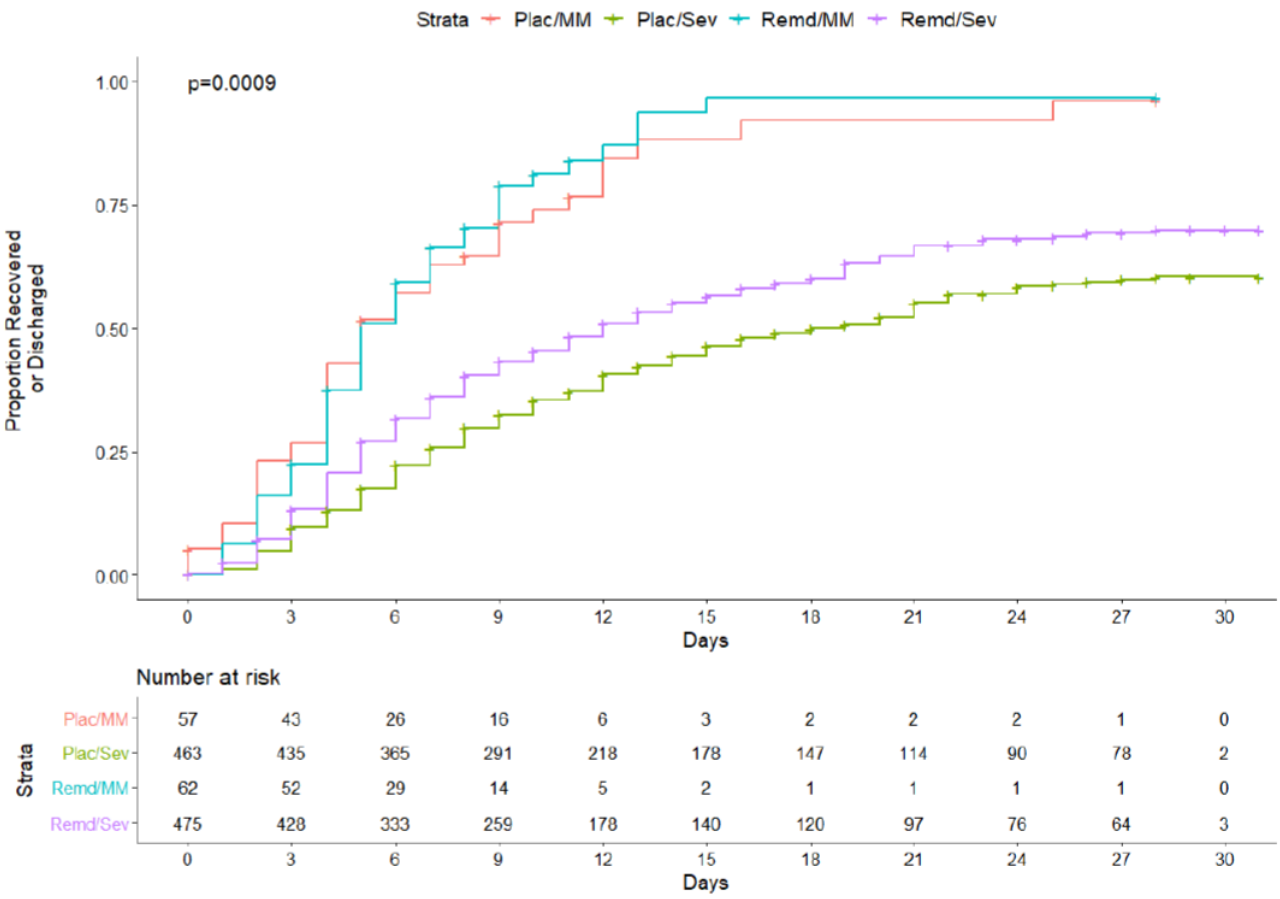


Table 13 Outcomes Overall and According to Score on the Ordinal Scale (ITT-population) *

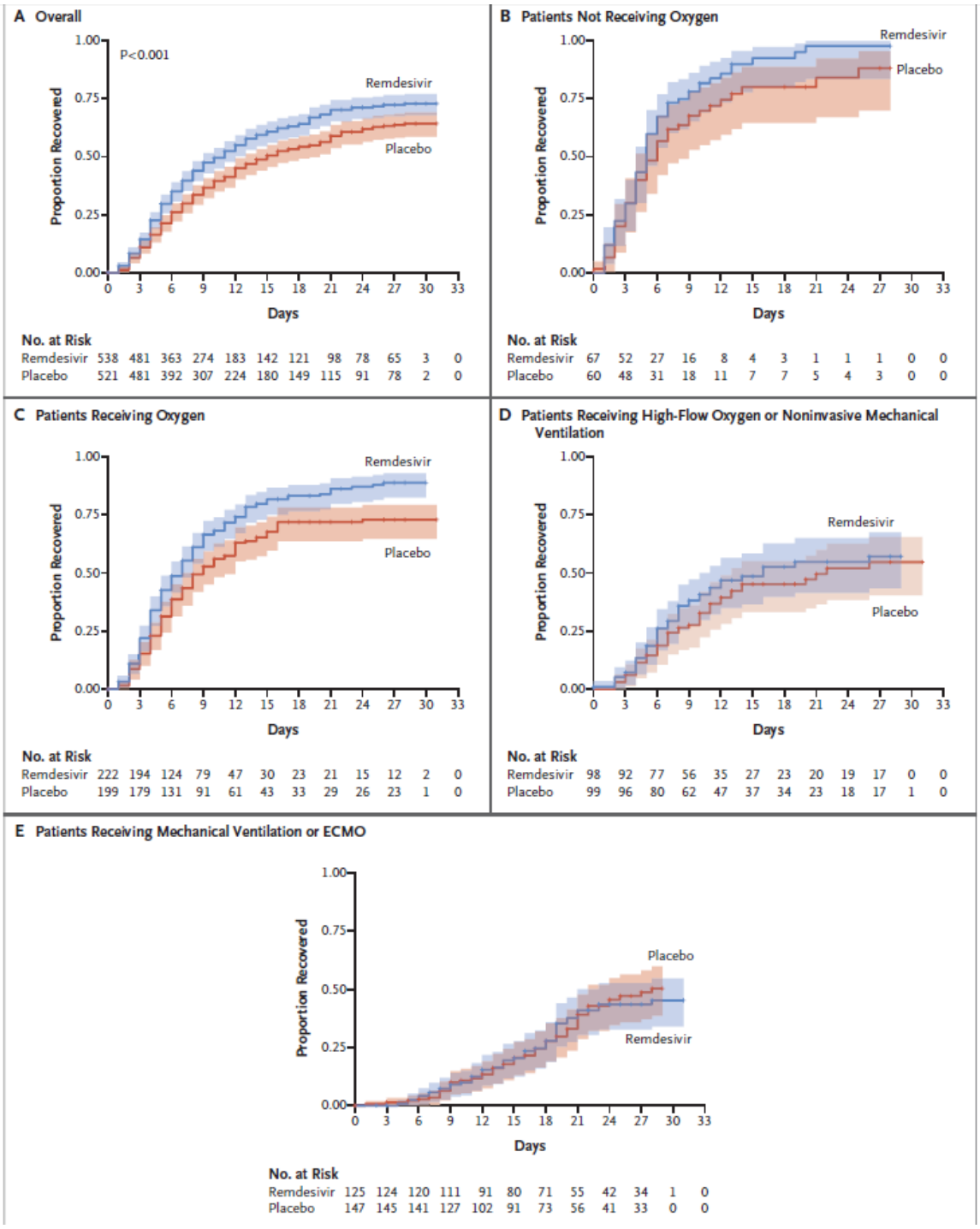
	Overall*		Ordinal Score at Baseline							
			4		5		6		7	
	Remdesivir (N=538)	Placebo (N=521)	Remdesivir (N=67)	Placebo (N=60)	Remdesivir (N=222)	Placebo (N=199)	Remdesivir (N=98)	Placebo (N=99)	Remdesivir (N=125)	Placebo (N=147)
Recovery										
No. of recoveries	334	273	61	47	177	128	47	43	45	51
Median time to recovery (95% CI) — days	11 (9–12)	15 (13–19)	5 (4–6)	6 (4–8)	7 (6–8)	9 (7–11)	16 (NE– 10)	22 (NE– 12)	NE–NE	28 (NE– 22)
Rate ratio (95% CI)†	1.32 (1.12–1.55 [P<0.001])		1.38 (0.94–2.03)		1.47 (1.17–1.84)		1.20 (0.79–1.81)		0.95 (0.64–1.42)	
Mortality										
Hazard ratio (95% CI)	0.70 (0.47–1.04)		0.46 (0.04–5.08)		0.22 (0.08–0.58)		1.12 (0.53–2.38)		1.06 (0.59–1.92)	
No. of deaths by day 14	32	54	1	1	4	19	13	13	13	19
Kaplan–Meier estimate — % (95% CI)	7.1 (5.0–9.9)	11.9 (9.2–15.4)	1.5 (0.2–10.1)	2.5 (0.4–16.5)	2.4 (0.9–6.4)	10.9 (7.1–16.7)	15.2 (9.0–25.0)	14.7 (8.7–24.3)	11.3 (6.7–18.8)	14.1 (9.2–21.2)
Ordinal score at day 15 (±2 days) — no. (%)‡										
Patients with baseline and day 15 score data — no.	434	410	60	51	196	161	71	77	101	115
1	99 (22.8)	76 (18.5)	22 (36.7)	15 (29.4)	54 (27.6)	45 (28.0)	13 (18.3)	7 (9.1)	10 (9.9)	8 (7.0)
2	158 (36.4)	127 (31.0)	25 (41.7)	21 (41.2)	95 (48.5)	66 (41.0)	28 (39.4)	27 (35.1)	6 (5.9)	10 (8.7)
3	11 (2.5)	6 (1.5)	7 (11.7)	4 (7.8)	4 (2.0)	2 (1.2)	0	0	0	0
4	23 (5.3)	20 (4.9)	1 (1.7)	3 (5.9)	12 (6.1)	7 (4.3)	4 (5.6)	4 (5.2)	6 (5.9)	6 (5.2)
5	34 (7.8)	40 (9.8)	3 (5.0)	5 (9.8)	14 (7.1)	6 (3.7)	2 (2.8)	7 (9.1)	15 (14.9)	22 (19.1)
6	16 (3.7)	14 (3.4)	1 (1.7)	0 (0)	1 (0.5)	3 (1.9)	6 (8.5)	6 (7.8)	7 (6.9)	5 (4.3)
7	60 (13.8)	72 (17.6)	0 (0)	2 (3.9)	12 (6.1)	12 (7.5)	5 (7.0)	13 (16.9)	43 (42.6)	45 (39.1)
8	33 (7.6)	55 (13.4)	1 (1.7)	1 (2.0)	4 (2.0)	20 (12.4)	13 (18.3)	13 (16.9)	14 (13.9)	19 (16.5)
Odds ratio (95% CI)	1.50 (1.18–1.91 [P=0.001])		1.51 (0.76–3.00)		1.31 (0.89–1.92)		1.60 (0.89–2.86)		1.04 (0.64–1.68)	

*P values and confidence intervals have not been adjusted for multiple comparisons. NE denotes not possible to estimate.
† Recovery rate ratios and hazard ratios were calculated from the stratified Cox model; P values for these ratios were calculated with the stratified log-rank test. Recovery rate ratios greater than 1 indicate a benefit for remdesivir; hazard ratios less than 1 indicate a benefit for remdesivir.
‡ The ordinal score at day 15 is the patient's worst score on the ordinal scale during the previous day. In the remdesivir group, 103 patients did not have ordinal scale scores for the day 15 visit at the time of the data freeze (11 with mild-to-moderate illness and 92 with severe illness). In the placebo group, 109 patients did not have ordinal scale scores for the day 15 visit at the time of the data freeze (12 with mild-to-moderate illness and 97 with severe illness). Two patients died 15 days after randomization and are included in the ordinal scale scores but not in the estimate of mortality by day 14. Scores on the ordinal scale are as follows: 1, not hospitalized, no limitations of activities; 2, not hospitalized, limitation of activities, home oxygen requirement, or both; 3, hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection-control reasons); 4, hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (Covid-19–related or other medical conditions); 5, hospitalized, requiring any supplemental oxygen; 6, hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices; 7, hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); and 8, death. Odds ratios and P values were calculated with the use of a proportional odds model. Odds ratio values greater than 1 indicate a benefit for remdesivir. Source: Beigel et al, NEJM ,2020

Cumulative recovery estimates are shown in the overall population (Panel A), in patients with a baseline score of 4 on the ordinal scale (not receiving oxygen;Panel B), in those with a baseline score of 5 (receiving oxygen; Panel C), in those with a baseline score of 6 (receiving high-flow oxygen or noninvasive mechanical ventilation; Panel D), and in those with a baseline score of 7 (receiving mechanical ventilation or ECMO; Panel E).

A key secondary analysis (the primary analysis according to the original protocol) used the proportional odds model on the 8-point ordinal scale at Day 15. The odds of improvement in the ordinal scale were higher in the RDV group as determined by a proportional odds model at the Day 15 visit when compared to the placebo group (OR, 1.50; 95% CI, 1.18 to 1.91; p = 0.001; n = 844)

Figure 13 Kaplan–Meier Estimates of Cumulative Recoveries

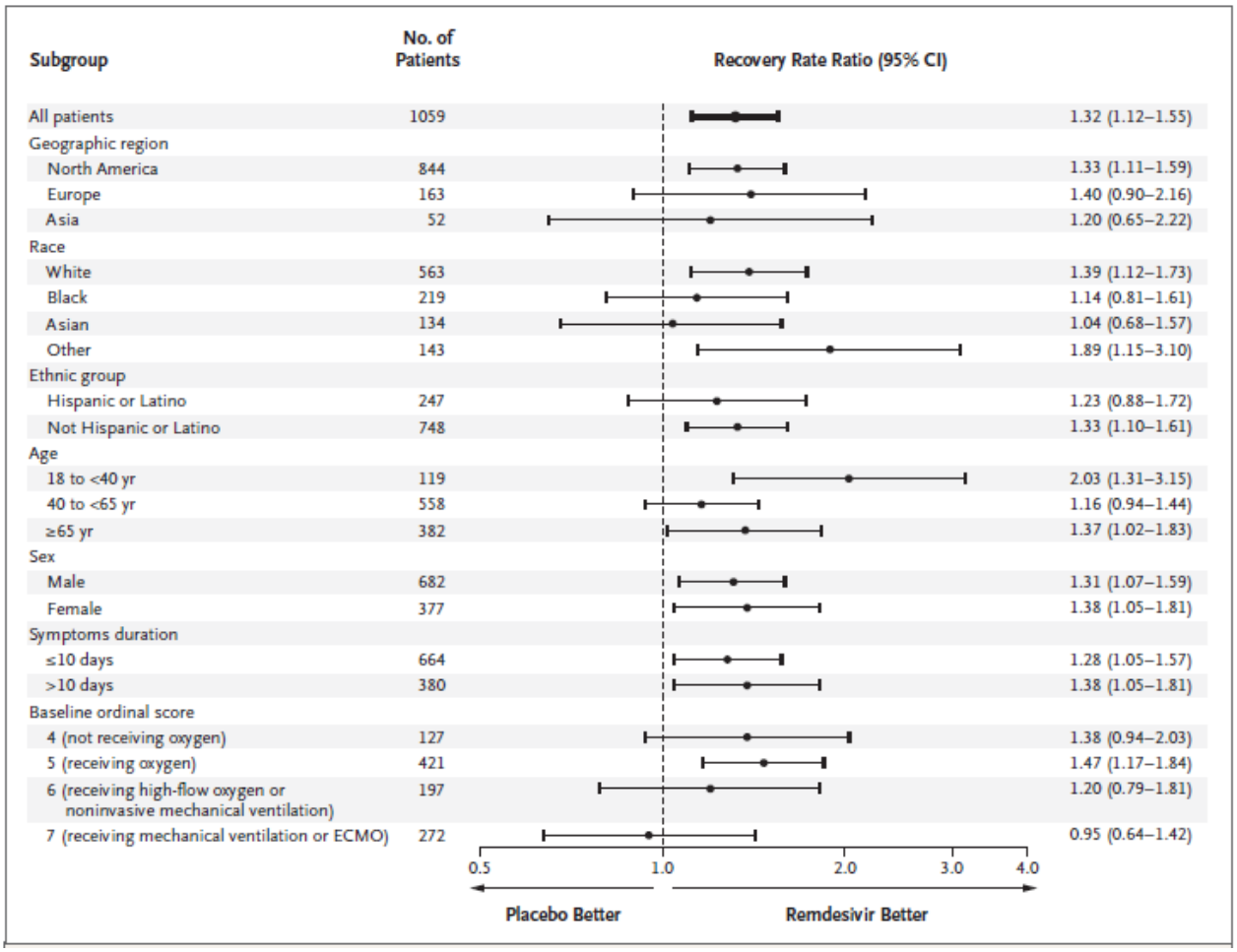


Cumulative recovery estimates are shown in the overall population (Panel A), in patients with a baseline score of 4 on the ordinal scale (not receiving oxygen;Panel B), in those with a baseline score of 5 (receiving oxygen; Panel C), in those with a baseline score of 6 (receiving high-flow oxygen or noninvasive mechanical ventilation; Panel D), and in those with a baseline score of 7 (receiving mechanical ventilation or ECMO; Panel E). Source: Beigel et al, NEJM ,2020

Patients who underwent randomization during the first 10 days after the onset of symptoms had a rate ratio for recovery of 1.28 (95% CI, 1.05 to 1.57; 664 patients), whereas patients who underwent randomization

more than 10 days after the onset of symptoms had a rate ratio for recovery of 1.38 (95% CI, 1.05 to 1.81; 380 patients)

Figure 14 Time to Recovery According to Subgroup.



The widths of the confidence intervals have not been adjusted for multiplicity and therefore cannot be used to infer treatment effects. Race and ethnic group were reported by the patients. Source: Beigel et al, NEJM ,2020

Key secondary outcomes

The Kaplan–Meier estimates of mortality by 14 days reported in the NEJM publication were 7.1% (32/538 patients) and 11.9% (54/521 patients) in the remdesivir and placebo groups, respectively showing a hazard ratio for death of 0.70 (95% CI 0,47 to 1.04). An analysis with adjustment for baseline ordinal score as a stratification variable showed a hazard ratio for death of 0.74 (95% CI, 0.50 to 1.10).

For reliable conclusions on mortality, the final results on 28-day mortality with complete follow-up are required.

Figure 15 Kaplan-Meier Plot of time to death

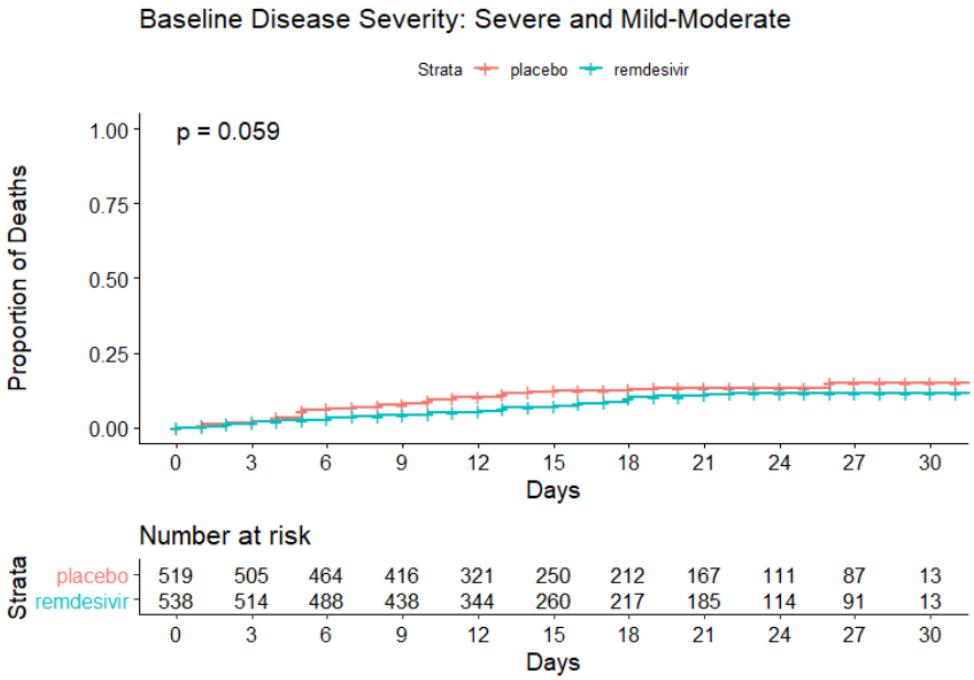
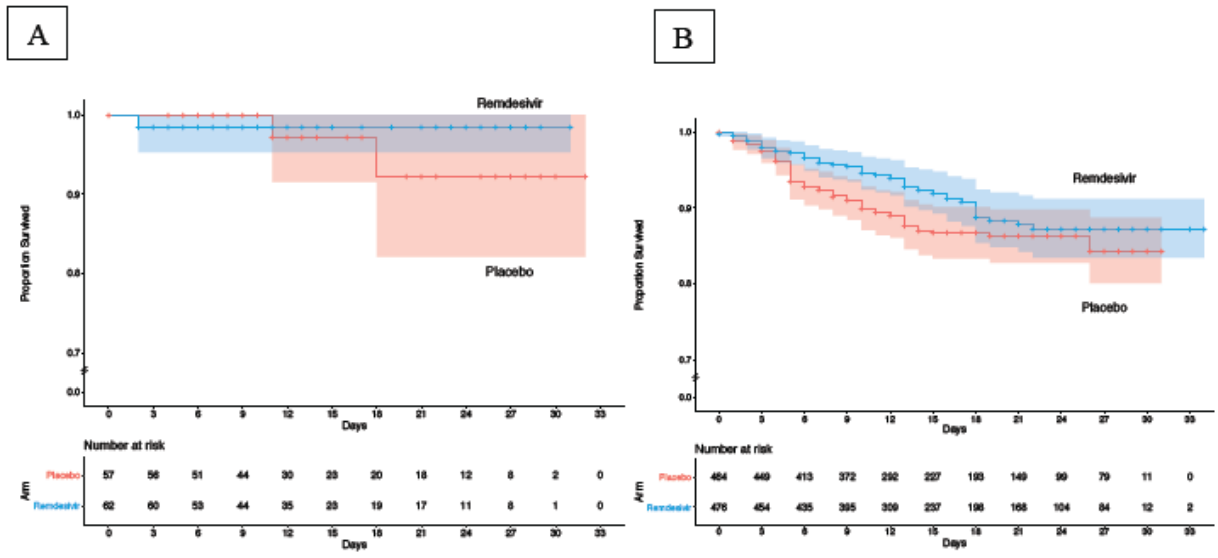
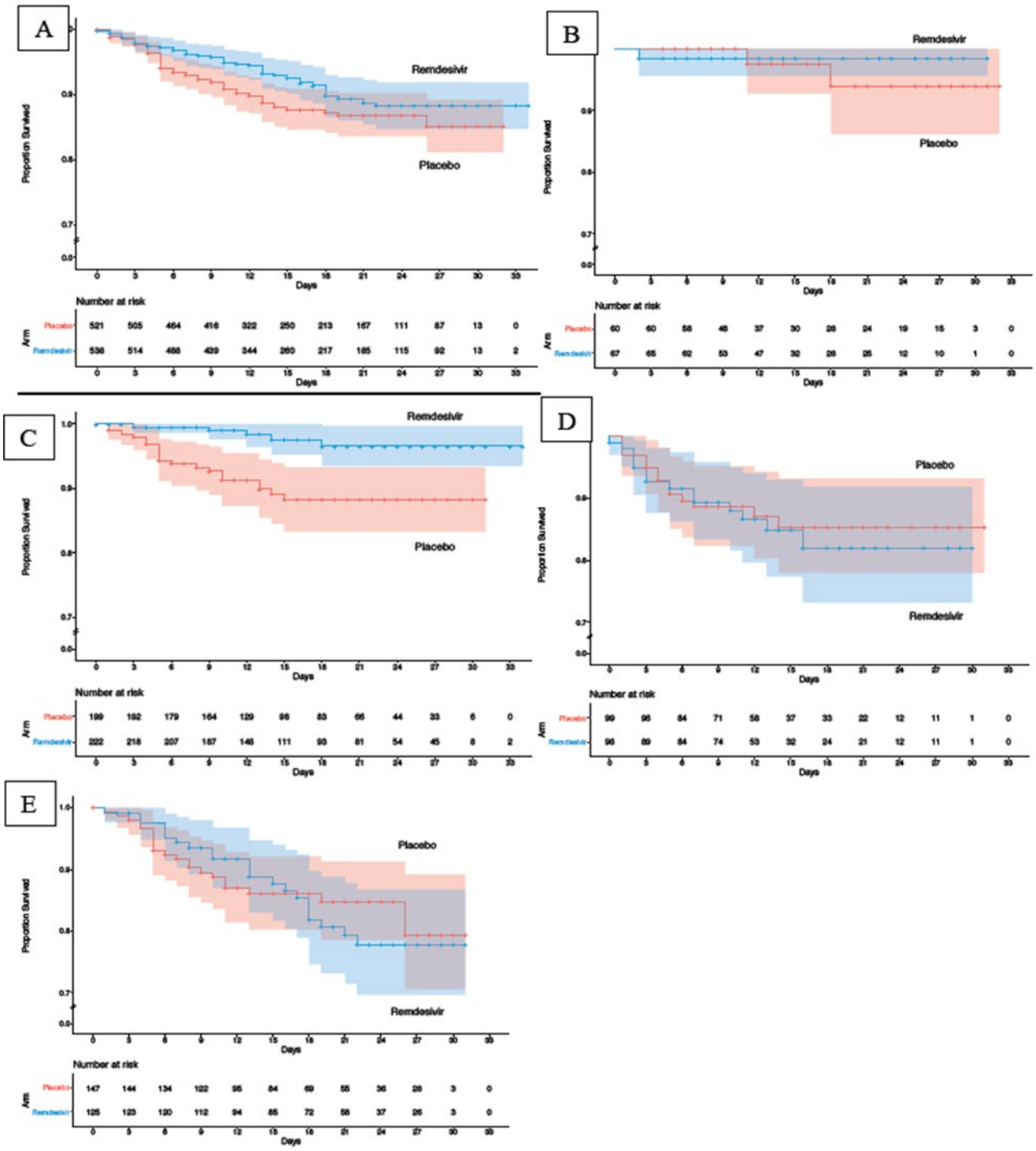


Figure 16 Kaplan–Meier Estimates of Survival by Disease Severity.



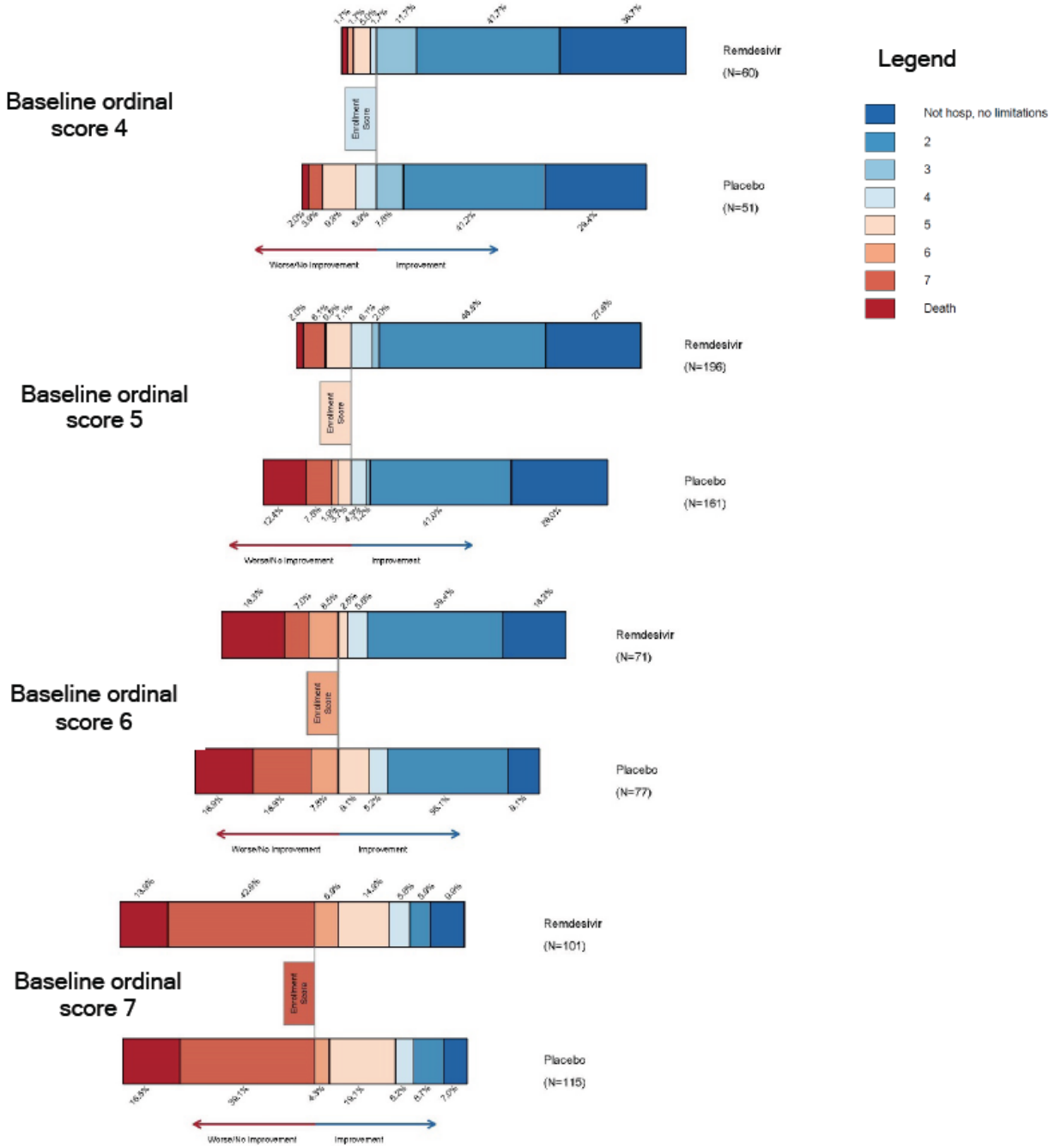
Panel A shows the estimates (and 95% confidence bands) in patients with mild-moderate disease, and Panel B in patients with severe disease.

Figure 17 Kaplan–Meier Estimates of Survival by Baseline Ordinal Scale.



