EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

03 April 2020
EMA/178637/2020 – Rev.1
Human Medicines Division

Summary on compassionate use

Remdesivir Gilead

International Nonproprietary Name: remdesivir

Procedure No. EMEA/H/K/5622/CU

Note

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

In addition, where indicated in [brackets], clinical information currently not yet published and hence confidential, redacted. This summary will be re-published including these data as soon as they are publicly available.

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1 Background information on the procedure

1.1 Submission of the dossier

Estonia, Greece, The Netherlands and Romania on 25 and 26 March 2020 requested from the Agency (EMA) a CHMP opinion on the compassionate use for the above-mentioned medicinal product in accordance with Article 83(3) of Regulation (EC) No 726/2004.

The legal basis for this application refers to:

Article 83(3) of Regulation (EC) No 726/2004

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

Rapporteur: Dr Janet König (DE), Multinational Team with AT (Quality)

Co-Rapporteur: Dr Filip Josephson (SE)

1.2 Steps taken for the assessment of the product

- The dossier was received by the EMA on 27 March 2020.
- The Applicant responded on 31 March 2020 and 01 April 2020 to questions raised by the Rapporteurs.
- The Rapporteur's Joint Assessment Report was circulated to all CHMP members and the company on 01 April 2020
- The procedure was discussed in an extraordinary CHMP meeting on 2 April 2020
- The opinion was adopted on 02 April 2020

2 General conditions for the manufacturer

2.1 Manufacturers

Manufacturers responsible for import and batch release in the European Economic Area

Both dosage forms:

Facility	Function
Fisher Clinical Services GmbH Im Woerth 3 Weil am Rhein, 79576 Germany	Importation and labeling
Fisher Clinical Services UK Limited Langhurstwood Road Horsham RH12 4QD United Kingdom	Importation and labeling
Gilead Sciences Ireland UC IDA Business and Technology Park Carrigtohill, Co. Cork Ireland	Importation, testing and QP release

Conclusion:

The applicant confirms that the manufacturing steps conducted at each facility are in full compliance with current Good Manufacturing Practices (cGMP) guidelines. Additionally, appropriate GMP certificates for the manufacturing / importation / batch release sites could be found at EudraGMPDP database.

2.2 Conditions of distribution

Medicinal product subject to restricted medical prescription. Treatment should be initiated in hospital setting only.

The company has stated in their submission that clinical trials are being prioritized to evaluate safety and efficacy for the treatment of COVID-19. CHMP supports this position and considers that the compassionate use programmes should be used for patients for which it is not possible to participate in a clinical trial. In light of the pandemic situation CHMP also considers that it is important to have the product made available to interested EU Member States in a fair and transparent manner.

2.3 Conditions for update of Compassionate Use to be implemented by the company

In accordance with Article 83(4) of Regulation (EC) No 726/2004, any change or new data having an impact on the CHMP compassionate use opinion as adopted by the CHMP, related to the conditions of use, distribution and targeted population of product, shall be communicated to the Agency (EMA) in order to update the CHMP Compassionate Use opinion as appropriate.

2.4 Conditions for safety monitoring to be implemented by the company

In accordance with Article 83(6) of Regulation (EC) No 726/2004, the pharmacovigilance rules and responsibilities defined in Articles 28(1) and 28(2) of the Regulation (EC) No 726/2004 are applicable to medicinal products for which an opinion on the conditions for compassionate use has been adopted. Therefore, the company shall ensure that these pharmacovigilance rules and responsibilities are fulfilled.

The company shall submit every 6 months a periodic safety update report. In addition, the company shall submit to EMA monthly expedited summary safety reports, following the format described in the CHMP Opinion.

2.5 Conditions for safety monitoring to be implemented by the Member States.

In accordance with Article 83(6) of Regulation (EC) No 726/2004, the pharmacovigilance rules and Responsibilities defined in Article 28(1) and (2) of the Regulation (EC) No 726/2004 referring to centrally authorised medicinal products as defined in articles 3(1) and (2) are applicable to medicinal products for which an opinion on the conditions for compassionate use has been adopted. Therefore, the Member States shall ensure that these pharmacovigilance rules and responsibilities are fulfilled.

3 Scientific discussion

3.1 Introduction

As requested by the CHMP, the company submitted a dossier to support the compassionate use of the product.

Remdesivir when used as part of a compassionate use programme, is indicated for the treatment of adults with coronavirus disease 2019 (COVID-19) who require invasive mechanical ventilation.

Inclusion Criteria

- Willing and able to provide written informed consent, or with a legal representative who can provide informed consent, or enrolled under ICH E6(R2) 4.8.15 emergency use provisions as deemed necessary by the investigator (participants ≥ 18 years of age)
- Age ≥ 12 years
- Hospitalized with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) by Polymerase chain reaction (PCR) or known contact of confirmed case with syndrome consistent with COVID-19 with PCR pending
- Requiring invasive mechanical ventilation (e.g., via endotracheal intubation or tracheostomy)
- Adequate renal function with estimated glomerular filtration rate ≥ 30 ml/min by local laboratory measure
- ALT ≤ 5 x upper limit of normal (ULN) by local laboratory measure

Exclusion Criteria

- Hypersensitivity to the active substance(s) or to any of the excipients
- Evidence of multiorgan failure
- The use of more than one pressor for septic shock (the use of 1 pressor at low/medium doses for inotropic support due to the use of sedation and paralytics while on the ventilator is allowed)
- ALT ≥ 5 x upper limit of normal (ULN) by local laboratory measure
- Renal failure (eGRF < 30 mL/min) or dialysis or continuous Veno-Venous Hemofiltration
- Participation in any other clinical trial of an experimental agent treatment for COVID-19

Background

SARS-CoV-2 was identified as the cause of an outbreak of respiratory illness (COVID-19) that was first detected in Wuhan, China, in December 2019. 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}. 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}. 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) 2020c}. 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}.

There are currently no approved effective therapeutic agents available for the treatment of COVID-19. The availability of a potentially effective antiviral agent with a favorable benefit/risk profile would address a serious unmet medical need for the treatment of patients with COVID-19. Remdesivir (GS-5734) is a single diastereomer monophosphoramidate prodrug of a nucleoside analog that is intracellularly metabolized into an analog of adenosine triphosphate that inhibits viral RNA polymerases and has broad spectrum activity against members of the filoviruses (eg, EBOV, MARV), CoVs (eg, SARS-CoV, MERS-CoV), and paramyxoviruses (eg, respiratory syncytial virus [RSV], Nipah virus [NiV], and Hendra virus).

There are several ongoing or planned studies on the clinical efficacy and safety of remdesivir for the treatment of COVID-19. (Table 1)

Table 1. Ongoing or planned studies on the clinical efficacy and safety of remdesivir for the treatment of COVID-19

Study Number	Study Title	Study Status
GS-US-540-5773 (SIMPLE)	A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants with Severe COVID-19	Ongoing
GS-US-540-5774 (SIMPLE)	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
IN-US-540-5755	Individual Patient Use Protocol for Wuhan Coronavirus	Ongoing
CO-US-540-5764	A Phase 3 Randomized, Double-blind, Placebo-controlled Multicenter Study to Evaluate the Efficacy and Safety of Remdesivir in Hospitalized Adult Patients With Mild and Moderate 2019-nCoV Respiratory Disease	Ongoing
CO-US-540-5776 (NIAID)	A Multicenter, Adaptive, Randomized Blinded Controlled Trial on the Safety and Efficacy Study of Investigational Therapeutics for the Treatment of 2019-nCoV	Ongoing
CO-US-540-5758	A Phase 3 Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Remdesivir Combined with Standard of Care (SOC) in Hospitalized Adult Patients with Severe 2019-nCoV Respiratory Disease	Planned
CO-US-540-5804	Multi-centre, adaptive, randomized trial of the safety and efficacy of treatments of COVID-19 in hospitalized adults	Planned
GS-US-540-5821	Expanded Access Treatment Protocol: Remdesivir (RDV; GS-5734) for the Treatment of SARS-CoV2 (CoV) Infection	Planned
CO-US-540-5824 (WHO)	Multi-centre, adaptive, randomized trial of the safety and efficacy of treatments of COVID-19 in hospitalized adults	Planned

There is an ongoing single-patient compassionate use programme conducted both in the EU and outside the EU (Study IN-US-540-5755).

Remdesivir is currently not approved for marketing in any country.

3.2 Quality aspects

Introduction

Remdesivir is a single stereoisomer monophosphoramidate prodrug of a nucleoside analog that is being developed for the treatment of coronavirus (CoV) disease.

Remdesivir for compassionate use is provided in two dosage forms, a solution formulation and a lyophilized formulation. The standard term "Concentrate for solution for infusion" will be used in this document for the solution formulation, and the standard term "Powder for concentrate for solution for infusion" will be used for the lyophilized formulation.

The concentrate for solution for infusion is supplied as a sterile, preservative-free, clear, colourless to yellow, aqueous-based concentrated solution containing 5 mg/mL remdesivir to be diluted into infusion fluids prior to IV administration (see Annex I, 5.1 Preparation of the medicinal product to be administered).

The powder for concentrate for solution for infusion is a preservative-free, white to off-white to yellow, lyophilized solid containing 100 remdesivir to be reconstituted with sterile water for injection and diluted into IV infusion fluids prior to IV administration (see Annex I, 5.1 Preparation of the medicinal product to be administered).

Detailed information regarding study drug administration, reconstitution, and dilution instructions are stated to be provided in a pharmacy manual provided to the investigators.

Drug Substance

The chemical name for 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. The molecular formula is $C_{27}H_{35}N_6O_8P$ and the molecular weight is 602,6 g/mol.

Remdesivir is a white to off-white or yellow non hygroscopic solid, practically insoluble in water and soluble in ethanol. Remdesivir has six chiral centres and is produced as a single stereoisomer. Different polymorphic forms exist and the active substance is manufactured as Form II or mixtures of Form II and another crystalline form. The mixture of forms and Form II show similar solubility and do not result in differences in finished product performance. The active substance is dissolved before final I.V. administration.

The active substance has been appropriately characterised by a range of analytical techniques.

The chemical synthesis was briefly described. The starting materials are relatively complex and only one synthetic step followed by deprotection and crystallisation is presented. The level of detail is brief, although some information on solvents used in previous steps and no use of class I solvents or intentionally added elements is stated. In total, the information on the manufacturing process is considered sufficient for use of the active substance in clinical trials and compassionate use programs. It is expected that this section is further extended for any upcoming applications.

Impurities have been evaluated and proposed structures for five impurities present in the remdesivir active substance are presented. One of the impurities, which is the diastereomer of remdesivir, is controlled as a specified impurity in the active substance specification.

A short discussion regarding assessment of mutagenic and potentially mutagenic impurities is presented and is acceptable considering the acute, potentially life-saving use. It is expected that this section is further extended for any upcoming applications.

Control of Drug Substance

The active substance specification covers appearance, identification, clarity of solution, water content, assay, impurity content by UPLC, optical rotation, residual solvents by GC, elemental impurities and microbiological examination. Analytical methods used are briefly described and adequately validated. Tests and acceptance limits are adequately justified. It is stated that the limit for specified impurity diastereomer is qualified in toxicological studies and the limit is considered acceptable. The limit for any individual unspecified impurity is high but is acceptable considering actual levels of unspecified impurities observed during stability. It is also stated that "any unspecified impurity exceeding the qualification threshold specified in ICH Q3A(R2) will be appropriately qualified by toxicological studies". Batch analysis data for four clinical batches of remdesivir active substance was presented and the results comply with specification.

Stability

The active substance packaging has been described. A retest period of up to 60 months may be applied for when stored below 30°C. Stability data for one representative clinical batch of remdesivir over 48 months at long-term conditions (30°C/75 % RH) and 6 months at accelerated conditions (40°C/75 % RH) are available. The results are within specification limits and no significant changes are observed. A retest period of 60 months is acceptable.

Drug Product – Powder for concentrate for solution for infusion

The finished product is a is a preservative-free, white to off-white or yellow lyophilized solid available in two strengths containing 100 mg remdesivir as active substance.

Powder for concentrate for solution for infusion, 100 mg, contains 100 mg remdesivir that is to be reconstituted with 19 mL of sterile water for injection and diluted into intravenous infusion fluids prior to intravenous administration.

Following reconstitution, each vial contains a 5 mg/mL remdesivir concentrated solution with sufficient volume to allow withdrawal of 20 ml (100 mg remdesivir).

Pharmaceutical Development

Remdesivir finished product contains the excipients betadex sulfobutyl ether sodium, hydrochloric acid and/or sodium hydroxide. Water for injections is used in the process and is removed during lyophilization. Betadex sulfobutyl ether sodium is used in the formulation as a solubilizing agent due to the limited aqueous solubility of remdesivir. All excipients are compendial (USP/NF/Ph Eur).

After reconstitution, the product should be diluted into intravenous fluids prior to intravenous administration. A compatibility study of 150 mg remdesivir (no longer part of this CU application) diluted in 250 ml infusion bags of 0.9 % sodium chloride in water (saline) and 5 % glucose (dextrose) in water has been performed. The chemical stability and compatibility of the diluted infusion formulation was studied at room temperature, exposed to ambient room lighting, for up to 24 hours. Results for remdesivir strength (%) and total degradation products (%) are stable and little or no change was observed. As the concentration of the active substance in the reconstituted solution for the tested 150 mg strength is the same i.e. 5 mg/ml, as the 100 mg strength which is proposed to be used in the Compassionate Use, it is acceptable that no compatibility studies of Remdesivir have been performed in mentioned infusion fluids.

Based on the presented data following in-use conditions are acceptable:

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C. From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of

microbial contamination, the product should be used immediately. If not used immediately, in-use storage tomes and conditions are the responsibility of the user.