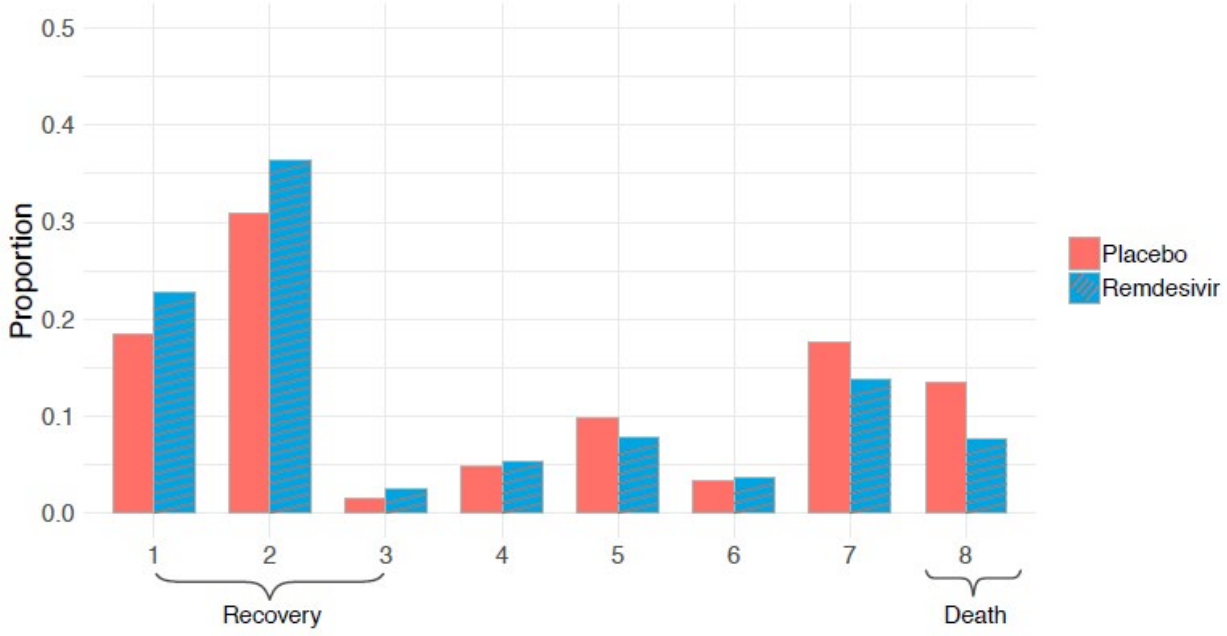
Panel A shows the estimates (and 95% confidence bands) in the overall population, Panel B in those with baseline ordinal scale = 4, Panel C in those with baseline ordinal scale = 5, Panel D in those with baseline ordinal scale = 6, and Panel E in those with baseline ordinal scale = 7.

Figure 18 Day 15 outcomes by baseline ordinal scale in the intent-to-treat population.



Bar plots are shifted to compare improvement versus no improvement / worsening compared to the baseline ordinal score category (i.e., the "Enrollment Score"). Movement to the right of the enrollment score line reflect improvement by Day 15. Movement to the left of the enrollment line reflect no change in ordinal status (same color same color as the "Enrollment Score" box) or worsening by Day 15.

Figure 19 Histogram of ordinal scores at Day 15 by treatment arm



No virological outcomes are available. Currently, proof of antiviral activity *in vivo* is lacking for RDV.

Study title: A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants with Severe COVID-19 (GS-US-540-5773)

Methods

This ongoing open-label trial compared 5-day and 10-day remdesivir durations for the treatment of patients with severe COVID-19.

The study has a part A and a part B, with part A constituting the sample for the inferential analysis, and part B an expansion cohort with broader inclusion criteria and applying the 10-day RDV regimen only.

There was no stratification of randomisation.

Study participants

Included patients were aged ≥12 years, hospitalised with SARS-CoV-2 infection confirmed by RT-PCR testing. Radiographic evidence of pulmonary infiltrates was required or SpO2 ≤94% on room air or requirement for supplemental oxygen.

Exclusion criteria disallowed patients on mechanical ventilation (as of 15 Mach expanded to mechanical ventilation for ≥5 days, incl. ECMO), patients with multiorgan failure, ALT or AST >5 times the upper limit of normal, or creatinine clearance <50 mL/min.

The most severely ill patients were excluded from this study.

Treatments

Remdesivir (from lyophilized formulation) was administered intravenously at a dose of 200 mg on Day 1 followed by 100 mg on subsequent five or ten days. There was no placebo or standard of care group.

Concomitant medications

Concomitant use of investigational agents such as approved HIV protease inhibitors like lopinavir/ritonavir, chloroquine, etc. while receiving RDV was prohibited.

Outcomes/endpoints

The pre-specified primary efficacy analysis was to examine results on a 7-point (until April 06 on a 6-point) ordinal scale at Day 14 using a proportional odds model. The scale used the following categories:

1. Death;
2. Hospitalized, on invasive mechanical ventilation or ECMO;
3. Hospitalized, on non-invasive ventilation or high flow oxygen devices;
4. Hospitalized, requiring low flow supplemental oxygen;
5. Hospitalized, not requiring supplemental oxygen – requiring ongoing medical care (COVID-19 related or otherwise);
6. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care (other than per protocol RDV administration);
7. Not hospitalized.

The endpoint will be derived by combining the available death, hospital discharge alive and ordinal scale assessment reported by the site, where death supersedes discharge alive and discharge alive supersedes the ordinal scale score reported by the site.

The Full Analysis Set (FAS) is the primary analysis set for efficacy analysis and includes all patients randomized into Part A of the study that have received at least 1 dose of RDV.

The primary endpoint was to be analyzed using a proportional odds model including treatment as the independent variable and baseline score as a continuous covariate.

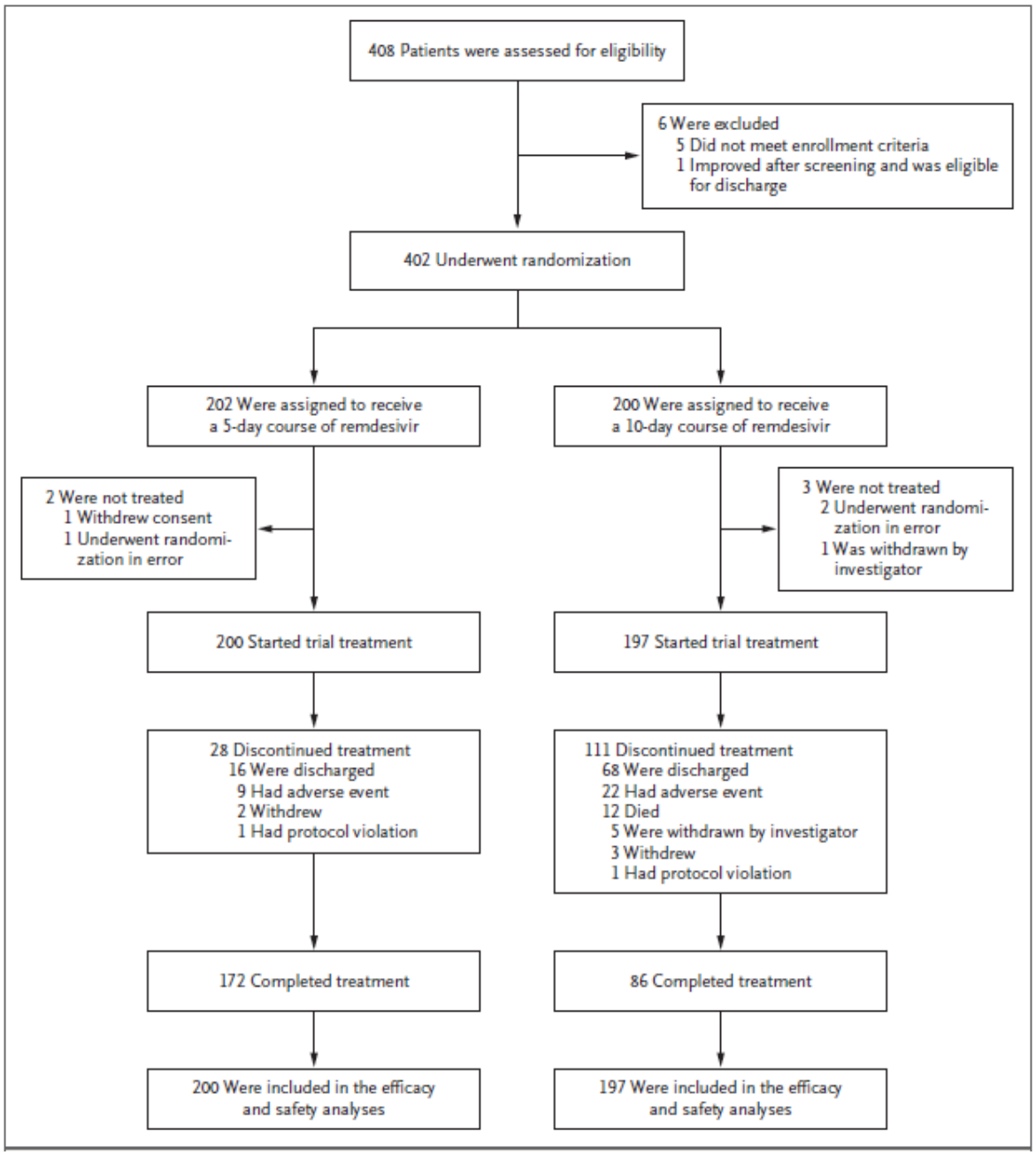
Virological investigations

SARS-CoV-2 testing may include RT-qPCR to detect or quantify SARS-CoV-2 or virus sequencing results. If feasible, OP, saliva, sputum, stool, and/or blood samples may be collected and assayed using RT-qPCR to quantify SARS-CoV-2 viral load. Pre-treatment and posttreatment samples with detectable SARS-CoV-2 may be sequenced for resistance monitoring of the viral polymerase gene if possible. Results have not been presented.

Participant flow

A total of 402 patients were randomized in a 1:1 ratio to the 5-day and 10-day remdesivir groups. The sponsor excluded 5 patients who were randomized but not treated, and the primary analysis set included 200 patients in the 5-day group and 197 patients in the 10- day group. Relevant information in terms of patient flow, such as protocol deviations, follow-up and analysis sets, are missing.

Figure 20: Enrolment and Randomization.



Source: Goldman et al, NEJM 2020

- **Blinding (masking)**

Blinding of treatment assignments or data was not performed in this study.

- **Statistical methods**

The null hypothesis being tested is whether the odds of improvement on the ordinal scale is the same for the two treatment groups (i.e., whether the common odds ratio is equal to 1). The odds ratio and 95% confidence interval will be provided. If a participant is discharged prior to Day 14, the Day 14 ordinal scale category is considered to be not hospitalized.

The protocol does not define a directional alternative hypothesis, but evidently only in case the 10 day treatment arm was superior to the 5 day treatment arm, a drug effect would have been isolated.

No multiplicity adjustment was planned due to this interim analysis, as it comprises the primary analysis for Part A.

Values for missing data were not imputed.

The primary analysis concerning the baseline adjustment as specified in the protocol was changed in the SAP dated April 22, 2020.

Conduct of the study

As the study is ongoing, no clinical study report in line with ICH E3 (CPMP/ICH/137/95) is currently available.

Comprehensive information on protocol violations has not been presented.

Baseline data

Table 14: Study 5773 – Demographic and Clinical Characteristics of the Patients at Baseline According to Remdesivir Treatment Group. *

Characteristic	5-Day Group (N=200)	10-Day Group (N=197)
Median age (IQR) — yr	61 (50–69)	62 (50–71)
Male sex — no. (%)	120 (60)	133 (68)
Race — no./total no. (%)†		
White	142/200 (71)	134/192 (70)
Black	21/200 (10)	23/192 (12)
Asian	20/200 (10)	25/192 (13)
Other	17/200 (8)	10/192 (5)
Median body-mass index (IQR)‡	29 (25–34)	29 (25–33)
Coexisting conditions of interest — no. (%)		
Diabetes	47 (24)	43 (22)
Hyperlipidemia	40 (20)	49 (25)
Hypertension	100 (50)	98 (50)
Asthma	27 (14)	22 (11)
Clinical status on the 7-point ordinal scale — no. (%)§		
2: Receiving invasive mechanical ventilation or ECMO	4 (2)	9 (5)
3: Receiving noninvasive ventilation or high-flow oxygen	49 (24)	60 (30)
4: Receiving low-flow supplemental oxygen	113 (56)	107 (54)
5: Not receiving supplemental oxygen but requiring medical care	34 (17)	21 (11)
Median duration of hospitalization before first dose of remdesivir (IQR) — days	2 (1–3)	2 (1–3)
Median duration of symptoms before first dose of remdesivir (IQR) — days	8 (5–11)	9 (6–12)
Median AST level (IQR) — U/liter¶	41 (29–58)	46 (34–67)
Median ALT level (IQR) — U/liter	32 (22–50)	36 (23–58)
Median creatinine clearance by Cockcroft–Gault (IQR) — ml/min	106 (80–142)	103 (80–140)

* Percentages may not total 100 because of rounding. ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and IQR interquartile range.
† Race was reported by the patients.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ P = 0.02 for the comparison between the 5-day group and the 10-day group by the Wilcoxon rank-sum test.
¶ P = 0.008 for the comparison between the 5-day group and the 10-day group by the Wilcoxon rank-sum test.

Source: Goldman JD et al ,NEJM 2020

With the exception of male gender, it appears that baseline characteristics in terms of demographics (age, gender, BMI, race) and baseline comorbidities (diabetes, hyperlipidaemia, hypertension, asthma) are relatively well balanced between treatment groups. It is unclear how many patients were recruited at sites within the EU.

The overall distribution of clinical status was statistically significantly different between the RDV 5-day group and the RDV 10-day group (p = 0.019), with greater proportions of participants in the 2 highest disease severity categories (i.e., on invasive mechanical ventilation or ECMO and on noninvasive ventilation or high-flow oxygen devices) for the RDV 10-day group than for the RDV 5-day group.

The age range was 20-98 years. Adolescents were not included in the study.

Although concomitant use of drugs with potential antiviral activity against SARS-CoV-2 was prohibited, a considerable number of patients received non study antiviral drugs, i.e. (hydroxy)chloroquine, LPV/rtv, DRV/rtv, DRV/cobi, tocilizumab, interferon-beta, ribavirin, or oseltamivir, for some patients more than one agent was given.

Table 15 Study 5773- Exposure to study drug

Subjects, n (%)		Treatment A N = 200	Treatment B N=197	Total N=397
Number of Days Received, n (%)	1 Day	2 (1)	4 (2)	6 (2)
	2 Days	6 (3)	9 (5)	15 (4)
	3 Days	8 (3)	10 (5)	18 (5)
	4 Days	11 (6)	10 (5)	21 (5)
	5 Days	172 (86)	20 (10)	192 (48)
	6 Days	1 (0.5)	11 (6)	12 (3)
	7 Days	--	19 (10)	19 (5)
	8 Days	--	15 (8)	15 (4)
	9 Days	--	14 (7)	14 (4)
	10 Days	--	85 (43)	85 (21)
Number of Doses Received, median (IQR)		5 (5, 5)	9 (5, 10)	5 (5, 8)

In the 10-day treatment group, only 43% of the patients received remdesivir for 10 days and 27% in this group received only an up to 5-day course.

The applicant notes that, given the stretched health care resources during the pandemic, it seemed appropriate to allow for patients to be discharged from the hospital as soon as medically indicated, regardless of whether they had completed the full assigned course of treatment with remdesivir. As a result, only 44% of patients in the 10-day treatment group completed the full course of therapy.

Outcomes and estimations

The primary endpoint was clinical outcome at Day 14. After adjusting for baseline clinical status, participants receiving a 10-day course of RDV had a similar distribution in clinical status at Day 14 as those receiving a 5-day course (p = 0.1443; see table below)

Table 16 Study 5773 -Clinical outcomes at Day 14

Characteristic	5-Day Group (N=200)	10-Day Group (N=197)	Baseline-Adjusted Difference (95% CI)*
Clinical status at day 14 on the 7-point ordinal scale — no. of patients (%)			P=0.14†
1: Death	16 (8)	21 (11)	
2: Hospitalized, receiving invasive mechanical ventilation or ECMO	16 (8)	33 (17)	
3: Hospitalized, receiving noninvasive ventilation or high-flow oxygen	9 (4)	10 (5)	
4: Hospitalized, requiring low-flow supplemental oxygen	19 (10)	14 (7)	
5: Hospitalized, not receiving supplemental oxygen but requiring ongoing medical care	11 (6)	13 (7)	
6: Hospitalized, not requiring supplemental oxygen or ongoing medical care	9 (4)	3 (2)	
7. Not hospitalized	120 (60)	103 (52)	
Time to clinical improvement (median day of 50% cumulative incidence‡)	10	11	0.79 (0.61 to 1.01)
Clinical improvement — no. of patients (%)			
Day 5	33 (16)	29 (15)	0.2% (−7.0 to 7.5)
Day 7	71 (36)	54 (27)	−5.0% (−14.0 to 4.0)
Day 11	116 (58)	97 (49)	−4.8% (−14.1 to 4.6)
Day 14	129 (64)	107 (54)	−6.5% (−15.7 to 2.8)
Time to recovery (median day of 50% cumulative incidence‡)	10	11	0.81 (0.64 to 1.04)
Recovery — no. of patients (%)			
Day 5	32 (16)	27 (14)	0.1% (−7.0 to 7.1)
Day 7	71 (36)	51 (26)	−6.0% (−14.8 to 2.7)
Day 11	115 (58)	97 (49)	−3.7% (−12.8 to 5.5)
Day 14	129 (64)	106 (54)	−6.3% (−15.4 to 2.8)
Time to modified recovery (median day of 50% cumulative incidence‡)	9	10	0.82 (0.64 to 1.04)
Modified recovery — no. of patients (%)			
Day 5	51 (26)	41 (21)	−2.3% (−10.5 to 5.9)
Day 7	84 (42)	69 (35)	−3.4% (−12.6 to 5.8)
Day 11	128 (64)	106 (54)	−5.7% (−14.6 to 3.2)
Day 14	140 (70)	116 (59)	−6.7% (−15.3 to 1.9)

* Differences are expressed as rate differences, except in the case of time to clinical improvement, time to recovery, and time to modified recovery, for which differences are expressed as hazard ratios; for these time-to-event end points, the hazard ratio and its 95% confidence interval were estimated from a cause-specific proportional-hazards model including treatment and baseline clinical status as covariates. For events at prespecified time points (e.g., days 5, 7, 11, and 14), the difference in the proportion of subjects with an event under evaluation between treatment groups and the 95% confidence interval were estimated from the Mantel–Haenszel proportions adjusted according to baseline clinical status.
† The P value was calculated from a Wilcoxon rank-sum test stratified by baseline clinical status.
‡ Clinical improvement was defined as an improvement of at least 2 points from baseline on the 7-point ordinal scale; recovery was defined as an improvement from a baseline score of 2 to 5 to a score of 6 or 7; and modified recovery was defined as an improvement from a baseline score of 2 to 4 to a score of 5 to 7 or from a score of 5 to a score of 6 or 7. Cumulative incidence functions were calculated for each treatment group for days to the event under evaluation (i.e., clinical improvement, recovery, or modified recovery), with death as the competing risk. Data for patients not achieving the event under evaluation at the last assessment were censored on the day of the last clinical assessment. Patients who died before achieving the event under evaluation were considered to have experienced a competing event
Source: Goldman JD et al NEJM 2020

The reported results of the primary analysis of the proportional odds model at Day 14 shows an estimated odds ratio (adjusted for baseline imbalances) of 0.79 on a scale with values less than 1.00 favouring the 5-day duration, with a 95% confidence interval from 0.61 to 1.04. Thus, there was a numerical trend showing improved outcomes in the 5-day group, although this difference was not statistically significant.

The result of the primary analysis as specified in the protocol was not presented. The p-value of the unadjusted analysis (primary analysis as specified in the protocol) is p=0.035 (indicating a statistically significant difference between both treatments in favour of the 5-day regimen with an OR of 0.67 and a 95% confidence interval of (0.46, 0.97).

The median duration of hospitalization among patients discharged on or before day 14 was 7 days (interquartile range, 6 to 10) for the 5-day group and 8 days (interquartile range, 5 to 10) for the 10-day group. Numerically more patients were discharged from the hospital in the 5-day group than in the 10-day group (60%, vs. 52%).

14-day mortality was numerically lower in the 5-day vs. the 10-day group (8%, vs. 11%).

No virological outcomes are available.

According to the protocol, 28-day mortality data will be collected.

Ancillary analyses

To justify the proposed treatment duration, the applicant presented a post-hoc comparison of treatment arms based on day 5 status to identify groups that may benefit from an additional 5 days of therapy. Among patients receiving mechanical ventilation or ECMO at day 5, 40% (10 of 25) in the 5-day group had died by day 14, as compared with 17% (7 of 41) in the 10-day group. Comparing both treatments with respect to the day 14 status adjusted for IMV on day 5 (yes/no) does not yield a significant treatment effect nor a significant treatment-by-IMV on day 5 interaction, indicating that the different treatment effects might still be a chance finding. In addition, 17 patients appear to be missing in the evaluation.

Study title: A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants with moderate COVID-19 (Study Code: GS-US-540-5774)

Interim analysis was performed based on a data cut-off 26 May 2020. The SAP was authored on 25 May 2020 in this open-label study. Thus, the level of pre-specification of the analysis plan is unclear.

Methods

This is a Phase 3 randomized, open-label, multi-center study of RDV therapy in participants with moderate COVID-19.

In Part A, approximately 600 participants who meet all eligibility criteria may be randomized in 1:1:1 ratio into one of the following treatment groups: RDV for 5 days; RDV for 10 days; standard of care alone. Randomization was not stratified. Part B is an expanded access protocol.

Study participants

Patients were adult, or aged ≥ 12 and >18 years and weighing ≥ 40 kg, hospitalized and requiring medical care for COVID-19, with SpO2 > 94% on room air at screening, and with radiographic evidence of pulmonary infiltrates. Exclusion criteria included evidence of severe hepatic impairment (ALT or AST > 5 times ULN) or renal impairment (CrCl < 50 mL/min).

Treatments

Remdesivir was administered intravenously at a dose of 200 mg on Day 1 followed by 100 mg on subsequent days, for a scheduled 5 or 10 days depending on study arm. The control arm received standard of care alone.

Concomitant medications

Concomitant use of investigational agents such as approved HIV protease inhibitors like lopinavir/ritonavir, chloroquine, interferon, etc while receiving RDV is prohibited due to lack of evidence on additive or synergistic effects and potential for an increased risk of transaminase elevations.

Outcomes/endpoints

The primary efficacy endpoint is clinical status assessed by a 7-point ordinal scale on Day 11. The ordinal scale is as follows:

1. Death

2. Hospitalized, on invasive mechanical ventilation or ECMO

3. Hospitalized, on non-invasive ventilation or high flow oxygen devices

4. Hospitalized, requiring low flow supplemental oxygen

5. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care

6. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care

(other than per protocol RDV administration)

7. Not hospitalized,

The endpoint is derived by combining the available death, hospital discharge, and ordinal scale assessment reported by the site, where death supersedes discharge and discharge supersedes the ordinal scale score reported by the site.

Blinding, masking, randomisation and statistical methods

Subjects who met eligibility criteria were randomized in a 1:1:1 ratio; randomization was not stratified.

Blinding of treatment assignments or data was not performed in this study.

The primary endpoint was to be analysed using a proportional odds model, to compare each RDV

(5-day or 10-day) group with the SOC group, including treatment as the independent variable.

The 25 May SAP states that, for control for Type I error rate, the statistical significance of RDV treatment effect was to be assessed based on the Bonferroni method. Each hypothesis (5-day RDV vs. SOC and 10-day RDV vs. SOC) will be tested at alpha level of 0.025. This information is not found in the original protocol of this open-label study.

No multiplicity adjustment was planned due to the interim analysis, as it comprises the primary analysis for Part A.

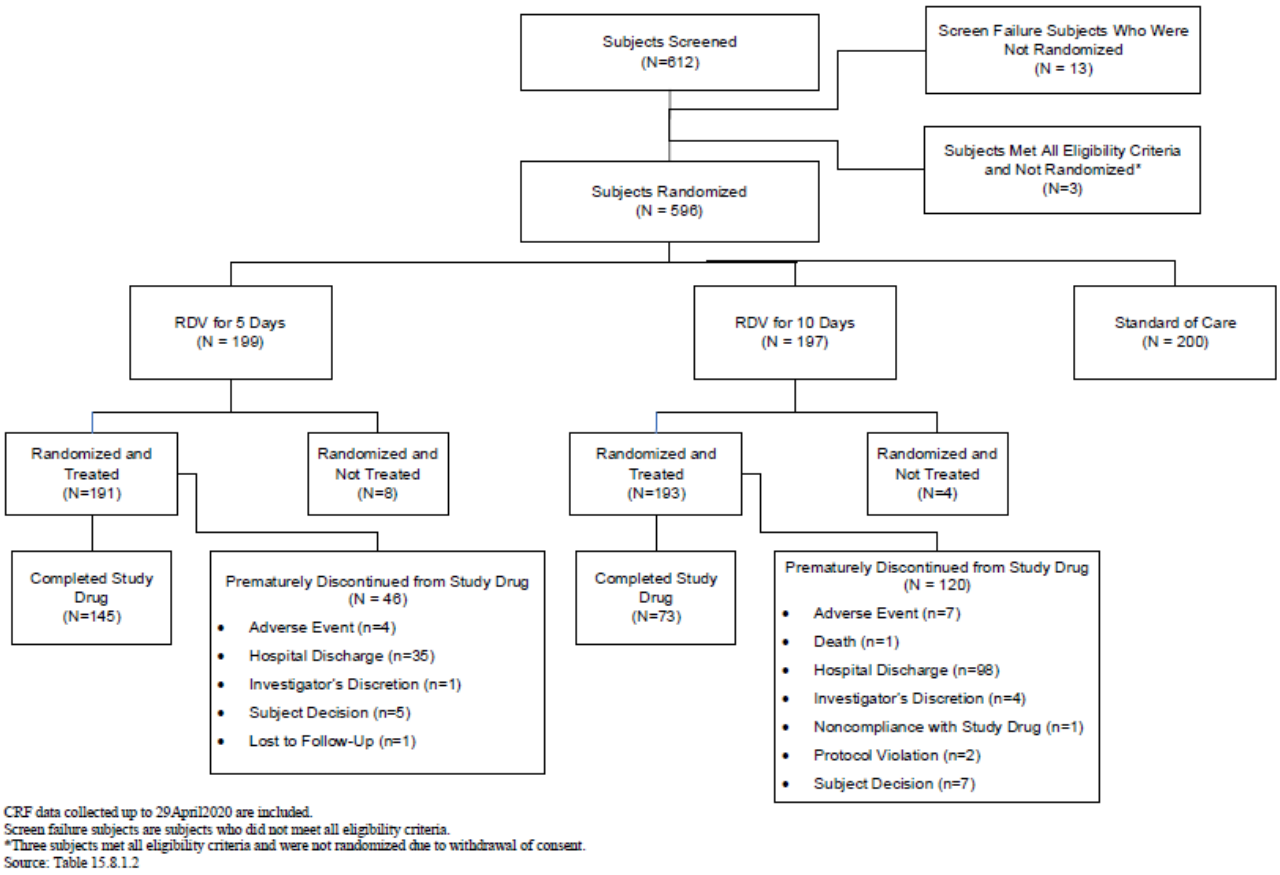
The proportion of participants in each category was to be summarized by treatment group. The assumption of odds proportionality was to be assessed using a score test and reported.

The primary analysis set for efficacy analysis is the Full Analysis Set (FAS), which includes all participants who (1) are randomized into Part A of the study and (2) have received at least 1 dose of study treatment if randomized to one of the RDV treatment groups. Participants in the SOC arm who have had protocol Day 1 visit are included in the FAS.

Values for missing data were not imputed according to the protocol. According to SAP missing data was replaced by last observation carried forward for the ordinal scale.

Figure 21: Study -5774, Enrolment and Randomization

Participant flow



CRF data collected up to 29April2020 are included.
Screen failure subjects are subjects who did not meet all eligibility criteria.
*Three subjects met all eligibility criteria and were not randomized due to withdrawal of consent.
Source: Table 15.8.1.2

Conduct of the study

As the study is ongoing, no clinical study report in line with ICH E3 (CPMP/ICH/137/95) is currently available. While approximately 37% of the participants have been recruited in Europe, 44% come from the USA. 12 patients randomised to either of the RDV arms who were not treated, were excluded from analysis.

No information on concomitant use of other antiviral medications was provided.

Baseline data

Most participants were male (61.1%), with a median age (range) of 57 (12 to 95) years; most participants were white (61.3%) and not Hispanic or Latino (81.9%). The most common comorbidities were hypertension (39.0%), hyperlipidaemia (15.4%), and cough (14.6%).

Table 17: Study 5774 – Demographic and Clinical Characteristics of the Patients at Baseline According to Remdesivir Treatment Group. *

	RDV For 5 Days (N=191)	RDV For 10 Days (N=193)	SOC (N=200)	Total (N=584)	p-value
Age (Years)					
N	191	193	200	584	0.7607
Mean (SD)	56 (14.6)	55 (15.5)	55 (15.1)	56 (15.1)	
Median	58	56	57	57	
Q1, Q3	48, 66	45, 66	45, 66	46, 66	
Min, Max	12, 90	20, 94	23, 95	12, 95	
Age Categories (Years)					
< 50	58 (30.4%)	67 (34.7%)	65 (32.5%)	190 (32.5%)	0.9832
>= 50 to <65	84 (44.0%)	74 (38.3%)	77 (38.5%)	235 (40.2%)	
>= 65 to <75	31 (16.2%)	26 (13.5%)	38 (19.0%)	95 (16.3%)	
>= 75	18 (9.4%)	26 (13.5%)	20 (10.0%)	64 (11.0%)	
Sex at Birth					
Male	114 (59.7%)	118 (61.1%)	125 (62.5%)	357 (61.1%)	0.8500
Female	77 (40.3%)	75 (38.9%)	75 (37.5%)	227 (38.9%)	
Race					
American Indian or Alaska Native	2 (1.1%)	0	1 (0.6%)	3 (0.6%)	0.8317
Asian	34 (18.8%)	31 (17.6%)	37 (20.8%)	102 (19.1%)	
Black	35 (19.3%)	37 (21.0%)	27 (15.2%)	99 (18.5%)	
Native Hawaiian or Pacific Islander	1 (0.6%)	1 (0.6%)	1 (0.6%)	3 (0.6%)	
White	109 (60.2%)	107 (60.8%)	112 (62.9%)	328 (61.3%)	
Not Permitted	5	5	7	17	
Other	5	12	15	32	
Ethnicity					
Hispanic or Latino	25 (13.4%)	42 (22.6%)	34 (18.3%)	101 (18.1%)	0.0691
Not Hispanic or Latino	162 (86.6%)	144 (77.4%)	152 (81.7%)	458 (81.9%)	
Not Permitted	4	7	13	24	
- Missing -	0	0	1	1	
Baseline Weight (kg)					
N	186	187	197	570	0.2840
Mean (SD)	79.8 (19.97)	83.3 (20.68)	80.8 (19.22)	81.3 (19.97)	
Median	78.0	80.0	77.2	78.1	
Q1, Q3	66.0, 90.7	67.8, 95.1	69.0, 88.9	68.0, 90.7	
Min, Max	45.0, 180.0	43.7, 172.3	35.8, 153.7	35.8, 180.0	
Baseline Height (cm)					
N	187	186	193	566	0.6374
Mean (SD)	168.9 (10.39)	170.0 (9.83)	169.3 (10.11)	169.4 (10.11)	
Median	168.0	170.0	168.0	170.0	
Q1, Q3	162.6, 176.0	163.0, 177.8	162.6, 177.9	162.6, 177.0	
Min, Max	144.8, 200.0	147.3, 193.0	149.9, 193.0	144.8, 200.0	
Baseline Body Mass Index (kg/m^2)					
N	185	183	191	559	0.2373
Mean (SD)	27.8 (6.51)	28.9 (6.77)	28.2 (6.65)	28.3 (6.64)	
Median	26.7	27.6	26.7	27.1	
Q1, Q3	23.8, 30.4	24.5, 32.2	23.5, 31.1	24.1, 31.1	
Min, Max	17.2, 76.9	16.1, 63.2	15.9, 53.9	15.9, 76.9	

For race and ethnicity, 'Not Permitted', 'Missing' and 'Other' were excluded from the percentage calculation and p-value calculation.
Not Permitted = local regulators did not allow collection of race/ethnicity information. All but 3 values of 'Other' are unknown, not specified, etc.
For categorical data, p-value was from the CMH test (general association statistic for nominal data and row mean scores differ statistic for ordinal data). For continuous data, p-value was from the Kruskal-Wallis test.
Data Extracted: CRF Data, Lab Data: 26MAY2020
Source: .../interim_part_a/version1/prog/t-demog.sas v9.4 Output file: t-demog.pdf 01JUN2020:22:07

Table 18: **Study -5774, Other Baseline Characteristics - Safety Analysis Set**

	RDV For 5 Days (N=191)	RDV For 10 Days (N=193)	SOC (N=200)	Total (N=584)	p-value
Clinical Status (7-Point Ordinal Scale)					
2 - Hospitalised, on invasive mechanical ventilation or ECMO	0	0	0	0	0.0781
3 - Hospitalised, on non-invasive ventilation or high flow oxygen devices	2 (1.0%)	1 (0.5%)	2 (1.0%)	5 (0.9%)	
4 - Hospitalised, requiring low flow supplemental oxygen	29 (15.2%)	23 (11.9%)	36 (18.0%)	88 (15.1%)	
5 - Hospitalised, not requiring supplemental oxygen - requiring ongoing medical care	160 (83.8%)	163 (84.5%)	160 (80.0%)	483 (82.7%)	
6 - Hospitalised, not requiring supplemental oxygen - no longer requires ongoing medical care	0	6 (3.1%)	2 (1.0%)	8 (1.4%)	
Duration of Hospitalisation prior to Study Day 1 (Days)					
N	191	193	199	583	0.6273
Mean (SD)	3 (4.4)	3 (4.6)	3 (3.6)	3 (4.2)	
Median	2	2	2	2	
Q1, Q3	1, 3	1, 3	1, 3	1, 3	
Min, Max	0, 36	0, 30	0, 33	0, 36	
Duration of Symptoms prior to Study Day 1 (Days)					
N	191	189	197	577	0.0253
Mean (SD)	9 (6.5)	8 (5.7)	9 (5.2)	9 (5.8)	
Median	8	8	9	8	
Q1, Q3	5, 11	5, 11	6, 11	5, 11	
Min, Max	1, 48	1, 40	1, 34	1, 48	
ALT (U/L)					
N	191	193	200	584	0.8702
Mean (SD)	39 (31.3)	40 (35.4)	42 (35.5)	40 (34.1)	
Median	30	28	30	29	
Q1, Q3	19, 51	21, 47	19, 49	19, 50	
Min, Max	6, 221	4, 229	5, 289	4, 289	
AST (U/L)					
N	186	187	193	566	0.9772
Mean (SD)	42 (28.2)	41 (29.5)	42 (30.9)	42 (29.5)	
Median	32	34	34	33	
Q1, Q3	25, 48	23, 48	24, 49	24, 49	
Min, Max	8, 147	9, 215	8, 229	8, 229	
Baseline Oxygen Support Status					
Invasive Mechanical Ventilation	0	0	0	0	0.2070
High Flow Oxygen	2 (1.0%)	1 (0.5%)	2 (1.0%)	5 (0.9%)	
Low Flow Oxygen	29 (15.2%)	23 (11.9%)	36 (18.0%)	88 (15.1%)	
Room Air	160 (83.8%)	169 (87.6%)	162 (81.0%)	491 (84.1%)	

For Clinical Status: Category 5 includes medical care (COVID 19 related or otherwise); Category 6 excludes per protocol RDV administration.
Category 7 (Not Hospitalized) and Category 1 (Death) are not included in this table.
Baseline was the last available value recorded on or prior to dosing for RDV groups and Study Day 1 for SOC. For clinical status for SOC, baseline
was the eCRF record labeled 'Day 1 Predose.'
For oxygen support status, p-value was from the CMH test (row mean scores differ statistic). For clinical status and continuous data, p-value was
from the Kruskal-Wallis test.
Data Extracted: CRF Data, Lab Data: 26MAY2020
Source: .../interim_part_a/version1/prog/t-basechar.sas v9.4 Output file: t-basechar.pdf 01JUN2020:22:07

The median duration of symptoms at baseline was 9 days, similar to the NIAID-ACTT study, and the majority of patients did not require supplemental oxygen at baseline.

In the 10-day treatment group, 38% of the patients received remdesivir for 10 days and almost 50% in this group received only an up to 5-day course.

***Table 19: Study 5774, Exposure to Study Drug - Safety Analysis* Set**

	RDV For 5 Days (N=191)	RDV For 10 Days (N=193)
Number of Doses Received		
N	191	193
Mean (SD)	4 (1.1)	6 (3.2)
Median	5	6
Q1, Q3	5, 5	3, 10
Min, Max	1, 5	1, 10
Number of Doses Received		
1 Dose	7 (3.7%)	8 (4.1%)
2 Doses	12 (6.3%)	19 (9.8%)
3 Doses	17 (8.9%)	24 (12.4%)
4 Doses	9 (4.7%)	21 (10.9%)
5 Doses	146 (76.4%)	19 (9.8%)
6 Doses	0	9 (4.7%)
7 Doses	0	10 (5.2%)
8 Doses	0	7 (3.6%)
9 Doses	0	3 (1.6%)
10 Doses	0	73 (37.8%)

Data Extracted: CRF Data, Lab Data: 26MAY2020

Outcomes and estimations

For the primary endpoint clinical status at Day 11, a statistically significant improvement in clinical status at Day 11 for participants receiving a 5-day course of RDV compared with those receiving SOC alone was found (OR, 1.65; 95% CI, 1.09 to 2.48; p=0.017) based on the LOCF-analysis (Table 26). Based on the Observed cases (OC)-analysis, as prespecified in the protocol, no difference for either RDV compared to SOC was seen (RDV 5d vs. SOC p=0.059).

Data concerning the length of the hospital stay, do not indicate a positive effect of RDV (5-day: 8 days, 10-day: 8 days; SOC: 7 days.

Table 20 Study -5774: Analysis of Clinical Status (7 Point Ordinal Scale) on Day 11 Using Proportional Odds with Baseline Adjustment (FAS)

Clinical Status	Parameter Estimate (SE)	OR (95% CI)	P-Value	Score Test for Proportionality of Odds P-Value
RDV for 5 days/SOC	0.50 (0.210))	1.65 (1.092, 2.483)	0.0174	< 0.3960
RDV for 10 days/SOC	0.27 (0.203)	1.31 (0.880, 1.952)	0.1826	< 0.0001

CI = confidence interval; eCRF = electronic case report form; FAS = Full Analysis Set; OR = odds ratio; RDV = remdesivir (GS-5734™); SE = standard error; SOC = standard of care
Clinical status is based on an ordinal scale from 1 = Death to 7 = Not hospitalized.
Clinical status was derived from death, hospital discharge, and the ordinal scale as follows: 1 for all days on or after the death date; 7 for all days on or after discharged alive date; ordinal scale using the last available postbaseline record for missing assessment.
Source: GS-US-540-5774 Part A Interim Analysis, Table 15.9.1.1.1

There was a statistically significant difference in the distribution in clinical status at Day 11 for participants receiving a 5-day course of RDV compared with those receiving SOC alone, while participants receiving a 10-day course of RDV had a similar distribution as those receiving SOC alone (see table below).

Table 21 Study -5774: Clinical Status (7 Point Ordinal Scale) on Day 11 (FAS)

Clinical Status, n (%)	RDV for 5 Days (N = 191)	RDV for 10 Days (N = 193)	SOC (N = 200)	RDV for 5 Days vs SOC P-Value[a]	RDV for 10 Days vs SOC P-Value[a]
7 – Not hospitalized	134 (70.2)	125 (64.8)	120 (60.0)		
6 – Hospitalized, not requiring supplemental oxygen or ongoing medical care	7 (3.7)	9 (4.7)	8 (4.0)		
5 – Hospitalized, not requiring supplemental oxygen, but requiring ongoing medical care	38 (19.9)	44 (22.8)	46 (23.0)		
4 – Hospitalized, requiring low-flow supplemental oxygen	7 (3.7)	12 (6.2)	11 (5.5)	0.0171	0.1826
3 – Hospitalized, on noninvasive ventilation or high-flow oxygen device	5 (2.6)	0	7 (3.5)		
2 – Hospitalized, on invasive mechanical ventilation or ECMO	0	1 (0.5)	4 (2.0)		
1 – Death	0	2 (1.0)	4 (2.0)		

ECMO = extracorporeal membrane oxygenation; FAS = Full Analysis Set; RDV = remdesivir (GS-5734™); SOC = standard of care

a P-value based on Wilcoxon Rank Sum test comparing RDV for 5/10 days vs SOC (stratified by baseline clinical status for postbaseline days).

Clinical status was derived from death, hospital discharge, and the ordinal scale as follows: 1 for all days on or after the death date; 7 for all days on or after discharged alive date; ordinal scale using the last available postbaseline record for missing assessment.

Source: GS-US-540-5774 Part A Interim Analysis, Table 15.9.1.2.1

For other efficacy endpoints of interest, at Day 11, ≥ 2-point improvements in the clinical ordinal scale were reported in 70.2% of participants who received a 5-day course of RDV and 65.3% of participants who received a 10 day course of RDV compared with 60.5% of those who received SOC alone. Clinical recovery at Day 11 was achieved in a numerically greater proportion of participants in the RDV 5-day group (73.8%) than the RDV 10-day group (68.4%) and the SOC group (64.0%).

Table 22 Study -5774: Other clinical Outcomes at Day 11 (FAS)

Outcome, n (%)	RDV for 5 Days (N = 191)	RDV for 10 Days (N = 193)	SOC (N = 200)	RDV for 5 Days vs SOC		RDV for 10 Days vs SOC	
				P-Value	Baseline-Adjusted Difference in Proportions (95% CI)	P-Value	Baseline-Adjusted Difference in Proportions (95% CI)
≥ 2-point Improvement in Ordinal Scale	134 (70.2)	126 (65.3)	121 (60.5)	0.0557	9.7 (0.1, 19.1)	0.3484	4.8 (-5.0, 14.4)
≥ 1-point Improvement in Ordinal Scale	146 (76.4)	135 (69.9)	132 (66.0)	0.0257	10.4 (0.9, 19.4)	0.4495	3.9 (-5.5, 13.2)
Recovery	141 (73.8)	132 (68.4)	128 (64.0)	0.0386	9.8 (-0.3, 19.0)	0.3941	4.4 (-5.0, 13.8)
Death	0	2 (1.0)	4 (2.0)	0.0171	NC	0.1826	NC
≥ 1-point Worsening in Ordinal Scale	6 (3.1)	12 (6.2)	22 (11.0)	NC	NC	NC	NC
≥ 2-point Worsening in Ordinal Scale	3 (1.6)	3 (1.6)	12 (6.0)	NC	NC	NC	NC

CI = confidence interval; FAS = Full Analysis Set; NC = not calculated; RDV = remdesivir (GS-5734™); SOC = standard of care
Source: GS-US-540-5774 Part A Interim Analysis, Tables 15.9.1.2.1, 15.9.2.4.4, 15.9.2.5.4, 15.9.2.6.4, and 15.9.1.8

Virological endpoint

The proportion of patients with to SARS-CoV-2 PCR negativity was an extrapolatory endpoint.

No consistent effect of RDV with respect to cease of viral shedding was observed.

Study title: A Phase 3 Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Remdesivir in Hospitalized Adult Patients with Severe COVID-19. (GS-US 540-5758)

Methods

This was an investigator-initiated, randomised, placebo-controlled, double-blind trial performed at ten hospitals in Wuhan, Hubei, China.

Study participants

Adult patients, RT-PCR positive for SARS-CoV-2, had pneumonia confirmed by chest imaging or had oxygen saturation of 94% or lower on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of 300 mm Hg or less, and were within 12 days of symptom onset.

Exclusion criteria included hepatic cirrhosis; alanine aminotransferase or aspartate aminotransferase more than five times the upper limit of normal; known severe renal impairment (estimated glomerular filtration rate <30 mL/min per 1·73 m²) or receipt of continuous renal replacement therapy, haemodialysis, or peritoneal dialysis;

Treatments

Patients received either intravenous remdesivir (from lyophilized formulation) 200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions) or the same volume of placebo infusions for a total of 10 days. Blinded placebo was provided by Gilead.

Concomitant medications

The use of other experimental treatments for COVID-19, including lopinavir–ritonavir, was permitted.

Outcomes/endpoints

Eligible patients were randomly assigned (2:1) to either the remdesivir group or the placebo group. Randomisation was stratified according to the level of respiratory support as follows: (1) no oxygen support or oxygen support with nasal duct or mask; or (2) high-flow oxygen, non-invasive ventilation, invasive ventilation, or extracorporeal membrane oxygenation.

The primary clinical endpoint was time to clinical improvement within 28 days after randomisation. Clinical improvement was defined as a two-point reduction in patients' admission status on a six-point ordinal scale, or live discharge from the hospital, whichever came first. The six-point scale was as follows:

6=death

5= hospital admission for extracorporeal membrane oxygenation or mechanical ventilation

4= hospital admission for noninvasive ventilation or high-flow oxygen therapy

3= hospital admission for oxygen therapy (but not requiring high-flow or non-invasive ventilation)

2= hospital admission but not requiring oxygen therapy

1= discharged or having reached discharge criteria (defined as clinical recovery—ie, normalisation of pyrexia, respiratory rate <24 breaths per minute, saturation of peripheral oxygen >94% on room air, and relief of cough, all maintained for at least 72 h)

Secondary endpoints included all-cause mortality until day 28.

Overall, the study chronology and important milestones of clinical trial conduct are missing and conflicting information is available in the public domain on the change of the primary endpoint.

The original design required a total of 325 events across both groups, which would provide 80% power under a one-sided type I error of 2·5% if the hazard ratio (HR) comparing remdesivir to placebo is 1·4, corresponding to a change in time to clinical improvement of 6 days assuming that time to clinical improvement is 21 days on placebo.

Assuming an 80% event rate within 28 days across both groups and a dropout rate of 10% implied that about 453 patients should be recruited for this trial.

The primary efficacy analysis was done on an intention to- treat (ITT) basis with all randomly assigned patients. Time to clinical improvement was assessed after all patients had reached day 28; no clinical improvement at day 28 or death before day 28 were considered as right censored at day 28.

Virological investigations

NP and OP swabs, expectorated sputa as available, and faecal or anal swab specimens were collected on days 1, 3, 5, 7, 10, 14, 21, and 28 for viral RNA detection and quantification. Virological measures included the proportions of patients with viral RNA detected and viral RNA load (measured by quantitative RT-PCR).

Virological testing was done at a central lab using quantitative real-time RT-PCR. At baseline, the upper (nasopharyngeal or oropharyngeal swabs) and lower respiratory tract specimens were tested for detection of E-gene, RNA-dependent RNA polymerase gene, and N-gene, then samples on the subsequent visits were quantitatively and qualitative assessed for E-gene.

Participant flow

158 patients were assigned to receive remdesivir and 79 to receive placebo; one patient in the placebo group withdrew their previously written informed consent after randomisation, so 158 and 78 patients were included in the ITT population.

Conduct of the study

Between 6 Feb 2020 and 12 March 2020, 255 patients were screened, of whom 237 were eligible.

No patients were enrolled after March 12, because of the control of the outbreak in Wuhan and on the basis of the termination criteria specified in the protocol, the data safety and monitoring board recommended that the study be terminated, and data analysed on 29 March.

When all the other assumptions stayed the same, with the actual enrolment of 236 participants, the statistical power was reduced from 80% to 58%.

Baseline data

Baseline characteristics were overall reasonably balanced between groups.

Patients are somewhat older on average than in the NIAID study. As anticipated, there is a higher proportion of men than women, and randomisation in this small study is not fully balanced. Similar to the NIAID study, hypertension and type 2 diabetes are the most prevalent comorbidities. Notably, 29% and 38% of patients in the remdesivir and placebo arms received concomitant interferon beta, and two-thirds of patients received corticosteroids during the study. Such data are not available for the NIAID study, but it is likely that such comedications were considerably less common there.

Median time from symptom onset to therapy is very similar to the NIAID study, whereas the proportion of patients requiring invasive mechanical ventilation at baseline are very few in the study by Wang et al, compared to 26% in the NIAID study.

Outcomes and estimations

158 patients on RDV and 78 patients on placebo were included in the ITT-analysis. In the ITT-population, the time to clinical improvement in the remdesivir group was not significantly different to that of the control group. Time to clinical improvement was (median 21·0 days [IQR 13·0–28·0] in the remdesivir group vs 23·0 days [15·0–28·0] in the placebo group; HR 1·23 [95% CI 0·87–1·75].

In an exploratory analysis in the subgroup of patients receiving remdesivir or placebo within 10 days of symptom onset in the ITT-population, those receiving remdesivir had a numerically faster time to clinical improvement than those receiving placebo (median 18·0 days [IQR 12·0–28·0] vs 23·0 days [15·0–28·0]; HR 1·52 [0·95–2·43], which would be in line with what is known for other antivirals in acute viral infections.

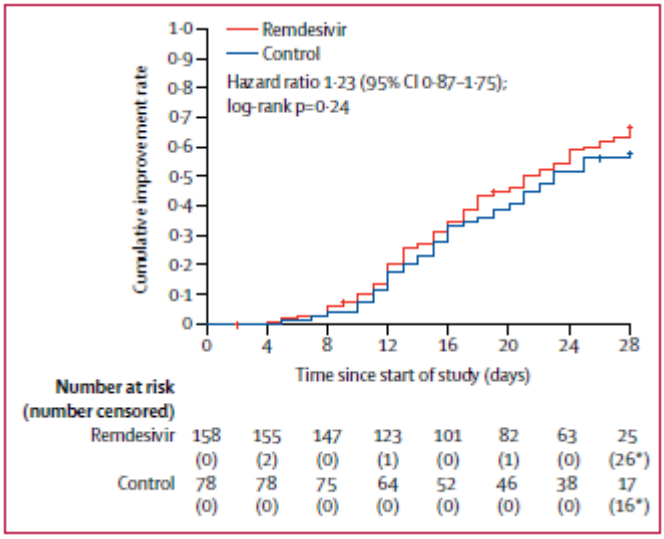
28-day all-cause mortality was similar between the two groups (22 [14%] died in the remdesivir group vs 10 (13%) in the placebo group; difference 1·1% [95% CI –8·1 to 10·3]).

Table 23: Main outcomes (ITT-analysis)

	Remdesivir group (n=158)	Placebo group (n=78)	Difference*
Time to clinical improvement	21·0 (13·0 to 28·0)	23·0 (15·0 to 28·0)	1·23 (0·87 to 1·75)†
Day 28 mortality	22 (14%)	10 (13%)	1·1% (–8·1 to 10·3)
Early (≤10 days of symptom onset)	8/71 (11%)	7/47 (15%)	–3·6% (–16·2 to 8·9)
Late (>10 days of symptom onset)	12/84 (14%)	3/31 (10%)	4·6% (–8·2 to 17·4)
Clinical improvement rates			
Day 7	4 (3%)	2 (3%)	0·0% (–4·3 to 4·2)
Day 14	42 (27%)	18 (23%)	3·5% (–8·1 to 15·1)
Day 28	103 (65%)	45 (58%)	7·5% (–5·7 to 20·7)
Duration of invasive mechanical ventilation, days	7·0 (4·0 to 16·0)	15·5 (6·0 to 21·0)	–4·0 (–14·0 to 2·0)
Duration of invasive mechanical ventilation in survivors, days‡	19·0 (5·0 to 42·0)	42·0 (17·0 to 46·0)	–12·0 (–41·0 to 25·0)
Duration of invasive mechanical ventilation in non-survivors, days‡	7·0 (2·0 to 11·0)	8·0 (5·0 to 16·0)	–2·5 (–11·0 to 3·0)
Duration of oxygen support, days	19·0 (11·0 to 30·0)	21·0 (14·0 to 30·5)	–2·0 (–6·0 to 1·0)
Duration of hospital stay, days	25·0 (16·0 to 38·0)	24·0 (18·0 to 36·0)	0·0 (–4·0 to 4·0)
Time from random group assignment to discharge, days	21·0 (12·0 to 31·0)	21·0 (13·5 to 28·5)	0·0 (–3·0 to 3·0)
Time from random group assignment to death, days	9·5 (6·0 to 18·5)	11·0 (7·0 to 18·0)	–1·0 (–7·0 to 5·0)

Source: Lang et al, Lancet 2020 (for the complete table, please check the article)

Figure 22: Time to clinical improvement in the intention-to-treat population Adjusted hazard ratio for randomisation stratification was 1 ·25 (95% CI 0 ·88–1 ·78). *Including deaths before day 28 as right censored at day 28, the number of patients without clinical improvement was still included in the number at risk.



Source: Lang et al, Lancet 2020

In patients with use of remdesivir within 10 days after symptom onset, 28-day mortality was not significantly different between the groups, Neither were duration of invasive mechanical ventilation, nor length of oxygen support, hospital length of stay, days from randomisation to discharge, days from randomisation to death and distribution of six-category scale at day 7, day 14, and day 28 different between the two groups.

Virological outcomes

Of 236 patients (158 in the remdesivir group and 78 in the placebo group) who were RT-PCR positive at enrolment, 37 (19%) of the 196 with data available had undetectable viral RNA on the NP and OP swab taken at baseline.

The mean baseline viral load of nasopharyngeal and oropharyngeal swabs was 4·7 log10 copies per mL (SE 0·3) in the remdesivir group and 4·7 log10 copies per mL (0·4) in the control group. Viral load decreased over time similarly in both groups. No differences in viral load were observed when stratified by interval from symptom onset to start of study treatment. In the 106 patients from whom expectorated sputa could be obtained, when adjusted for baseline sputum viral load at enrolment, the remdesivir group showed no significant difference at day 5 from placebo, but a slightly more rapid decline in load (p=0·0672)

The cumulative rate of undetectable viral RNA of nasopharyngeal and oropharyngeal swabs by day 28 was 153 (78%) of 196 patients, and the negative proportion was similar among patients receiving remdesivir and those receiving placebo.

Summary of main studies

The following table summarise the efficacy results from the NIAID ACTT study supporting the present application. The summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections) and also need to be updated once more data is available.

Summary of efficacy for trial NIAID ACTT

<table>
<tr><td colspan="3"><u>Title: A Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Adults - Short Title: Adaptive COVID-19 Treatment Trial (CO-US-540-5776)</u></td></tr>
<tr><td>Study identifier</td><td colspan="2">DMID Protocol Number: 20-0006</td></tr>
<tr><td>Design</td><td colspan="2">This study is an adaptive, randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of novel therapeutic agents in hospitalized adults diagnosed with COVID-19. The study is a multicenter trial that is currently conducted in approximately 60 sites globally.

The primary endpoint was “Time to recovery Day1 through D29”.

Main inclusion criteria were lab confirmed SARS-CoV-2 infection and admission to hospital. Patients were hospitalised with COVID-19, and had either pulmonary infiltrates, or hypoxia, or both.</td></tr>
<tr><td></td><td>Duration of main phase:
Duration of Run-in phase:
Duration of Extension phase:</td><td>10d treatment duration
None
Follow up until D29</td></tr>
<tr><td>Hypothesis</td><td colspan="2">Superiority</td></tr>
<tr><td>Treatments groups</td><td>Remdesivir</td><td>10d, n=541</td></tr>
<tr><td></td><td>Placebo</td><td>10d, n=522</td></tr>
</table>

Endpoints and definitions	Primary endpoint	time to recovery	Day of recovery is defined as the first day on which the subject satisfies one of the following three categories from the ordinal scale: • Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care; • Not hospitalized, limitation on activities and/or requiring home oxygen; • Not hospitalized, no limitations on
	Key secondary endpoint	clinical status (8-point ordinal scale) at Day 15	• Death; • Hospitalized, on invasive mechanical ventilation or ECMO; • Hospitalized, on non-invasive ventilation or high flow oxygen devices; • Hospitalized, requiring supplemental oxygen; • Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise); • Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care; • Not hospitalized, limitation on activities and/or requiring home
	Secondary endpoint	Mortality	o 14-day mortality o 29-day mortality
Database lock	N/A		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	Remdesivir	Placebo	
	Number of subjects	541	522	
	time to recovery	11 (9-12)	15 (13-19)	Any severity
	time to recovery	5 (4-7)	5 (4-7)	Mild/Moderate
	time to recovery	12 (10-14)	18 (15-21)	Severe

Effect estimate per comparison	Primary endpoint	Comparison groups	
		HR (95% CI) p-value	Any severity 1.312 (1.118-1.541), 0.0009
			Mild/Moderate 1.081 (0.725-1.609), 0.703

			Severe 1.362 (1.143-1.1623), 0.0005

Clinical studies in special populations

With the submission of the efficacy data from clinical studies the applicant should provide data in patients from 65 years and onwards.

2.5.3. Discussion on clinical efficacy

Basis of the Application for conditional marketing authorisation

COVID-19 inarguably represents the most significant public health emergency of our time. There are no products with established efficacy and regulatory approval in the EU. There is significant unmet medical need. In addition, the medicinal product under assessment is intended for use in an emergency situation, in response to public health threats duly recognised by the WHO and the EC.

Remdesivir exhibits *in vitro* activity against SARS-CoV-2 with nanomolar EC_{50}'s. There are clinical effects in non-stringent animal models of COVID-19, as well as SARS-CoV and MERS-CoV disease. These, however, may be understood to represent mainly post-exposure prophylaxis rather than the treatment scenario. In the non-lethal rhesus macaque model of SARS-CoV-2, antiviral effects were only noted in lungs, but not in upper respiratory secretions. The reasons for this are not understood.

It is important to note that the appropriate matrix for quantifying SARS-CoV-2 viral load has not been established. Further, there is no validated quantitative PCR, or a WHO reference standard. Therefore, the sensitivity of virological methods to detect antiviral activity is uncertain. Moreover, as seen in for instance the study by Wang et al, it is not uncommon that patients with evident COVID-19 and positive screening or diagnostic sample, test negative in NP or OP secretions at baseline. The clinical significance of this is not understood.

The initial rolling review formally started subsequent to the announcement, on 30th April 2020, by the NIAID, that the ACTT(1)-study was formally positive and would now be unblinded, all patients being offered remdesivir.

On 5th June 2020, the application for a conditional marketing authorisation was submitted.

Only top line data is available for this pivotal trial, as well as for three other RCTs providing further information. Thus, data are presently non-comprehensive.

Target populations and endpoints in COVID-19

There is no regulatory guidance on SARS-CoV-2 drug development. In most large studies of drugs with a presumed antiviral mechanism of action, target populations have been dichotomised into the "moderate" (SpO2 on room air above 93-94%) and "severe" (SpO2 below this level or in need of supplementary oxygen- or other respiratory support). Other important potential effect modifiers include time from symptom onset to treatment initiation. The notion of the importance of this, is extrapolated from influenza, where this is known to impact the efficacy of treatment. There is presently no regulatory guidance or precedent specifying a particular preferred primary endpoint for studies in this indication. An impact on mortality would be the most clinically relevant as well as scientifically persuasive outcome of a study in COVID-19. However, this may not be readily demonstrated in a study program, due to its limited size and/or limited effects of the treatment administered.

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

On the other hand, agents for the treatment of influenza have been approved based on an impact on time to recovery.

The definition of recovery has been variable in the three studies assessed. In the NIAID-ACTT-study three categories of an ordinal scale were collapsed to provide the definition of recovery. Thus, the primary endpoint of the NIAID-ACTT study, pivotal to this application, could be considered to capture clinical benefit.

The pivotal NIAID-ACTT1 study (CO-US-540-5776)

This study is not sponsored by the applicant. No CSR or TFL are available. It has been assessed based on the SAP and the publication by Beigel et al, 2020 (NEJM 2020).

This double-blinded, placebo-controlled study compared RDV for ten days with placebo in 1063 patients hospitalised with moderate or severe COVID-19. Severe cases dominated, and 26% of patients required IMV or ECMO at baseline. Of note, only 33% of the participants received the planned 10 doses of RDV.

The study, which had a time-to-event design, was unblinded after a primary analysis indicating that RDV decreased median time to recovery from 15 to 11 days, with a p-value of 0.0009. The recovery rate ratio was 1.32 (95% CI 1.12 to 1.55; p<0.001). After adjustment for baseline imbalances, this was essentially unchanged with a recovery rate ratio of 1.31 (95%CI, 1.12 to 1.54, based on 1017 patients).

The efficacy demonstration was confined to the severe stratum (patients with pneumonia and need for supplemental oxygen), whereas no effect could be shown in the mild-moderate stratum which recruited approximately 120 patients. Moreover, no difference was seen in time to recovery in patients who started remdesivir when they were already on mechanical ventilation or ECMO (extracorporeal membrane oxygenation).

While patient follow-up is still ongoing with final outcome data missing for approximately 28% of the participants, it is unlikely that the final analysis of the primary endpoint could over-ride the inferential analysis.

Estimated 28-day all-cause mortality was 7.1% in the RDV group and 11.9% in the placebo group, with a HR of 0.70 (95%CI 0.47 to 1.04). While mortality estimates in patients on low flow supplemental oxygen favour remdesivir, those in the subgroup of patient on IMV/ECMO at baseline, are trending in favour of placebo. The analysis of the full set of 28-day mortality is pending and will be submitted as soon as these data become available.

Clinical status per ordinal scale at day 15 was the primary endpoint according to the original protocol. This also showed a statistically significant effect of remdesivir over placebo.

There was no apparent difference in efficacy depending on whether therapy was started within or after 10 days of symptoms. In accordance with the above, this is somewhat surprising.

The extent of use of concomitant medications, including corticosteroids, that might impact the course of COVID-19 is presently not known due to limitations of available data.

Virological endpoints were exploratory and sampling non-mandatory per protocol. The lack of mechanistic proof of the antiviral activity of RDV is an important limitation on the evidence base for its efficacy.

Additional clinical evidence

Study **GS-US 540 5773** is an open-label RCT and was performed in a "severe" population, but with very few patients on IMV/ventilator. The study failed to demonstrate a dose/duration - response relationship, since 10 days treatment was not better than 5 days. Noteworthy, mortality in the 10-day arm was not different from the mortality in the placebo arm in the NIAID-study, while severity of disease of the patients included was overall less. Overall, there seem to be trends in favour of 5-day therapy. It is of note that only a proportion of 44% in the 10-day treatment arm received a full treatment course. While the study did neither include a standard of care arm nor was it designed as non-inferiority study, it seems to indicate, if taken together with results from the placebo-controlled NIAID ACTT1-study, that a treatment course of 5 days does not lead to any loss of efficacy. This conclusion does not apply to those requiring IMV at baseline, as these were not represented in the study.

It must be noted that the overall level of evidence from this study is weak, particularly due to the lack of blinding and potential subjectivity in primary outcome.

Study **GS-US 540 5774** was performed in a "mild/moderate" population. Due to several flaws in study design (e.g. no blinding, potential subjectivity in primary outcome, potential post-hoc adjustment of primary analysis), it is uncertain whether this trial was positive in a statistical sense, and inferences of efficacy cannot presently have this study as a basis.

The placebo-controlled study in severely ill patients (**GS-US 540-5758**, China severe) was underpowered due to its premature termination following the falling incidence of COVID-19 in Wuhan. With a remaining power of 58% no beneficial effect for remdesivir was shown. It is notable that, compared to the NIAID-ACTT study, patients received less intensive ventilatory support at baseline. However, 28-day mortality was 13% versus 14% for placebo- and remdesivir-treated patients, which is in the same range as the (preliminary) mortality figures of the NIAID-ACTT trials.