Water for Injection may be used as reconstitution solution. Saline solution (0.9% NaCl) and 5% Glucose (Dextrose solution) may be used as diluents.

Container closure system

The container closure system consists of a 30 mL Type I clear glass vial, a 20 mm rubber stopper and an aluminum overseal with a plastic flip-off cap.

Adventitious Agents

No excipients of human or animal origin are used.

Manufacture of the Product

The finished product is produced under aseptic conditions. In summary, the process steps include dissolution of betadex sulfobutyl ether sodium in water for injection, pH adjustment and dissolution of remdesivir, dilution with sufficient quantity of water for injection, pH adjustment, bioburden reduction via filtration, sterile filtration, vial filling, stopper insertion, lyophilization, and capping.

Sterilization of equipment and closures is accomplished using steam sterilization. The glass vials are sterilized and depyrogenated using dry heat.

The limit for bioburden of the bulk solution prior to sterile filtration was stated and is acceptable. Two filters are used in sequence. Filter integrity is tested. Media fill studies have been performed. Vials are visually inspected.

Overall, the manufacturing process and in process controls are sufficiently described for use of the drug product in clinical trials and compassionate use programs.

Product Specification

The finished product specification includes tests for appearance, identification, reconstitution, assay, degradation products, pH of solution, water content, uniformity of dosage units, sterility, bacterial endotoxins and particulate matter. The analytical methods are briefly described and validation for relevant methods are presented. Batch analyses data for one clinical batch (100 mg) is presented and the results comply with specification. Additionally, results for two clinical batches of 150mg strength (no longer part of this CU application) are submitted in support. Results also comply with specification. The impurity profile of the finished product is consistent with the impurity profile observed in the active substance. Two impurities that are potentially formed by hydrolysis, are controlled as specified impurities in the finished product specification. One of them is the active species and metabolite of the pro-drug remdesivir. Tests and acceptance limits in the finished product specification are justified. It is stated that the limit for the other specified impurity is qualified in toxicological studies. The limit for any unspecified degradation product at shelf-life is high but is considered acceptable since it is stated that "any new unspecified degradation product exceeding the qualification threshold specified in ICH Q3B(R2) will be appropriately qualified by additional toxicology data". Also, actual levels of unspecified degradation products observed during stability are relatively low.

Stability of the Product

12 months stability data for one batch (100 mg) at long-term condition (30°C/75 % RH) was provided. Additionally, 36 months stability data for one batch of 150mg strength (no longer part of this CU procedure) are submitted in support. Also, 6 months of accelerated stability data (40°C/75% RH) for both batches are available. The results comply with specification. Results for specified and unspecified degradation products are well within specification. Results for total degradation products varies but

remain within the specification limit. Based on the available stability data, the finished product has been assigned a shelf life of 51 months at the storage condition "Store below 30°C" (39 months plus 12 months is used for assigning the shelf life instead of 36 months + 12 months since the initiation of stability program was delayed by 3 months). The proposed shelf-life and storage condition is considered acceptable. The shelf-life may be extended to 60 months when 48 months long-term stability data is available, which is also considered acceptable.

Drug Product – Concentrate for solution for infusion

Remdesivir concentrate for solution for infusion, 100 mg (5 mg/ml), is a sterile, preservative-free, clear, colourless to slightly yellow, aqueous-based concentrated solution for dilution into intravenous fluids, available in 20 ml vials.

Each 20 mL vial contains sufficient volume to allow withdrawal of 20 mL, equivalent to 100 mg remdesivir.

The finished product is stored frozen and is thawed and diluted prior to intravenous infusion.

Pharmaceutical Development

Remdesivir concentrate for solution for infusion contains the excipients water for injection, betadex sulfobutyl ether sodium, hydrochloric acid and/or sodium hydroxide. Betadex sulfobutyl ether sodium is used in the formulation as a solubilizing agent due to the limited aqueous solubility of remdesivir. All excipients are compendial (USP/NF/Ph Eur).

As no formulation development is described, comparison is drawn to the other presentation (powder for concentrate for solution for infusion). It is shown that the amount of the excipient betadex sulfobutyl ether sodium is varying in both presentation: in the powder for concentrate for solution for infusion 165 mg/ml reconstituted solution prior to dilution are included, while in the concentrate for solution for infusion prior to dilution 300 mg/ml are included (both calculated with 5 mg/ml API). Pharmacokinetic comparison of both dosage forms is reported in table 67 of the IB. These data have been generated using finished product of both dosage forms according to the respective final compositions as described in P.1 of the provided IMPDs. Based on the presented data no further information regarding formulation development is required in the course of the Compassionate Use.

It is stated that the finished product, when exposed to a typical autoclaving cycle of 121 °C for 30 minutes, results in significant degradation of remdesivir. Therefore, the product is sterile filtered under aseptic conditions as opposed to terminal sterilization. The justification for aseptic manufacturing is considered acceptable.

The concentrated solution is to be diluted in intravenous fluids prior to intravenous administration. A compatibility study, covering the dose range of 3 mg to 300 mg remdesivir, diluted in 250 ml infusion bags of 0,9 % sodium chloride in water (saline) has been performed. The chemical stability and compatibility of the diluted infusion formulations was studied at room temperature, exposed to normal room lighting, for up to 24 hours. Results for remdesivir assay (%) and total degradation products (%) are stable and little or no change is observed. Microbiological stability for 3 mg and 225 mg remdesivir diluted into 250 ml 0.9% and 0.45 % sodium chloride in water has also been studied during 24 hours in room temperature. No microbial growth or increase in bacterial endotoxin level was observed during the storage period.

Based on the presented data (presented for both dosage forms) following in-use conditions are acceptable:

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C. From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage tomes and conditions are the responsibility of the user.

Saline solution (0.9% NaCl) and 5% Glucose (Dextrose solution) may be used as diluents.

Container closure system

The container closure system consists of a 20 ml Type I clear glass vial, a coated butyl rubber stopper, and an aluminium seal with a polypropylene flip-off cap.

Adventitious Agents

No excipients of human and animal origin are used.

Manufacture of the Product

In summary, the manufacturing process steps include dissolution and mixing, pH adjustment, q.s. with water for injection, pH adjustment, bioburden reduction via filtration, sterile filtration, vial filling, stopper insertion, and capping.

Sterilization of equipment and closures is accomplished using a pass-through steam sterilizer. The glass vials are sterilized and depyrogenated using dry heat.

The limit for bioburden of the bulk solution prior to sterile filtration was stated and is acceptable. Two filters are used in sequence. Filter integrity is tested. Media fill studies have been performed. Vials are visually inspected.

Overall, the manufacturing process and in process controls are sufficiently described for use of the drug product in clinical trials and compassionate use programs.

Product Specification

The finished product specification includes tests for appearance, identification, assay, impurity content, pH, sterility, bacterial endotoxins, particulate matter and volume in container. The analytical methods are briefly described and a summary of the validation for the method for identification, assay and degradation products was presented. Batch analyses data for one development batch, representative of clinical batches, is available and the results comply with specification. The impurity profile of the finished product is consistent with the impurity profile observed in the active substance. Two impurities are potentially formed by hydrolysis and are controlled as specified impurities in the finished product specification. One of them is the active species and metabolite of the pro-drug remdesivir. Tests and acceptance limits in the finished product specification are justified. It is stated that the limit for the other specified impurity is qualified in toxicological studies, it is however noted that the limit is higher than the corresponding limit in the powder for concentrate for solution for infusion. Nonetheless, the limit is considered acceptable. The limit for any unspecified degradation product at shelf-life is high but is considered acceptable since it is stated that "any new unspecified degradation product exceeding the qualification threshold specified in ICH Q3B(R2) will be appropriately qualified by additional toxicology data". Also, no unspecified degradation products are observed during stability.

Stability of the Product

36 months of long-term stability data at -20°C and 12 months accelerated data at 5°C are provided for one batch of finished product, which is stated to be representative for clinical batches. Samples

have been placed at upright and inverted configurations. The results comply with specification. At the accelerated storage condition, One of the hydrolysis formed impurities increases during 12 months but remains within the specification limit. No other degradation products are observed. Total degradation products remained unchanged at the long-term storage condition. Based on the available stability data, a 48-month shelf-life is proposed at "Store in a freezer (−25°C to −10°C)". The proposed shelf-life and storage condition is considered acceptable. The shelf-life may be extended to 60 months when 48 months long-term stability data is available, which is also considered acceptable.

In the absence of freeze-thaw studies, the drug product should not be frozen and thawed repeatedly.

Overall assessment on Quality

Only brief information on active substance and finished product quality is provided. In the course of an application for marketing authorisation a complete module 3, which is in line with all relevant guidance documents and pharmacopoeial requirements, is expected to be presented.

3.3 Non-clinical aspects

Introduction

Remdesivir was originally developed against EBOLA virus disease.

The case for the investigation and compassionate use of remdesivir rests on in vitro data and preclinical efficacy data for various coronaviruses, and a PK bridge to human exposure. All pivotal nonclinical in vivo studies were 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, thus representative of the clinical formulations.

Data submitted

The assessment based on the submitted IB edition 5 (21 February 2020). The applicant has also submitted references to a number of scientific publications. No study reports have been submitted.

Pharmacology

Mode of action:

The sponsor states that remdesivir has been designed to efficiently deliver the monophosphate nucleoside analog GS-441524 into cells. Inside cells, the GS-441524 monophosphate undergoes rapid conversion to the pharmacologically active nucleoside triphosphate form GS-443902. Efficient metabolism of remdesivir and/or the diastereomeric mixture GS-466547 to the nucleoside triphosphate GS-443902 has been demonstrated in multiple cell types.

Biochemical studies demonstrate that the nucleoside triphosphate GS-443902 acts as an analog of adenosine triphosphate (ATP) and competes with the natural ATP substrate to selectively inhibit EBOV RNA-dependent RNA polymerase. The primary mechanism of inhibition is the incorporation of the nucleoside triphosphate GS-443902 into nascent RNA chains by EBOV RNA-dependent RNA polymerase, causing delayed RNA chain termination during the process of viral replication [Tchesnokov 2019]. Delayed chain termination has also been shown to be the mechanism of action of remdesivir inhibition of the MERS-CoV (preliminary data), RSV [Warren 2016], and NiV [Jordan 2018] polymerases.

Primary Pharmacology:

Remdesivir inhibits viral RNA polymerases and has broad spectrum activity against members of the filoviruses (eg, EBOV, MARV), CoVs (eg, SARS-CoV, MERS-CoV), and paramyxoviruses (eg, respiratory syncytial virus [RSV], Nipah virus [NiV], and Hendra virus).

In vitro susceptibility of coronaviruses

In HAE cells, remdesivir efficiently inhibited both MERS-CoV and SARS-CoV replication with IC50 values of 0.074 and 0.069 μM, respectively. In both HAE and Calu-3 cells, no cytotoxicity was observed at 10 μM remdesivir, the highest concentration tested, demonstrating that remdesivir has a favorable in vitro selectivity index {Sheahan 2017}.

Results from initial in vitro testing performed at the China CDC in collaboration with Gilead Sciences showed that remdesivir has potent antiviral activity against SARS-CoV-2 in Vero cells (EC50 = 0.137 μM; preliminary data). In another study conducted by the Wuhan Institute of Virology, remdesivir also showed in vitro activity against SARS-CoV-2 in Vero cells (EC50 = 0.77 μM) {Wang 2020}.

The in vitro development of resistance to remdesivir in CoVs has been assessed by cell culture passaging of MHV in the presence of the remdesivir nucleoside analog GS-441524. After 23 passages, 2 mutations were selected in the nsp12 polymerase at residues conserved across CoVs: F476L and V553L. Compared with wild-type virus, recombinant MHV containing the F476L mutation showed 2.4-fold reduced susceptibility to remdesivir, and MHV containing V553L demonstrated 5-fold reduced susceptibility, while the double mutant conferred 5.6-fold reduced susceptibility to remdesivir in vitro.

No resistance data have been submitted specific to SARS-Cov2.

Efficacy in disease models of coronaviruses

Efficacy of Remdesivir Against SARS-CoV (not SARS-CoV-2) in Mice

Mice were inoculated intranasally with 104 pfu/50 μL (prophylactic) or 103 pfu/50 μL (therapeutic) of SARS-CoV, and the effect of subcutaneous administration of remdesivir on viral load in lung tissue, disease-related clinical signs, lung function assessments, and lung histopathology was assessed on Day 4 post-infection (Table 2).

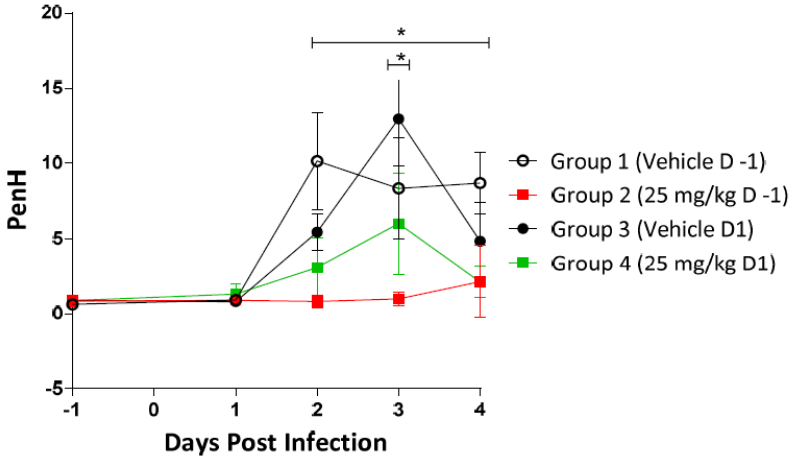
Table 2. PC-399-2033: Design of Efficacy Study of Remdesivir administered subcutaneously against SARC-CoV in mice.