While based on a rather similar ordinal scale (a two-point reduction in patients' admission status), the primary outcome measure was different from that of the NIAID-ACTT. Study GS-US 540-5758 did not show any statistically significant difference for the primary endpoint (nor for mortality). Only in the subgroup of patients starting therapy within ten days of symptom onset, the point estimate on the primary endpoint was trending in favour of remdesivir.

As yet, no in-vivo antiviral effect of remdesivir has been shown. The sensitivity of the methods used has not been established, and the sample sizes are limited and heterogeneous with respect to matrix. The applicant committed to present the virology report from the NIAID-ACTT1 study and any other virology data becoming available from patients with COVID-19.

Evaluation of the evidence for efficacy

The regulatory evaluation of RDV efficacy is presently hampered by limitations in the comprehensiveness of data provided, with only top line results available from the pivotal trial, and no CSR's available for any of the RCT that have reported results. Still, some conclusions can be drawn.

The results of the primary analysis in the NIAID-ACTT(1) study provides statistically compelling evidence of a clinically relevant impact on time to recovery. This effect was constrained to the dominant stratum of patients with "severe disease", whereas no effect could be demonstrated in the stratum with mild/moderate disease. The CHMP considered that the benefit of remdesivir in less ill patients without hypoxia or without respiratory distress has not been shown. Available data from the study GS-US-540-5774 are neither considered to support such use.

The supportive studies provide support for the notion that a full 10-day course is frequently not necessary with remdesivir. Further, only a minority of the patients in the NIAID-ACTT(1) study received the planned 10 doses, mostly because of discharge or death.

With respect to Day-28 all-cause mortality the preliminary analysis indicated a numerical benefit for remdesivir. The full dataset will be submitted for a comprehensive review once they are available.

Assessment of paediatric data on clinical efficacy

Pursuant to Article 17 and 21 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0201/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0201/2020 was not yet completed as some measures were deferred.

Additional efficacy data needed in the context of a conditional Marketing Authorization (CMA)

In the framework of the conditional marketing authorisation, to complete efficacy, the applicant should fulfil, post-approval, the specific obligations (SOs) as referred below in the conclusion.

2.5.4. Conclusions on the clinical efficacy

Whereas in the context of a CMA the benefit of remdesivir is considered adequately shown for patients with COVID-19 with pneumonia and need for supplemental oxygen; this is not the case for patients with mild/moderate disease (i.e. SpO2>94% without tachypnoea or symptoms of respiratory distress).

Data from study 5773 seems to indicate that 5 days suffice for patients not requiring IMV. In addition, considering the results from study 5774 there was no incremental effect of 10 days of treatment over 5 days. Therefore, considering the available data, the Committee recommended that the total duration of treatment should be at least 5 days and not more than 10 days. The use of remdesivir should be confined to healthcare facilities in which patients can be monitored closely.

During the procedure, several major objections were raised relating to the indication and in order to further clarify efficacy data. With the available data up to now, the Committee agreed to restrict the indication to patients who need supplement oxygen as explained before. Considering that the applicant accepted the indication agreed by the Committee, the information provided in the responses and the measures to be taken by the applicant after authorisation, the major objections were therefore considered solved.

CHMP has considered that these available data would support granting a Conditional Marketing Authorisation taking into account the public health emergency of international concern declared by WHO and EU.

In conclusion, based on the current dossier, Veklury may be approved as a conditional Marketing Authorisation with a list of specific obligations that need to be fulfilled, as detailed in the assessment report (see discussion section).

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a CMA:

- In order to confirm the efficacy and safety of remdesivir, the applicant should submit the final clinical study report (CSR) of Study CO-US-540-5776 (NIAID-ACTT1).
- In order to confirm the efficacy and safety of remdesivir in patients on IMV/ECMO, the applicant should submit the published final D28 mortality data by ordinal scale categories of Study CO-US-540-5776 (NIAID-ACTT1). In addition, the applicant should discuss potential imbalance in the use of corticosteroids and effect modification in Study CO-US-540-5776.

- In order to confirm the efficacy and safety of remdesivir, the applicant should submit the final CSR for Part A (Day 28) of Study GS-US-540-5773.
- In order to confirm the efficacy and safety of remdesivir, the applicant should submit the final CSR for Part A (Day 28) of Study GS-US-540-5774.

2.6. Clinical safety

Patient exposure

Overall, the Applicant presented safety data from sources which include 1936 individuals who received at least 1 dose of IV RDV, including 1630 with COVID-19; 175 with EVD; and 131 healthy participants in the Phase 1 studies (see table below).

Table 24 Summary of the Extent of Exposure to Intravenously Administered RDV

Study ID	Number Who Received RDV	Dose Regimen of IV RDV
Studies in Participants with COVID-19		
CO-US-540-5776 {Beigel 2020a}	531 hospitalized participants with COVID-19	200 mg on Day 1 100 mg/day for up to 9 days (up to 10 days total)
GS-US-540-5773 {Goldman 2020}	397 hospitalized participants with severe COVID-19	200 mg on Day 1 100 mg/day for 4 or 9 days (5 or 10 days total)
GS-US-540-5774	384 hospitalized participants with moderate COVID-19	200 mg on Day 1 100 mg/day for 4 or 9 days (5 or 10 days total)
CO-US-540-5758 {Wang 2020}	155 hospitalized participants with COVID-19	200 mg on Day 1 100 mg/day for up to 9 days (up to 10 days total)
IN-US-540-5755	163 hospitalized patients with COVID-19	200 mg on Day 1 100 mg/day for up to 9 days (up to 10 days total)
Studies in Healthy Participants		
GS-US-399-1812	78 healthy participants	3 to 225 mg – single dose
GS-US-399-1954	16 healthy participants	150 mg/day for up to 14 days
GS-US-399-5505	29 healthy participants	200 mg on Day 1 100 mg/day for 4 or 9 days (5 or 10 days total)
GS-US-399-4231	8 healthy participants	150 mg – single dose
Study in Participants with Ebola Virus		
CO-US-399-5366 (PALM) {Mulangu 2019}	175 participants with EVD	200 mg on Day 1 100 mg/day for 9 to 13 days (10 to 14 days total)

COVID-19 = coronavirus disease 2019; EVD = Ebola virus disease; ID = identification; IV = intravenous; RDV = remdesivir (GS-5734™)

Adverse events

Clinical studies in COVID-19

CO-US-540-5776

The following information about AEs reported in NIAID ACTT-1 study (CO-US-540-5776) is available:

Grade 3 or 4 non-serious AEs occurred in 156 (28.8%) participants in the RDV group and 172 (33.0%) in the placebo group. In the following table grade 3 or 4 non-serious AEs occurring in 5 or more subjects are listed by PTs.

Table 25 Non-Serious Grade 3 or 4 Adverse Events Occurring in 5 or More Subjects in Any Preferred Term by Treatment Group

MedDRA System Organ Class	Preferred Term	Remdesivir (N = 541) No.(%)	Placebo (N = 522) No.(%)
Any System Organ Class	Any Preferred Term	156 (28.8)	172 (33.0)
Blood and lymphatic system disorders	Anemia[a]	22 (4.1)	25 (4.8)
	Lymphopenia[b]	1 (0.2)	10 (1.9)
Cardiac disorders	Atrial fibrillation	3 (0.6)	6 (1.1)
General disorders and administration site conditions	Pyrexia	27 (5.0)	17 (3.3)
Infections and infestations	Pneumonia	8 (1.5)	2 (0.4)
Investigations	Hemoglobin decreased[a]	22 (4.1)	23 (4.4)
	Glomerular filtration rate decreased[c]	20 (3.7)	17 (3.3)
	Aspartate aminotransferase increased[d]	15 (2.8)	20 (3.8)
	Lymphocyte count decreased[b]	13 (2.4)	18 (3.4)
	Blood glucose increased[e]	12 (2.2)	6 (1.1)
	Alanine aminotransferase increased[d]	8 (1.5)	9 (1.7)
	Blood bilirubin increased	7 (1.3)	8 (1.5)
	Blood creatinine increased[c]	8 (1.5)	4 (0.8)
	Prothrombin time prolonged	7 (1.3)	3 (0.6)
	Blood albumin decreased	6 (1.1)	3 (0.6)
	Transaminases increased[d]	3 (0.6)	6 (1.1)
	Creatinine renal clearance decreased[c]	3 (0.6)	5 (1.0)
Metabolism and nutrition disorders	Hyperglycemia[e]	10 (1.8)	11 (2.1)
	Acidosis	5 (0.9)	5 (1.0)
	Hypoalbuminemia	4 (0.7)	5 (1.0)
	Alkalosis	4 (0.7)	2 (0.4)
Psychiatric disorders	Delirium	4 (0.7)	4 (0.8)
Renal and urinary disorders	Acute kidney injury[c]	15 (2.8)	17 (3.3)
Respiratory, thoracic and mediastinal disorders	Hypoxia[f]	7 (1.3)	9 (1.7)
	Dyspnea[f]	6 (1.1)	3 (0.6)
	Respiratory distress[f]	3 (0.6)	5 (1.0)
Uncoded	Uncoded	30 (5.5)	34 (6.5)
Vascular disorders	Hypotension	12 (2.2)	7 (1.3)
	Hypertension	11 (2.0)	4 (0.8)
	Deep vein thrombosis	6 (1.1)	9 (1.7)

No. = number of subjects reporting at least one event.
Bacteraemia has been redacted from the table as it occurred in only one treatment group.
[a] The combined number of subjects with either anaemia and/or haemoglobin decreased are 43 for Remdesivir and 47 for Placebo.
[b] The combined number of subjects with either lymphopenia and/or lymphocyte count decreased are 14 for Remdesivir and 28 for Placebo.
[c] The combined number of subjects with either glomerular filtration rate decreased, acute kidney injury, blood creatinine increased and/or creatinine renal clearance decreased are 40 for Remdesivir and 38 for Placebo.
[d] The combined number of subjects with either transaminases increased, aspartate aminotransferase increased and/or alanine aminotransferase increased are 22 for Remdesivir and 31 for Placebo.
[e] The combined number of subjects with either hyperglycaemia and/or blood glucose increased are 22 for Remdesivir and 17 for Placebo.
[f] The combined number of subjects with either hypoxia, dyspnoea and/or respiratory distress are 16 for Remdesivir and 17 for Placebo.

GS-US-540-5773

The overall incidence of AEs, study drug-related AEs, study drug related SAEs, and death were similar between the RDV 5 day and 10-day treatment groups (see table below).

More participants in the RDV 10-day group than the RDV 5-day group had Grade ≥ 3 AEs, SAEs, and AEs leading to discontinuation, likely due to the differences in baseline disease characteristics, whereby the RDV 10-day group had significantly worse clinical status than those randomized to the RDV 5-day group (p = 0.019; Section 4.2.2).

Table 26 GS-US-540-5773: Overall Summary of Adverse Events (Safety Analysis Set)

	RDV for 5 Days (N = 200)	RDV for 10 Days (N = 197)	RDV for 5 Days vs 10 Days	
			P-Value	Baseline Clinical Status Adjusted P-Value[a]
Any AE	141 (70.5%)	145 (73.6%)	0.5042	0.8658
Any Grade 3 or higher AE	61 (30.5%)	84 (42.6%)	0.0126	0.0604
Any study drug-related AE	33 (16.5%)	38 (19.3%)	0.5135	0.3609
Any Grade 3 or higher study drug-related AE	8 (4.0%)	10 (5.1%)	0.6377	0.6478
Any SAE	42 (21.0%)	68 (34.5%)	0.0035	0.0113
Any study drug-related SAE	3 (1.5%)	4 (2.0%)	0.7224	0.7334
Any AE leading to discontinuation	9 (4.5%)	20 (10.2%)	0.0344	0.0657
Death	19 (9.5%)	25 (12.7%)	0.3402	0.6822

AE = adverse event; AIDS = acquired immunodeficiency syndrome; MedDRA = Medical Dictionary for Regulatory Activities; RDV = remdesivir (GS-5734™); SAE = serious adverse event

a P-value comparing the percentages of participants between treatment groups was from Cochran-Mantel-Haenszel test stratified by baseline clinical status.

Adverse events were coded using MedDRA 22.1.

Severity grades were defined by Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 July 2017.

Death refers to deaths that occurred between the first dose date and the last dose date plus 30 days (inclusive).

Source: GS-US-540-5773 Part A Interim Analysis, Table 15.11.2.1.1.1; GS-US-540-5773 Part A Interim Analysis, Adhoc Table req10607.8

An exploratory analysis sought to evaluate whether the difference in AEs reported in the RDV 10-day group was due to the differences in baseline clinical status, the increased duration of hospitalization for receiving study drug, or cumulative toxicity of RDV.

The nominal values show higher rates of grade 3/4 AE's as well as SAE's in the 10 day arm, also during the five first days when treatment was similar When comparing Days 1 through 5 and adjusting for baseline clinical status, there was no statistical difference in AE profile between treatment groups.

Within the RDV 10-day group, the AE profile was then evaluated during the first 5 days of therapy and compared to the second 5 days of therapy. While participants experienced additional AEs during Days 6 through 10, the proportion of participants experiencing all types of AE was lower during Days 6 through 10 than during Days 1 through 5 (death was reported for the same number of participants in each period, table below).

Table 27 GS-US-540-5773: Summary of Adverse Events During Days 1 to 5 and Days 6 to 10 (Safety Analysis Set)

	RDV for 5 Days		RDV for 10 Days	
	Days 1 to 5 (N = 200)	**Days 6 to 10 (N = 198)**	**Days 1 to 5 (N = 197)**	**Days 6 to 10 (N = 188)**
Any AE	120 (60.0%)	59 (29.8%)	122 (61.9%)	67 (35.6%)
Any Grade 3 or higher AE	46 (23.0%)	17 (8.6%)	62 (31.5%)	28 (14.9%)
Any study drug-related AE	30 (15.0%)	3 (1.5%)	26 (13.2%)	13 (6.9%)
Any Grade 3 or higher study drug-related AE	8 (4.0%)	0	8 (4.1%)	2 (1.1%)
Any SAE	31 (15.5%)	12 (6.1%)	45 (22.8%)	21 (11.2%)
Any study drug-related SAE	3 (1.5%)	0	4 (2.0%)	0
Any AE leading to study drug discontinuation	9 (4.5%)	NA	14 (7.1%)	6 (3.2%)
Death	2 (1.0%)	11 (5.6%)	9 (4.6%)	9 (4.8%)

AE = adverse event; AIDS = acquired immunodeficiency syndrome; MedDRA = Medical Dictionary for Regulatory Activities; NA = not applicable; RDV = remdesivir (GS-5734™); SAE = serious adverse event
Adverse events were coded using MedDRA 22.1.
Severity grades were defined by Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 July 2017.
Death refers to deaths that occurred between the first dose date and the last dose date plus 30 days (inclusive).
Adverse events with onset/deaths on Days 1 to 5 or AEs with onset/deaths on Days 6 to 10 are included.
The denominator for Days 6 to 10 is participants in the Safety Analysis Set excluding participants who died prior to Day 6.
Source: GS-US-540-5773 Part A Interim Analysis, Adhoc Table req10607.9

In the following table AEs occurring in ≥3% of patients are outlined.

Table 28 GS-US-540-5773: Adverse Events Occurring in ≥ 3% of Participants Overall by Treatment Group (Safety Analysis Set)

	RDV for 5 Days (N = 200)	**RDV for 10 Days (N = 197)**	**Total (N = 397)**
Nausea	20 (10.0%)	17 (8.6%)	37 (9.3%)
Acute respiratory failure	12 (6.0%)	21 (10.7%)	33 (8.3%)
Alanine aminotransferase increased	11 (5.5%)	15 (7.6%)	26 (6.5%)
Constipation	13 (6.5%)	13 (6.6%)	26 (6.5%)
Aspartate aminotransferase increased	10 (5.0%)	13 (6.6%)	23 (5.8%)
Hypokalaemia	10 (5.0%)	12 (6.1%)	22 (5.5%)
Hypotension	9 (4.5%)	12 (6.1%)	21 (5.3%)
Insomnia	10 (5.0%)	11 (5.6%)	21 (5.3%)
Respiratory failure	7 (3.5%)	14 (7.1%)	21 (5.3%)
Acute kidney injury	4 (2.0%)	15 (7.6%)	19 (4.8%)
Corona virus infection	7 (3.5%)	10 (5.1%)	17 (4.3%)
Diarrhoea	8 (4.0%)	8 (4.1%)	16 (4.0%)
Anaemia	6 (3.0%)	7 (3.6%)	13 (3.3%)
Anxiety	4 (2.0%)	9 (4.6%)	13 (3.3%)

	RDV for 5 Days (N = 200)	RDV for 10 Days (N = 197)	Total (N = 397)
Hyperglycaemia	6 (3.0%)	7 (3.6%)	13 (3.3%)
Pyrexia	9 (4.5%)	3 (1.5%)	12 (3.0%)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; RDV = remdesivir (GS-5734™)
Adverse events were coded using MedDRA 22.1.
Preferred terms are presented by descending order of the total frequencies.
Multiple AEs were counted only once per participant per preferred term.
Source: GS-US-540-5773 Part A Interim Analysis, Table 15.11.2.1.3

Table 29 Study GS-US-540-5773 (Part A Interim Analysis) - Treatment-Emergent Study Drug-Related Adverse Events by System Organ Class and Preferred Term Safety Analysis Set

	RDV For 5 Days (N=200)	RDV For 10 Days (N=197)	Total (N=397)
Number of Subjects Experiencing Any Treatment-Emergent Study Drug-Related AEs	33 (16.5%)	40 (20.3%)	73 (18.4%)
Number of Subjects Experiencing Any Treatment-Emergent Study Drug-Related Adverse Event by System Organ Class And Preferred Term			
Blood and lymphatic system disorders	1 (0.5%)	0	1 (0.3%)
Leukopenia	1 (0.5%)	0	1 (0.3%)
Cardiac disorders	1 (0.5%)	0	1 (0.3%)
Atrial fibrillation	1 (0.5%)	0	1 (0.3%)
Gastrointestinal disorders	13 (6.5%)	8 (4.1%)	21 (5.3%)
Nausea	9 (4.5%)	5 (2.5%)	14 (3.5%)
Constipation	3 (1.5%)	3 (1.5%)	6 (1.5%)
Vomiting	4 (2.0%)	0	4 (1.0%)
Diarrhoea	1 (0.5%)	0	1 (0.3%)
Dyspepsia	1 (0.5%)	0	1 (0.3%)
General disorders and administration site conditions	2 (1.0%)	1 (0.5%)	3 (0.8%)
Infusion site pain	1 (0.5%)	0	1 (0.3%)
Infusion site phlebitis	1 (0.5%)	0	1 (0.3%)
Injection site erythema	0	1 (0.5%)	1 (0.3%)
Hepatobiliary disorders	0	3 (1.5%)	3 (0.8%)
Hypertransaminasaemia	0	2 (1.0%)	2 (0.5%)
Hepatitis	0	1 (0.5%)	1 (0.3%)
Infections and infestations	1 (0.5%)	0	1 (0.3%)
Pneumonia streptococcal	1 (0.5%)	0	1 (0.3%)
Investigations	16 (8.0%)	25 (12.7%)	41 (10.3%)
Alanine aminotransferase increased	4 (2.0%)	14 (7.1%)	18 (4.5%)
Aspartate aminotransferase increased	5 (2.5%)	11 (5.6%)	16 (4.0%)
Transaminases increased	5 (2.5%)	4 (2.0%)	9 (2.3%)
Hepatic enzyme increased	3 (1.5%)	2 (1.0%)	5 (1.3%)
Liver function test increased	2 (1.0%)	1 (0.5%)	3 (0.8%)
Blood potassium decreased	0	1 (0.5%)	1 (0.3%)
Heart rate irregular	0	1 (0.5%)	1 (0.3%)
Metabolism and nutrition disorders	2 (1.0%)	0	2 (0.5%)
Hypertriglyceridaemia	2 (1.0%)	0	2 (0.5%)
Nervous system disorders	1 (0.5%)	2 (1.0%)	3 (0.8%)
Headache	1 (0.5%)	1 (0.5%)	2 (0.5%)
Dizziness	0	1 (0.5%)	1 (0.3%)
Paraesthesia	0	1 (0.5%)	1 (0.3%)
Psychiatric disorders	2 (1.0%)	1 (0.5%)	3 (0.8%)
Insomnia	2 (1.0%)	1 (0.5%)	3 (0.8%)
Respiratory, thoracic and mediastinal disorders	0	1 (0.5%)	1 (0.3%)
Oropharyngeal pain	0	1 (0.5%)	1 (0.3%)
Skin and subcutaneous tissue disorders	0	3 (1.5%)	3 (0.8%)
Rash	0	2 (1.0%)	2 (0.5%)
Pruritus	0	1 (0.5%)	1 (0.3%)
Rash macular	0	1 (0.5%)	1 (0.3%)
Vascular disorders	0	1 (0.5%)	1 (0.3%)
Flushing	0	1 (0.5%)	1 (0.3%)

GS-US-540-5774

The overall incidence of AEs was as follows: RDV for 5 days: 50.8%, 97 participants; RDV for 10 days: 54.9%, 106 participants; SOC: 45.0%, 90 participants. The overall incidence of Grade ≥ 3 AEs, serious AEs, and deaths were generally comparable between the 3 groups.

Table 30 GS-US-540-5774: Overall Summary of Adverse Events (Safety Analysis Set)

	RDV for 5 Days (N = 191)	**RDV for 10 Days (N = 193)**	**SOC (N = 200)**
Any AE	97 (50.8%)	106 (54.9%)	90 (45.0%)
Any Grade 3 or higher AE	20 (10.5%)	21 (10.9%)	24 (12.0%)
Any study drug-related AE	36 (18.8%)	24 (12.4%)	NA
Any Grade 3 or higher study drug-related AE	6 (3.1%)	5 (2.6%)	NA
Any SAE	8 (4.2%)	7 (3.6%)	18 (9.0%)
Any study drug-related SAE	1 (0.5%)	0	NA
Any AE leading to study drug discontinuation	4 (2.1%)	7 (3.6%)	NA
Death	2 (1.0%)	2 (1.0%)	4 (2.0%)

AE = adverse event; AIDS = acquired immunodeficiency syndrome; MedDRA = Medical Dictionary for Regulatory Activities; NA = not applicable; RDV = remdesivir (GS-5734™); SAE = serious adverse event
Adverse events were coded using MedDRA 22.1.
Severity grades were defined by Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 July 2017.
Source: GS-US-540-5774 Part A Interim Analysis, Table 15.11.2.1.1.1

Table 31 GS-US-540-5774: Adverse Events Occurring in ≥ 3% of Participants in Any Treatment Group by Treatment Group (Safety Analysis Set)

	RDV for 5 Days (N = 191)	**RDV for 10 Days (N = 193)**	**SOC (N = 200)**
Nausea	19 (9.9%)	18 (9.3%)	6 (3.0%)
Diarrhoea	10 (5.2%)	10 (5.2%)	14 (7.0%)
Hypokalaemia	9 (4.7%)	13 (6.7%)	4 (2.0%)
Headache	10 (5.2%)	10 (5.2%)	5 (2.5%)
Constipation	8 (4.2%)	5 (2.6%)	9 (4.5%)
Alanine aminotransferase increased	8 (4.2%)	6 (3.1%)	5 (2.5%)
Phlebitis	7 (3.7%)	7 (3.6%)	5 (2.5%)
Pyrexia	2 (1.0%)	8 (4.1%)	7 (3.5%)
Rash	7 (3.7%)	4 (2.1%)	6 (3.0%)
Insomnia	7 (3.7%)	2 (1.0%)	7 (3.5%)
Hypotension	6 (3.1%)	6 (3.1%)	1 (0.5%)
Hypertransaminasaemia	3 (1.6%)	6 (3.1%)	3 (1.5%)
Hypocalcaemia	6 (3.1%)	6 (3.1%)	0

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; RDV = remdesivir (GS-5734™); SOC = standard of care
Adverse events were coded using MedDRA 22.1.
Preferred terms are presented by descending order of the total frequencies.
Multiple AEs were counted only once per participant per preferred term.
Source: GS-US-540-5774 Part A Interim Analysis, Table 15.11.2.1.3

Table 32 Study GS-US-540-5774 (Part A Interim Analysis) - Treatment-Emergent Study Drug-Related Adverse Events by System Organ Class and Preferred Term Safety Analysis Set

	RDV For 5 Days (N=191)	For 10 Days (N=193)
Number of Subjects Experiencing Any Treatment-Emergent Study Drug-Related Adverse Event	36 (18.8%)	24 (12.4%)
Number of Subjects Experiencing Any Treatment-Emergent Study Drug-Related Adverse Event by System Organ Class And Preferred Term		
Eye disorders	3 (1.6%)	0
Conjunctival haemorrhage	1 (0.5%)	0
Dry eye	1 (0.5%)	0
Eye pruritus	1 (0.5%)	0
Gastrointestinal disorders	18 (9.4%)	8 (4.1%)
Nausea	13 (6.8%)	7 (3.6%)
Diarrhoea	3 (1.6%)	3 (1.6%)
Vomiting	1 (0.5%)	3 (1.6%)
Abdominal pain	1 (0.5%)	0
Constipation	1 (0.5%)	0
Flatulence	1 (0.5%)	0
General disorders and administration site conditions	3 (1.6%)	4 (2.1%)
Fatigue	1 (0.5%)	1 (0.5%)
Infusion site erythema	1 (0.5%)	1 (0.5%)
Infusion site pain	1 (0.5%)	1 (0.5%)
Chest pain	0	1 (0.5%)
Infusion site pruritus	1 (0.5%)	0
Infusion site swelling	0	1 (0.5%)
Pyrexia	1 (0.5%)	0
Hepatobiliary disorders	2 (1.0%)	5 (2.6%)
Hypertransaminasaemia	2 (1.0%)	4 (2.1%)
Cholestasis	0	1 (0.5%)
Infections and infestations	2 (1.0%)	0
Lymphangitis	1 (0.5%)	0
Urinary tract infection	1 (0.5%)	0
Injury, poisoning and procedural complications	1 (0.5%)	0
Fall	1 (0.5%)	0
Investigations	7 (3.7%)	6 (3.1%)
Alanine aminotransferase increased	7 (3.7%)	3 (1.6%)
Aspartate aminotransferase increased	5 (2.6%)	3 (1.6%)
Blood alkaline phosphatase increased	0	1 (0.5%)
Blood bilirubin increased	1 (0.5%)	0
Gamma-glutamyltransferase increased	0	1 (0.5%)
Heart rate decreased	1 (0.5%)	0
Transaminases increased	0	1 (0.5%)
Metabolism and nutrition disorders	1 (0.5%)	0
Hypercalcaemia	1 (0.5%)	0
Musculoskeletal and connective tissue disorders	3 (1.6%)	0
Back pain	1 (0.5%)	0
Musculoskeletal pain	1 (0.5%)	0
Myalgia	1 (0.5%)	0

Nervous system disorders	5 (2.6%)	3 (1.6%)
Headache	4 (2.1%)	3 (1.6%)
Dizziness	1 (0.5%)	0
Dysgeusia	1 (0.5%)	0
Psychiatric disorders	1 (0.5%)	1 (0.5%)
Insomnia	1 (0.5%)	0
Sleep disorder	0	1 (0.5%)
Renal and urinary disorders	0	1 (0.5%)
Acute kidney injury	0	1 (0.5%)
Skin and subcutaneous tissue disorders	5 (2.6%)	2 (1.0%)
Rash	5 (2.6%)	1 (0.5%)
Pruritus	1 (0.5%)	0
Rash papular	0	1 (0.5%)
Vascular disorders	2 (1.0%)	0
Phlebitis	2 (1.0%)	0

CO-US-540-5758

In CO-US-540-5758, overall, adverse events were reported in 102 (66%) of 155 patients in the RDV group and 50 (64%) of 78 in the placebo group. The following adverse events were reported in more than one patient:

Table 33 CO-US-540-5758 - Adverse events

	Remdesivir group (n=155)		Placebo group (n=78)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Adverse events (in ≥2% of patients in any treatment group)				
Any	102 (66%)	13 (8%)	50 (64%)	11 (14%)
Hypoalbuminaemia	20 (13%)	0	12 (15%)	1 (1%)
Hypokalaemia	18 (12%)	2 (1%)	11 (14%)	1 (1%)
Increased blood glucose	11 (7%)	0	6 (8%)	0
Anaemia	18 (12%)	1 (1%)	12 (15%)	2 (3%)
Rash	11 (7%)	0	2 (3%)	0
Thrombocytopenia	16 (10%)	4 (3%)	5 (6%)	3 (4%)
Increased total bilirubin	15 (10%)	1 (1%)	7 (9%)	0
Increased blood lipids	10 (6%)	0	8 (10%)	0
Increased white blood cell count	11 (7%)	0	6 (8%)	0
Hyperlipidaemia	10 (6%)	0	8 (10%)	0
Increased blood urea nitrogen	10 (6%)	0	5 (6%)	0
Increased neutrophil	10 (6%)	0	4 (5%)	0
Aspartate aminotransferase increased	7 (5%)	0	9 (12%)	0
Constipation	21 (14%)	0	12 (15%)	0
Nausea	8 (5%)	0	2 (3%)	0
Diarrhoea	5 (3%)	0	2 (3%)	0
Vomiting	4 (3%)	0	2 (3%)	0
Reduced serum sodium	4 (3%)	0	2 (3%)	0
Increased serum potassium	4 (3%)	2 (1%)	1 (1%)	0

Source: modified from Wang et al, Lancet 2020

Clinical studies in Ebola

No information about reported AEs is available.

PK studies

Based on pooled available AE data from Gilead-sponsored Studies GS-US-399-1812, GS-US-399-1954, GS-US-399-4321, and GS-US-399-5505, AEs observed in at least 5 subjects across these 4 studies are presented in table below.

Table 34: GS-US-399-1812, GS-US-399-1954, GS-US-399-4231, and GS-US-399-5505: Adverse Events Occurring in ≥ 5 Subjects (Safety Analysis Sets)

Preferred Term	Remdesivir[a] (N = 138)
Phlebitis	8
Constipation	7
Headache	6
Ecchymosis	5
Nausea	5
Pain in extremity	5

a Includes 131 subjects who received remdesivir and 7 subjects who received placebo. Data from placebo subjects was included because Study GS-US-399-5505 is still blinded. Data from Studies GS-US-399-4231 and GS-US-399-5505 is preliminary.

Single-patient compassionate use in COVID-19

The table below provides information about treatment-emergent AEs by baseline oxygen support status.