Group, No. of Animals (N)	Treatment (Subcutaneous, Twice Daily)
Group 1, N = 5	Vehicle, Days –1 to 4
Group 2, N = 10	Remdesivir 25 mg/kg, Days –1 to 4
Group 3, N = 4	Vehicle, Days 1 to 4
Group 4, N = 11	Remdesivir 25 mg/kg, Days 1 to 4

Source: IB Edition 5 21 February 2020, Table 29

Prophylactic administration of 25 mg/kg remdesivir subcutaneously twice daily, initiated 1 day prior to virus inoculation (Group 2), improved pulmonary function (ie, reduced Penh scores) , reduced virus titers in the lung , and reduced SARS-CoV-induced weight loss compared to control vehicle-treated animals (Group 1). Similarly, therapeutic administration of the same remdesivir dosing regimen initiated 1 day post-infection improved weight loss, viral load in lung (Table 3), and lung function (Figure 1), albeit to a lesser extent than the prophylactic regimen.

Figure 1. PC-399-2033: Effect of Remdesivir twice-daily subcutaneously. Prophylactic and Therapeutic administration on lung function in SARS-CoV infected mice.



Whole-body plethysmography was used to measure pulmonary function in SARS-CoV-infected mice treated with remdesivir, either 1 day prior to infection (Group 2) or 1 day post-infection (Group 4). Penh is a surrogate measure of bronchoconstriction or airway obstruction. Asterisks indicate statistical significance by 2-way ANOVA with Sidek's multiple comparison test.

Source: IB Edition 5 21 February 2020, Figure 9

Table 3. PC-399-2033: Effect of Remdesivir twice-daily subcutaneously. Prophylactic and Therapeutic administration on lung viral load in SARS-CoV infected mice.

Group, No. of Animals (N)	Treatment (Subcutaneous, Twice Daily)	Day 4 Lung Viral Load (PFU/lobe)
Group 1, N = 5	Vehicle, Days –1 to 4	3.1×10^6
Group 2, N = 10	Remdesivir 25 mg/kg, Days –1 to 4	9.5×10^{4a}
Group 3, N = 4	Vehicle, Days 1 to 4	1.7×10^6
Group 4, N = 11	Remdesivir 25 mg/kg, Days 1 to 4	3.9×10^{5b}

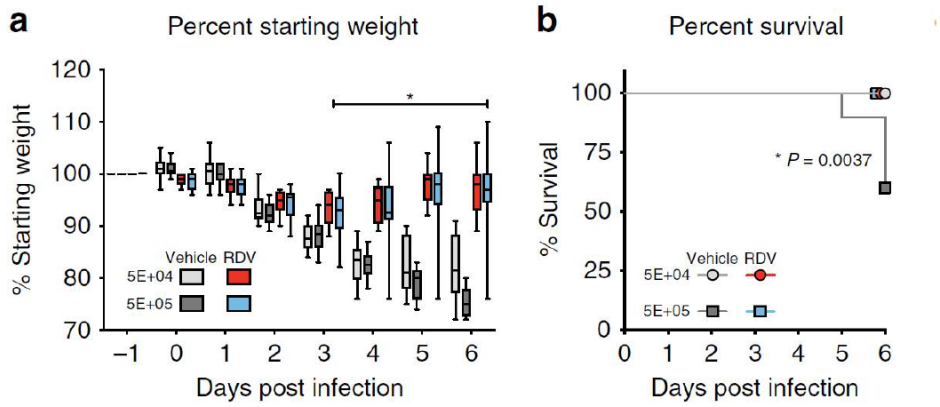
a p = 0.0007 calculated using the Mann-Whitney test comparing Group 2 with Group 1.
b p = 0.0059 calculated using the Mann-Whitney test comparing Group 4 with Group 3.

Source: IB Edition 5 21 February 2020, Table 30

Efficacy of Remdesivir Against MERS-CoV in Mice

In a prophylactic study, remdesivir (25 mg/kg, twice daily) was administered subcutaneously 1 day prior to intranasal infection in mice with 5 * 104 PFU or 5 * 105 PFU of MERS-CoV. Prophylactic remdesivir significantly diminished MERS-CoV-induced weight loss compared with control vehicle-treated animals and also prevented mortality in mice administered a lethal dose (ie, 5 *105 PFU) of MERS-CoV (Figure 2). Prophylactic remdesivir also significantly reduced virus lung titers on Days 4 and 6 post-infection (Figure 3), decreased lung hemorrhage scores, and diminished the pathological features of acute lung injury compared with control vehicle-treated animals. In contrast, a similarly designed study conducted in the same mouse model demonstrated that prophylactic LPV/RTV-IFNb slightly reduced viral loads but did not impact other disease parameters [Sheahan 2020].

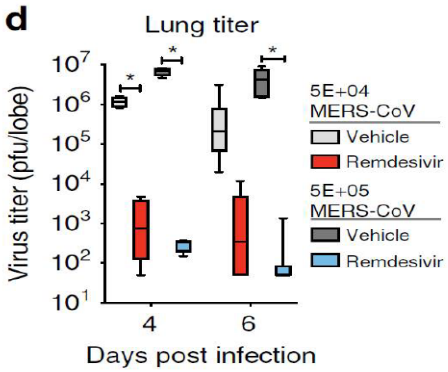
Figure 2 Effect of Prophylactic Remdesivir twice-daily subcutaneously on weight loss and mortality in MERS-CoV infected mice.



Panel a: Asterisks indicate statistically significant differences ($P < 0.05$) as determined by 2-way ANOVA with Tukey's multiple comparison test.
Panel b: Survival analysis by Mantel–Cox test ($P < 0.05$).
Source: {Sheahan 2020}

Source: IB Edition 5 21 February 2020, Figure 10

Figure 3 Effect of Prophylactic Remdesivir twice-daily subcutaneously on lung viral load in MERS-CoV infected mice.



Day 4, n = 4 per group; Day 6, all remaining animals.
Asterisks indicate statistically significant differences ($P < 0.05$) as determined by 2-way ANOVA and Sidek's multiple comparison test.
Source: {Sheahan 2020}

Source: IB Edition 5 21 February 2020, Figure 11

In a therapeutic study, remdesivir (25 mg/kg, twice daily) was administered subcutaneously 1 day after intranasal infection of mice with 5 * 104 PFU of MERS-CoV. The effect of therapeutic treatment with lopinavir/ritonavir (LPV/RTV) in combination with 2 different doses of interferon beta (IFNb) was also assessed as part of the same study (Table 4).

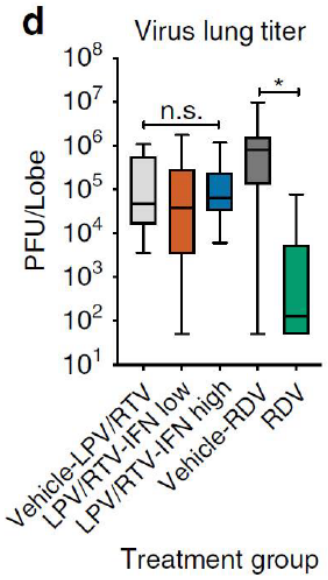
Table 4. Design of Therapeutic Efficacy Study of Twice-Daily Subcutaneous Remdesivir Compared With Once-Daily Oral Lopinavir/Ritonavir Plus Interferon-Beta Against MERS-CoV in Mice

Group, No. of Animals (N)	Treatment	Administration
Group 1, N = 13	Remdesivir Vehicle, Days 1 to 5	Subcutaneous, Twice Daily
Group 2, N = 14	Remdesivir 25 mg/kg, Days 1 to 5	Subcutaneous, Twice Daily
Group 3, N = 15	LPV/RTV-IFNb Vehicle, Days 1 to 5	Oral, Once Daily
Group 4, N = 16	LPV/RTV-IFNb Low[a], Days 1 to 5	Oral, Once Daily
Group 5, N = 16	LPV/RTV-IFNb High[b], Days 1 to 5	Oral, Once Daily

IFNb = interferon beta; LPV = lopinavir; RTV = ritonavir
a IFNb low is 1 × human equivalent dose of 1.6 million international units (MIU)/kg.
b IFNb low is 25 × human equivalent dose of 40 MIU/kg.
Source: {Sheahan 2020}

Source: IB Edition 5 21 February 2020, Table 32

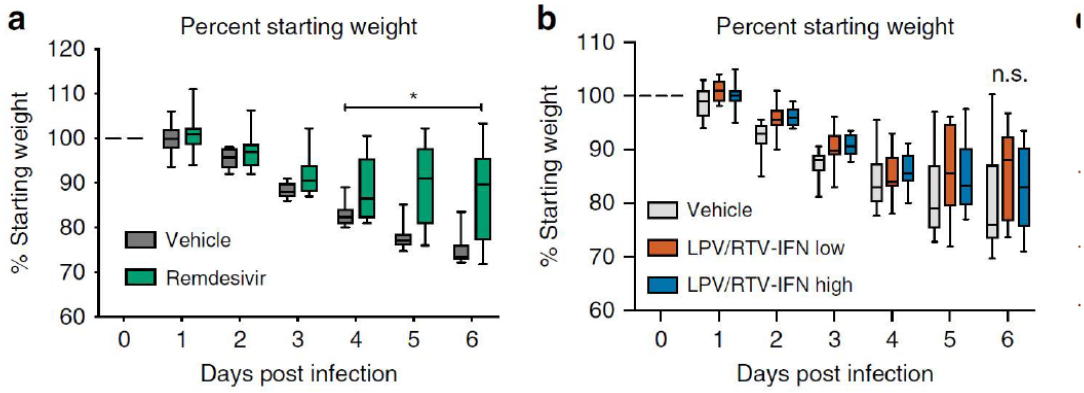
Figure 4. Effect of Therapeutic Twice-Daily Subcutaneous Remdesivir or Therapeutic Once-Daily Oral Lopinavir/Ritonavir Plus Interferon Beta on Lung Viral Load in MERS-CoV-Infected Mice



Asterisks indicate statistical significance by 1-way ANOVA with Kruskal-Wallis test.
Source: {Sheahan 2020}

Source: IB Edition 5 21 February 2020, Figure 13

Figure 5. Effect of Therapeutic Twice-Daily Subcutaneous Remdesivir or Therapeutic Once-Daily Oral Lopinavir/Ritonavir Plus Interferon Beta on Weight Loss in MERS-CoV-Infected Mice



n.s. = not significant
Asterisks indicate statistical differences by 2-way ANOVA with Tukey's multiple comparison test.
Source: {Sheahan 2020}

Source: IB Edition 5 21 February 2020, Figure 12

Prophylactic and Therapeutic Efficacy of 5 mg/kg Remdesivir Against MERS-CoV in Rhesus Monkeys

The prophylactic and therapeutic efficacy of a 5 mg/kg daily dose of remdesivir was determined in MERS-CoV-infected rhesus monkeys {De Wit 2020}. Vehicle or remdesivir 5 mg/kg was administered once daily using IV bolus injection beginning 24 hours prior to (prophylactic) or 12 hours after (therapeutic) MERS-CoV inoculation until Day 6 post-inoculation (Table 5). Animals were inoculated on Day 0 with a target dose of 7 * 106 tissue culture infectious dose 50 (TCID50) of MERS-CoV via the intranasal, ocular, oral, and intratracheal routes.

Table 5. PC-399-2037: Design of Prophylactic and Therapeutic Efficacy Studies of 5 mg/kg Intravenous Remdesivir Against MERS-CoV in Rhesus Monkeys

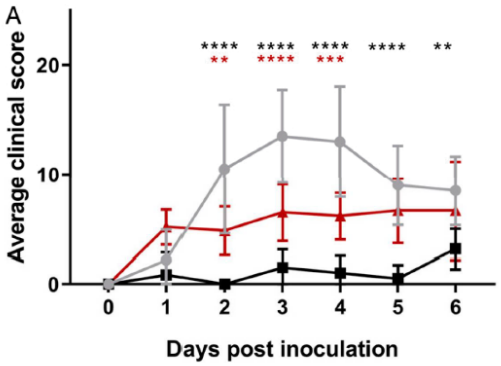
Group No.	No. of Animals (N)	Treatment (IV, Once Daily)
1	N = 6	Remdesivir 5 mg/kg, Days –1 to 5
2	N = 3	Vehicle, Days –1 to 5
3	N = 6	Remdesivir 5 mg/kg, Days 0.5 to 5
4	N = 3	Vehicle, Days 0.5 to 5

Source: {De Wit 2020}

Source: IB Edition 5 21 February 2020, Table 33

Both prophylactic and therapeutic remdesivir treatment significantly reduced MERS-CoV-induced clinical signs (Figure 6) and virus replication in respiratory tissues (Figure 7), and decreased presence and severity of lung lesions compared to vehicle-treated animals. These effects were more pronounced in the animals treated prophylactically.

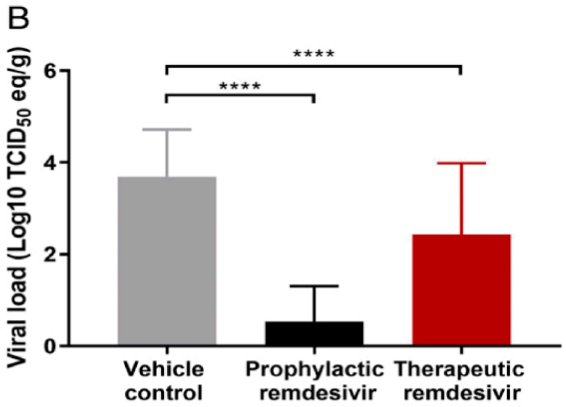
Figure 6. Effect of 5 mg/kg Intravenous Remdesivir Once-Daily Prophylactic or Therapeutic Administration on Clinical Score in MERS-CoV-Infected Rhesus Monkeys



Key: gray circles = vehicle control; black squares = prophylactic remdesivir; red triangles = therapeutic remdesivir
Two-way ANOVA with Dunnett's multiple comparisons; black asterisks indicate statistical significance between the vehicle control and prophylactic remdesivir groups and red asterisks indicate statistical significance between the vehicle control and therapeutic remdesivir groups. * P<0.05; ** P<0.01; *** P<0.001; **** P<0.0001. Vehicle control animals from the prophylactic and treatment groups were analyzed together.
Source: {De Wit 2020}

Source: IB Edition 5 21 February 2020, Figure 14

Figure 7. Effect of 5 mg/kg Intravenous Remdesivir Once-Daily Prophylactic or Therapeutic Administration on Lung Viral Load in MERS-CoV-Infected Rhesus Monkeys



Asterisks indicate statistically significant differences in a 2-way ANOVA with Dunnett's multiple comparisons. * P<0.05; ** P<0.01; *** P<0.001; **** P<0.0001.
Source: {De Wit 2020}

Source: IB Edition 5 21 February 2020, Figure 15

Prophylactic Efficacy of 10 mg/kg Remdesivir Against MERS-CoV Infection in Rhesus Monkeys

The prophylactic efficacy of a 10 mg/kg daily dose of remdesivir was determined in MERS-CoV-infected rhesus monkeys of Indian origin (Study PC-399-2038). Vehicle or remdesivir at 10 mg/kg was administered once daily for 7 days using IV bolus injection beginning 1 day prior to MERS-CoV inoculation (Table 6). Animals were inoculated on Day 0 with a target dose of 7 * 106 TCID50 of MERS-CoV via the intranasal, ocular, oral, and intratracheal routes.

Table 6. PC-399-2038: Design of Prophylactic Study of 10 mg/kg Intravenous Remdesivir Against MERS-CoV in Rhesus Monkeys

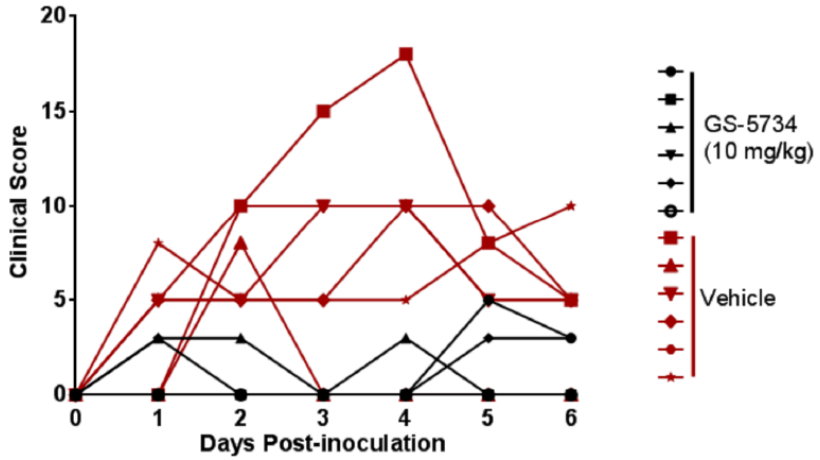
Table 34. PC-399-2038: Design of Prophylactic Study of 10 mg/kg Intravenous Remdesivir Against MERS-CoV in Rhesus Monkeys

Group No.	No. of Animals (N)	Treatment (IV, Once Daily)
1	N = 6	Remdesivir 10 mg/kg, Days –1 to 5
2	N = 6	Vehicle, Days –1 to 5

Source: IB Edition 5 21 February 2020, Table 34

Time-weighted average clinical scores were significantly higher in control vehicle-treated animals than in remdesivir-treated animals (p = 0.006; Figure 8). Clinical signs of respiratory disease, such as hunched posture and increased respiration rates observed in control vehicle-treated animals, were not observed in remdesivir-treated animals. At necropsy on Day 6 post-infection, viral RNA levels in lungs of remdesivir-treated animals were significantly reduced compared with vehicle-treated controls (Table 7). Animals treated with a 10 mg/kg dose of remdesivir displayed changes in serum creatinine and BUN suggestive of altered renal function (Study PC-399-2038).

Figure 8 PC-399-2038: Effect of 10 mg/kg Intravenous Remdesivir Once-Daily Prophylactic Administration on Clinical Score in MERS-CoV-Infected Rhesus Monkeys



Source: IB Edition 5 21 February 2020, Figure 16

Table 7. PC-399-2038: Effect of 10 mg/kg Intravenous Remdesivir Once-Daily Prophylactic Administration on Lung Viral Load in MERS-CoV-Infected Rhesus Monkeys

Group, No. of Animals (N)	Treatment (IV, Once Daily, Days −1 to 5)	Day 6 Average Lung Viral Load (Log_{10} $TCID_{50}$ Eq/g) (SD)
Group 1, N = 6	Remdesivir 10 mg/kg	0.26 (0.66)[a]
Group 2, N = 6	Vehicle	3.58 (0.89)

P-value was calculated from unpaired t-test comparing remdesivir-treated animals to control vehicle-treated animals.
a p = 0.0022.

Source: IB Edition 5 21 February 2020, Table 35

No in vivo studies have been conducted in SARS/MERS-CoV infected animals where treatment was initiated later than one day after viral inoculation. Furthermore, no data have been referred to on the efficacy of remdesivir in any animal model with SARS-CoV-2. Therefore, the efficacy seen in the cited animal models must be bridged from SARS-Cov and MERS to SARS-Cov2 via similar EC50 values and presumed similarity of pathogenesis.

Secondary Pharmacology:

Remdesivir and the nucleoside analog GS-441524 were broadly profiled in a suite of in vitro toxicity assays, including cytotoxicity in multiple human cell types and mitochondrial function testing under various conditions. These results were considered in the context of systemic exposures observed in healthy human subjects administered 200-mg remdesivir IV. The dose of 200 mg represents the currently proposed maximum dose for the treatment of patients with acute EVD, MVD, or COVID-19, and/or subjects recovering from EVD. Administration of remdesivir 200 mg results in Day 1 peak systemic concentrations (Cmax) of 9.0 µM for remdesivir and 0.5 µM for GS-441524. Concentrations of remdesivir associated with biological effects in the individual toxicity assays. To put these effects in the context of the clinical systemic drug exposure, individual margins for each assay are also presented based on the in vitro and in vivo free drug concentrations. The margins are > 3.5-fold in most of the assays. Only 3 assays, including cytotoxicity in PHH, cytotoxicity in PC-3 cells under aerobic conditions, and spare mitochondrial respiration in PC-3 cells, show a < 2-fold margin.

It should be noted, however, that these narrower margins are observed in vitro under constant prolonged exposures to remdesivir for several days. In comparison, the systemic clinical exposures to drug concentrations > 1 µM are transient, lasting only for the duration of IV infusion (ie, 1 hour) due to fast systemic clearance.

The nucleoside analog GS-441524 was largely devoid of any effects at high concentrations, with the exception of effects on the proliferation of various hematopoietic stem cells, with CC50 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 remdesivir. In conclusion, both remdesivir and the nucleoside analog GS-441524 exhibit good margins in most in vitro toxicity assays. A relatively narrow in vitro cytotoxicity margin (ie, ratio of CC50 and clinical Cmax) for a 200-mg IV infusion of approximately 0.3-fold was determined for remdesivir in PHH following 5-days incubation, which may be informative in further understanding the liver transaminase elevations observed in healthy human subjects following multiple doses of remdesivir.

Molecular target screening studies (evaluated against a panel of up to 87 targets consisting of receptors, ion channels, and transporters) with GS-441524 and GS-466547 showed no significant binding (> 50%) at 10 µM.

Safety pharmacology:

Studies were conducted to examine the potential effects of remdesivir on the respiratory, CNS, and cardiovascular systems after IV administration. In a respiratory safety study in rats, remdesivir had no effect on tidal volume or minute volume; however, respiration rates were increased from 0.75 to 6 hours postdose in animals administered ≥ 20 mg/kg.

Respiration rates returned to control levels by 24 hours postdose, resulting in a NOEL for respiratory function in male rats of 5 mg/kg, at exposures approximately 2-fold above the estimated GS-441524 Cmax at the currently proposed 200-mg maximum clinical dose.

Remdesivir had no effect on the CNS of rats and no effect on cardiovascular parameters in monkeys. at dose levels up to 50 and 10 mg/kg, respectively. Resulting in a 18-fold safety margin at the NOEL (50 mg/kg) in rats and in an approximately 2.5-fold safety margin at the NOEL (10 mg/kg) in monkeys at the currently proposed 200-mg maximum clinical dose.

Additional remdesivir did show only a weak inhibition in vitro of the hERG channel, IC20 and IC50 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.

Pharmacokinetics

ADME:

Absorption, distribution, and metabolism studies support the selection of Wistar-Han rat and cynomolgus monkey for the assessment of remdesivir toxicology. Both rat and monkey formed the intermediate metabolite GS-704277 and the nucleoside metabolite GS-441524. GS-441524 is the predominant metabolite observed in all nonclinical studies.

Remdesivir is not suitable for oral delivery as its poor hepatic stability would likely result in almost complete first-pass clearance.

Additional it was investigated that the IM route was also suboptimal for the administration of remdesivir. Studies assessing IM administration did shown a slow and variable release from muscle, evidence for IM metabolism, and delayed appearance of the pharmacologically active triphosphate GS-443902 in PBMCs. Therefore, it was concluded that IV administration delivers GS-443902 more rapidly and consistently into target cells.

Following IV administration of [14C]remdesivir to rats and monkeys, radioactivity was widely distributed in most tissues. High levels of radioactivity were observed in kidney, kidney medulla, liver, and arterial wall. Little or no radioactivity was detected in brain tissues of rats, suggesting that [14C]remdesivir-derived radioactivity crosses the blood:brain barrier poorly. Low levels of radioactivity were detected in testis in both rats and monkeys, suggesting that [14C]remdesivir-derived radioactivity can cross the blood:testis barrier. No melanin binding was observed. The predominant circulating metabolite was the nucleoside analog GS-441524 in both rats and monkeys.

Studies in rats and monkeys indicating that renal and biliary excretion were the major routes of elimination.

Drug-Drug- Interactions:

It was shown in vitro that remdesivir is a substrate for CYP2C8, CYP2D6, and CP3A4.

Remdesivir is a substrate for OATP1B1 and P-gp. However, the impact of these transporters on remdesivir disposition is likely minimized by the parenteral route of administration. Remdesivir is an inhibitor of CYP3A4, OATP1B1, OATP1B3, BSEP, MRP4, and NTCP in vitro, but its potential to be the perpetrator of clinically significant drug-drug interactions is limited by its rapid clearance. GS-704277 and GS-441524 are not inhibitors of human BSEP, MRP2, MRP4, or NTCP transporters. While hepatocyte donor-dependent induction of mRNA levels of CYP1A2 and CYP2B6 was observed, remdesivir showed no induction of CYP3A4 mRNA or CYP3A4/5 activity. No evidence for induction by GS-441524 or GS-704277 was observed. Consistently, no potential for induction of enzymes or transporters via PXR or AhR was detected in reporter cell lines.

Toxicology

No single-dose toxicity studies with remdesivir have been conducted. The nonclinical toxicologic profile of remdesivir has been characterized in a comprehensive set of safety evaluations that includes GLP compliant 2 and 4 w- long repeat-dose toxicity studies in rats and cynomolgus monkeys, a complete set of reproductive and developmental toxicity studies in rats and rabbits, and a standard battery of genotoxicity evaluations. The safety program also includes a mechanistic study in rats addressing a nephrotoxic potential of remdesivir, a non- GLP study in cynomolgus evaluating safety of IM injections of remdesivir and a 2-week study in rhesus monkeys of Indian origin and in vitro assays investigating hemolytic potential. Exposure margins are generally given in relation to exposure to the predominant metabolite in plasma GS-441524.

Repeated dose toxicity:

Repeat-dose toxicity studies in rats (5, 20, 50 mg/kg for 14 days and 1, 3, 10 mg/g for 4 weeks) and studies in monkeys (1, 3, 10 mg/kg for 14 days and 4 weeks) after intravenous injections identified the kidney as target organ. In both species, clinical chemistry, urinalysis, and/or urinary biomarkers were early predictors of the observed kidney changes.

In rats microscopic changes in the kidney were seen in males administered ≥ 3 mg/kg/day and in females administered 10 mg/kg/day, and were consistent with a regenerative process secondary to a sustained, low-level injury to the cortical tubules; findings included basophilic tubules and karyomegaly. These findings were associated with increased kidney weights and/or ratios for males.

Assessment of interaction of remdesivir and its major systemic metabolites, GS-704277 and the nucleoside analog GS-441524, with human and rat renal OATs showed that GS-704277, but not remdesivir or GS-441524, is an effective substrate of rat OAT3 and exhibits rat OAT3-dependent cytotoxicity, suggesting it may have a role in the observed renal adverse effects in rats. GS-704277 is not a substrate for human OATs, suggesting a reduced potential for renal adverse effects in human compared with rat due to lower renal accumulation.

There were no liver changes in rats or monkeys based on clinical chemistry parameters, liver weight, or microscopic observations.

Based on the nature and severity of the kidney changes in rats after 4 weeks, the NOAEL for remdesivir is 3 mg/kg/day (GS-441524: Day 28 Cmax 208 and 127 ng/mL in males and females, respectively; Day 28 AUC0-24 1000 and 493 ng•h/mL in males and females, respectively; GS-704277: Day 28 Cmax 1020 and 288 ng/mL in males and females, respectively; Day 28 AUC0-24 424 and 167 ng•h/mL in males and females, respectively). At the 3 mg/kg/day dose, GS-441524 AUCs were approximately 0.3-fold lower versus exposures at the currently proposed 200-mg maximum clinical dose.