Table 35 IN-US-540-5755: Overall Summary of Treatment-Emergent Adverse Events by Baseline Oxygen Support Status – All Patients (Compassionate Use Analysis Set)

	Invasive (N = 104)	Noninvasive (N = 58)	Overall (N = 163)
Patients with any TEAE	58 (55.8%)	24 (41.4%)	82 (50.3%)
Patients with any TESAE	29 (27.9%)	9 (15.5%)	38 (23.3%)
Patients with TEAEs leading to discontinuation of RDV	8 (7.7%)	5 (8.6%)	13 (8.0%)
Death	27 (26.0%)	6 (10.3%)	33 (20.2%)

e-CRF=electronic case reports form; MedDRA=Medical Dictionary for Regulatory Activities; PDT=Pacific Daylight Time; RDV=remdesivir (GS-5734™); TEAE=treatment-emergent adverse event; TESAE=treatment-emergent serious adverse event
One patient had no record on oxygen support status at baseline or postbaseline, and hence was excluded from the analysis by baseline oxygen support status.
Compassionate Use Analysis Set included all patients who received the first dose of RDV on or prior to 14 March 2020, per data entered in eCRFs as of 27 March 2020 10:00 AM PDT.
Adverse events were coded using MedDRA 22.1
Source: Table 7.1.4 and listing 8

The following treatment-emergent AEs were reported in >2% of patients overall by baseline oxygen support status:

Table 36 IN-US-540-5755: Treatment-Emergent Adverse Events Reported in ≥ 2% of Patients Overall by Baseline Oxygen Support Status – All Patients (Compassionate Use Analysis Set)

	Invasive (N = 104)	Noninvasive (N = 58)	Overall (N = 163)
Investigations	21 (20.2%)	7 (12.1%)	28 (17.2%)
Transaminases increased	5 (4.8%)	3 (5.2%)	8 (4.9%)
Alanine aminotransferase increased	3 (2.9%)	2 (3.4%)	5 (3.1%)
Aspartate aminotransferase increased	3 (2.9%)	2 (3.4%)	5 (3.1%)
Hepatic enzyme increased	3 (2.9%)	2 (3.4%)	5 (3.1%)
Respiratory, thoracic and mediastinal disorders	18 (17.3%)	5 (8.6%)	23 (14.1%)
Respiratory failure	10 (9.6%)	1 (1.7%)	11 (6.7%)
Acute respiratory distress syndrome	4 (3.8%)	1 (1.7%)	5 (3.1%)
Infections and infestations	16 (15.4%)	3 (5.2%)	19 (11.7%)
Corona virus infection	6 (5.8%)	1 (1.7%)	7 (4.3%)
Septic shock	3 (2.9%)	1 (1.7%)	4 (2.5%)
Renal and urinary disorders	16 (15.4%)	2 (3.4%)	18 (11.0%)
Acute kidney injury	7 (6.7%)	1 (1.7%)	8 (4.9%)
Renal failure	4 (3.8%)	1 (1.7%)	5 (3.1%)
Renal impairment	5 (4.8%)	0	5 (3.1%)
Gastrointestinal disorders	2 (1.9%)	10 (17.2%)	12 (7.4%)
Diarrhoea	1 (1.0%)	6 (10.3%)	7 (4.3%)
Skin and subcutaneous tissue disorders	8 (7.7%)	4 (6.9%)	12 (7.4%)
Rash	3 (2.9%)	2 (3.4%)	5 (3.1%)
Vascular disorders	9 (8.7%)	2 (3.4%)	11 (6.7%)
Hypotension	7 (6.7%)	1 (1.7%)	8 (4.9%)
General disorders and administration site conditions	7 (6.7%)	3 (5.2%)	10 (6.1%)
Multiple organ dysfunction syndrome	5 (4.8%)	0	5 (3.1%)
Pyrexia	2 (1.9%)	2 (3.4%)	4 (2.5%)

AE =adverse event, eCRF = electronic case report form; MedDRA = Medical Dictionary for Regulatory Activities;
PDT = Pacific Daylight Time; RDV=remdesivir (GS-5734™); TEAE=treatment-emergent adverse event
One patient had no record on oxygen support status at baseline or postbaseline, and hence was excluded from the analysis by baseline oxygen support status.
Compassionate use Analysis Set included all patients who received the first dose of RDV on or prior to 14 March 2020, per data entered in eCRF`s as of 27 March 2020 10:00 AM PDT.
Treatment-emergent AE`s were coded sing MedDRA 22.1
System organ classes are presented by descending order of the total frequencies, and preferred terms within the system organ class are presented by descending order of the total frequencies.
Multiple TEAE`s were counted only once per patient for each system organ class and preferred term, respectively.
Source: Table 7.2.4

Serious adverse event and deaths

Clinical studies in COVID-19

CO-US-540-5776

The following information about SAEs is available from NIAID ACTT-1 study:

Serious AEs (SAEs) were reported for 114 (21.1%) participants in the RDV group and 141 (27.0%) participants in the placebo group; 4 events (2 in each group) were judged by site investigators to be related to RDV or placebo. The table below provides information about SAEs reported during study CO-US-540-5776.

Table 37 Serious Adverse Events Occurring in 5 or More Subjects in Any Preferred Term by Treatment Group

MedDRA System Organ Class	Preferred Term	Remdesivir (N = 541) No.(%)	Placebo (N = 522) No.(%)
Any System Organ Class	Any Preferred Term	114 (21.1)	141 (27.0)
Cardiac disorders	Cardiac arrest	6 (1.1)	5 (1.0)
	Atrial fibrillation	4 (0.7)	2 (0.4)
Infections and infestations	Septic shock	6 (1.1)	7 (1.3)
	Pneumonia viral	3 (0.6)	7 (1.3)
Investigations	Glomerular filtration rate decreased[a]	3 (0.6)	2 (0.4)
Renal and urinary disorders	Acute kidney injury[a]	4 (0.7)	7 (1.3)
Respiratory, thoracic and mediastinal disorders	Respiratory failure	28 (5.2)	42 (8.0)
	Acute respiratory failure	9 (1.7)	12 (2.3)
	Respiratory distress[b]	9 (1.7)	10 (1.9)
	Hypoxia[b]	4 (0.7)	5 (1.0)
	Pneumothorax	3 (0.6)	3 (0.6)
	Pulmonary embolism	3 (0.6)	3 (0.6)
Surgical and medical procedures	Mechanical ventilation	1 (0.2)	5 (1.0)
	Endotracheal intubation	2 (0.4)	3 (0.6)
Uncoded	Uncoded	19 (3.5)	22 (4.2)
Vascular disorders	Hypotension	2 (0.4)	12 (2.3)
	Shock	4 (0.7)	3 (0.6)

No. = number of subjects reporting at least one event.
Renal impairment has been redacted from the table as it occurred in only one treatment group.
[a] The combined number of subjects with either glomerular filtration rate decreased and/or acute kidney injury are 7 for Remdesivir and 9 for Placebo.
[b] The combined number of subjects with either hypoxia and/or respiratory distress are 13 for Remdesivir and 15 for Placebo.

GS-US-540-5773

Overall, 44 deaths were reported; 19 (9.5%) in the RDV 5-day group and 25 (12.7%) in the RDV 10 day group.

The SAEs reported in > 1% of participants overall are presented by treatment group in the table below.

Table 38 GS-US-540-5773: Serious Adverse Events Occurring in > 1% of Participants Overall by Treatment Group (Safety Analysis Set)

	RDV for 5 Days (N = 200)	**RDV for 10 Days (N = 197)**	**Total (N = 397)**
Acute respiratory failure	10 (5.0%)	18 (9.1%)	28 (7.1%)
Corona virus infection	7 (3.5%)	10 (5.1%)	17 (4.3%)
Respiratory failure	5 (2.5%)	10 (5.1%)	15 (3.8%)
Respiratory distress	3 (1.5%)	4 (2.0%)	7 (1.8%)
Septic shock	2 (1.0%)	5 (2.5%)	7 (1.8%)
Acute respiratory distress syndrome	1 (0.5%)	5 (2.5%)	6 (1.5%)

	RDV for 5 Days (N = 200)	RDV for 10 Days (N = 197)	Total (N = 397)
Hypoxia	2 (1.0%)	4 (2.0%)	6 (1.5%)
Dyspnoea	4 (2.0%)	1 (0.5%)	5 (1.3%)
Pneumonia viral	3 (1.5%)	2 (1.0%)	5 (1.3%)
Pneumothorax	2 (1.0%)	3 (1.5%)	5 (1.3%)
Transaminases increased	3 (1.5%)	2 (1.0%)	5 (1.3%)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; RDV = remdesivir (GS-5734™)
Adverse events were coded using MedDRA 22.1.
Preferred terms are presented by descending order of the total frequencies.
Multiple AEs were counted only once per participant per preferred term.
Source: GS-US-540-5773 Part A Interim Analysis Table 15.11.4.1

The following SAEs were rated as study drug-related.

Table 39 Study GS-US-540-5773 (Part A Interim Analysis) - Treatment-Emergent Study Drug-Related Serious Adverse Events by System Organ Class and Preferred Term – Safety Analysis Set

	RDV For 5 Days (N=200)	RDV For 10 Days (N=197)	Total (N=397)
Number of Subjects Experiencing Any Treatment-Emergent Study Drug-Related Serious AEs	3 (1.5%)	4 (2.0%)	7 (1.8%)
Number of Subjects Experiencing Any Treatment-Emergent Study Drug-Related Serious Adverse Event by System Organ Class And Preferred Term			
Hepatobiliary disorders	0	1 (0.5%)	1 (0.3%)
Hypertransaminasaemia	0	1 (0.5%)	1 (0.3%)
Investigations	3 (1.5%)	3 (1.5%)	6 (1.5%)
Transaminases increased	3 (1.5%)	2 (1.0%)	5 (1.3%)
Hepatic enzyme increased	0	1 (0.5%)	1 (0.3%)

GS-US-540-5774

Overall, 8 deaths were reported; 2 (1.0%) in the RDV 5-day group, 2 (1.0%) in the RDV 10-day group, and 4 (2.0%) in the SOC group.

The SAEs reported in ≥ 1% of participants in any treatment group are presented in the table below. No event was reported for ≥ 1% of participants in either RDV group.

Table 40 GS-US-540-5774: Serious Adverse Events Occurring in ≥ 1% of Participants in Any Treatment Group by Treatment Group (Safety Analysis Set)

	RDV for 5 Days (N = 191)	RDV for 10 Days (N = 193)	SOC (N = 200)
Any SAE	8 (4.2%)	7 (3.6%)	18 (9.0%)
Acute respiratory failure	0	0	5 (2.5%)
Respiratory distress	0	1 (0.5%)	2 (1.0%)
Respiratory failure	1 (0.5%)	0	2 (1.0%)

	RDV for 5 Days (N = 191)	RDV for 10 Days (N = 193)	SOC (N = 200)
Cardiac arrest	0	0	2 (1.0%)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; RDV = remdesivir (GS-5734™); SAE = serious adverse event; SOC = standard of care
Adverse events were coded using MedDRA 22.1.
Preferred terms are presented by descending order of the total frequencies.
Multiple AEs were counted only once per participant per preferred term.
Source: GS-US-540-5774 Part A Interim Analysis Table 15.11.4.5

Overall, in one case the SAE was rated as study drug-related (RDV 5-days group: heart rate decreased).

CO-US-540-5758

Serious adverse events were reported in 28 (18%) of 155 patients in the RDV group and 20 (26%) of 78 in the placebo group. The following serious adverse events were reported in more than one patient:

Table 41 CO-US-540-5758 - Serious adverse events

	Remdesivir group (n=155)		Placebo group (n=78)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Serious adverse events				
Any	28 (18%)	9 (6%)	20 (26%)	10 (13%)
Respiratory failure or acute respiratory distress syndrome	16 (10%)	4 (3%)	6 (8%)	4 (5%)
Cardiopulmonary failure	8 (5%)	0	7 (9%)	1 (1%)
Pulmonary embolism	1 (1%)	1 (1%)	1 (1%)	1 (1%)
Recurrence of COVID-19	1 (1%)	0	0	0
Cardiac arrest	1 (1%)	0	0	0
Acute coronary syndrome	0	0	1 (1%)	1 (1%)
Tachycardia	0	0	1 (1%)	0
Septic shock	1 (1%)	0	1 (1%)	1 (1%)

Source: modified from Wang et al, Lancet 2020

	Remdesivir group (n=155)		Placebo group (n=78)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Lung abscess	0	0	1 (1%)	1 (1%)
Sepsis	0	0	1 (1%)	1 (1%)
Bronchitis	0	0	1 (1%)	1 (1%)
Thrombocytopenia	1 (1%)	1 (1%)	0	0
Increased D-dimer	0	0	1 (1%)	1 (1%)
Haemorrhage of lower digestive tract	1 (1%)	1 (1%)	0	0
Ileus	0	0	1 (1%)	0
Deep vein thrombosis	1 (1%)	1 (1%)	1 (1%)	1 (1%)
Acute kidney injury	1 (1%)	0	0	0
Diabetic ketoacidosis	0	0	1 (1%)	1 (1%)
Multiple organ dysfunction syndrome	1 (1%)	0	2 (3%)	0

Source: modified from Wang et al, Lancet 2020

Clinical studies in Ebola

CO-US-399-5366

In the PALM study, a total of 9 SAEs judged by the site investigator as not related to underlying EVD were reported for participants receiving RDV. Of these, an event of hypotension, which occurred during administration of the loading dose and led to fatal cardiac arrest, was considered related to RDV. The independent pharmacovigilance committee noted that the death could not be readily distinguished from underlying fulminant EVD.

PREVAIL IV

No SAEs occurred in 38 Men Who Survived Ebola Virus infections under a comparable dosing regimen. There was one individual dose reduction for transaminase elevations.

PK studies

No information about reported SAEs is available.

Single-patient compassionate use

In the following table treatment-emergent serious adverse events reported during single-patient compassionate use are outlined.

Table 42 *IN-US-540-5755: Treatment-Emergent Serious Adverse Events Reported in ≥ 2 Patients Overall by Baseline Oxygen Support Status - All Patients (Compassionate Use Analysis Set)*

	Invasive (N = 104)	Noninvasive (N = 58)	Overall (N = 163)
Respiratory, thoracic and mediastinal disorders	13 (12.5%)	5 (8.6%)	18 (11.0%)
Respiratory failure	9 (8.7%)	1 (1.7%)	10 (6.1%)
Acute respiratory distress syndrome	2 (1.9%)	1 (1.7%)	3 (1.8%)
Respiratory distress	0	2 (3.4%)	2 (1.2%)
Infections and infestations	10 (9.6%)	2 (3.4%)	12 (7.4%)
Corona virus infection	5 (4.8%)	0	5 (3.1%)
Septic shock	2 (1.9%)	1 (1.7%)	3 (1.8%)
Pneumonia	2 (1.9%)	0	2 (1.2%)
Sepsis	1 (1.0%)	1 (1.7%)	2 (1.2%)
Renal and urinary disorders	7 (6.7%)	1 (1.7%)	8 (4.9%)
Acute kidney injury	6 (5.8%)	0	6 (3.7%)
Renal failure	3 (2.9%)	1 (1.7%)	4 (2.5%)
Vascular disorders	6 (5.8%)	0	6 (3.7%)
Hypotension	6 (5.8%)	0	6 (3.7%)
General disorders and administration site conditions	5 (4.8%)	0	5 (3.1%)
Multiple organ dysfunction syndrome	3 (2.9%)	0	3 (1.8%)

eCRF = electronic case report form; MedDRA = Medical Dictionary for Regulatory Activities;
PDT = Pacific Daylight Time; RDV=remdesivir (GS-5734™); SAE=serious adverse event, TESAE=treatment-emergent serious adverse event
One patient had no record on oxygen support status at baseline or postbaseline, and hence was excluded from the analysis by baseline oxygen support status.
Compassionate use Analysis Set included all patients who received the first dose of RDV on or prior to 14 March 2020, per data entered in eCRF`s as of 27 March 2020 10:00 AM PDT.
Treatment-emergent SAE`s were coded sing MedDRA 22.1
System organ classes are presented by descending order of the total frequencies, and preferred terms within the system organ class are presented by descending order of the total frequencies.
Multiple TESAE`s were counted only once per patient for each system organ class and preferred term, respectively.
Source: Table 7.3.4

Laboratory findings

Clinical studies in COVID-19

CO-US-540-5776

No additional information regards to laboratory findings is available. See also sections above.

GS-US-540-5773

Summaries of graded laboratory abnormalities for Study GS-US-540-5773 are provided in the table below. Laboratory abnormalities of Grade 3 or higher were experienced by 27.2% of participants in the RDV 5-day group and 33.5% of participants in the RDV 10-day group.

Table 43 GS-US-540-5773: Summary of Graded Laboratory Abnormalities (Safety Analysis Set)

	RDV for 5 Days (N = 200)	**RDV for 10 Days (N = 197)**	**Total (N = 397)**
Maximum Treatment-Emergent Toxicity Grade	195	191	386
Any Grade	152 (77.9%)	160 (83.8%)	312 (80.8%)
Grade 1	46 (23.6%)	25 (13.1%)	71 (18.4%)
Grade 2	53 (27.2%)	71 (37.2%)	124 (32.1%)
Grade 3	43 (22.1%)	38 (19.9%)	81 (21.0%)
Grade 4	10 (5.1%)	26 (13.6%)	36 (9.3%)

AIDS = acquired immunodeficiency syndrome; RDV = remdesivir (GS-5734™)
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.
Participants were counted once for the maximum postbaseline severity for each laboratory test under evaluation.
Severity grades were defined by Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 July 2017.
Source: GS-US-540-5773 Part A Interim Analysis, Table 15.11.6.4.1

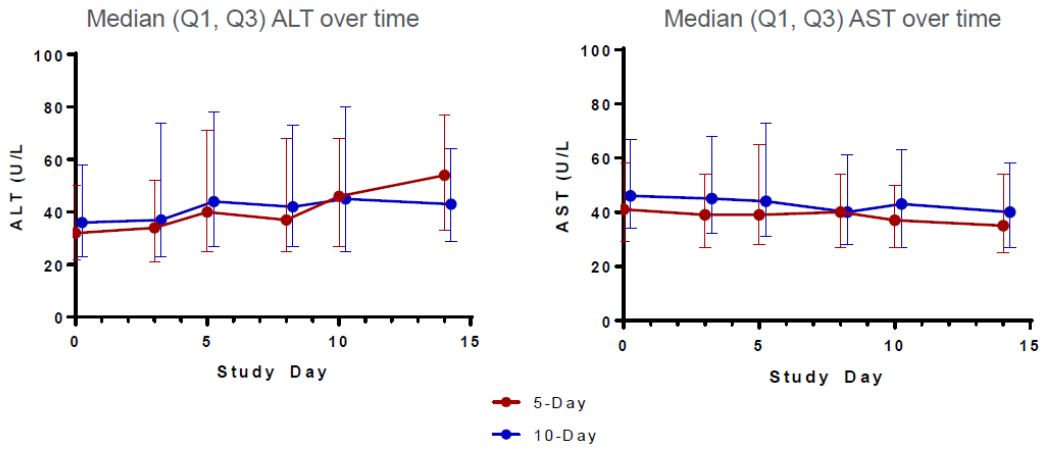
Table 44 GS-US-540-5773: Summary of Grade 3 or 4 Laboratory Abnormalities (Safety Analysis Set)

	RDV for 5 Days (N = 200)	**RDV for 10 Days (N = 197)**	**Total (N = 397)**
Maximum Treatment-Emergent Toxicity Grade	195	191	386
All Grade 3 or 4	53 (27.2%)	64 (33.5%)	117 (30.3%)
Hemoglobin (Decreased)	195	191	386
Grade 3	11 (5.6%)	12 (6.3%)	23 (6.0%)
Grade 4	0	2 (1.0%)	2 (0.5%)
Platelets (Decreased)	195	191	386
Grade 3	2 (1.0%)	1 (0.5%)	3 (0.8%)
Grade 4	0	0	0
ALT (Increased)	194	191	385
Grade 3	8 (4.1%)	11 (5.8%)	19 (4.9%)
Grade 4	4 (2.1%)	5 (2.6%)	9 (2.3%)
AST (Increased)	194	190	384
Grade 3	11 (5.7%)	7 (3.7%)	18 (4.7%)
Grade 4	3 (1.5%)	4 (2.1%)	7 (1.8%)
Creatinine (Increased)	195	191	386
Grade 3	5 (2.6%)	7 (3.7%)	12 (3.1%)
Grade 4	4 (2.1%)	22 (11.5%)	26 (6.7%)
Serum Glucose (Hyperglycemia)	186	187	373

	RDV for 5 Days (N = 200)	RDV for 10 Days (N = 197)	Total (N = 397)
Grade 3	19 (10.2%)	14 (7.5%)	33 (8.8%)
Grade 4	0	1 (0.5%)	1 (0.3%)
Total Bilirubin (Hyperbilirubinemia)	193	190	383
Grade 3	1 (0.5%)	3 (1.6%)	4 (1.0%)
Grade 4	0	1 (0.5%)	1 (0.3%)
Creatinine Clearance (Decreased)	193	188	381
Grade 3	13 (6.7%)	13 (6.9%)	26 (6.8%)
Grade 4	5 (2.6%)	23 (12.2%)	28 (7.3%)

AIDS = acquired immunodeficiency syndrome; ALT = alanine aminotransferase; AST = aspartate aminotransferase; RDV = remdesivir (GS-5734™)
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.
Participants were counted once for the maximum postbaseline severity for each laboratory test under evaluation.
Severity grades were defined by Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 July 2017.
Source: GS-US-540-5773 Part A Interim Analysis, Table 15.11.6.4.2

Figure 23 GS-US-540-5773 Laboratory Values: ALT and AST - Gilead Severe Simple Trial



GS-US-540-5774

Summaries of graded laboratory abnormalities for study GS-US-540-5774 are provided in the table below. Laboratory abnormalities of Grade 3 or higher were experienced by 12.8% of participants in the RDV 5-days group, 16.2% of participants in the RDV 10-days group, and 17.7% of participants in the SOC group. The only significant difference on Day 10 was observed for ALT, where the median change from baseline in ALT was higher in the SOC group compared with the RDV 5-day and 10-day groups.

Table 45 GS-US-540-5774: Summary of Graded Laboratory Abnormalities (Safety Analysis Set)

	RDV for 5 Days (N = 191)	RDV for 10 Days (N = 193)	SOC (N = 200)
Maximum Treatment-Emergent Toxicity Grade	180	179	186

	RDV for 5 Days (N = 191)	RDV for 10 Days (N = 193)	SOC (N = 200)
Any Grade	131 (72.8%)	128 (71.5%)	136 (73.1%)
Grade 1	54 (30.0%)	41 (22.9%)	37 (19.9%)
Grade 2	54 (30.0%)	58 (32.4%)	66 (35.5%)
Grade 3	18 (10.0%)	25 (14.0%)	25 (13.4%)
Grade 4	5 (2.8%)	4 (2.2%)	8 (4.3%)

AIDS = acquired immunodeficiency syndrome; RDV = remdesivir (GS-5734™); SOC = standard of care
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.
Participants were counted once for the maximum postbaseline severity for each laboratory test under evaluation.
Severity grades were defined by Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 July 2017.
Source: GS-US-540-5774 Part A Interim Analysis, Table 15.11.6.4.1

Table 46 GS-US-540-5774: Summary of Grade 3 or 4 Laboratory Abnormalities (Safety Analysis Set)

	RDV for 5 Days (N = 191)	RDV for 10 Days (N = 193)	SOC (N = 200)
Maximum Treatment-Emergent Toxicity Grade	180	179	186
All Grade 3 or 4	23 (12.8%)	29 (16.2%)	33 (17.7%)
Hemoglobin (Decreased)	179	178	184
Grade 3	4 (2.2%)	2 (1.1%)	8 (4.3%)
Grade 4	2 (1.1%)	0	2 (1.1%)
Platelets (Decreased)	179	178	184
Grade 3	0	0	1 (0.5%)
Grade 4	3 (1.7%)	0	0
WBC (Decreased)	179	178	184
Grade 3	1 (0.6%)	3 (1.7%)	2 (1.1%)
Grade 4	1 (0.6%)	1 (0.6%)	0
ALT (Increased)	179	177	182
Grade 3	4 (2.2%)	6 (3.4%)	10 (5.5%)
Grade 4	0	0	3 (1.6%)
AST (Increased)	177	175	182
Grade 3	3 (1.7%)	2 (1.1%)	6 (3.3%)
Grade 4	1 (0.6%)	0	5 (2.7%)
Creatinine (Increased)	180	179	184
Grade 3	1 (0.6%)	3 (1.7%)	4 (2.2%)
Grade 4	0	1 (0.6%)	4 (2.2%)
Serum Glucose (Hyperglycemia)	180	177	181

	RDV for 5 Days (N = 191)	RDV for 10 Days (N = 193)	SOC (N = 200)
Grade 3	7 (3.9%)	5 (2.8%)	4 (2.2%)
Grade 4	0	0	0
Total Bilirubin (Hyperbilirubinemia)	177	176	181
Grade 3	1 (0.6%)	3 (1.7%)	1 (0.6%)
Grade 4	0	1 (0.6%)	1 (0.6%)
Creatinine Clearance (Decreased)	178	176	182
Grade 3	4 (2.2%)	7 (4.0%)	9 (4.9%)
Grade 4	0	2 (1.1%)	4 (2.2%)

AIDS = acquired immunodeficiency syndrome; ALT = alanine aminotransferase; AST = aspartate aminotransferase; RDV = remdesivir (GS-5734™); SOC = standard of care; WBC = white blood cell
The denominator for percentage is the number of participants in the Safety Analysis Set with at least 1 postbaseline value for the test under evaluation.
Participants were counted once for the maximum postbaseline severity for each laboratory test under evaluation.
Severity grades were defined by Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 July 2017.
Source: GS-US-540-5774 Part A Interim Analysis, Table 15.11.6.4.2

CO-US-540-5758

No specific information about laboratory findings is available.

Clinical studies in Ebola

No additional information regards to laboratory findings is available.

PK studies

No additional information regards to laboratory findings is available.

Single-patient compassionate use

The following data were provided for single-patient compassionate use:

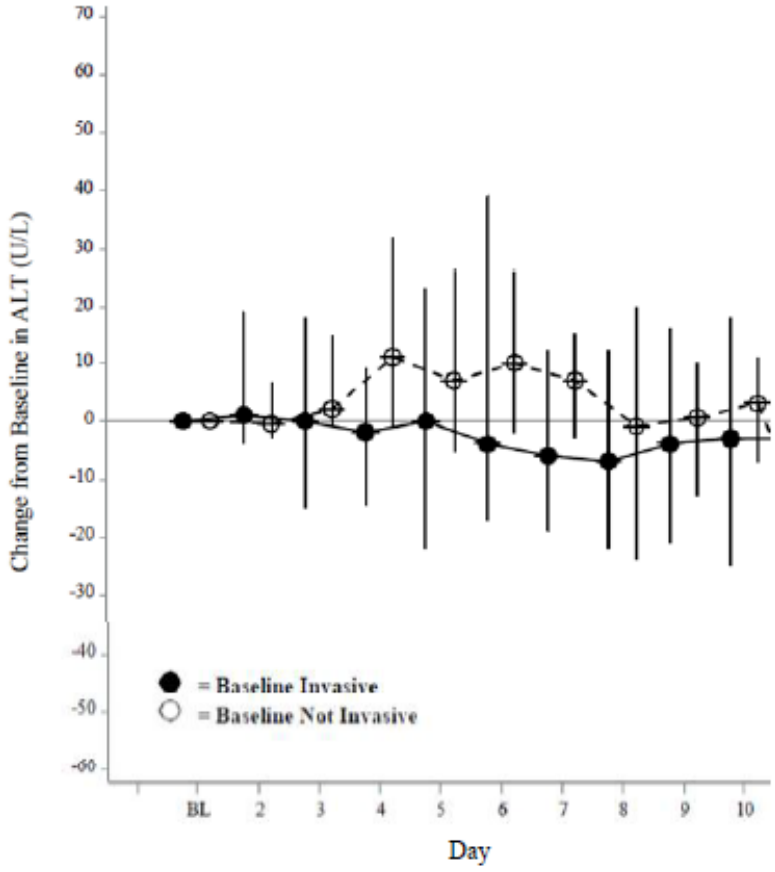
Table 47 IN-US-540-5755: Treatment-Emergent Liver-Related Laboratory Abnormalities by Baseline Oxygen Support Status – All Patients (Compassionate Use Analysis Set)

	Invasive (N = 104)	Noninvasive (N = 58)	Overall (N = 163)
ALT (Increased)	95	49	144
Grade 1	20 (21.1%)	13 (26.5%)	33 (22.9%)
Grade 2	14 (14.7%)	5 (10.2%)	19 (13.2%)
Grade 3	7 (7.4%)	1 (2.0%)	8 (5.6%)
Grade 4	0	0	0
Any Grade	41 (43.2%)	19 (38.8%)	60 (41.7%)
AST (Increased)	89	47	136
Grade 1	21 (23.6%)	10 (21.3%)	31 (22.8%)
Grade 2	14 (15.7%)	10 (21.3%)	24 (17.6%)
Grade 3	8 (9.0%)	1 (2.1%)	9 (6.6%)
Grade 4	1 (1.1%)	0	1 (0.7%)
Any Grade	44 (49.4%)	21 (44.7%)	65 (47.8%)
Alkaline Phosphatase (Increased)	75	37	112
Grade 1	15 (20.0%)	2 (5.4%)	17 (15.2%)
Grade 2	9 (12.0%)	1 (2.7%)	10 (8.9%)
Grade 3	0	0	0
Grade 4	0	0	0
Any Grade	24 (32.0%)	3 (8.1%)	27 (24.1%)

	Invasive (N = 104)	Noninvasive (N = 58)	Overall (N = 163)
Total Bilirubin (Hyperbilirubinemia)	89	43	132
Grade 1	2 (2.2%)	0	2 (1.5%)
Grade 2	8 (9.0%)	1 (2.3%)	9 (6.8%)
Grade 3	7 (7.9%)	4 (9.3%)	11 (8.3%)
Grade 4	10 (11.2%)	2 (4.7%)	12 (9.1%)
Any Grade	27 (30.3%)	7 (16.3%)	34 (25.8%)

ALT = alanine aminotransferase; AST=aspartate aminotransferase; DAIDs=Division of AIDS; eCRF=electronic case report form; PDT=Pacific Daylight Time; RDV=remdesivir (GS-5734™)
One Patient had no record on oxygen support status at baseline or postbaseline; and hence was excluded from the analysis by baseline oxygen support status
Compassionate Use Analysis Set included all patients who received the first dose of RDV on or prior to 14 March 2020, per data entered in eCRFs as of 27 March 2020 10:00 AM PDT.
The DAIDS Table for Grading the Severity of Adults and Paediatric Adverse Event Version 2.1 (July 2017) was used for assigning toxicity grades (0 to 4) to laboratory results for analysis.
The denominator for percentage was the number of patients in the Compassionate Use Analysis Set with at least 1 postbaseline value for the test under evaluation
Patients were counted once for the maximum postbaseline severity for each laboratory test under evaluation.
Source: Adhoc Table 10585.8.1.4

Figure 24 IN-US-540-5755: Median (Q1, Q3) Change From Baseline in Alanine Aminotransferase Through Day 10 by Baseline Oxygen Support Status – All Patients (Compassionate Use Analysis Set)



Baseline Invasive (n=):	86	63	67	68	61	62	57	43	47	47
Baseline Not Invasive (n=):	50	28	29	25	24	25	21	15	19	14

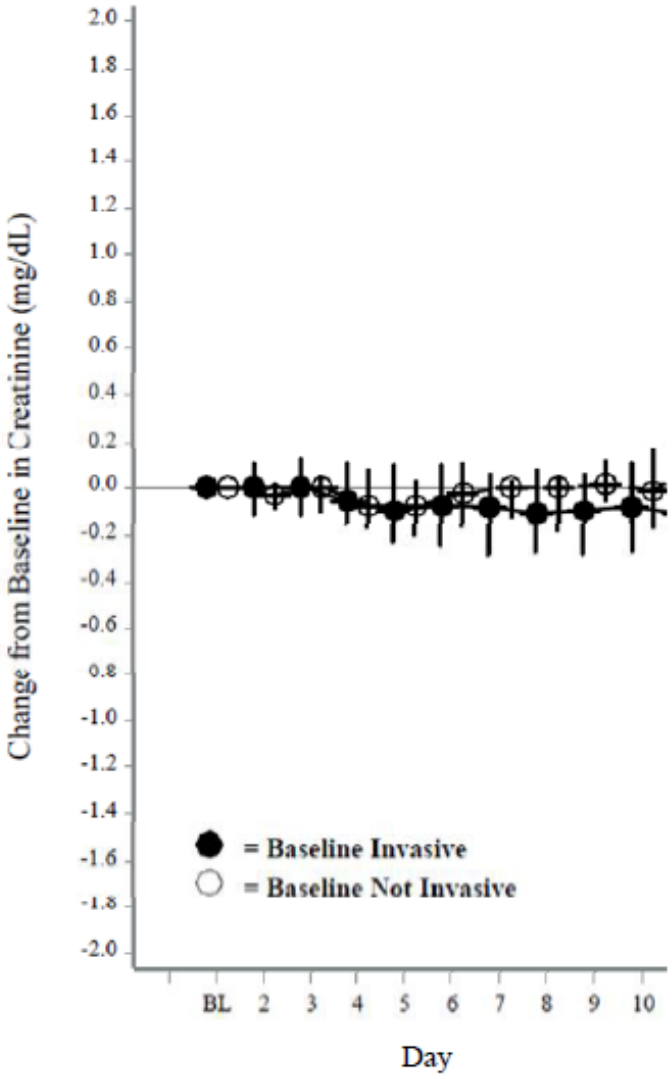
ALT = alanine aminotransferase; BL = baseline; eCRF = electronic case report form; PDT = Pacific Daylight Time; Q1 = first quartile; Q3 = third quartile; RDV = remdesivir (GS-5734™)
Compassionate Use Analysis Set included all patients who received the first dose of RDV on or prior to 14 March 2020, per data entered in eCRFs as of 27 March 2020 10:00 AM PDT.
Reference line represents no change from baseline (ie, y = 0).
Source: Adhoc Figure 10585.7.4

Table 48 IN-US-540-5755: Treatment-Emergent Serum Creatinine Abnormalities by Baseline Oxygen Support Status – All Patients (Compassionate Use Analysis Set)

	Invasive (N = 104)	Noninvasive (N = 58)	Overall (N = 163)
Creatinine (Increased)	95	53	148
Grade 1	1 (1.1%)	1 (1.9%)	2 (1.4%)
Grade 2	9 (9.5%)	6 (11.3%)	15 (10.1%)
Grade 3	7 (7.4%)	2 (3.8%)	9 (6.1%)
Grade 4	13 (13.7%)	2 (3.8%)	15 (10.1%)
Any Grade	30 (31.6%)	11 (20.8%)	41 (27.7%)

DAIDs=Division of AIDS; eCRF=electronic case report form; PDT=Pacific Daylight Time; RDV=remdesivir (GS-5734™)
One Patient had no record on oxygen support status at baseline or postbaseline; and hence was excluded from the analysis by baseline oxygen support status
Compassionate Use Analysis Set included all patients who received the first dose of RDV on or prior to 14 March 2020, per data entered in eCRFs as of 27 March 2020 10:00 AM PDT.
The DAIDS Table for Grading the Severity of Adults and Paediatric Adverse Event Version 2.1 (July 2017) was used for assigning toxicity grades (0 to 4) to laboratory results for analysis.
The denominator for percentage was the number of patients in the Compassionate Use Analysis Set with at least 1 postbaseline value for the test under evaluation
Patients were counted once for the maximum postbaseline severity for each laboratory test under evaluation.
Source: Adhoc Table 10585.8.1.4

Figure 25 IN-US-540-5755: Median (Q1, Q3) Change From Baseline in Serum Creatinine Through Day 10 by Baseline Oxygen Support Status – All Patients (Compassionate Use Analysis Set)



Baseline Invasive (n=):	93	76	78	77	71	77	70	63	65	57
Baseline Not Invasive (n=):	51	34	36	35	30	31	26	24	26	18

BL = baseline; eCRF = electronic case report form; PDT = Pacific Daylight Time; Q1 = first quartile; Q3 = third quartile; RDV = remdesivir (GS-5734™)
Compassionate Use Analysis Set included all patients who received the first dose of RDV on or prior to 14 March 2020, per data entered in eCRFs as of 27 March 2020 10:00 AM PDT.
Reference line represents no change from baseline (ie, y = 0).
Source: Adhoc Figure 10585.9.4

Safety in special populations

No information about safety in special populations has been provided in the course of this procedure. No studies in patients with renal or hepatic impairment were investigated. See also PK assessment.