The NOAEL in monkey after 4 weeks of treatment was 10 mg/kg/day (Day 28 mean combined sexes: remdesivir AUC0-24 of 1330 ng•h/mL and Cmax of 1160 ng/mL; GS-441524 AUC0-24 of 2070 ng•h/mL and Cmax of 288 ng/mL; GS-704277 AUC0-24 of 849 ng•h/mL and Cmax of 680 ng/mL). At the NOAEL, margins of exposures are approximately 0.5-fold for remdesivir and 0.9-fold for GS-441524 versus the 200-mg clinical dose.

Additional non-GLP studies were conducted, the diastereomeric mixture GS-466547 has been administered to male cynomolgus monkeys by IM injection once daily for 7 days and remdesivir has been administered to male rhesus monkeys by IV injection once daily for 7 days.

As the IM injection is not the intended administration in humans, no further data will be presented and discussed.

In the IV study of rhesus monkeys of Indian origin (TX-399-2021), remdesivir was administered at 0, 5, 10, and 20 mg/kg/day for 7 days. Remdesivir-related morbidity, with subsequent early euthanasia, was noted in a single 20 mg/kg/day animal. The cause of moribundity was attributed to remdesivir-related kidney findings. Clinical observations noted prior to early euthanasia included hypoactivity, labored respiration, partial closure of the eye(s), dermal atonia, red mucoid feces, decreased body temperature and red or brown material around the anogenital area. Microscopically, this animal also had ulcerations or necrosis in the stomach, jejunum, colon, and rectum, and decreased cellularity of the lymphoid follicles in the spleen. No remdesivir-related clinical findings were noted for the surviving animals or effects on food consumption. Nonadverse, remdesivir-related slight body weight losses and lower body weight gains were noted at ≥ 10 mg/kg/day during the dosing period; animals showed improvement during the 10-day recovery period. Changes in hematology, coagulation, serum chemistry, and urinalysis indicated kidney injury and/or dysfunction. These effects were dose dependent, and correlated with histopathology findings of renal tubular atrophy and basophilia and casts. Macroscopic findings at the primary necropsy included discoloration or pale kidneys in a single 20 mg/kg/day animal, which correlated microscopically to tubular atrophy and basophilia, and a small thymus in a single 10 mg/kg/day animal, which correlated microscopically to mild decreased lymphocytes in the cortex of the thymus. Pale kidneys in one 20 mg/kg/day recovery animal correlated microscopically to moderate interstitial fibrosis. There were no remdesivir-related macroscopic findings noted at the recovery necropsy. 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 findings were considered adverse at all dose levels as there was a loss of tubules and resulting interstitial fibrosis in 1 recovery animal, suggesting progression to chronicity. A NOAEL was not determined in this study.

Table 8. Estimated Margins for Remdesivir and the Nucleotide MetaboliteGS-441524 Relative to Exposure at a 200-mg Clinical Dose

Species, Route, Duration	NOAEL (mg/kg/day)	NOAEL AUC_{0-24} (µg•h/mL)[a]		Human Dose (mg)	AUC Margin[b]	
		Remdesivir	GS-441524		Remdesivir	GS-441524
Rat, IV, 4 weeks	3	NA	748	200	NA	0.3
Monkey, IV, 4 weeks	10	1330	2070	200	0.5	0.9

NA = not applicable (plasma concentrations of remdesivir were not measurable at the 3 mg/kg/day dose); NOAEL = no observed adverse effect level

a Males and females combined.

b Margins of exposure were calculated using Day 1 exposure (AUC_{0-24}) in human at the 200-mg clinical dose (Study GS-US-399-5505).

Source: IB Edition 5 21 February 2020, Table 61

Genotoxicity:

Remdesivir was non genotoxic in a standard battery of in vitro and in vivo studies.

Reproductive and development toxicity:

A complete set of developmental and reproductive toxicity studies have been conducted with remdesivir.

In the reproductive and development toxicity studies, the only notable finding was a decrease in corpora lutea, a consequent decrease in implantation sites and viable embryos, and lower ovary and uterus/cervix/oviduct weights in the rat fertility study; these changes were observed at a systemically toxic dose. There were no remarkable findings in male rats in the fertility study, no adverse findings in the developmental toxicity studies in rats and rabbits, and no adverse changes in the pre- and postnatal study in rats.

EFD-Rats: At the NOAEL 20 mg/kg/day (GD 17 GS-441524 AUC0-24 and Cmax values of 8740 ng•h/mL and 1580 ng/mL, respectively, and GS-704277 AUC0-24 and Cmax values of 3420 ng•h/mL and 8620 ng/mL, respectively), the margin of exposures is approximately 3.9-fold for GS-441524 versus the 200-mg clinical dose.

EFD-Rabbits: At the NOAEL 20 mg/kg/day (GD 17: remdesivir AUC0-24 and Cmax values of 2830 ng•h/mL and 2950 ng/mL, respectively; GS-441524 AUC0-24 and Cmax values of 8930 ng•h/mL and 1680 ng/mL, respectively, and GS-704277 AUC0-24 and Cmax values of 11,700 ng•h/mL and 13,200 ng/mL, respectively), the margins of exposures are approximately 0.5-fold for remdesivir and 4.0-fold for GS-441524 versus the 200-mg clinical dose.

PPN-Rats: Due to the lack of adverse effects at any dose, the NOAEL was 10 mg/kg/day for F0 maternal systemic toxicity (LD 10 GS-441524 and GS-704277 Cmax values of 572 and 2680 ng/mL, respectively, and AUC0-24 values of 2310 and 1190 ng•h/mL, respectively) and 10 mg/kg/day for F1 developmental/neonatal, F1 parental systemic, F1 reproductive, and F2 neonatal/early postnatal toxicity (PND 10 GS-441524 Cmax value of 4.51 ng/mL in F1 pups). At the NOAEL, the margin of exposures is approximately 1.0-fold for GS-441524 versus the 200-mg clinical dose.

Other toxicity studies:

Remdesivir were compatible with monkey, rat, and human whole blood and plasma.

Data on phototoxic potential is missing for the substance.

To explore the potential etiology of remdesivir nephrotoxicity observed in rat repeat-dose toxicity studies, remdesivir and its major systemic metabolites GS-441524 and GS-704277 were tested for their interaction with human and rat renal OATs (Study PC-399-2020). Rat OAT3 expression increased the cytotoxicity of the intermediate metabolite GS-704277 by approximately 15-fold. In addition, intracellular accumulation of the active triphosphate metabolite GS-443902 increased in rat OAT3-expressing cells following exposure to GS-704277. In contrast, the cytotoxicity of GS 704277 changed minimally (< 2-fold) in cells expressing rat OAT1, human OAT1, or human OAT3 transporters compared with control cells. The expression of neither rat nor human OATs significantly changed cytotoxicity or intracellular triphosphate accumulation upon incubation with remdesivir or the nucleoside metabolite GS-441524. These data indicate that the intermediate metabolite GS-704277, but not remdesivir or the nucleoside metabolite GS-441524, is an effective substrate of rat OAT3 and exhibits rat OAT3-dependent cytotoxicity. In contrast, GS-704277 is not a substrate for human OATs, suggesting a reduced potential for renal adverse effects in human compared with rat due to lower renal accumulation.

Discussion on non-clinical aspects

Empirical nonclinical data on antiviral activity of remdesivir on SARS-CoV-2 is currently limited to a few in vitro observations. Information supportive of clinical activity mainly extrapolated from in vivo studies with other Coronavirus types (i.e. SARS CoV and MERS-CoV), that are presumed to have similar pathogenesis and viral susceptibility as does covid-19 and SAR-Cov2. These studies indicate that prophylactic treatment is more effective than when remdesivir is given after viral challenge. Furthermore, there are no data on the initiation of treatment more than one day after challenge. The case supporting the potential efficacy of remdesivir in the proposed use is further discussed below, in the section on benefits and risks. The case for the PK bridge from animal models to humans is discussed below, in the section on clinical pharmacology.

The non-clinical studies are considered sufficient in scope and extent to support the duration of clinical use. The data presented adequately describes the pharmacological and toxicological properties of remdesivir.

Secondary pharmacology studies indicate that primary human hepatocytes may be sensitive to remdesivir cytotoxicity at clinically relevant exposures. This may correlate with transient increases in liver enzymes that have been observed in healthy volunteers after repeated dosing with remdesivir and is monitorable.

Safety pharmacology studies in rats indicated that remdesivir may transiently increase respiratory rate at 2.5-fold the maximum clinical exposure. In addition, an in vitro hERG assay indicated an inhibitory potential 6-fold clinical exposure. No adverse effects on respiration or EKG after repeated exposure have been recorded.

Remdesivir has low potential for drug-drug interactions.

In repeat-dose toxicity studies in rats and monkeys, kidney (i.e. kidney tubular epithelium) was identified as the primary target organ of remdesivir toxicity. After repeated-dosing signs of kidney injury and/or reduced function was evident as indicated by biomarkers at clinically relevant exposures. At higher exposures than required for inducing kidney toxicity, three unscheduled mortalities were noted across the nonclinical studies. One of these deaths, a high-dose female rhesus monkey, was likely secondary to kidney injury. For the remaining two deaths (2/25 high-dose female rats, on day 14 and 19 in the 4 w repeat dose study) the relationship of remdesivir in uncertain. Given that kidney toxicity was observed at lower exposures than these deaths (which allows for monitoring of signs of remdesivir toxicity) and the vital indication targeted with this CUP, this issue is not pursued here. However, a more thorough investigation of the findings in rats are expected in a future application. None-the-less it will have to be taken into consideration in the overall benefit-risk assessment and addressed in future applications. Another issue that would need future clarification by the applicant is an observation that doses used in the repeated-dose toxicity studies were not high enough to provide information 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.).

Remdesivir were negative *in vitro* and *in vivo* genotoxicity studies.

Remdesivir administration had no effect on reproductive functions in males or on embryo-fetal and peri-postnatal development. However, exposure to remdesivir or its metabolites were not sufficiently high to fully exclude lack of reproductive/developmental toxicity. Furthermore, 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). These reproductive risks have been taken into

consideration in the recommendations regarding pregnant women and women of child-bearing potential.

An assessment on phototoxic potential is missing in the provided dossier for remdesivir. Considering that the patients are in intensive care and likely not at risk for a phototoxic reaction lack of this information is acceptable. For future applications, the phototoxic potential of remdesivir treatment is expected to be addressed in line with ICH guideline S10 on photosafety evaluation of pharmaceuticals.

The potential pharmacodynamic interactions of remdesivir and its functional consequences is not considered in the non-clinical part.

Overall conclusion on non-clinical aspects

Remdesivir has shown antiviral activity in animal models of SARS-CoV and MERS-CoV disease.

To conclude the nonclinical part, a few concerns and deficiencies were identified regarding the nonclinical safety studies, but these are either manageable by recommendations / warnings in the CU protocol (e.g. restrictions in inclusion of patients with reduced kidney / liver functions) or acceptable given the vital indication and that patients are in intensive care. From a non-clinical point of view there are no issues that prohibit the use of remdesivir at the proposed dose regime and the intended patient population.

There is also no concern for inclusion of women of childbearing potential. The Applicant is proposing that the use of remdesivir in pregnant woman is not recommended. Remdesivir has been used for treatment of Ebola in a few pregnant women (Mulangu S, Dodd L, Davey R, Mbaya O, Proschan M, Mukadi D, et al. A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. NEJM. 2019;381(24):2293–2203). Based on the data provided no safety or efficacy issue in pregnant woman can be predicted. In addition, the safety profile of remdesivir is incompletely characterized. The Committee acknowledged this fact and consider that the use of Remdesivir is not recommended in pregnant women at the moment.

3.4 *Clinical aspects*

Data submitted

The assessment based on the submitted IB edition 5 (21 February 2020). The applicant has also submitted references to a number of scientific publications. No study reports have been submitted.

Pharmacokinetics

Remdesivir (GS-5734) is a single diastereomer monophosphoramidate prodrug of a monophosphate nucleoside analog (GS-441524). The rapid decline in plasma levels of remdesivir are accompanied by the sequential appearance of the intermediate metabolite GS-704277 and the nucleoside metabolite GS-441524. Inside cells, the GS-441524 monophosphate undergoes rapid conversion to the pharmacologically active analog of adenosine triphosphate (GS-443902) that inhibits viral RNA polymerases.

- Absorption

IV administration, F=100 %. The Sponsor claims that remdesivir is not suitable for oral delivery as its poor hepatic stability would likely result in almost complete first-pass clearance.

Following an IV infusion of 200 mg remdesivir to healthy human subjects, the AUC0-24 values were 4.8 µM•h for remdesivir and 7.7 µM•h for the nucleoside metabolite GS-441524 (**Study GS-US-399-5505**). In addition, following a 30-minute IV infusion of remdesivir lyophilized formulation, similar plasma exposures to remdesivir, GS-704277, and GS-441524 were observed between rhesus monkeys and human subjects administered remdesivir at doses of 5 mg/kg and 75 mg, respectively (**Study GS-US-399-1812**).

Following single-dose IV administration of remdesivir solution formulation over 2 hours at doses ranging from 3 to 225 mg in Study GS-US-399-1812, remdesivir and GS-441524, the major circulating metabolite, exhibited a linear PK profile. Following administration of remdesivir IV over 2 hours at doses of 75 and 150 mg, both the lyophilized and solution formulations provided comparable remdesivir PK parameters, indicating similar formulation performance. Remdesivir 75 mg lyophilized formulation infused IV over 30 minutes provided similar PBMC exposures of GS-443902, the active triphosphate metabolite, as remdesivir 150 mg lyophilized formulation infused IV over 2 hours.