Immunological events

No information about immunological events reported in clinical trials has been provided in the course of this procedure.

Safety related to drug-drug interactions and other interactions

No information about safety related to drug-drug interactions has been provided in the course of this procedure.

Adverse events of special interest

Hepatic safety

With once-daily dosing of RDV 150 mg for 14 days (a higher dose than used in participants with COVID-19), transient Grade 1 or 2 elevations in ALT and transient Grade 1 elevations in AST were observed in 75% of healthy participants (Study GS-US-399-1954). In some participants, ALT and AST elevations were associated with transient Grade 1 increased prothrombin time; however, there was no other evidence of hepatic effects.

The incidence of hepatic AEs was similar across all treatment groups in Study GS-US-540-5774.

One participant in the RDV 10-day group had an SAE of ALT increased, that was not considered related to study treatment. Six participants in the RDV 10-day group and 1 participant in the RDV 5-day group discontinued study drug due to AEs of liver enzyme elevation.

Table 49 GS-US-540-5774: Liver-related Adverse Events by Treatment Group (Safety Analysis Set)

	RDV for 5 Days (N = 191)	**RDV for 10 Days (N = 193)**	**SOC (N = 200)**
Alanine aminotransferase increased	8 (4.2%)	6 (3.1%)	5 (2.5%)
Aspartate aminotransferase increased	5 (2.6%)	5 (2.6%)	5 (2.5%)
Hypertransaminasaemia	3 (1.6%)	6 (3.1%)	3 (1.5%)
Transaminases increased	3 (1.6%)	4 (2.1%)	0
Cholestasis	1 (0.5%)	1 (0.5%)	1 (0.5%)
Blood bilirubin increased	1 (0.5%)	1 (0.5%)	0
Liver function test increased	1 (0.5%)	0	1 (0.5%)
Blood alkaline phosphatase increased	0	1 (0.5%)	0
Gamma-glutamyltransferase increased	0	1 (0.5%)	0

The incidence of liver-related AEs was similar between RDV-treated participants and placebo-treated participants in Study CO-US-540-5758 (Wang et al, 2020).

Renal safety

The kidney was identified as a target organ of toxicity for RDV in nonclinical studies.

Notably, acute kidney injury has been commonly observed among patients with COVID-19 requiring hospitalization.

The incidence of Grade 3 or 4 renal related non serious AEs was similar between the RDV and placebo groups. The same applies for the incidence renal-related SAE: acute kidney injury: RDV: 0.7% (4 participants); placebo 1.3% (7 participants); glomerular filtration rate decreased: RDV: 0.6% (3 participants); placebo 0.4% (2 participants).

In the GS-US-540-5773, the incidence of Grade 3 or 4 laboratory abnormalities in serum creatinine and CrCl was higher in the RDV 10-day group compared to in the RDV 5-day group. In an exploratory analysis, the difference in incidence between the groups was already evident at Day 5 of the study, when both groups had received the same duration of treatment.

In Study GS-US-540-5774, the incidence of renal-related AEs was low and similar across all treatment groups. There were no renal-related SAEs in the RDV 5-day or 10-day groups. One participant in the SOC group had an SAE of acute kidney injury.

In Study CO-US-540-5758, the only renal-related AE reported in ≥ 2% of participants in a treatment group was increased blood urea nitrogen (6% of participants in both the RDV and placebo groups). There was 1 SAE of acute kidney injury in the RDV group (not Grade 3 or 4) and no renal SAEs in the placebo group. One participant discontinued drug due to Grade 3 or 4 acute kidney injury in the RDV group.

Discontinuation due to adverse events

Clinical studies in COVID-19

CO-US-540-5776

Thirty-six patients had RDV treatment discontinued before day 10 because of an AE or a SAE other than death.

GS-US-540-5773

The proportion of participants who discontinued RDV due to AEs was 4.5% (9 participants) in the RDV 5-day group and 10.2% (20 participants) in the RDV 10-day group, with 7.1% (14 participants) in the RDV 10-day group discontinuing by Day 5; the difference between treatment groups was not statistically significant once differences in baseline clinical status were controlled for. The AEs leading to discontinuation of study drug that were reported in > 1 participant overall are presented by treatment group in the table below. Additional AEs leading to discontinuation of study drug were reported in 1 participant each and included thrombocytopenia, pneumonia, blood creatinine increased, and respiratory failure in the RDV 5 day group, and anemia, injection site erythema, rash, septic shock, AST increased, glomerular filtration rate decreased, renal failure, acute respiratory failure, and respiratory disorder in the RDV 10-day group.

Table 50 GS-US-540-5773: Adverse Events Leading to Discontinuation Reported in > 1 Participant Overall by Treatment Group (Safety Analysis Set)

	RDV for 5 Days (N = 200)	**RDV for 10 Days (N = 197)**	**Total (N = 397)**
Acute kidney injury	0	5 (2.5%)	5 (1.3%)
Transaminases increased	3 (1.5%)	1 (0.5%)	4 (1.0%)
Alanine aminotransferase increased	0	2 (1.0%)	2 (0.5%)
Hypertransaminasaemia	0	2 (1.0%)	2 (0.5%)

Hepatic enzyme increased	1 (0.5%)	1 (0.5%)	2 (0.5%)
Liver function test increased	1 (0.5%)	1 (0.5%)	2 (0.5%)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; RDV = remdesivir (GS-5734™)
Adverse events were coded using MedDRA 22.1.
Preferred terms are presented by descending order of the total frequencies.
Multiple AEs were counted only once per participant per preferred term.

Source: GS-US-540-5773 Part A Interim Analysis Table 15.11.5.1

GS-US-540-5774

The proportion of participants who discontinued study drug due to AEs was 2.1% in the RDV 5-days group, and 3.6% in the RDV 10-days group (most commonly due to liver enzyme elevation) (see table below).

Table 51 GS-US-540-5774: Adverse Events Leading to Study Drug Discontinuation by Treatment Group (Safety Analysis Set)

	RDV for 5 Days (N = 191)	**RDV for 10 Days (N = 193)**
Any AE leading to discontinuation of study drug	4 (2.1%)	7 (3.6%)
Alanine aminotransferase increased	1 (0.5%)	3 (1.6%)
Aspartate aminotransferase increased	0	2 (1.0%)
Blood alkaline phosphatase increased	0	1 (0.5%)
Blood bilirubin increased	0	1 (0.5%)
Heart rate decreased	1 (0.5%)	0
Transaminases increased	0	1 (0.5%)
Rash	2 (1.0%)	0
Hypertransaminasaemia	0	1 (0.5%)
Acute respiratory failure	0	1 (0.5%)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; RDV = remdesivir (GS-5734™)
Adverse events were coded using MedDRA 22.1.
Preferred terms are presented by descending order of the total frequencies.
Multiple AEs were counted only once per participant for each system organ class and preferred term, respectively.
Source: GS-US-540-5774 Part A Interim Analysis Table 15.11.5.1

CO-US-540-5758

More patients in the RDV group than the placebo group discontinued study drug because of adverse events or serious adverse events as outlined below.

Table 52 CO-US-540-5758 - Events leading to discontinuation

	Remdesivir group (n=155)		Placebo group (n=78)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4

Events leading to drug discontinuation				
Any	18 (12%)	3 (2%)	4 (5%)	1 (1%)
Respiratory failure or acute respiratory distress syndrome	7 (5%)	1 (1%)	1 (1%)	0
Secondary infection	4 (3%)	0	7 (9%)	2 (3%)
Cardiopulmonary failure	3 (2%)	0	1 (1%)	0
Nausea	1 (1%)	0	0	0
Vomiting	1 (1%)	0	0	0
Ileus	0	0	1 (1%)	0
Increased alanine aminotransferase	2 (1%)	1 (1%)	0	0
Rash	2 (1%)	0	0	0
Poor appetite	1 (1%)	0	0	0
Increased total bilirubin	1 (1%)	0	0	0
Acute kidney injury	1 (1%)	1 (1%)	0	0
Seizure	0	0	1 (1%)	0
Aggravated schizophrenia	0	0	1 (1%)	1 (1%)
Aggravated depression	0	0	1 (1%)	1 (1%)

Source: Wang et at, Lancet 2020

Clinical studies in Ebola

No information is available.

PK studies

No information is available.

Single-patient compassionate use

Overall, 13 patients (8.0%) discontinued RDV due to AEs. Most of these patients discontinued due to AEs associated with renal dysfunction (4 patients) or elevated liver function tests (5 patients; the sponsor notes that for one patient, the AEs leading to discontinuation of RDV were initially reported as hepatitis and worsening hepatitis, which the requesting physician clarified to be only elevated transaminases without any clinical demonstration of hepatitis).

Two patients discontinued due to multiple organ failure, 1 patient due to systolic dysfunction, and 1 patient due to respiratory distress.

The following AEs were also reported as leading to discontinuation of RDV: maculopapular rash in a patient with transaminase elevations; rash in a patient with elevated transaminases (initially reported as hepatitis and worsening hepatitis); and hypotension in a patient with creatinine renal clearance abnormal and renal failure.

A C-QT model was developed based on the data from study GS-US-399-1954, including RDV and the two metabolites GS-441524 and GS-704277. In general, model development was conducted according to guidelines. While there is no indication of a QT-prolonging potential at therapeutic concentrations, a limitation is the lack of information on the impact of supratherapeutic concentrations. Therefore, a potential risk of QT-prolongation cannot be completely excluded.

Post marketing experience

N/A

2.6.1. Discussion on clinical safety

The safety database for RDV is relatively large and satisfies ICH-E1 requirements. Overall, 1,467 patients have received RDV for up to ten days (the maximal proposed duration) within randomised clinical trials in COVID-19. A further 163 patients have been reported from the compassionate use program. No integrated summary of safety, however, has been presented, nor are there available CSR's from any of the randomised controlled trials that are pivotal or supportive to the application. Therefore, in this respect, safety data are deemed non-comprehensive. Furthermore, the understanding of patient factors such as co-morbidities, drug-drug interactions or disease severity, that may impact the tolerability of RDV, is incomplete.

Overall, RDV seems well tolerated, with less than 10% of patients discontinuing due to AE's in the studies where information is available.

The assessment of the available data from individual Phase 2/3 studies investigating COVID-19 came to the following observations:

CO-US-540-5776:

The overall rate of AEs, SAEs and discontinuation rate due to AEs was comparable between RDV and placebo group. Complete information about all AEs recorded is not available and needs to be presented with the study report at the latest. Compared to placebo group incidences of AEs after treatment with RDV were only slightly higher for PTs hyperglycaemia/blood glucose increased (4.1 vs. 3.3%), blood creatinine increased (1.5 vs. 0.8%), prothrombin time prolonged (1.5 vs. 0.8%), and hypertension (2.0 vs. 0.8%). Regards to SAEs only 4 events (2 out of 114 SAEs in the RDV group and 2 out of 141 SAEs in the placebo group) were judged by the site investigators to be related to RDV or placebo which is a very low rate. Furthermore, no deaths were considered to be related to treatment with RDV.

The analysis of safety from this study is not complete, due to the limitations of available information.

GS-US-540-5773:

The overall rate and severity of AEs tended to be lower in the treatment group who received RDV for 5 days compared to the 10 days RDV group. Nausea, acute respiratory failure, ALT increased and constipation were the most frequently reported PTs. The rate of most reported PTs was comparable between 5 days RDV group and 10 days RDV group (e.g. nausea, constipation, AST increased, hypokalemia). However, for single PTs the rate of AEs tended to be lower in the 5 days RDV group (e.g. acute respiratory failure, acute kidney injury).

The rate of study drug-related AEs (5 days RDV 17%, 10 days RDV 19%) was comparable between treatment groups. According to the provided interim report the most frequently reported study drug related AEs were nausea (5-days group 4.5 % vs. 10-days group 2.5%), ALT and AST increased (5-days group 4.5 % vs. 10-days group 11.2%), constipation (5-days group 1.5 % vs. 10-days group 1.5%), and vomiting (5-days group 2 % vs. 10-days group 0%). Other ADRs were single cases or cases reported twice.

The rate of deaths was slightly higher in the RDV 10-days group (25 [12.7%]) compared to the RDV 5-days group (19 [9.5%]).

The occurrence of SAEs tended to be lower in the 5-days RDV group. The most frequently reported SAE were acute respiratory failure (5 days group 5%, 10-days group 9.1%), respiratory failure (5 days group 2.5%, 10-days group 5.1%), respiratory distress (5 days group 1.5%, 10-days group 2.0%), and septic shock (5 days group 1%, 10-days group 2.5%).

The rate of study-drug related SAEs (5-days RDV group 3 cases of transaminases increased [1.5%], 10-days group RDV 4 cases related to hepatic enzyme increased [2%]) was comparable between treatment groups.

More patients in the 10-days RDV group discontinued treatment due to AEs. According to the Applicant this difference between treatment groups was not statistically significant once differences in baseline clinical status were controlled for.

Overall, the higher incidence of AEs in the 10-day arm of the 5773 study is noted; however, the difference in AE's here is clearly apparent already in the first 5 days where the assigned treatment is similar. Therefore, this is largely driven by baseline differences in disease severity. The findings from the 5773 study are not replicated in the 5774 study, which also compared these durations of treatment.

GS-US-540-5774:

The rate of AEs was 50.8% in the RDV 5-days group, 54.9% in the RDV 10-days group and 45.0% in the SOC group.

Nausea, diarrhoea, hypokalaemiae, headache, constipation and ALT increased were the most commonly reported AEs. The rates of most AEs were comparable between treatment groups. Hypokalaemia was more frequently reported in RDV 10-days group (6.7%) compared to RDV 5-days group (4.7%). Constipation (5-days group 4.2%, 10-days group 2.6%) and rash (5-days group 3.7%, 10-days group 2.1%) were more commonly registered in the 5-days group. When comparing to the SOC group the following PTs were more frequently reported in the RDV groups: nausea, hypokalaemia, headache, hypotension and transaminase increased.

Study drug-related AEs occurred in a higher frequency in RDV 5-days group (18.8%) compared to RDV 10-days group (12.4%). There was no placebo in this open-label study

According to the provided interim report the most frequently reported study drug related AEs were nausea (5-days group 6.8% vs. 10-days group 3.6%), ALT and AST increased (5-days group 6.3% vs. 10-days group 3.2%), headache (5-days group 2.1 % vs. 10-days group 1.6%), diarrhoea (5-days group 1.6% vs. 10-days group 1.6%), rash (5-days group 2.6 % vs. 10-days group 0.5%) and vomiting (5-days group 0.5 % vs. 10-days group 1.6%). Other ADRs were single cases or cases reported twice. In 6 cases (3.1%) in the 5-days group and 5 cases (2.6%) in the 10-days group ADRs were rated as grade 3 or higher.

The rate of deaths was comparable between RDV 5-days group (1.0%) compared to the RDV 10-days group (1.0%]).

Occurrence of SAEs were comparable between RDV groups (5-days group 4.2% vs. 10 days group 3.6%). The rate of SAEs was higher in the SOC group (9.9%). All SAEs were single cases or appeared twice.

In only one case the SAE was rated as study drug-related (RDV 5-days group: heart rate decreased).

Overall, slightly more patients in the 10-days RDV group discontinued treatment due to AEs (3.6% vs. 2.1%). The reason for discontinuation in most cases was liver enzyme elevation.

CO-US-540-5758:

AEs presented by the Applicant (based on publication by Wang et al. 2020) were in general comparable between RDV and placebo group. Only rash (7% vs. 3%) and thrombocytopenia (10% vs. 6%) were reported more frequently in the RDV group. SAEs were less reported in the RDV group compared to the placebo group. According to the publication, all deaths during the observation period were judged by the site investigators to be unrelated to the intervention.

Regards to laboratory findings, overall, changes in ALT/AST, total bilirubin, haemoglobin, platelets, creatinine and hyperglycemia were reported after treatment with RDV.

Overall, RDV seems to be well tolerated in clinical studies. However, a completed safety assessment of RDV is not currently possible based on data available.

Furthermore, the warning related to hypersensitivity reactions has been also added in line with FDA labelling and the respective cases discussed.

Full clinical study reports and an integrated summary of safety should be submitted as soon as they are available. This is recorded as a specific obligation that the applicant must fulfil,

Additional safety data needed in the context of a conditional

In the framework of the conditional marketing authorisation, to complete data and analysis on safety, the applicant should fulfil post-approval the specific obligations (SOs) described below in the conclusion.

2.6.2. Conclusions on the clinical safety

Available data on RDV safety are non-comprehensive, due to the incompleteness of data presentation. Available data, however, indicates that RDV is well tolerated. Apart from a likely possibility of causing transaminitis, no signature toxicity has been seen. Regards to hypersensitivity reactions a warning was added.

Section 4.8 of the SmPC will be updated after submitting CSRs and Module 2.7.4 with complete information about adverse reactions reported during clinical studies.

An updated analysis of safety will be delivered as a specific obligation in the context of a CMA.

The CHMP considers the following measures necessary to address the missing safety data in the context of a CMA:

- In order to confirm the efficacy and safety of remdesivir, the applicant should submit the final clinical study report (CSR) of Studies: CO-US-540-5776 (NIAID-ACTT1), GS-US-540-5774 and GS-US-540-5774 (see description in conclusion on clinical efficacy)
- In order to confirm the safety profile of remdesivir, the applicant should submit in Module 2.7.4 an analysis of all available safety data from clinical trials CO-US-540-5776, GS-US-540-5773, GS-US-540-5774 and CO-US-540-5758 when completed, including case narratives, detailed information about adverse reaction and exposure data as well as an analysis of occurrence and aggravation of AEs, SAEs and ADRs associated with increasing exposure.

2.7. Risk Management Plan

Safety concerns

The applicant submitted for evaluation an RMP version 1.0 dated 24 June 2020, with the following summary of safety concerns:

Important Identified Risks	Hypersensitivity including Infusion-Related Reaction
Important Potential Risks	Hepatotoxicity
	Nephrotoxicity
Missing Information	Safety in patients with hepatic impairment

	Safety in patients with severe renal impairment
	Safety in pregnant and lactating women

A certain degree of hepatic toxicity is already labelled as a transaminase increase in SmPC and severe liver damage cannot be excluded due to the currently low quality of safety data provided: currently no case narratives are available, and no adverse drug reactions analysis is available from the NIAID study. Therefore, there is currently significant uncertainty with regard the level and frequency of severe hepatotoxicity potentially caused by remdesivir in clinical practice. Consequently, hepatotoxicity has been included as an important potential risk in the RMP, together with measures to further assess and minimize this risk.

As non-clinical data as well as case-reports from the compassionate use program showed signs of nephrotoxicity, and SBECD may also contribute to renal toxicity, this risk was included as an important potential risk in the RMP, together with measures to further evaluate and minimise it.

Cases of hypersensitivity including infusion-related reactions following administration of RDV have been reported. Signs and symptoms ranged from throat itching to significant hypotension. Therefore, it was considered that "Hypersensitivity including infusion-related reactions" is warranted to be included in the RMP as an important identified risk. The potentially higher nephrotoxicity of the 'concentrate for injection solutions' due to the higher concentration of Betadex will be addressed within the important potential risk of "nephrotoxicity" prior to marketing the concentrate for solution.

The inclusion of "Safety in patients with hepatic impairment" and "Safety in patients with severe renal impairment" as missing information and the proposals how to further evaluate these risks is supported.

In addition, the inclusion of "Safety in pregnant and lactating women" as missing information is supported. The applicant will further evaluate this missing information within category 3 study IN-US-540-5755 as the patient compassionate use program allows pregnant women to request treatment with RDV.

Having considered the data in the safety specification the CHMP considers the list of safety concerns appropriate.

Pharmacovigilance plan

Routine pharmacovigilance measures include:

- The use of *Postmarketing pregnancy report forms* and *Postmarketing pregnancy outcome report forms*. The *Postmarketing pregnancy report form* will be updated by the MAH to clearly indicate a request for the contact details of the healthcare professional following the pregnant woman (e.g. obstetrician/gynaecologist).
- Monthly summary safety reports submitted to EMA, including spontaneously reported data and data from compassionate use and expanded access programs, for the duration of the COVID-19 pandemic.

Additional pharmacovigilance activities:

Activity (Status)	Summary of Objectives	Safety Concerns Addressed	Milestones	Due dates
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				
Study GS-US-540-5773	To evaluate the safety of RDV including in	Hypersensitivity including Infusion-Related	Submission of clinical study report (Part A,	31 December 2020

Activity (Status)	Summary of Objectives	Safety Concerns Addressed	Milestones	Due dates
A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir in Participants with Severe COVID-19 (Ongoing)	patients with renal impairment.	Reaction Safety in patients with severe renal impairment	Day 28 analysis)	
Study GS-US-540-5774 A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734) in Participants with Moderate COVID-19 Compared to Standard of Care Treatment (Ongoing)	To provide information on the safety of RDV compared to standard of care in patients with COVID-19.	Hypersensitivity including Infusion-Related Reaction Hepatotoxicity Nephrotoxicity Safety in patients with hepatic impairment Safety in patients with severe renal impairment	Submission of clinical study report (Part A Day 11)	31 December 2020
Study CO-US-540-5776 (ACTT-1): A Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Adults (Ongoing)	To provide information on the safety of RDV compared to placebo in patients with COVID-19.	Infusion-related reaction Hepatotoxicity Nephrotoxicity Safety in patients with hepatic impairment Safety in patients with severe renal impairment	Submission of published manuscript with final D28 mortality Submission of the final clinical study report	31 August 2020 31 December 2020
Category 3 - Required additional pharmacovigilance activities				
Remdesivir pregnancy safety report	To provide information on pregnant women and birth outcomes with the use of RDV during pregnancy from the compassionate use program (IN-US-540-5755) and expanded access program (GS-US-540-5821).	Safety in pregnancy	Submission of report	Yearly, within annual renewal
Phase 1 study in subjects with hepatic impairment (Planned)	To evaluate the pharmacokinetics of RDV and its metabolite(s) in subjects with hepatic impairment	Safety in patients with hepatic impairment	Submission of study report	30 November 2021

Activity (Status)	Summary of Objectives	Safety Concerns Addressed	Milestones	Due dates
Phase 1 study in subjects with renal impairment and subjects with end-stage renal disease on dialysis (Planned)	To evaluate the pharmacokinetics of RDV and its metabolite(s) in subjects with severe renal impairment and subjects with end-stage renal disease on dialysis	Safety in patients with severe renal impairment	Submission of study report	30 September 2021

Having considered the data submitted, the PRAC and CHMP are of the opinion that the proposed post-authorisation pharmacovigilance plan is sufficient to identify and characterise the risks of the product.

The PRAC and CHMP also consider that routine pharmacovigilance activities are sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Safety concern	Routine risk minimization activities
Hypersensitivity including Infusion-Related Reaction	Routine risk communication: SmPC section 4.4 and 4.8 PL section 2 and 4
Hepatotoxicity	Routine risk minimization activities recommending specific clinical measures to address the risk: SmPC section 4.4 includes recommendations for hepatic laboratory testing. PL section 2
Nephrotoxicity	Routine risk minimization activities recommending specific clinical measures to address the risk: SmPC section 4.4 includes recommendations for monitoring renal function. PL section 2 Not marketing the solution for infusion until the specific obligation is fulfilled[1]
Safety in patients with hepatic impairment	Routine risk communication: SmPC section 4.2, 4.4, 4.8 and 5.2 PL section 2
Safety in patients with severe renal impairment	Routine risk communication: SmPC section 4.2, 4.4 and 5.2 PL section 2
Safety in pregnant and lactating women	Routine risk communication: SmPC section 4.6 PL section 2

[1] The applicant has proposed that this formulation is not marketed until there is reassurance on the potential nephrotoxic effect of the betadex sulfobutyl ether sodium (β-cyclodextrin) excipient. A specific obligation is imposed on the concentrate for solution for infusion formulation with a due date in August 2020

The PRAC and CHMP, having considered the data submitted, was of the opinion that the proposed routine risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

Conclusion

The CHMP and PRAC consider that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

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. The PSUR cycle is based on a birth date determined by the compassionate use programme for this product.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation (DLP 01/10/2020).

2.9. New Active Substance

The applicant compared the structure of remdesivir with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers remdesivir to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons: considering the limited amount of time available during the evaluation of this procedure the company will be conducting a user consultation shortly after the marketing authorisation has been issued to fulfil the relevant legal requirement. CHMP recommends conducting and submit the readability testing as soon after authorisation as possible.

2.10.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

The justification of the company was based on the fact that the vial labels used for both remdesivir formulations are too small to accommodate full labelling particulars. Moreover, the full labelling particulars will be included on the carton label which will contain only 1 vial per carton for single use only and which once opened is to be used immediately. Additionally, the medicinal product is not intended to be delivered directly to the patient and is administered to the patient by the healthcare professional who will have the information and knowledge on correct and safe use of the product. On the basis of the above the Group accepted the request to use minimum particulars for the 20ml vial label of both Remdesivir 100mg concentrate for solution for infusion, and Remdesivir 100 mg powder for concentrate for solution for infusion.

2.10.3. Quick Response (QR) code

A request to include a QR code in the labelling and package leaflet for the purpose of providing statutory information in all EU languages has been submitted by the applicant and has been found acceptable.

The following elements have been agreed to be provided through a QR code:

1. A public section which will contain the following public domain information in the local language:

- SmPC

- PL with HCPL attached

- where required the blue box information,

2. A HCP section which will contain the following information in the local language:

- SmPC

- PL with HCPL attached.

2.10.4. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Veklury (remdesivir) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU and it is approved under a conditional marketing authorisation.

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

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

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

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

3.1.2. Available therapies and unmet medical need

Currently, there are no medicinal products for the treatment of COVID-19 approved in the European Union (EU)[2]. Patients with this condition are treated with relevant supportive care, including e.g., oxygen, mechanical ventilation and other life support, as required.

Several immunomodulating therapies such as glucocorticoids, convalescent plasma, and anticytokine therapies, are also currently under investigation in patients with severe disease. In this context, an impact of dexamethasone treatment on mortality in patients with hypoxia has recently been reported. It remains however that there is no medicinal product authorised in the EU for the treatment of COVID-19

3.1.3. Main clinical studies

There are presently (top-line) data from four RCTs to inform on the clinical efficacy and safety of remdesivir (RDV). There are no CSRs for either of these studies.

The four trials include:

- *A Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Adults (CO-US-540-5776)*

[2] A nationally authorised chloroquine product in Poland (Arechin) has the therapeutic indication that includes supportive treatment of SARS-Cov-2 infection. However, such authorisation does not exist in other member states and there is no scientific evidence on the efficacy of this chloroquine that would be comparable to the extent of evidence on remdesivir, as discussed in this report.

This trial is termed "NIAID-ACTT(1)" below. The sponsor is the National Institute of Allergy and Infectious Diseases (NIAID). The assessment of this study rests mainly on the publication by Beigel et al, NEJM, Epub: May 22, 2020.

https://www.nejm.org/doi/full/10.1056/NEJMoa2007764

This study is pivotal to the application.