Table 9. GS-US-399-1812: Summary Statistics of Remdesivir Plasma Pharmacokinetic Parameters Following a Single 2-Hour Intravenous Infusion of Remdesivir Solution Formulation in Healthy Adult Subjects (Cohorts 1-6; Pharmacokinetic Analysis Set)

PK Parameter[a]	Cohort 1 Remdesivir 3 mg (N = 8)	Cohort 2 Remdesivir 10 mg (N = 8)	Cohort 3 Remdesivir 30 mg (N = 8)	Cohort 4 Remdesivir 75 mg (N = 8)	Cohort 5 Remdesivir 150 mg (N = 8)	Cohort 6 Remdesivir 225 mg (N = 8)
AUC_{inf} (h•ng/mL)	—	230.0 (28.4)	773.9 (22.9)	1999.6 (27.1)	2976.1 (19.0)	5274.7 (11.6)
AUC_{last} (h•ng/mL)	67.1 (17.2)	230.0 (16.1)	767.5 (23.2)	1989.9 (27.3)	2965.4 (19.1)	5261.7 (11.7)
C_{max} (ng/mL)	57.5 (31.1)	220.8 (31.2)	693.9 (18.6)	1626.0 (38.6)	2280.0 (30.1)	4421.3 (16.0)
T_{max} (h)	2.03 (2.01, 2.04)	2.01 (2.00, 2.03)	2.02 (2.00, 2.03)	2.03 (2.03, 2.05)	2.00 (1.98, 2.04)	1.97 (1.95, 1.98)
$t_{1/2}$ (h)	—	0.66 (0.54, 0.79)	0.81 (0.61, 0.91)	0.90 (0.82, 1.07)	0.99 (0.92, 1.06)	1.05 (0.96, 1.21)

a All PK parameters are presented as mean (%CV) except T_{max} and $t_{1/2}$, which are presented as median (Q1, Q3). Plasma AUC_{inf} was not calculable for Cohort 1.

Source: IB Edition 5 21 February 2020, Table 63

Following multiple once-daily IV administration, remdesivir plasma PK was consistent with that observed after single-dose administration, with no accumulation, consistent with its t1/2 of approximately 1 hour. Metabolite GS-441524 reached steady-state by Day 4, and accumulated approximately 1.9-fold (based on AUC) after multiple daily dosing, consistent with its t1/2 of approximately 24.5 hours.

Table 10 GS-US-399-5505: Summary Statistics of Remdesivir Plasma Pharmacokinetic Parameters Following 30-Minute IV Infusion(s) of Remdesivir 200 mg on Day 1 and 100 mg Daily for 4 Days in Healthy Adult Subjects (Preliminary Analysis)

PK Parameter[a]	Remdesivir Day 1 (N = 8)	Remdesivir Day 5 (N = 7)
Cohort 1 (5-day dosing)		
C_{max} (ng/mL)	5440 (20.3)	2610 (12.7)
AUC[b] (h•ng/mL)	2920 (20.6)	1560 (13.9)
$t_{1/2}$ (h)	0.98 (0.82, 1.03)	0.89 (0.82, 1.09)

a All PK parameters are presented as mean (%CV) except $t_{1/2}$, which is presented as median (Q1, Q3).
b $AUC_{0\text{-}24}$ is presented for Day 1. AUC_{tau} is presented for Day 5.

Source: IB Edition 5 21 February 2020, Table 74

Table 11. GS-US-399-5505: Summary Statistics of Nucleoside Metabolite GS-441524 Plasma Pharmacokinetic Parameters Following 30-minutes IV Infusion(s) of Remdesivir 200 mg on Day 1 and 100 mg Daily for 4 Days in Healthy Adult Subjects (Preliminary Analysis)

PK Parameter[a]	GS-441524 Day 1 (N = 8)	GS-441524 Day 5 (N = 7)
Cohort 1 (5-day dosing)		
C_{max} (ng/mL)	152 (25.9)	142 (30.3)
AUC[b] (h•ng/mL)	2240 (29.1)	2230 (30.0)
$t_{1/2}$ (h)	NA	25.3 (24.10, 30.32)

NA = not applicable
a All PK parameters are presented as mean (%CV) except $t_{1/2}$, which is presented as median (Q1, Q3).
b $AUC_{0\text{-}24}$ is presented for Day 1. AUC_{tau} is presented for Day 5.

Source: IB Edition 5 21 February 2020, Table 75

- Distribution

Remdesivir had moderate protein binding in all species, with a free fraction ranging from 8.0% in rat to 14.2% in cynomolgus monkey. The free fraction in human was 12.1%. GS-704277 and GS-441524 exhibited very low protein binding in plasma from all species (mean free fraction ranging from 85% to 127%).

- Metabolism

The stability of remdesivir in human plasma was determined (Study AD-399-2012) and the half-life was determined to be 69 minutes. Remdesivir was more unstable in rat plasma (t1/2 ≤ 0.9 min), and the Sponsor explains this with higher esterase activity in rodent plasma.

The metabolic stability of remdesivir was assessed in intestinal S9 from Sprague-Dawley rat, beagle dog, and human, and hepatic S9 from Sprague-Dawley rat, beagle dog, cynomolgus monkey, rhesus monkey, and human (Study AD-399-2014). Across species, remdesivir was moderately stable in intestinal extract (t1/2 = 40.3 to 114.1 minutes) but unstable in hepatic extract (t1/2 < 3.9 minutes). Remdesivir was relatively stable in human intestinal S9 (t1/2 = 114.1 minutes).

To determine if remdesivir is a substrate for cytochrome P450 enzyme (CYP) enzymes, 5 μM remdesivir was incubated with 7 individual complementary DNA-expressed human CYP enzyme preparations coexpressed with human nicotinamide adenine dinucleotide phosphate CYP reductase (Study AD-399-2011). There was no detectable metabolism of remdesivir by recombinant CYP1A2, CYP2B6, CYP2C9, or CYP2C19. Remdesivir was metabolized by CYP2C8, CYP2D6, and CYP3A4. The rate of CYP3A4 metabolism was 42.1% of that of the positive control, simvastatin.

Although remdesivir is a substrate for CYP2C8, CYP2D6, and CYP3A4 in vitro, the Sponsor argues that its metabolism is likely to be predominantly mediated by hydrolase activity.

Metabolism data on intermediate metabolite GS-704277, the nucleoside metabolite GS-441524 and the pharmacologically active analog of adenosine triphosphate GS-443902 has not been reported.

Available preliminary data from the mass balance study (GS-US-339-4231) confirm that remdesivir is extensively metabolized. Additional plasma metabolite profiling analyses from the mass balance study (see below) are ongoing.

Clinical Study **GS-US-399-4231**: Remdesivir Human Absorption, Distribution, Metabolism, and Excretion Study:

Available preliminary data from this study confirm that remdesivir is extensively metabolized.

The total combined mean recovery of [14C]-radioactivity in feces and urine was approximately 92%, with most of the radioactive dose recovered from urine (approximately 74%). The predominant species detected in urine were GS-441524 (49%), followed by remdesivir (10%) and other metabolites, accounting for 6% of total radioactive dose (each less than 2%). In feces, M14 accounted for 12% of the radioactive dose; all other metabolites were in trace amounts, accounting for 1% of total radioactivity (each less than 0.5%). Additional plasma metabolite profiling analyses are ongoing.

Peripheral Blood Mononuclear Cell Pharmacokinetics of the Active Triphosphate Metabolite GS-443902

Peripheral blood mononuclear cell PK parameters for the active triphosphate metabolite GS-443902 after administration of single IV doses (75 and 150 mg) of remdesivir lyophilized formulation (Cohorts 7-9) are presented in Table 12. The median t1/2 of GS-443902 in PBMCs was comparable between the 75- and 150-mg doses administered IV over 2 hours (35.95 to 42.68 hours). Following IV administration of 75 mg remdesivir lyophilized formulation over 30 minutes (Cohort 9), GS-443902 exposure (AUCinf) in PBMCs was similar to that achieved with 150 mg remdesivir lyophilized formulation administered IV over 2 hours (Cohort 8).

Table 12 GS-US-399-1812: Summary Statistics of Peripheral BloodMononuclear Cell Pharmacokinetic Parameters of the Active Triphosphate Metabolite GS-443902 Following a Single Intravenous Infusion of Remdesivir Lyophilized Formulation in Healthy Adult Subjects (Cohorts 7-9; PK Analysis Set; Sensitivity Analysis)

GS-443902 PBMC PK Parameter[a]	Cohort 7 Remdesivir 75 mg 2-Hour Infusion (N = 10)	Cohort 8 Remdesivir 150 mg 2-Hour Infusion (N = 10)	Cohort 9 Remdesivir 75 mg 30-Minute Infusion (N = 9)
AUC_{inf} (h•ng/mL)	176.2 (23.1)	294.7 (28.3)	394.3 (49.9)
$t_{1/2}$ (h)	42.68 (30.61, 47.41)	35.95 (27.27, 41.50)	48.79 (26.61, 69.52)

a AUC_{inf} is presented as mean (%CV); $t_{1/2}$ is presented as median (Q1, Q3). One subject in Cohort 9 did not receive the full volume of the IV dose; data for this subject was excluded.

Source: IB Edition 5 21 February 2020, Table 69

Peripheral Blood Mononuclear Cell Pharmacokinetics of the Nucleoside Metabolite GS-441524

Peripheral blood mononuclear cell PK parameters the nucleoside metabolite GS-441524, which reflect total levels of PBMC-associated GS-441524 intracellular metabolites (GS-441524 and its monophosphate, diphosphate, and active triphosphate [GS-443902] forms) after administration of single IV doses (3 to 225 mg) of remdesivir solution formulation (Cohorts 1-6) are presented in Table 13.

GS-441524 exposures in PBMCs (AUCinf) increased across the dose range evaluated. The median t1/2 of GS-441524 in PBMCs was comparable across the 3 to 225 mg dose range (32.23 to 48.38 hours).

Table 13. GS-US-399-1812: Summary Statistics of Peripheral Blood Mononuclear Cell Pharmacokinetic Parameters of the Nucleoside Metabolite GS-441524 Following a Single 2-Hour Intravenous Infusion of Remdesivir Solution Formulation in Healthy Adult Subjects (Cohorts 1-6; Pharmacokinetic Analysis Set)

GS-441524 PBMC PK Parameter[a]	Cohort 1 Remdesivir 3 mg (N = 8)	Cohort 2 Remdesivir 10 mg (N = 8)	Cohort 3 Remdesivir 30 mg (N = 8)	Cohort 4 Remdesivir 75 mg (N = 8)	Cohort 5 Remdesivir 150 mg (N = 8)	Cohort 6 Remdesivir 225 mg (N = 8)
AUC_{inf} (h•ng/mL)	11.6 (74.3)	37.1 (31.7)	91.0 (39.9)	414.1 (37.3)	463.7 (36.6)	863.2 (32.5)
$t_{1/2}$ (h)	48.38 (30.75, 101.37)	43.12 (33.43, 52.09)	43.58 (25.23, 54.29)	38.63 (29.91, 41.01)	39.47 (32.68, 43.11)	32.23 (28.99, 42.60)

a AUC_{inf} is presented as mean (%CV); $t_{1/2}$ is presented as median (Q1, Q3).

Source: IB Edition 5 21 February 2020, Table 68

- Formulations (bioequivalence/relative bioavailability)

In Clinical Study **GS-US-399-1812**: Remdesivir Single-Ascending Dose Study, nine dose cohorts were evaluated in the study. Following screening and Day −1 procedures, eligible subjects were randomized 4:1 within each of Cohorts 1-6 to receive remdesivir solution formulation (n = 8) or matching placebo (n = 2) on Day 1.

In each of Cohorts 7-9, subjects were randomized 5:1 within each cohort to receive remdesivir lyophilized formulation (n = 10) or matching placebo (n = 2) on Day 1.

The study was not primarily designed for a bioequivalence/relative bioavailability comparison between the different formulations, but data may be extracted as follows:

Table 14 GS-US-399-1812: Statistical Comparison of Plasma Pharmacokinetic Parameters for Remdesivir and the Nucleoside Analog GS-441524 Between the Lyophilized and Solution Formulations of Remdesivir (Cohorts 4, 5, 7, and 8; Pharmacokinetic Analysis Set)

	Remdesivir 75 mg			Remdesivir 150 mg		
	GLSM			GLSM		
	Cohort 7: Lyophilized Formulation (N = 10)	Cohort 4: Solution Formulation (N = 8)	% GLSM Ratio (Lyophilized/Solution) (90% CI)	Cohort 8: Lyophilized Formulation (N = 10)	Cohort 5: Solution Formulation (N = 8)	% GLSM Ratio (Lyophilized/Solution) (90% CI)
Remdesivir PK Parameter						
AUC_{inf} (h•ng/mL)	1817.00	1941.53	93.59 (77.71, 112.70)	3192.39[a]	2933.39	108.83 (91.98, 128.76)
AUC_{last} (h•ng/mL)	1809.53	1931.48	93.69 (77.73, 112.91)	3199.24	2922.80	109.46 (93.16, 128.60)
C_{max} (ng/mL)	1657.30	1478.18	112.12 (77.10, 163.03)	2572.82	2183.17	117.85 (88.97, 156.09)
GS-441524 PK Parameter						
AUC_{inf} (h•ng/mL)	2166.00	2411.15	89.83 (74.57, 108.22)	4233.57	4589.67	92.24 (78.62, 108.22)
AUC_{last} (h•ng/mL)	2056.30	2313.81	88.87 (73.47, 107.50)	4100.62	4464.28	91.85 (78.19, 107.90)
C_{max} (ng/mL)	75.98	83.61	90.88 (74.92, 110.25)	143.27	148.14	96.71 (77.97, 119.95)

CI = confidence interval; GLSM = geometric least-squares mean
Solution and lyophilized formulations administered via 2-hour infusion are compared.
a n = 9 for this parameter.

Source: IB Edition 5 21 February 2020, Table 67

Although not formally bioequivalent in this comparison, the results indicate that the formulations result in comparable plasma concentrations.

- Elimination and Excretion

Study **GS-US-399-4231** was single-center, open-label, mass balance Phase 1 study of remdesivir administered as a single, IV dose of radiolabeled [14C]-remdesivir in healthy subjects (n=8).

The total combined mean recovery of [14C]-radioactivity in feces and urine was approximately 92%, with most of the radioactive dose recovered from urine (approximately 74%). The predominant species detected in urine were GS-441524 (49%), followed by remdesivir (10%) and other metabolites, accounting for 6% of total radioactive dose (each less than 2%). In feces, M14 accounted for 12% of the radioactive dose; all other metabolites were in trace amounts, accounting for 1% of total radioactivity (each less than 0.5%).

Notable, the excipient SBECD is renally cleared.

- Drug-Drug Interactions

No in vivo interaction studies have been performed, but the ability of the parent compound remdesivir to inhibit CYP enzymes and transporters, as well its the inducing capacity, has been tested in vitro. For remdesivir, the regulatory cut off, 50 X Cmax(unbound) is 54,6 µM based on a Cmax of 5440 ng/ml (loading dose) and 12 % fraction unbound.

CYP inhibition

The potential for remdesivir to inhibit CYP enzymes was evaluated using human hepatic microsomes and monitoring specific CYP-mediated transformations of probe substrates (Study AD-399-2010). Remdesivir was a weak inhibitor of CYP1A2, CYP2C9, CYP2C19, and CYP2D6. Remdesivir had an IC50 for CYP3A of 1.6 µM.

CYP induction

The potential of induction of CYP enzymes (CYP1A2, CYP2B6, and CYP3A4) following exposure of human hepatocytes to remdesivir, and its major systemic metabolites, GS-704277 and the nucleoside analog GS-441524, was assessed by quantitating messenger RNA (mRNA) levels and CYP enzyme activities (Study AD-399-2027). In hepatocytes from 1 of the 3 donors, remdesivir showed induction of mRNA levels of CYP1A2 and CYP2B6 by 5.7-fold and 5.4-fold, respectively. Such induction was not observed in hepatocytes from the other 2 donors. Remdesivir showed no induction of CYP3A4 mRNA or CYP3A4/5 activity. GS-441524 and GS-704277 showed no induction of CYP enzymes tested in the study.

Transporter substrate

Remdesivir was found to be a substrate for OATP1B1 but not for OATP1B3.

Remdesivir was assessed as a substrate for the efflux transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) (Study AD-399-2007). Remdesivir was found to be a substrate for P-gp but not BCRP.

In cells overexpressing human organic anion transporters (OAT) 1 and 3, no evidence for transport of remdesivir and its major systemic metabolites, GS-704277 and the nucleoside analog GS-441524, was observed (Study PC-399-2020; IB Edition 5 21 February 2020 Section 3.3.6.2).

Transporter Inhibition

The potential for remdesivir to inhibit drug transporters was assessed in vitro in transfected cell lines expressing OATP1B1, OATP1B3, P-gp, and BCRP (Study AD-399-2005). Remdesivir did not inhibit P-gp at the highest concentration tested (40 µM), but inhibited OATP1B1- and OATP1B3with IC50 values of 2.8 and 2.1 µM, respectively.

Remdesivir inhibited BSEP-, MRP4- and NTCP-mediated probe substrate transport, with calculated IC50 values of 22, 5.1, and 72 µM, respectively. No interaction of remdesivir with MRP2 was observed at up to 100 µM. The major metabolite GS-704277 showed 25% and 44% inhibition of MRP2- and NTCP-mediated transport, respectively, at the 100 µM test concentration Whereas no interaction with BSEP or MRP4 was observed. The nucleoside metabolite GS-441524 showed 24% inhibition of NTCP-mediated transport at the 100 µM test concentration, but no interaction with BSEP, MRP2, or MRP4 was observed.

- Special Populations

<u>Hepatic impairment</u>

There are no specific studies conducted with RDV in patients with hepatic impairment. 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.

Given the benefit-risk ratio in patients with acute CoV infection, no dose modification is recommended at the present time. Remdesvir is contraindicated in patients with severe hepatic impairment.

Renal impairment

There are no specific studies conducted with RDV in patients with renal impairment.

The parent compound remdesivir has only minor renal excretion, but as 49% of a radioactive dose was found as the metabolite GS-441524 in urine, renal impairment may theoretically increase plasma exposure to this metabolite.

Both formulations (Solution Formulation, Remdesivir (GS-5734) and Lyophilized Formulation, Remdesivir (GS-5734)) contain sulfobutylether β-cyclodextrin sodium (SBECD) as a solubility enhancer. The excipient SBECD is renally cleared and accumulates in patients with decreased renal function. Given the benefit-risk ratio in patients with acute CoV infection, no dose modification is recommended at the present time in patients with mild and moderate renal impairment. Remdesivir is contraindicated in patients with severe renal impairment.

Paediatric population

Some evidence of the use of remdesivir in paediatric patients comes from the treatment of Ebola disease (Mulangu S. et al A randomized controlled trial of Ebola virus disease therapeutics. N Engl J Med 2019;381:2293-303) although data are limited, especially in younger children. At the moment there is no data available in children with COVID-19.

The PK bridge between animal models and humans

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 (Table 15).

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 15. Pharmacokinetics of RDV in Plasma and Nucleoside Triphophate Metabolite GS-443902 (PBMCs) following repeat RDV doses (30-min IV infusion) to healthy Rhesus Monkeys (5mg/kg) and healthy humans (100mg)

PK Parameter	Mean (SD)	
	Healthy Rhesus Monkeys	Healthy Human Subjects
	RDV 5 mg/kg Test Treatment (N=8)	RDV 100 mg Reference Treatment (N=26)
Plasma RDV		
AUC (h*ng/mL)	1430 (230)	1585.3* (263.6)
C_{max} (ng/mL)	3350 (390)	2228.8 (427.3)
PBMC GS-443902		
C_{24h} (µM)	7.1 (6.7)	10.2 (5.05)*

AUC: healthy rhesus monkeys AUC0-24; healthy human subjects AUCtau
* N=25

Source: Applicant's response to LoQ dated 31.03.2020, Table 1

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 (Table 16) 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 16. Pharmacokinetics of RDV in Plasma and Nucleoside Triphosphate Metabolite GS-443902 (PBMCs) following 200mg single dose of RDV to healthy volunteers.

PK Parameter	Mean (%CV)
	Healthy Human Subjects
	RDV 200 mg (N=28)
Plasma RDV	
AUC_{0-24} (h*ng/mL)	2862.5 (18.6)
C_{max} (ng/mL)	4377.9 (23.5)
C_{last} (ng/mL)	8.8 (57.7)
$T_{1/2}$ (h) (median, Q1,Q3)	0.9 (0.8, 1.03)
PBMC GS-443902	
AUC_{0-24h} (h*µM)	157.4 (32.9)
C_{max} (µM)	9.8 (46.6)
C_{24h} (µM)	6.9 (45.8)

Source: Applicant's response to LoQ dated 31.03.2020, Table 2

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/mL (Table 15). Additionally, trough (C24h) PBMC concentrations of nucleoside triphosphate metabolite GS-443902 following a 200 mg dose (Table 16) are comparable to values seen in rhesus monkeys.

Overall conclusion on Clinical Pharmacokinetics

The assessment has been based on IB (edition 5, 21 February 2020) and not the actual study reports. Based on the level of information given in the IB, no large risks for patients associated with PK characteristics of remdesivir or its metabolites (e. g. interaction potential / restrictions/other dose for special populations) are seen. Of note, several aspects regarding PK would be subject to further assessment in a future marketing authorisation applications (MAA) but are not further pursued here given the severity and urgency of the situation.

Some in vitro interaction results may indicate a potential for drug interactions (in vitro inhibition of e g CYP3A4 and the hepatic uptake transporter OATPs) but the in vivo relevance is likely low given the transient exposure to remdesivir following IV infusion. The interaction potential of the metabolites of remdesivir is still largely unknown.

There is no data available on the pharmacokinetics of remdesivir in patients with renal or hepatic impairment. As the parent compound is believed to be rapidly cleaved by hydrolases, the effect of hepatic impairment on remdesivir plasma levels is likely low. 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.

No renal or hepatic abnormalities were attributed to remdesivir patients with acute Ebola virus disease who received treatment with remdesivir under the PALM and MEURI protocols who had moderate to severe liver and renal abnormalities at presentation. Adequate organ function is ensured by inclusion and exclusion criteria (estimated glomerular filtration rate ≥ 30 ml/min; ALT ≤ 5 x upper limit of normal), dose modification is not recommended at the present time. Remdesivir should not be given with other known hepatotoxic drugs.

Regarding bioequivalence between the remdesivir solution formulation and remdesivir lyophilized formulation data indicate that the formulations may be seen as interchangeable in terms of achieving comparable plasma concentrations.

The PK bridge between rhesus monkey experience and humans has been reasonably substantiated, although data pertain to healthy monkeys and humans, rather than those with COVID-19.

Clinical efficacy

There are no clinical efficacy data to support the compassionate use of remdesivir coming from patients with infection for COVID-19. There are currently several ongoing and planned clinical studies with this regard.

Discussion / Overall conclusion on clinical efficacy

The hypothesis of clinical efficacy rests on in *vitro* data, animal disease model outcomes, and a PK bridge to humans.

Clinical safety

As of 14 February 2020, four **Phase 1 PK studies** sponsored by the Applicant have been conducted in which 138 healthy subjects have been dosed with remdesivir. Studies investigated single-dose, 2-hour IV administration of remdesivir solution formulation at doses ranging from 3 to 225 mg, single-dose IV administration of remdesivir lyophilized formulation for 30 minutes (75 mg) or 2 hours (75 and 150 mg) and multiple-dose IV administration of remdesivir 150 mg once daily for 7 or 14 days.

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 17.

Table 17. 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.

Source: IB Edition 5 21 February 2020, Table 62

Transient treatment-emergent elevations in ALT and AST were observed during the studies in healthy volunteers, none of which were graded in the single-ascending dose study, and all of which were Grade 1 or Grade 2 in the multiple-dose studies. Some ALT and AST elevations were associated with graded PT elevations; however, there were no graded changes in INR. Laboratory results for these subjects indicated no systemic sign of drug reaction.

In a phase II study (**PREVAIL IV**) with remdesivir 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.

PALM study,

The PALM Study was an open-label, 1:1:1:1 randomized, parallel, interventional Phase 2/3 study designed to assess the efficacy and safety of IV investigational treatments in patients with EVD: ZMappTM, a triple monoclonal antibody; REGN-EB3 (REGN3470-3471-3479), a coformulated mixture of 3 human IgG1 monoclonal antibodies; mAb114, a single monoclonal antibody; and remdesivir {Mulangu 2019}. The primary endpoint was death at 28 days.

Patients with Ebola Virus Disease in the remdesivir group received a loading dose on Day 1 (200 mg in adults and adjusted for body weight in paediatric patients), followed by a daily maintenance dose (100 mg in adults) starting on Day 2 and continuing for 9 to 13 days, depending on viral load.

A total of 681 patients with EVD were enrolled and randomized at Ebola Treatment Centers to receive treatment, 175 participants were randomized to receive remdesivir. All enrolled patients received standard care, which consisted of administration of IV fluids, daily clinical laboratory testing, correction of hypoglycemia and electrolyte imbalances, and administration of broad-spectrum antibiotic agents and antimalarial agents.

During the course of the study, the data and safety monitoring board recommended that patients be assigned only to the MAb114 and REGN-EB3 groups for the remainder of the trial; the recommendation was based on the results of an interim analysis that showed superiority of these groups to ZMapp and remdesivir with respect to mortality.

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 remdesivir. Of these, an event of hypotension, which occurred during administration of the loading dose and led to fatal cardiac arrest, was considered related to remdesivir. The independent pharmacovigilance committee noted that the death could not be readily distinguished from underlying fulminant EVD.

Overall conclusion on clinical safety

The safety profile of remdesivir, which is not approved for any indication, is incompletely characterised. Most of the clinical experience relates to Ebola virus disease, which differs profoundly in its clinical characteristics from SARS-CoV2. However, there are hitherto no safety findings precluding the further development of remdesivir, in COVID-19 and the safety profile is compatible with compassionate use in the proposed target population.

Transaminase increases are presently the only adverse effect that appears clearly linked to remdesivir use. Special attention should be paid to elevations of transaminases, hypersensitivity reactions, renal events, pregnancy and unexpected adverse reactions in the periodic safety reports and the expedited summary safety reports.

The current contraindication on starting remdesivir therapy concomitant vasopressors use is based on this being an indication of end organ failure, where there are no safety data. However, the use of pressor at low/medium doses for inotropic support due to the use of sedation and paralytics while on the ventilator is allowed. On the other hand, once a patient initiates treatment with remdesivir, subsequent use of pressors is not a reason for discontinuation of remdesivir.