- *A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Severe COVID-19 (GS-US-540-5773)*

  The sponsor is the applicant, Gilead Sciences. The assessment of this study rests mainly on the publication by Goldman et al, NEJM, Epub: May 27, 2020.

  https://www.nejm.org/doi/full/10.1056/NEJMoa2015301

- *A phase 3 randomized study to evaluate the safety and antiviral activity of Remdesivir (GS-5734™) in participants with moderate COVID-19 compared to standard of care treatment (GS-US-540-5774)*

  The sponsor is the applicant, Gilead Sciences. The assessment of this study rests mainly on a document ("part-a-dmc-interim tfls.pdf") submitted by the applicant and a press release.

  https://www.gilead.com/news-and-press/press-room/press-releases/2020/6/gilead-announces-results-from-phase-3-trial-of-remdesivir-in-patients-with-moderate-covid-19

- *A Phase 3 Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Remdesivir in Hospitalized Adult Patients With Severe COVID-19.*

  The sponsor is Capital Medical University, China. The assessment of this study rests on a publication by Wang et al, Lancet, Epub: April 29, 2020.

  https://doi.org/10.1016/S0140-6736(20)31022-9

3.2. Favourable effects

The **pivotal NIAID-ACTT(1) (GS-US 540 5776)** study is a randomised, double-blinded and placebo-controlled study conducted in hospitalised patients with COVID-19, with evidence of lower respiratory tract involvement. Treatment with remdesivir/placebo was for up to 10 days. The primary endpoint was the time to recovery (defined as no longer being hospitalised or being hospitalised but no longer requiring medical care). At the time of the primary analysis, 1063 patients had been randomised. The analysis population included 1059 patients for whom the authors had at least some post-baseline data available (538 in the remdesivir group and 521 in the placebo group).

According to the inferential analysis, the median difference in time to recovery is 4 days favouring the remdesivir group. In the primary endpoint remdesivir was hence superior to placebo in the treatment of hospitalized participants with COVID-19 (HR: 1.32, 95% CI 1.12 to 1.55; p<0.001). This effect is evident regardless of whether the duration of symptoms at treatment initiation was more or less than 10 days.

In the stratum of patients with "severe disease" (with pneumonia and need for supplemental oxygen), representing approximately 90% of patients in the study, the difference in median time to recovery was 12 versus 18 days, The RR was 1.36 (95% CI 1.143-1.1623;,p<0.001).

No difference in time to recovery was seen in the stratum of "mild-moderate disease".

In the overall study population, the Kaplan–Meier estimates of mortality by 14 days were 7.1% (32/538 patients) and 11.9% (54/521 patients) in the remdesivir and placebo groups, respectively showing a hazard ratio for death of 0.70 (95% CI 0,47 to 1.04).

The GS-US-540-5773 study is an ongoing randomised, open-label study comparing 5-day and 10-day remdesivir durations in patients with "severe" COVID-19. The pre-specified primary efficacy analysis was to examine results on a 7-point ordinal scale at Day 14 using a proportional odds model. The Day-14 primary analysis included 397 patients, 200 patients in the 5-day treatment group and 197 patients in the 10-day treatment group.

The reported results of the primary analysis of the proportional odds model at Day 14 shows an estimated odds ratio (adjusted for baseline imbalances) of 0.79 on a scale with values less than 1.00 favouring the 5-day duration, with a 95% confidence interval from 0.61 to 1.04.

The GS-US-540-5774 study is an ongoing randomised, open-label study comparing 5-day remdesivir with SOC and 10-day remdesivir with SOC in patients with "moderate" COVID-19. The study is conducted in two parts. In Part A, eligible participants are randomized in a 1:1:1 ratio to either 5-day and 10-day remdesivir durations or SOC. The pre-specified primary efficacy analysis was to examine results on a 7-point ordinal scale at Day 11 using a proportional odds model. The Day 11 primary analysis included 584 patients, 191 patients in the 5-day treatment group, 193 patients in the 10-day treatment group and 200 patients in the SOC-arm.

Based on the LOCF-analysis treatment with RDV for 5 days resulted in significantly greater improvements in clinical status at Day 11 compared with SOC alone (OR, 1.65; 95% CI 1.09 to 2.48; p = 0.0174). Treatment with RDV for 10 days did not result in significantly greater improvements in clinical status at Day 11 compared with SOC alone (OR, 1.31; 95% CI, 0.88 to 1.95; p = 0.1826).

Study CO-US-540-5758 (reported by Wang et al) was a randomised, double-blinded and placebo-controlled study conducted in Chinese patients with "severe" COVID-19. The study was terminated early due to the epidemiological development and was therefore underpowered (power of 58%) compared to assumptions. At the time of study termination, 237 patients had been randomised.

The primary clinical endpoint was time to clinical improvement. Clinical improvement was defined as a two-point reduction in patients' admission status on a six-point ordinal scale. Treatment with RDV/placebo was for 10 days.

The median time to clinical improvement was 21 days for remdesivir versus 23 days for placebo. The HR (on a scale with values greater than 1.00 favouring remdesivir) was 1.23; p=0.24. Day 28 all-cause mortality rates were similar in the two treatment groups. Mortality rates were 22/158 (13.9%) for the remdesivir group versus 10/78 (12.8%) for the placebo group.

3.3. Uncertainties and limitations about favourable effects

The identified quality issues concerning the active substance and finished product manufacture, the proposed control strategy for the active substance and finished product, and the in-use stability of the powder formulation, to be addressed through fulfilment of specific obligations, pose some uncertainties with regard to the batch to batch consistency between the product batches studied in pharmaceutical and (pre-)clinical development and future commercial batches.

Clinical study reports are presently not available for any of the four RCTs. Hence, the assessment of effects presently lacks the generally required granularity.

The efficacy demonstration rests on the NIAID-ACTT(1)-study. A complete follow-up with analyses of the data is missing for approximately 1/3 of the patients. Therefore, evaluation of the full 28-day all-cause mortality, has not been possible.

Other issues including information on methods for maintenance of blinding, as well as the concomitant use of other agents with putative impact on COVID-19, such as corticosteroids, remains to be fully analysed.

Subgroup data from the NIAID-ACTT(1) study show no apparent beneficial effect of remdesivir in the most severely ill patients, i.e. those on invasive mechanical ventilation or extracorporeal membrane oxygenation (IMV/ECMO) upon start of therapy. For the latter group an effect has neither been seen for the time to recovery (Rate Ratio 0.95) nor for mortality (HR: 1,06 as per data freeze 28th April 2020).

Also, median time to recovery did not differ between remdesivir and placebo for the stratum of patients with mild/moderate disease. Furthermore, presently available data from the study -5774 do not suffice to draw conclusions on efficacy in these disease stages. A lack of blinding and an endpoint allowing considerable room for subjectivity, paired with uncertainties in the conduct of the primary analysis, render the results of this study not robust: The level of pre-specification of the SAP in the study -5774 is unclear (e.g., the Bonferroni alpha split between the RDV 5d vs SOC and RDV 10d vs SOC is mentioned in the SAP produced after database lock in this open label study, but not in the protocol). Even if the analysis in the SAP is accepted, the finding of a statistically significant difference of 5-day RDV vs SOC does not appear robust, as only the LOCF-imputed, but not the OC-analysis showed a statistically significant difference of 5 days remdesivir versus standard of care. Therefore, it is unclear whether this study is formally positive on its primary endpoint.

The submitted data provide no clear picture on the duration of therapy. Studies -5773 and 5774 failed to show an advantage of the longer treatment. They may even be indicative of detrimental effect of longer use. It has to be pointed out, however, that less than 50% of the patients in each of these studies received a full 10-day treatment course. And while the pivotal NIAID ACTT(1) study was designed to prove efficacy of a 10-day treatment course, factually only one third of the patients received a full treatment course. Based on these data rather a 5-day treatment course appears generally indicated. Another uncertainty is the present lack of in-vivo proof of concept of anti SARS-CoV-2 activity.

3.4. Unfavourable effects

The safety database for RDV is relatively large and satisfies ICH-E1 requirements. 1467 patients have received RDV for up to ten days (the maximal proposed duration) within randomised clinical trials in COVID-19. A further 163 patients have been reported from the compassionate use program.

Overall, RDV seems well tolerated, with less than 10% of patients discontinuing due to AE's in the studies where information is available.

In the NIAID-ACTT(1) study the most commonly reported grade 3/4 AE's are anaemia, acute kidney injury and increased transaminases. There is no difference in frequency compared to placebo. The most common serious AE's are respiratory failure and similar terms; such events are more common in the placebo arm.

In Gilead Simple trial GS-US-540-5773 the overall rate and severity of AEs tended to be lower in the treatment group who received RDV for 5 days compared to the 10 days RDV group; however, the difference in AE's here is clearly apparent already in the first 5 days where the assigned treatment is similar. Therefore, this is impacted by baseline differences in disease severity.

Nausea, acute respiratory failure, ALT increased and constipation were the most reported PTs. The rate of most reported PTs was comparable between 5 days RDV group and 10 days RDV group (e.g. nausea, constipation, AST increased, hypokalaemia). The rate of study drug-related AEs (5 days RDV 17%, 10 days RDV 19%) and the rate of study-drug related SAEs (5 days RDV 2%, 10 days RDV 2%) were comparable between treatment groups. According to the provided interim report the most frequently reported study drug related AEs were nausea (5-days group 4.5 % vs. 10-days group 2.5%), ALT and AST increased (5-days group 4.5 % vs. 10-days group 11.2%), constipation (5-days group 1.5 % vs. 10-days group 1.5%), and vomiting (5-days group 2 % vs. 10-days group 0%). The rate of study-drug related SAEs (5-days RDV group

3 cases of transaminases increased [1.5%], 10-days group RDV 4 cases related to hepatic enzyme increased [2%]) was comparable between treatment groups.

In Gilead Moderate Simple trial GS-US-540-5774 nausea, diarrhoea, hypokalaemia, headache, constipation and ALT increased were the most commonly reported AEs. The rates of most AEs were comparable between treatment groups. Hypokalaemia was more frequently reported in RDV 10-days group (6.7%) compared to RDV 5-days group (4.7%). Constipation (5-days group 4.2%, 10-days group 2.6%) and rash (5-days group 3.7%, 10-days group 2.1%) were more commonly registered in the 5-days group. When comparing to the SOC group the following PTs were more frequently reported in the RDV groups: nausea, hypokalaemia, headache, hypotension and transaminase increased. The occurrence of SAEs was comparable between RDV groups.

Study drug-related AEs occurred in a higher frequency in RDV 5-days group (18.8%) compared to RDV 10-days group (12.4%). According to the provided interim report the most frequently reported study drug related AEs were nausea (5-days group 6.8% vs. 10-days group 3.6%), ALT and AST increased (5-days group 6.3% vs. 10-days group 3.2%), headache (5-days group 2.1 % vs. 10-days group 1.6%), diarrhoea (5-days group 1.6% vs. 10-days group 1.6%), rash (5-days group 2.6 % vs. 10-days group 0.5%) and vomiting (5-days group 0.5 % vs. 10-days group 1.6%). In only one case the SAE was rated as study drug-related (RDV 5-days group: heart rate decreased).

In China trial CO-US-540-5758 AEs were in general comparable between RDV and placebo group. Only rash (7% vs. 3%) and thrombocytopenia (10% vs. 6%) were reported more frequently in the RDV group. SAEs were less reported in the RDV group compared to the placebo group. According to the publication, all deaths during the observation period were judged by the site investigators to be unrelated to the intervention.

Regards to laboratory findings, overall, changes in ALT/AST, total bilirubin, haemoglobin, platelets, creatinine and hyperglycaemia were reported after treatment with RDV. However, due to missing causality assessment, missing information about medical history and concomitant medication as well as partially missing placebo group a profound assessment is not possible.

In healthy volunteers, transaminitis was seen at multiple daily doses of 150 mg prompting a partial clinical hold by the FDA. This led to strict inclusion and discontinuation criteria in further clinical trials. Data from the clinical trials appear reassuring in this respect, but the applicant’s proposed monitoring seems relevant. Furthermore, there is a preclinical signal on renal tubular toxicity, which is not clearly noticeable in available clinical data.

The warning in section 4.4 of the SmPC related to hypersensitivity reactions was added. Overall RDV seems adequately tolerated, also in severely ill patients.

3.5. Uncertainties and limitations about unfavourable effects

No integrated summary of safety has been presented, nor are there available CSR from any of the randomised controlled trials that are pivotal or supportive to the application. Therefore, in this respect, safety data are deemed non-comprehensive. Furthermore, the understanding of patient factors such as co-morbidities, drug-drug interactions or disease severity, that may impact the tolerability of RDV, is incomplete.

The findings of more side effects with 10 days of remdesivir versus 5 days in the 5773 study are uncertain since the difference is apparent also in the first five days of treatment when exposure to the drug is similar between arms. Further, notwithstanding the randomisation, patients in the 5-day arm were more severely ill at baseline in the ten-day arm. The findings, such as that of an increased rate of acute kidney injury with longer therapy, is not replicated in the 5774 study. Moreover, there is no increase in severe or serious renal events above placebo in the NIAID-ACTT(1) study.

There is, however, a nonclinical signal on renal tubular toxicity, which is not clearly noticeable in available clinical data. Given the limitations in available clinical safety data reporting, this remains an important potential risk, to be addressed in the RMP and further followed up post marketing.

Due to the lack of a tQT study, or information on systematic ECG monitoring at supratherapeutic doses, the potential risk of QT prolongation is deemed incompletely characterised. Based on in vitro data, the torsadogenic risk should be low; however, the non-clinical safety pharmacology studies are also inconclusive due to low drug exposure. Although there are limitations in the safety data presentation, it is noted that clinical data do not give rise a concern about cardiac safety.

Transaminitis is considered an identified risk, and to be addressed in the product information (Section 4.4 and 4.8). Although there is no signal from the available data of severe hepatotoxicity or DILI, this is still considered an important potential risk, to be addressed in the RMP and further followed up post marketing. In addition, the risk of "Hypersensitivity including infusion related reaction" has been included as important identified risk in the RMP.

Section 4.8 of the SmPC will to be updated after submitting CSRs and Module 2.7.4 with complete information about adverse reactions reported during clinical studies.

The human mass balance study indicates presence of a currently unknown major metabolite M27 in plasma, and it is unknown if this metabolite is adequately covered in the nonclinical safety studies, or what is its interaction potential.

3.6. Effects Table

Effects Table for Remdesivir

Effect	Short Description	Unit	RDV	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Recovery[1]	Day of recovery	Median time [95%CI]	11 days [9-12]	15 days [13-19]	**SoE:** RR: 1.32, (1.12, 1.55), p<0.001; **Unc:** Median TTR **did not differ** between RDV and placebo for the stratum of **patients with mild/moderate disease**. **Unc:** No beneficial effect of RDV in **critically ill patients**, i.e. those on IMV or ECMO upon start of therapy **(TTR: RR 0.95).** **Unc:** Unclear if the actually performed analysis corresponds to the originally planned primary analysis.	(1)
Clinical status[2]	Clinical status on a 7-point ordinal scale at day 15	Odds of improvement	OR:1.50 (1.18, 1.91) p = 0.001		**SoE:** 1.50 (1.18, 1.91), p = 0.001, ((OR); p-value) **Unc:** Patients with missing data were excluded from analysis. **Unc:** P-value and confidence intervals have not been adjusted for multiple comparisons.	(1)
Mortality	Kaplan–Meier estimates of mortality by 14 days	% [95% CI]	11.9% (54/521	7.1% (32/538	**Unc:** HR for death 0.70 (95% CI 0.47 to 1.04). **Unc:** incomplete dataset, **lacking 28-day all-cause mortality** analysis **Unc:** The Kaplan–Meier estimates of mortality by 28 days are not reliable given the large number of patients that did not yet complete day 29 visit. **Unc:** No beneficial effect of RDV in **critically ill patients**, i.e. those on ventilation, high-flow oxygenation, IMV or ECMO upon start of therapy **(HR: 1.12/1.06)**.	(1)

Effect	Short Description	Unit	RDV	Control	Uncertainties/ Strength of evidence	References
Antiviral effect		c/ml	N/A	N/A	**Unc:** Lack of *in vivo* data that demonstrate antiviral effect (POC) **Unc:** No data presented from the NIAID-ACTT1 study **Unc:** Available data from study -5774 and -5857 do not show any apparent antiviral effect of RDV.	(1,2,3,4),
Unfavourable Effects						
Important potential risk	Hepatotoxicity fo RDVNephrotoxicity of RDV and SBECD Hypersensitivity including Infusion-Related Reaction				**SoE:** Hepato and nephrotoxicity**:** overall**,** no difference in frequency compared to placebo **Unc:** Lack of data	(1, 2, 3,4)

Abbreviations: SoE: strength of evidence ,UnC: uncertainties RRR: Recovery Rate Ratio, LD: loading dose, MD maintenance dose, IV: intravenous RDV: Remdesivir, PBO: Placebo, POC: Proof of concept, OR: Odds Ratio; HR: Hazard Ratio, IMV: invasive mechanical ventilation, ECMO: extracorporal membrane oxygenation, TTR: Time to Recovery, SOC: Standard of Care

Notes: (1) Study NIAID-ACTT1 (GS-US 540 5776), (2) Study Simple Severe (GS-US-540-5773), (3) Study Simple Moderate (GS-US-540-5774), (4) China Study (GS-US-540-5857)

[1] Day of recovery is defined as the first day on which the subject satisfies one of the following categories (a) Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care; (b) Not hospitalized, limitation on activities and/or requiring home oxygen; (c)Not hospitalized, no limitations on activities. Day of recovery Recovery is evaluated up until Day 29.

[2] Ordinal scale of clinical status 1. Death; 2. Hospitalized, on invasive mechanical ventilation or ECMO; 3. Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4. Hospitalized, requiring low flow supplemental oxygen; 5. Hospitalized, not requiring supplemental oxygen – requiring ongoing medical care (COVID-19 related or otherwise); 6. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care (other than per protocol RDV administration); 7. Not hospitalized

[3]Time to clinical improvement is defined as a two-point reduction in patients' admission status on a six-point ordinal scale

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

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

The identified quality issues discussed in this report and to be addressed through fulfilment of specific obligations, pose some uncertainties with regard to the batch to batch consistency between the product batches studied in pharmaceutical and (pre-)clinical development and future commercial batches. However, the submitted data indicate that currently manufactured batches are actually of a quality that is appropriate and comparable to that of clinical development batches. Considering the emergency context of this application the above identified quality issues are thus considered to be compatible with the granting of a CMA. However, to ensure that the quality of future batches will also remain appropriate and comparable to that of clinical development batches over the entire life cycle of the medicinal product these issues are expected to be addressed though fulfilment of specific obligations, within the defined due dates.

The efficacy demonstration rests on preliminary data from the NIAID ACTT(1) study. The inferential analysis from this study shows that treatment with remdesivir results in a shorter time to recovery as compared to placebo. This effect is only evident in the stratum of patients with severe disease, where the difference in medians is 12 days for remdesivir versus 18 days for placebo. There was no indication of benefit in the stratum of patients with mild-moderate disease. At the present level of analysis, efficacy in such patients is neither considered to be supported by outcomes of the study -5774. Therefore, the indication is limited to those patients with COVID-19 pneumonia that require supplemental oxygen (patients with hypoxia, or symptoms of respiratory distress).

The adverse effect reported seems generally mild and remdesivir seems well tolerated, also in severely ill patients. Hepatotoxicity and nephrotoxicity were determined as adverse events of special interest (AESIs).

3.7.2. Balance of benefits and risks

Due to its promising effects in animal models of coronavirus disease, the CHMP expressed an opinion according to article 83, regarding the compassionate use of this drug in the context of the COVID-19 pandemic. Initially this was restricted to patients on IMV; however, after the presentation of top line data from the NIAID-ACTT(1) study confirming the efficacy of remdesivir, this opinion was expanded to cover all patients with severe COVID-19.

Article 83 provides an CHMP opinion on compassionate use, the implementation of which is up to the member states, which have different legal provisions with respect to forms of emergency authorisation.

In the present case, the applicant is not the sponsor of the pivotal trial. It has sponsored two of the supplemental trials; results from these trials have emerged during the rolling review of remdesivir, but no CSRs are presently available for any of the key studies. Therefore, the level of granularity as well as scrutiny of available data is lower than in the standard case.

Recognising the need to ascertain a timely access to treatments in the context of the public health emergency of COVID-19, the CHMP considered that the CMA legislation provides the most appropriate EU regulatory tool to achieve this goal.

Thus, while available data allow for a conclusion on B/R, these are not deemed comprehensive in the sense of usual data requirements for a standard authorisation. In the context of the COVID-19 pandemic, the non-comprehensiveness of clinical data here relates to the non-availability of the data at the time of the application, rather than, as in the usual case of a CMA, limitations in the extent of data. These missing data will be submitted once studies are completed. Also, quality data is currently not comprehensive, but this has been found acceptable in the emergency context and will be complemented though fulfilment of specific obligations.

Overall, in the context of a CMA a positive benefit/risk balance of remdesivir is considered adequately shown for patients with COVID-19 with pneumonia requiring supplemental oxygen.

3.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

As comprehensive data on the product are not available, a conditional marketing authorisation is relevant.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a life-threatening disease. In addition, the COVID-19 pandemic constitutes an emergency situation. It is a public health threat duly recognised by the World Health Organisation as well as the EU.

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed.
- It is likely that the applicant will be able to provide comprehensive data. The CHMP has identified specific obligations concerning pharmaceutical (quality), efficacy and safety data, which are expected to provide comprehensive data for this product. No concerns have been identified with the ability to complete these specific obligations, as the applicant has indicated that they consider respective due dates as feasible. In addition, the clinical studies from which clinical data has been requested are already ongoing.
- Unmet medical needs will be addressed, as currently there are no safe and effective medicinal products for the treatment of COVID-19 that would be approved in the European Union.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. COVID-19 inarguably represents the most significant public health emergency of our time. In this context it is considered that the benefits to public health of the immediate availability of RDV outweigh the risks inherent in the fact that additional quality, efficacy and safety data are still required.

3.8. Conclusions

The overall benefit/risk balance for remdesivir is positive for the following indication:

Veklury is indicated for the treatment of coronavirus disease 2019 (COVID 19) in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen (see section 5.1).

As available data are non-comprehensive, granting of a conditional marketing authorisation is relevant, and in line with provisions of Article 14-a of Regulation (EC) No 726/2004 it is supported.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Veklury is favourable in the following indication:

Veklury is indicated for the treatment of coronavirus disease 2019 (COVID 19) in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen (see section 5.1).

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

In view of the declared Public Health Emergency of International Concern and in order to ensure early supply, this medicinal product is subject to a number of quality related specific obligations. Implementation of these outstanding quality changes, including the necessary variations to the terms of the marketing authorisation, has to be completed by the 30 June 2021 at the latest, in line with the agreed plan for the update of the Quality dossier for this product. A progress report has to be included in the annual renewal application.

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription. (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation (DLP 01/10/2020).

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

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

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

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	**Due date**
In order to improve the impurity control strategy, lower the risk of contamination and assure comprehensive control throughout the lifecycle of the product, the MAH should, as agreed, re-define the starting materials of active substance synthesis, update all dossier documentation accordingly and implement the re-defined starting materials. The corresponding variation application must be submitted no later than by August 2020.	June 2021
In order to ensure batch to batch consistency the MAH should expand description of the active substance synthesis with more details regarding yields, process conditions, unambiguously specifying when each process stage is applicable, materials used and their specifications, and defining the batch size. Further, process parameter ranges should be further justified or tightened.	August 2020
In order to further substantiate the control strategy for the active substance the MAH should further elaborate the impurities discussion with regard to the formation of potential impurities in the current and redefined starting materials, the representativeness of the active substance used in the toxicological programme versus the commercial product, the contamination of the active substance by elemental impurities, and the proposed justification regarding the suitability and adequateness of the proposed controls.	August 2020
In order to improve the control strategy for the active substance the MAH should revise the active substance specification by including the parameter "microbial limits", by revising the proposed limits for assay, impurities, residual solvents, and water in line with batch data and/ or relevant guidelines and Ph. Eur. as applicable, and confirm that the analytical method can control unspecified impurities GS-832698 and GS-832699.	August 2020

In order to ensure batch to batch consistency of the Powder for Concentrate for Solution for Infusion the MAH should expand the description of the manufacture of the finished product with more details, by providing the actual process validation report, by justifying the level of betadex sulfobutyl ether sodium, by clearly defining the batch size in line with process validation studies and per manufacturing site, by defining process parameters and acceptance criteria and by introducing additional in-process controls.	August 2020
In order to confirm the appropriateness of aseptic processing of sterile bulk product for the Powder for Concentrate for Solution for Infusion the MAH should submit the media fill results.	August 2020
In order to improve the control strategy for the Powder for Concentrate for Solution for Infusion product the MAH should revise the excipient and finished product specifications by revising the limits for assay, impurities and water content in line with batch and stability data, relevant Ph.Eur. requirements and guidelines, as applicable.	August 2020
In order to further substantiate the recommendations for reconstitution and storage of the Powder for Concentrate for Solution for Infusion product the MAH should submit in-use stability data for reconstituted Powder for Concentrate for Solution for Infusion diluted to 100ml with 0.9% saline solution. Moreover, a justification for the different dilution regimens for Powder for Concentrate for Solution for Infusion (dilute to 100ml or 250ml) and Concentrate for Solution for Infusion (dilute to 250ml) should be provided. The potential for handling errors should be considered.	August 2020
In order to ensure batch to batch consistency of the Concentrate for Solution for Infusion the MAH should expand the description of the manufacture of the finished product with more details by providing the actual process validation report, by justifying the level of betadex sulfobutyl ether sodium, by clearly defining the batch size in line with process validation studies and per manufacturing site, by defining process parameters and acceptance criteria, by introducing additional in-process controls and by providing additional batch data.	August 2020
In order to confirm the appropriateness of aseptic processing of sterile bulk product for Concentrate for Solution for Infusion the MAH should submit the media fill results.	August 2020
In order to improve the control strategy for the Concentrate for Solution for Infusion product the MAH should revise the excipient and finished product specifications by revising the limits for assay, impurities and endotoxins in line with batch and stability data, relevant Ph. Eur. requirements and guidelines, as applicable.	August 2020

In order to confirm the efficacy and safety of remdesivir, the MAH should submit the final clinical study report (CSR) of Study CO-US-540-5776 (NIAID-ACTT1).	December 2020
In order to confirm the efficacy and safety of remdesivir in patients on IMV/ECMO, the MAH should submit the published final D28 mortality data by ordinal scale categories of Study CO-US-540-5776 (NIAID-ACTT1). In addition, the MAH should discuss potential imbalance in the use of corticosteroids and effect modification in Study CO-US-540-5776.	August 2020
In order to confirm the efficacy and safety of remdesivir, the MAH should submit the final CSR for Part A (Day 28) of Study GS-US-540-5773.	December 2020
In order to confirm the efficacy and safety of remdesivir, the MAH should submit the final CSR for Part A (Day 28) of Study GS-US-540-5774.	December 2020
In order to confirm the safety profile of remdesivir, the MAH should submit in Module 2.7.4 an analysis of all available safety data from clinical trials CO-US-540-5776, GS-US-540-5773, GS-US-540-5774 and CO-US-540-5758 when completed, including case narratives, detailed information about adverse reaction and exposure data as well as an analysis of occurrence and aggravation of AEs, SAEs and ADRs are associated with increasing exposure.	December 2020

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that remdesivir is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union

Appendix

1. Descriptions of the issues related to the different studies included as Specific Obligations that should be addressed by the applicant

Quality	
Active substance	
1. The applicant commits to redefine the starting materials (the corresponding variation to be submitted by August 2020, implementation to be completed by June 2021). The additional steps in the synthesis to be performed under GMP should improve the impurity control strategy, lower the risk of contamination and confirm appropriate control throughout the lifecycle of the medicinal product. In order to comply with the SOB the applicant is requested to consider the following: All dossier documentation should be updated accordingly. Information of the new starting materials, including their synthesis should be provided in dossier section S.2.3. It is outlined that additional starting material suppliers will be added post approval. Please note that not the supplier, but the manufacturer of the starting material should be included in the dossier. From the statement of the applicant, it cannot be concluded that the manufacturing synthesis of the starting materials remains unchanged. If the proposed additional starting material manufacturers use a substantially different route of synthesis or manufacturing conditions, with the short active substance synthesis currently used, this could change important quality characteristics of the active substance, such as qualitative and/or quantitative impurity profile or physico-chemical properties. Please note that additional starting material manufacturers would only be acceptable if the impurity profile of the active substance remains similar to that of active substance manufactured from material of the proposed starting material manufacturers. Adequate documentation in accordance with applicable regulatory requirements have to be provided in the course of a variation procedure. There is generally a high risk of formation and carry-over of impurities and contaminants potentially not covered by the proposed control strategy because of the sophisticated proposed starting material synthesis, which is not performed	In order to re-designate of the starting materials Due date: June 2021

under GMP. Additionally, it has to be noted in this context that it is also not clear whether there are purification steps upstream of the proposed starting materials that are relevant for the final active substance impurity profile. In line with ICH Q11 Q&A #5.11 addition of purification steps prior to a proposed starting material in order to avoid defining an earlier, upstream compound as the starting material would not be considered appropriate.	
2. The active substance synthesis should be described in more detail in order to ensure batch to batch consistency and thereby confirm the quality and safety of the medicinal product: a. Yields for each stage of remdesivir synthetic step are missing and should be outlined. b. Information on agitation conditions is missing and should be given. c. The description of the manufacturing process includes the expression "optionally" at several stages. The manufacturing process description should reflect the production of the process validation batches and the manufacturing of future batches. Unless the optional procedures described in the process description presented in S.2.2 are covered in the process validation and have shown not to affect active substance quality, they should be removed from the process description. d. The performed concentrations steps and the de-agglomeration step should be described more in detail in the process description. e. Filtration aids may be used for filtration and polish filtration may be used. If filtration aids and polish filtration is used, this should be clearly outlined in the process description and the filtration aids should also be reflected in the section control of materials. f. Relevant amounts of materials, reagents and solvents are laid down in the process description with quite wide ranges. Information on proven acceptable ranges for the preparation of remdesivir is given in S.2.6. For each step and parameter information on lower PAR (proven acceptable range), lower operating range, upper operating range, upper PAR and Gilead Alberta set point is given. Data to these ranges have not been provided	In order to ensure batch to batch consistency Due date: August 2020

and furthermore interactions between parameters have not been studies. Please provide data, which confirm that active substance of adequate quality can be produced in the mentioned ranges. Otherwise, the operating ranges should be tightened to represent normal operating ranges, i.e. common operational variability. g. Re-working procedures is not allowed and should not be included in the dossier. The information concerning rework procedures should be deleted. h. The batch size for remdesivir active substance production should be clearly stated in dossier section S.2.2. i. Adequate specifications for all solvents, recovered solvents (if applicable), reagents and auxiliary materials used in the manufacturing process are missing and should be provided. The specifications should include all quality relevant parameters (e.g. appearance, identity, assay, impurities). The active substance is used for parenteral use. The specification for water used in the last synthesis step should also include tests for microbial purity and endotoxins.	
3. The impurities discussion should be elaborated with more information in order to further substantiate the control strategy of the active substance and thereby confirming the quality and safety of the medicinal product: a. The applicant should discuss potential impurities formed from reagents and solvents used in the manufacture of one of the starting materials. This should include, but not be limited to, a discussion of the potential presence of residual cyanide in the starting material. b. The applicant should explain how a specified impurity is formed in the starting material synthesis. The risk of formation of other esters should also be addressed. c. The applicant should discuss how it is assured that active substance used in the toxicological program, purified with chromatography rather than crystallisation, is representative of the active substance to be used in commercial product. d. The capability of the process to purge a specified solvent to suitable levels should be demonstrated by the	In order to complete impurities discussion Due date: August 2020

applicant. Alternatively, a control of DBU to acceptable levels should be implemented in the process. e. The potential toxicity of two specified elemental impurities and risk of contamination of the active substance with unacceptable levels of the elements should be discussed by the applicant. f. The applicant should discuss how it has been assured that the laboratory experiments performed to demonstrate the purging capacity for impurities and residual solvents of the process are representative of the commercial scale process with regards to e.g. efficiency in extractions, washings and crystallizations. It is acknowledged that removal of impurities is largely dependent on compound properties such as reactivity, solubility, volatility, and ionizability. However, the efficiency of removal could also depend on manufacturing scale and this should be addressed. Further, the number of experiments of which the data rely on should be disclosed. g. The applicant should discuss the formation and control strategy for two identified potential impurities. h. A justification for why no control of three reported expected degradation products is needed in the active substance should be provided.	
4. The active substance specification should be revised in order to improve the control strategy and thereby confirm the quality and safety of the medicinal product: a. The parameter "microbial limits" is considered not necessary by the applicant due to no significant bioburden at batch release and during stability. This argument is not followed as for sterile products the microbial quality of the active substance is an essential quality parameter. In consequence the test for microbial limits should be included in the specification with the option to perform this test as skip test. b. The range for assay should be based on recent batch data rather than on theoretical considerations. Furthermore, total impurities levels should be taken into consideration as the specified range for assay and total impurities should correlate. The limit for "total impurities" should not solely be based on theoretical calculations, but also on recent batch data.	In order to revise active substance specification Due date: August 2020

c. The limits for impurities should not only be based on the maximum tolerable values found during toxicological studies but also on available batch data to ensure a consistently high-quality product. If some limits are above the ICH identification or qualification threshold (0.10 resp. 0.15%) and are toxicologically justified, a higher limit is acceptable in the range of recent batch data. According to this, limits for two specific impurities and are accepted to be higher than ICH threshold, but should be lowered based on recent batch data (primarily to batches of the 5734-BC-series). The approach described by J. Harvey et. al. for setting an acceptable limit for unspecified impurities based on duration of dosing is not accepted in a marketing application. The specification limit for unknown impurities should be adjusted to comply with ICH Q3A and Ph. Eur. 2034 general monograph. Further, the control strategy for all the impurities stated to be controlled as unspecified impurities should be revisited.	
d. The limits for residual solvents should be set with regard to option 1 of ICH guideline Q3C. Option 2 is only relevant, if the option 1 limit is not possible to set due to high solvent load of the active substance. As this is not the case for remdesivir, the proposed limits are not acceptable and should be lowered accordingly.	
e. The values found for residual water are consistently far below the proposed limit at release and at shelf life. This should be reflected in the specification, i.e. the limit should be lowered to more data driven values.	
f. It is stated that impurities GS-832698 and GS-832699 are controlled in the active substance as unspecified impurities. However, the analytical method used has not been validated with regards to the impurities. It should be confirmed that the analytical method used is able to detect GS-832698 and GS-832699 and that the impurities are thereby controlled as unspecified impurities in the active substance.	
g. The limit for unspecified organic volatile impurities should be adjusted to comply with ICH Q3A and Ph. Eur. general monograph 2034.	
Finished Product – Remdesivir Powder for Concentrate for Solution for Infusion	
5. The manufacture of the finished product should be described in more detail in order to ensure batch to	In order to ensure batch to

batch consistency and thereby confirm the quality and safety of the medicinal product: a. The level of betadex sulfobutyl ether sodium used should be justified by taking into account the content of the genotoxic impurity (1,4-butane sultone) in the betadex sulfobutyl ether sodium. b. The applicant states that the batch size may be scaled up or down proportionally based on commercial demand or manufacturing site equipment capacity. This statement is not acceptable and should be deleted from the dossier. Any batch size outside of the range of the finally approved batch sizes should be applied for in the course of a variation procedure. Please note that respective process validation data would be needed since the finished product is manufactured according to a non-standard process (see assessor´s comment on 4.1.2, P.2.3). c. It should be clarified whether or not both manufacturers manufacture each of the stated batch. d. Mixer speed at in one of the two proposed manufacturing sites is not yet defined. Numerical acceptance criteria should be given. e. Conditions of sterilisation of sterilising filters, glass vials and rubber stoppers should be included in the process description. f. Type of material, nominal pore size and number of filters should be stated for non-sterilising and sterilising filters in contact with the finished product or components of the finished product. Moreover, it should be stated whether the used filters (again non-sterilising and sterilising) are intended for single or multiple use. Additionally, filter area should be referenced for sterilising filters. g. Filter integrity test acceptance criteria should be given for sterilising filter. Moreover, filter integrity should not only be tested after, but also prior to sterilisation filtration. h. The maximum time between the start of bulk solution preparation and end of sterile filtration should be stated. i. Additionally, to total aseptic processing time information on the (sterile) bulk holding time before filling and on	batch consistency Due date: August 2020

the filling time should be included. j. Equipment working capacity should be indicated for lyophilisation step. k. Container closure integrity should be included as in-process control. l. Lyophilisation Process: Impact of Freezing Rate and Annealing Time on Quality Attributes and Manufacturing Efficiency should be discussed. m. An actual process validation report is still missing and should be submitted. Especially information on sampling (where, when and how was sampling done) is relevant to assess the appropriateness of the presented data to validate the manufacturing processes at both proposed manufacturing sites. Please also note that appearance of remdesivir powder should be explicitly detailed and should not be reported as `conforms´ in order to allow evaluation of colour of the finished product- and reconstituted solution of the reported batches.	
6. Media fill results should be submitted to confirm the appropriateness of the aseptic processing of sterile bulk product thereby confirming the quality and safety of the medicinal product: a. Media fill results should be presented from each of the manufacturing site for three complete runs, simulating the whole manufacturing process from mixing of bulk solution to sealing of vials including routine and worst-case interventions. The actual holding times of each step in the study should be stated.	In order to support appropriate aseptic processing of sterile bulk product Due date: August 2020
7. Excipient and finished product specifications should be revised in order to improve the control strategy and thereby confirm the quality, efficacy and safety of the medicinal product: a. Compliance with Ph.Eur. (2804) should be confirmed for Betadex sulfobutyl ether sodium. Compliance with USP is not sufficient. b. The limit for water content should be tightened and based on current batch data. c. The limit for assay during shelf-life is not based on current stability data. The assay during shelf-life should be tightened unless otherwise justified.	In order to revise excipient and finished product specifications Due date: August 2020

d. The specified limits for impurities are higher than the guideline's thresholds (ICH Q3B: reporting threshold 0.1 %, identification threshold 0.2 %, qualification threshold 0.2 % based on a maximum daily dose of 200 mg remdesivir). Proposed limits during release and shelf-life are either qualified by toxicological studies or the impurity is an (active) metabolite. The limits for specified degradation products and total impurities should be tightened based on actual batch- and stability results. e. The set limit for unspecified degradation products (at release and during shelf-life) is higher than the guideline's identification threshold (0.2%). This is generally not acceptable as this limit is applied for unknown impurities. The limit for unspecified degradation products should thus be lowered to NMT 0.2%.	
8. In-use stability data should be submitted in order to further substantiate the recommendations for reconstitution and storage of the medicinal product and thereby confirm the quality, efficacy and safety of the medicinal product. a. In-use stability data for reconstituted remdesivir powder for concentrate for solution for infusion diluted to 100ml with 0.9% saline solution should be provided to support the proposed in-use conditions as stated in SmPC section 6.3. b. A rationale for the different dilution regimens for remdesivir powder for concentrate for solution for infusion (dilute to 100ml or 250ml) and remdesivir concentrate for solution for infusion (dilute to 250ml) should be provided. It is noted that due to the risk of handling errors, different dilution regimens for the two dosage forms would not be acceptable without comprehensive justification.	In order to ensure In-use stability Due date: August 2020
Finished Product – Remdesivir Concentrate for Solution for Infusion	
9. The manufacture of finished product should be described in more detail in order to ensure batch to batch consistency and thereby confirm the quality and safety of the medicinal product: a. The level of betadex sulfobutyl ether sodium used	In order to ensure batch to batch consistency Due date: August 2020

should be justified by taking into account the content of the genotoxic impurity (1,4-butane sultone) in the betadex sulfobutyl ether sodium.

b. The applicant states that the batch size may be scaled up or down proportionally based on commercial demand or manufacturing site equipment capacity. This statement is not acceptable and should be deleted from the dossier. Any batch size outside of the range of the finally approved batch sizes should be applied for in the course of a variation procedure. Please note that respective process validation data would be needed since the finished product is manufactured according to a non-standard process.

c. Conditions of sterilisation of sterilising filters, glass vials, rubber stoppers and flip-off seals should be included in the process description.

d. Type of material, nominal pore size and number of filters should be stated for non-sterilising and sterilising filters in contact with the finished product or components of the finished product. Moreover, it should be stated whether the used filters (again non-sterilising and sterilising) are intended for single or multiple use. Additionally, filter area should be referenced for sterilising filters.

e. Filter integrity test acceptance criteria should be given for sterilising filter.

f. The maximum time between the start of bulk solution preparation and end of sterile filtration should be stated.

g. Information on the (sterile) bulk holding time before filling and on the filling time should be included.

h. Container closure integrity should be included as in-process control.

i. An actual process validation report is still missing and should be submitted. Especially information on sampling (where, when and how was sampling done) is relevant to assess the appropriateness of the presented data to validate the manufacturing processes at the proposed manufacturing site. Please also note that appearance of remdesivir concentrate should be explicitly detailed and should not be reported as `conforms´ in order to allow evaluation of solution colour of the reported batches.

j. Moreover, it is noticed that IPC and batch release results are reported for two consecutive batches and then again for another two batches, but only IPC results or not at all for one batch are reported for the batches in between. Batch release data are not reported for these batches. The reason for this selectively looking reporting of batch data should be stated and justified.	
10. Media fill results should be submitted to confirm the appropriateness of the aseptic processing of sterile bulk product thereby confirming the quality and safety of the medicinal product: a. Media fill results should be presented for three complete runs, simulating the whole manufacturing process from mixing of bulk solution to sealing of vials including routine and worst- case interventions. The actual holding times of each step in the study should be stated.	In order to support appropriate aseptic processing of sterile bulk product Due date: August 2020
11. Excipient and finished product specifications should be revised in order to improve the control strategy and thereby confirm the quality, efficacy and safety of the medicinal product: a. Compliance with Ph.Eur. (2804) should be confirmed for Betadex sulfobutyl ether sodium. Compliance with USP is not sufficient. b. The limit for assay during shelf-life is not based on actual stability data. The assay during shelf-life should be set tightened unless otherwise justified. c. The specified limits for impurities are higher than the guideline's thresholds (ICH Q3B: reporting threshold 0.1 %, identification threshold 0.2 %, qualification threshold 0.2 % based on a maximum daily dose of 200 mg remdesivir). Proposed limits during release and shelf-life are either qualified by toxicological studies or the impurity is an (active) metabolite. The limits for specified degradation products and total impurities should be based on actual batch- and stability results. d. The set limit for unspecified degradation products (at release and during shelf-life) is higher than the guideline's identification threshold (0.2%). This is generally not acceptable as this limit is applied for unknown impurities. The limit for unspecified degradation products should thus be lowered to NMT	In order to revise excipient and finished product specifications Due date: August 2020

0.2%. e. In the cover letter it is stated that proposed finished product is indicated for the treatment of adults and adolescents 12 years of age and older and weighing at least 40 kg with coronavirus disease 2019 (COVID-19). For adolescents weighing 40 kg the proposed endotoxin limit is too high and should be tightening (4.75 EU/mL is the highest acceptable endotoxin level for adolescent weighing 40kg).	
Clinical	
Efficacy	
12. In order to confirm the efficacy and safety of remdesivir, the MAH should submit the final clinical study report (CSR) of Study CO-US-540-5776 (NIAID-ACTT1). The CSR should provide answers to the following questions: a. Two different strengths were used: 150mg and 100mg. The Applicant should clarify how the doses to be applied were prepared by using the 150mg vials. b. The applicant should clarify, for how many patients the blinded placebo (as powder for infusion) was available and how it was distributed, i.e. if the same sites were given placebo/normal saline throughout the study. c. The factual blinding of the saline placebo at the study sites cannot be verified based on the available data. The applicant should clarify, which measures were taken at each of the study sites to maintain blinding of the study medication. d. Information on blinding of the tubes is contradictory between the MOP and the NEJM publication. This should be clarified. e. The Applicant should provide and analyse additional information such as routinely collected outcome scores on ICU (e.g. SOFA, SAPS, APACHE or Berlin criteria) in relation to treatment success. f. The Applicant should clarify if the assessment of the patient's status pertains to a single assessment on a given day or if this had to be confirmed or be maintained for a certain time.	Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Adults Due date: December 2020

g. For the protocol amendment changing the primary endpoint the Applicant should provide a list with names of approving authorities and dates of approval.

h. Additional effect measures to describe and summarize the treatment effect are requested, such as the recovery/discharge probability at fixed time points (day 7, 15, 22, 29) and the restricted mean survival time until day 29

i. Information on frequency, timing and reason of study discontinuation is requested by treatment arm, including inverse Kaplan-Meier curves.

j. For the primary endpoint, sensitivity analyses are requested to assess whether conclusions are robust to deviations from the non-informative censoring assumption.

k. Please provide the results of the planned sensitivity analyses exploring subjects who recover but subsequently report a clinical score > 3. The completeness of follow-up after recovery needs to be reported to allow conclusions whether sufficient data are available for the sensitivity analyses to provide meaningful additional information.

l. In the NEJM publication, there is an inconsistency between the results reported for the key secondary endpoint and the analysis of mortality reported in the supplementary material. In the analysis of the key secondary endpoint, 434 patients and 410 patients had baseline and day 15 score data in the remdesivir and the placebo group, respectively. However, according to the numbers of patients at risk at day 15 in the analysis of mortality, the numbers of patients known to be alive or died until day 15 were only 293 (260 at risk + 33 died) and 305 (250 at risk + 55 died) in the remdesivir group and in the placebo group, respectively. This issue needs to be clarified before results can be considered as valid.

m. For the final analysis of the key secondary endpoint with complete follow-up, it is expected that reasons for missing data and frequency should be reported, and sensitivity analyses with missing data imputation including placebo based multiple imputation should be provided.

n. While it is stated in the NEJM publication that data cutoff date was 22 April 2020, the reported figures with respect to recoveries do not match this date. As of April 22, 2020 482 recoveries have been reported. However, in table 2 (p.8 of the article) 607 recoveries are reported. It is stated in the appendix to the article that database freeze occurred on April 28, 2020. However, even then there is a discrepancy between the resulting figures as compared to the 28th April DSMB dataset. This should be clarified

o. It should be clarified if stratified enrolment was maintained until data cutoff.

p. Number, type of and reasons for protocol deviations should be described.

q. The charta and all meeting minutes of the DSMB should be submitted.

r. The monitoring plan (with clear responsibilities) and the high-level summary of the major outcomes of the visits as individual site and visit data should be provided

s. The baseline characteristics as well as the results should be displayed according to region.

t. As prognosis for IVM and ECMO are clearly different, more specific information as to the numbers for each of these subgroups should be presented, i.e. how many patients per arm were on IVM, how many on ECMO and what was their outcome.

u. The Applicant should display duration of symptoms as effect modifier and provide subgroup analyses according to duration of symptoms prior to initiation of therapy, e.g. by using categories such as ≤ 7 days, between 8 and ≤ 14 days and ≥ 15 days.

v. Concomitant medications at baseline and during the study should be reported.

w. Sensitivity analyses including only those discharged (and not deteriorating by day 29) should be provided.

x. Towards the end of the follow-up period of 29 days, the increases in recovery/discharge probability become smaller in both treatment groups such that a substantial proportion of patients is not yet released/recovered until day 29. This is probably partly explained by deceased patients who were censored at day 29. However, it may

also suggest that follow-up was too short for covering the complete time horizon of recovery. This issue should be clarified.

y. The reported mortality figures differ considerably between the report prepared for the DSMB (28th April 2020) and the published data (same datafreeze date). The Applicant should clarify.

z. It should be explained how/if a potential deterioration of patients' status (apart from death) after an initial improvement to categories 1,2 or 3 (defined as recovery) is accounted for.

aa. Sensitivity analyses should be conducted counting patients not recovered by day 29 (even if intermittently improved) as not recovered and this should be reflected accordingly in the analysis and KM-curve by censoring these patients at 29 days.

bb. The odds ratio resulting from the proportional odds model is difficult to interpret in terms of clinical relevance. In addition, the proportional odds assumption needs to be fulfilled. The cumulative probabilities for an outcome in a given category or worse allow an easier interpretation and should be provided (e.g. comparison of proportions of patients in the two worst categories 'death' or 'Hospitalized, on invasive mechanical ventilation or ECMO' between treatment groups)

cc. The analysis of the change in NEWS score should be presented.

dd. The per protocol analysis should be presented for all endpoints.

ee. The applicant should commit to deliver the full virology report as part of the SOB to provide the CSR for this study.

ff. It has been shown that patients treated up to 10 days after symptom onset appeared to benefit slightly less than those, in whom symptom onset was more than 10 days ago. Considering the experience with other antivirals, where "the earlier the better" is a paradigm, an explanation for this finding is lacking. The Applicant should explore this matter further by setting different cutoffs and as continuous variable as well as looking into potential cofactors.

gg. Based on the interim analysis, only one third of the patients has been treated with a full 10-day RDV treatment course. With the full analysis set this figure may increase to approximately 50% at most. Information, as to how the factual duration of therapy relates with outcomes is, however, missing. In view of the results of studies -5773 and -5774, indicative of similar or potentially even better outcomes with the 5-day as compared to the 10-day regimen, this information is urgently required	
13. In order to confirm the efficacy and safety of remdesivir in patients on IMV/ECMO, the MAH should submit the published final D28 mortality data by ordinal scale categories of Study CO-US-540-5776 (NIAID-ACTT1). In addition, the MAH should discuss potential imbalance in the use of corticosteroids and effect modification in Study CO-US-540-5776.	August 2020
14. In order to confirm the efficacy and safety of remdesivir, the MAH should submit the final CSR for Part A (Day 28) of Study GS-US-540-5773. The CSR should provide answers to the following questions: a. Information on protocol deviations seem incomplete and should be presented. b. Table 15.8.1.2 is included twice in the pdf, stating different figures. While the second table (p.8) specifies figures pertain to "data cut date", the footnote gives the date 10 April 2020 as date for collection of CRF data. The Applicant should clarify. c. The charta and all meeting minutes of the DSMB should be submitted. d. The monitoring plan (with clear responsibilities) and the high-level summary of the major outcomes of the visits as individual site and visit data should be provided. e. The Applicant is requested to report the dates defining the periods of recruitment and follow-up. f. The Applicant is requested to describe GCP inspection findings, if applicable.	A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of remdesivir This ongoing open-label trial compares 5-day and 10-day remdesivir durations for the treatment of patients with severe COVID-19. Due date: December 2020

g. The Applicant should clarify how many patients/sites were participating in Part A, as discrepant numbers have been provided

h. The Applicant is requested to present further details on comorbidities, eGFR as well as lab parameters predictive of outcome, such as CRP, lymphocyte count, D-dimer, and LDH at baseline (if available). In addition, figures describing the distribution of age, BMI and respiratory measures at baseline in both groups should be presented.

i. Concomitant use of the following is prohibited in participants receiving RDV However, according to listing 16.2.4.5 (part-a-dmc-interim-tfls.pdf) a considerable number of patients received non study antiviral drugs: (hydroxy)chloroquine, LPV/rtv, DRV/rtv, DRV/cobi, tocilizumab, interferon-beta, ribavirin, or oseltamivir, for some patients more than one agent was given. Summary listings/statistics have not been presented. Hence, it is not clear, how their use was distributed between the study groups, when during the course of the study/RDV-therapy these were administered and in which patients/ which clinical status of the patients. Hence, it is entirely unclear, if/how this may have influenced the study outcomes. The Applicant should provide the missing information and critically discuss any potential impact of use of these agents on the study results

j. The applicant is requested to describe in more detail the exposure to study drug, the reason for stopping treatment earlier in both, the 5- and 10-day treatment group as well as descriptive statistics for the resulting subgroups.

k. The applicant is asked to provide evidence that the lack of blinding has not introduced bias.

l. Baseline imbalances, as observed for the baseline clinical status status (significant) and gender (non-significant) indicating a shift to more cases in the 10-day group with a worse prognosis, may have been resulted from a potential deviation from the randomization scheme questioning the integrity of this open-label trial. The applicant is asked to provide evidence that the randomization was followed correctly.

m. Due to the lack of blinding, protocol changes during the trial may have affected the integrity of the trial. The applicant is asked to provide evidence that the SAP (finalized at the end of the 28-day period) has not been informed by the outcome of the trial.

n. Since the trial was open-label the SAP and the change in the primary analysis could have been informed by the outcome in the trial. Hence, the primary analysis as specified in the protocol would have to be considered as the primary inferential analysis and should be provided.

o. The primary endpoint was changed during the conduct of this open trial. The amendment was done after the study had started:

p. Considering a study duration of 14 days, some of the participants had already completed the study and thus were only evaluated on a 6-scale ordinal scale. It is not clear, how this change was accounted for in hindsight. The Applicant should comment.

q. The applicant should clarify the status of the trial with respect to the number of included patients and those who completed the 14 days at the time of the corresponding amendment and at the time of implementation of the amendment.

r. Due to the open-label nature of the study, the ordinal scale must be considered to be prone to potential bias, as neither objective criteria for the categorisation nor for discharge have been stated. Hence, it is in the full discretion of the investigators/study personnel. The Applicant should comment, if/which measures were taken to reduce bias in outcome assessment.

s. For the assessment of a public health benefit in the context of a CMA, the relevance of the primary endpoint is not clear (can any impact on health system resources be deduced from it?). Moreover, a single assessment of the patient's status on a given day/at a given time may be of questionable clinical relevance in view of the sometimes fluctuating course of disease. The Applicant should critically discuss these aspects.

t. The Applicant should comment, if apart from "time to first negative SARS-CoV-2 polymerase chain reaction (PCR)" any other virological assessment has been undertaken/is foreseen.

u. The evaluation of the validity of the proportionality assumption and the consequences for a potential change in the primary analysis remains unclear. The Applicant should comment and provide the comparison of cumulative proportions using different cut-offs in addition.

v. The applicant is asked to clarify the exact day of the data cut used for the primary analysis.

w. According to the protocol, missing data were not planned to be imputed and neither an estimand of interest nor any imputation method was specified. On the other hand, however, the SAP mentions that missing data imputation via LOCF was performed. The applicant should provide a justification and give a table on the number of patients by the last day at which the clinical status was known, treatment and clinical status at that day (where the reason for Hospital Discharge is not "Discharged Alive" and the subject has not died). Furthermore, sensitivity analyses using a longitudinal generalized linear mixed-effect model should be provided.

x. In the 10-day treatment group only 43% (44% according to the publication) of the patients received remdesivir for 10 days and 33% in this group received only a 5-day course. While for 52% of the patients the reasons were stopping early are described, information for 4% is missing and should be provided.

y. The applicant is asked to provide a clinical reasoning for the non-monotone dose (duration)-response.

z. The Applicant should provide data on the primary endpoint as well as mortality for the subgroups of patients on IMV/ECMO at baseline and no IMV/ECMO at baseline

aa. To allow comparison of the results of the different studies, time to recovery, 14-day and 28-day mortality should be presented according to baseline disease score.

bb. So far, all presented efficacy analyses are based on the full analysis set. The per-protocol analysis should be provided.

cc. According to listing 16.2.6 some patients were recorded as "score 7", while still in hospital and with need for

ongoing medical care or supplemental oxygen. The Applicant should clarify the cause for this ambiguous classification and the potential impact on the study results.

dd. Results were presented according to the three categories USA, Italy and Ex-Italy. This is an unusual way of displaying the data and obviously Italy stands as a proxy for worse outcome. The results in the different "countries" should be put in perspective with differences in baseline values and any other factors potentially influencing treatment outcome.

ee. The primary and secondary results should be displayed according to geographical region, i.e. North America, Europe, Asia

ff. The total numbers used in Table 44 do not fully match the fígures given in Table 15.9.1.2.1: "Clinical Status (7-Point Ordinal Scale) by Study Day" of the Interim Report of Study 5773, showing slightly higher numbers in all categories (n=42 for IMV/10d, n= 36 for high-flow O2/10d, n=70 for low-flow O2/5d, n=62 for for low-flow O2/10d, n= 37 for room air/5d). Table 15.9.1.2.1 suggests that the missing 17 patients may relate to those patients that discontinued the study before day 5, but this remains unclear. The applicant is asked to clarify

gg. Results are presented in the posthoc evaluation on Oxygen Support Status at Day 14 by Day 5 Oxygen Support Status (FAS):

hh. They suggest that conditional on not dying or being discharged until day 5 no difference is seen between both regimens with a numerical advantage for the 10d regimen in the IMV group (re. mortality and re. the overall OR). However, since 17 patients appear to be missing in the evaluation (see above), no complete appreciation of this finding is possible. The applicant is asked to explain.

ii. The regimen was known to the investigator from the beginning and baseline imbalances suggest that study populations differ right from the beginning. This may have introduced bias in the post-hoc analysis due to a potentially treatment dependent selection of the analysis population with respect to study discontinuation and discharge. The applicant is asked to clarify if the

results of the post-hoc analysis can still be used to support the proposed indication and treatment duration.	
14. In order to confirm the efficacy and safety of remdesivir, the MAH should submit the final CSR for Part A (Day 28) of Study GS-US-540-5774. The CSR should provide answers to the following questions: a. The date of database freeze for the presented interim analysis should be provided. b. The primary endpoint was changed to clinical status at Day 11. The amendment was done at the day of study start. However, as per Clinicaltrials.gov the study design was changed on April 6, 2020, one month after study start. Considering a study duration of up to 11 days, some of the participants had already completed the study and thus were only evaluated with regard to hospital discharge. It is not clear, how this change was accounted for in hindsight. The Applicant should comment. c. Due to the open-label nature of the study, the ordinal scale must be considered prone to potential bias, as neither objective criteria for the categorisation nor for discharge have been stated. Hence, it is in the full discretion of the investigators. The Applicant should comment, if/which measures were taken to reduce bias in outcome assessment. d. For the assessment of a public health benefit in the context of a CMA, the relevance of the primary endpoint is not clear (can any impact on health system resources be deduced from it?). The Applicant should comment. e. Moreover, a single assessment of the patient's status on a given day/at a given time may be of questionable clinical relevance (durability of response) in view of the sometimes fluctuating course of disease. The Applicant should comment. f. The primary endpoint was changed during the conduct of this open trial. The applicant should clarify the status of the trial with respect to the number of included patients and those who completed the 11 days at the	A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of remdesivir This ongoing open-label trial compares 5-day and 10-day remdesivir durations with SOC for the treatment of patients with moderate COVID-19. Due date: December 2020

time of the corresponding amendment and at the time of implementation of the amendment.

g. Missing data were replaced by last observation carried forward for the ordinal scale. Replacement of missing data was specified only in the SAP, while the protocol stated that "in general, values for missing data will not be imputed.". The influence of missing data handling on the conclusions from the study requires should be critically discussed.

h. It should be described whether measures were in place to ensure that persons in charge of protocol amendments and SAP have no knowledge of results from the ongoing study, and respective documentation should be provided. In addition, as some kind of review of data from the ongoing study was obviously conducted before finalizing the SAP, the respective review report needs to be provided. In particular, information on the data that were available for blinded review should be reported.

i. As the statistical testing and confidence interval should be consistent, nominal 97.5% confidence intervals (corresponding to adjusted 95% confidence intervals) should be reported.

j. Although the proportional odds model can be considered appropriate for testing the null hypothesis, the resulting proportional odds ratio is difficult to interpret in terms of clinical relevance. Clinical relevance needs to be evaluated in alternative ways, for example by comparing the cumulative proportions for observing clinical status of a given category or a better one between treatment groups, which should be provided. In addition, it is unclear what was the role of testing the proportional odds assumption. The Applicant should comment.

k. Patients from RDV groups who were not treated, were excluded from analysis. This is not in compliance with the ITT principle. The reasons for not treating patients should be reported and analyses including these patients should be provided.

l. Protocol deviation classified as important by the applicant were overall few and occurring most

frequently in the SOC-group. The Applicant should also present a summary listing of all protocol deviations.

m. Important information on administrative aspects (e.g. responsibilities for data management, statistics, IRT, randomisation, medical writing, etc) is missing. The Applicant is requested to present this information.

n. The charta and all meeting minutes of the DSMB should be submitted.

o. The monitoring plan (with clear responsibilities) and the high-level summary of the major outcomes of the visits as individual site and visit data should be provided.

p. The Applicant is requested to describe GCP inspection findings, if applicable.

q. One inclusion criterion was that patients had to have a SaO2> 94%. The Applicant should clarify, why, nonetheless, supplemental oxygen was required by 16% of the participants at baseline.

r. With respect to the study data from the US-sites some differences with the overall population are noted. Whites, participants younger than 50 years or older than 75 years, as well as patients requiring low flow oxygen were more likely to be in the 10-day RDV group. Duration of symptoms prior to study day 1 was significantly shorter in the 10-day group (P=0.0035). In view of these findings the applicant is asked to explain whether and how a deviation from the randomization scheme can be excluded.

s. It should be clarified, how many adolescents were included in this study.

t. Use of any agent with putative antiviral activity for SARS-CoV-2 was prohibited. However, information on concomitant use of other antiviral medications is missing and should be provided.

u. For comparability of the results (even though the endpoint differs in terms of its timing), time to recovery should be analysed according to baseline disease score.

v. In the 5-day and 10-day RDV group, 2 patients prematurely discontinued from study due to death but no deaths occurred for the 5-day RDV group in the analysis of clinical status at day 11. It is unclear when these deaths occurred. According to Table 15.9.2.9.1 Interim

Analysis, after day 11, 2 patients died in the 5-day RDV group, emphasizing the problem that 14-day mortality is not informative. Therefore, 28-day mortality data should be presented. w. To allow comparison of the results of the different studies, time to recovery, 14-day and 28-day mortality should be presented according to baseline disease score. x. So far, all presented efficacy analyses are based on the full analysis set. The per-protocol analysis should be provided as well. y. One of the exploratory endpoints is related to SARS-CoV-2 PCR negativity. However, the timing when this endpoint should be evaluated remains unclear, i.e. day 5, 10 and/or 11. z. The initial exploratory endpoint of "time to first negative SARS-CoV-2 PCR" was changed with protocol amendment 2 on April 29, 2020. It should be clarified if samples were to be taken from all sites/patients and the analysis for the initially specified endpoint should be provided as well. aa. The applicant is asked to clarify, at which of the participating sites virology data were collected and provide all available viral load and resistance data.	
Safety	
15. In order to confirm the safety profile of remdesivir, the MAH should submit in Module 2.7.4 an analysis of all available safety data from clinical trials CO-US-540-5776, GS-US-540-5773, GS-US-540-5774 and CO-US-540-5758 when completed, including case narratives, detailed information about adverse reaction and exposure data as well as an analysis of occurrence and aggravation of AEs, SAEs and ADRs are associated with increasing exposure.	No integrated summary of safety has been presented, nor are there available CSR's from any of the randomised controlled trials that are pivotal or supportive to the application. Furthermore, the understanding of patient factors such as co-morbidities, drug-drug interactions or disease severity, that may impact the tolerability of remdesivir, is incomplete. Due date: December 2020

* Classification: category 1= Annex II D condition; category 2= Annex II E specific obligations; category 3 = All other studies reflected only in the RMP (non-clinical, PK, PASS)