3.5 Pharmacovigilance

In order to ensure the safety monitoring of the patients, the following conditions have been adopted and are annexed to the CHMP opinion on compassionate use for remdesivir formulation as follows:

Conditions for safety monitoring to be implemented by the company

In accordance with Article 83(6) of Regulation (EC) No 726/2004, the pharmacovigilance rules and responsibilities defined in Articles 28(1) and (2) of the Regulation (EC) No 726/2004 referring to centrally authorised medicinal products as defined in articles 3(1) and (2) are applicable to medicinal products for which an opinion on the conditions for compassionate use has been adopted. Therefore, the company shall ensure that these pharmacovigilance rules and responsibilities are fulfilled.

The company should submit every 6 months a periodic safety update report.

In addition, the company should submit to EMA monthly expedited summary safety reports.

Requirements for the expedited summary safety reports

During a pandemic situation, the resources must be concentrated on a timely and effective monitoring of the safety profile of remdesivir used during the pandemic. Moreover, a 6-monthly cycle may be too long to allow assessment of the safety of remdesivir. Therefore, in addition to the 6-monthly or annual PSURs falling within the pandemic period, expedited summary safety reports should be submitted for review, accompanied by a summary of remdesivir distribution.

- Frequency of submission:

- The clock should start from the first Monday after the CHMP Opinion.
- First data-lock point is 30 days later.
- Expedited summary safety report submission to the Rapporteur and PRAC and CHMP members on Day 45.
- Rapporteur's assessment report is circulated to PRAC/CHMP members on Day 50.
- PRAC/CHMP report is circulated to the Applicant on Day 55.
- Submission of the expedited summary safety report to be monthly for the first 6 months.
- Periodicity should be reviewed by the MAH and the EMA at 6 monthly intervals.

- Format of the expedited summary safety report:

Spontaneously reported data and data from compassionate use or named patient use should be included in the expedited summary safety report. The report should include the following tables of aggregate data:

1. An overview for all cases per country, stratified according to type of report (medically confirmed or non-medically confirmed, spontaneous or solicited) and seriousness, for the period covered by the report and cumulatively.
2. An overview for all adverse reactions by SOC, High Level Term (HLT) and Preferred Term (PT), stratified according to type of report (medically confirmed or non-medically confirmed, spontaneous or solicited) and including the number of fatal reports and discontinuations due to adverse events, for the period covered by the report and cumulatively.
3. Adverse Events of Special Interest (AESI) stratified according to type of report (medically confirmed or non-medically confirmed, spontaneous or solicited). At a minimum, the AESI should include:
    - elevations of transaminases and hepatic events
    - hypersensitivity reactions
    - renal events
4. Serious unexpected adverse reactions (SOC, HLT, PTs) stratified according to type of report (medically confirmed or non-medically confirmed, spontaneous or solicited), for the period covered by the report and cumulatively.
5. All adverse reactions by age group, per SOC, HLT and PT, stratified according to type of report (medically confirmed or non-medically confirmed, spontaneous or solicited), for the period covered by the report and cumulatively. The following age groups should be used: 12-17 years, 18-64 years, 64-74 years, 75-84 years, 85 years and above.
6. All adverse reactions (SOC, HLT, PT) occurring in pregnant women, stratified according to type of report (medically confirmed or non medically confirmed, spontaneous or solicited), for the period covered by the report and cumulatively.

The following principles should be followed when compiling the data:

- Except for Table 1, all tables will be based on number of reactions (presented on PT level, sorted by System Organ Class [SOC] and High Level Term [HLT]) and not number of cases.

- "Cumulatively" means since the CHMP Opinion; events not reported during the periods of interest should not be presented in the tables.
- All non-medically confirmed events are those that have been entered into the database by the data-lock point. Those which have not yet been entered should be reported in the following expedited summary safety report.
- A line listing of fatal cases should be provided in an Annex.

A short summary should be provided in which validated signals and areas of concern are highlighted, taking into account information arising from any ongoing study. In the event of multiple signals, signal work-up may be prioritised and appropriate timelines for submission of a full signal evaluation report should be provided.

Conditions for safety monitoring to be implemented by the Member States

In accordance with Article 83(6) of Regulation (EC) No 726/2004, the pharmacovigilance rules and Responsibilities defined in Articles 28(1) and 28(2) of the Regulation (EC) No 726/2004 are applicable to medicinal products for which an opinion on the conditions for compassionate use has been adopted. Therefore, the Member State(s) shall ensure that these pharmacovigilance rules and responsibilities are fulfilled.

Additional EMA activities

Signal detection for remdesivir will be enhanced and accelerated during the pandemic.

3.6 Risk/benefit assessment and recommendation

Risk Benefit assessment

Severe acute respiratory syndrome CoV-2 is identified as the cause of an outbreak of respiratory illness that was first detected in Wuhan, China in December 2019. The virus causes respiratory illness in people and can spread from person to person [Center for Disease Control (CDC) 2020]. Common signs of infection include: fever, cough, shortness of breath, breathing difficulties, and other respiratory symptoms. In severe cases, COVID-19 can cause pneumonia, severe acute respiratory syndrome, kidney failure, and death [World Health Organization (WHO) 2020].

The Applicant is proposing the use of Remdesivir (RDV), when used as part of a compassionate use programme, for the treatment of patients with COVID-19 who require invasive mechanical ventilation. Such patients have been reported to have a mortality at and above 50%. There are no specific therapies with established efficacy and safety for the treatment of COVID-19. Thus, the target condition fulfils criteria for the compassionate use insofar as there is life-threatening illness which cannot be treated satisfactorily with any currently authorised medicine.

RDV is under investigation for the treatment of COVID-19, including several randomised controlled trials that include target populations overlapping that of the present compassionate use program. The assumption that RDV may be efficacious is mainly based on efficacy in animal models of SARS-Cov and MERS-Cov, in which RDV, when given prior to or one day after experimental infection, had better clinical and virological efficacy than vehicle alone or lopinavir/ritonavir with or without interferon beta1b.

These results are bridged from SARS-CoV or MER-CoV to SARS-Cov2 via in vitro data indicating that all these viruses are susceptible to RDV with EC50 values below 1 uM (=approximately 0.6 ug/mL). Furthermore, plasma exposure to RDV, as well as PBMC exposure to triphosphate metabolite GS-

443902, appear to support the assumption that the efficacy seen in Rhesus monkeys might also be seen in humans.

Major uncertainties include the relevance of the animal models for human COVID-19, as well as the fact that RDV was administered latest one day after viral challenge in the animal models. Furthermore, prophylactic administration appeared more effective that administration after challenge, indicating that, similar to other acute viral diseases, the benefit of remdesivir treatment may be greater the earlier treatment is started in relation to the onset of symptoms. From this point of view, treating patients that already have respiratory failure, and presumably in most cases would have been symptomatic for a while, may not represent the optimal use of RDV. On the other hand, there are reports that viral shedding as well as ICU stays tend to be more protracted with COVID-19 than usually seen for, e.g., influenza.

There are presently no clinical efficacy data to support the use of RDV. Furthermore, the safety profile of RDV is incompletely characterised. Nevertheless, the safety profile appears supportive of further studies in COVID-19. Hepatotoxicity is a clinically identified risk and should be monitored.

RDV is not approved in any jurisdiction. Consequently, patients with COVID-19 should presently preferably access RDV through clinical trials. However, given the dire prognosis in patients with covid-19 that require mechanical ventilation, compassionate use of RDV is considered reasonable in such patients that are not able to access a clinical trial.

With regards to the Paediatric indication, based on the limited data, no safety or efficacy issue in children below 12 years of age can be predicted. The Committee acknowledged this fact and considered that when more data become available the inclusion of children below this age should be also considered.

Finally, due to the current epidemiological situation it is foreseen that new data will be generated quickly in the context of the ongoing and planned clinical trials. These data will soon further characterise the safety and the efficacy profile of RDV.

In the context of the compassionate use of RDV for the above-mentioned targeted population and according to the conditions adopted by the CHMP, it is considered that the benefits outweigh the risks.

The Applicant is encouraged to initiate compassionate use programmes in all interested European Union Member States.

Recommendation

As part of the Opinion, the CHMP adopted conditions of use, conditions for distribution, patients targeted and conditions for safety monitoring addressed to Member States for product available for compassionate use (see appendix 1).

4 Revision 1

4.1 Background on revision 1

On 30 April 2020, the CHMP was made aware of additional information as regards the use of remdesivir from the NIAID ACTT-1 Study. Therefore, a revised CHMP opinion for the compassionate use of remdesivir and its conditions for use in the Union is being adopted.

This is a randomized, double-blind, placebo-control clinical study evaluated remdesivir 200 mg once daily for 1 day followed by remdesivir 100 mg once daily for 9 days (for a total of up to 10 days of intravenously administered therapy) in hospitalized adult patients with COVID-19.

Inclusion criteria were confirmed COVID-19 and either radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), OR SpO2 < / = 94% on room air, OR requiring supplemental oxygen, OR requiring mechanical ventilation. Severe disease was defined as hospitalization requiring supplemental oxygen, non-invasive ventilation, high-flow oxygen devices, invasive mechanical ventilation, or ECMO. The trial enrolled 1063 hospitalized patients in a 1:1 manner to receive remdesivir or placebo. The primary clinical endpoint was time to recovery at Day 29 after randomization.

Day of recovery was defined as the first day on which the subject satisfies one of the following three categories from the 8-point point ordinal scale: 3) Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care; 2) Not hospitalized, limitation on activities and/or requiring home oxygen; 1) Not hospitalized, no limitations on activities.

In an analysis of the primary endpoint performed [redacted], the median time to recovery was 11 days in the remdesivir group compared to 15 days in the placebo group [redacted] p<0.001). Follow-up for Day 29 all-cause mortality is still ongoing.

This section will be updated once the data had been published.

[Table with detailed outcome redacted]

4.2 Revised risk/benefit assessment and recommendation

Risk Benefit assessment

Expanding the CU target population from "requiring invasive mechanical ventilation due to COVID-19" to "severe COVID-19"is deemed reasonable based on preliminary results from the NIAID ACTT-1 Study which suggest a beneficial effect of remdesivir in the treatment of hospitalised patients with severe COVID-19. However, the complete study results have presently not been evaluated.

The rolling review (RR) of MAA for remdesivir has been formally started on 30 April 2020. More details on the available results of the NIAID ACTT-1 Study will be presented and discussed in the 1st AR of the RR.

Furthermore, a 10-day treatment course is recommended for patients requiring mechanical ventilation or ECMO and a 5-day treatment course is recommended in other patients hospitalized with severe COVID-19. Patients who receive a 5-day treatment course but do not demonstrate clinical improvement will be eligible to continue to receive RDV for an additional 5 days.

Paediatrics

On 1st May 2020 FDA issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product remdesivir for treatment of suspected or laboratory confirmed coronavirus disease 2019 (COVID-19) in adults and children hospitalized with severe disease. Dose recommendation for paediatric patients (> 7 days old) are given in the "FACT SHEET FOR HEALTH CARE PROVIDERS EMERGENCY USE AUTHORIZATION (EUA) OF REMDESIVIR (GS-5734™)" (https://www.fda.gov/media/137566/download). In the CHMP view, it will be necessary to first generate data in adult patients with COVID-19, as PK might differ between healthy volunteers and (ICU, eventually ventilated etc.) patients. These should be included first, before a reasonable dose

could be proposed for paediatric patients. Therefore, inclusion of paediatrics < 12 years of age is currently not recommended.

5 days vs. 10 days

According to the "FACT SHEET FOR HEALTH CARE PROVIDERS EMERGENCY USE AUTHORIZATION (EUA) OF REMDESIVIR (GS-5734)" a 10-day treatment course is recommended for patients requiring mechanical ventilation or ECMO and a 5-day treatment course is recommended in other patients hospitalized with severe COVID-19. Patients who receive a 5-day treatment course but do not demonstrate clinical improvement will be eligible to continue to receive RDV for an additional 5 days.

Study GS-US-540-5773 is an open-label study comparing 5-day and 10-day remdesivir durations for the treatment of patients with severe COVID-19. There is no placebo or SOC group. Inclusion criteria is confirmed COVID-19 and current hospitalization, radiographic evidence of pulmonary infiltrates, and SpO2 ≤94% on room air or requirement for supplemental oxygen. Exclusion criteria disallows patients on mechanical ventilation for ≥5 days and ECMO. The primary objective of this study is to evaluate the results on a 7-point ordinal scale through Day 14.

[Paragraph and table redacted]

Although the complete study results have presently not been evaluated, data suggest that the treatment course can be shortened to 5 days without any loss of efficacy, which may be favourable with respect to drug availability. Therefore, a treatment regimen that included a 10-day treatment course for patients requiring mechanical ventilation or ECMO and a 5-day course in other patients hospitalized with severe COVID-19 is recommended. Patients who receive a 5-day treatment course but do not demonstrate clinical improvement are eligible to continue to receive RDV for an additional 5 days.

Conclusion

Expanding the CU target population is deemed reasonable based on preliminary results from the NIAID ACTT-1 Study which suggest a beneficial effect of remdesivir in the treatment of hospitalised patients with severe COVID-19.

In addition, preliminary results from Study GS-US-540-5773 suggest that the treatment course can be shortened to 5 days without any loss of efficacy, which may be favourable with respect to drug availability. Therefore, a treatment duration of 5 days for patients not requiring mechanical ventilation or ECMO has been introduced. Patients who receive a 5-day treatment course but do not show clinical improvement, however, will be eligible to continue receiving remdesivir for an additional 5 days.

However, inclusion of paediatrics < 12 years of age is currently not recommended.

4.3 Revised Recommendation

As part of the Opinion, the CHMP adopted conditions of use, conditions for distribution, patients targeted and conditions for safety monitoring addressed to Member States for product available for compassionate use (see appendix 1).

5 Appendices

- Appendix 1 Conditions of use, conditions for distribution, patients targeted and conditions for safety monitoring addressed to Member States for product available for compassionate use.