16 December 2021
EMA/2138/2022
Committee for Medicinal Products for Human Use (CHMP)

Extension of indication variation assessment report

Invented name: Veklury

International non-proprietary name: remdesivir

Procedure No. EMEA/H/C/005622/II/0016

Marketing authorisation holder (MAH) Gilead Sciences Ireland UC

Note

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

Table of contents

List of abbreviations

ACTT Adaptive COVID-19 Treatment Trial

AE adverse event

AIDS acquired immunodeficiency syndrome

ALT alanine aminotransferase

AST aspartate aminotransferase

BMI body mass index

CI confidence interval

CLcr creatinine clearance

CMA conditional marketing authorisation

CoV coronavirus

COVID-19 coronavirus disease 2019

CSR clinical study report

ECMO extracorporeal membrane oxygenation

eCRF electronic case report form

Gilead Gilead Sciences

INR international normalized ratio

ITT intent-to-treat

MERS Middle East respiratory syndrome

NA not applicable

NIAID National Institute of Allergy and Infectious Diseases

O2 oxygen

Q1 first quartile

Q3 third quartile

RDV remdesivir (GS-5734™)

RNA ribonucleic acid

RRR recovery rate ratio

RSV respiratory syncytial virus

SAE serious adverse event

SARS-CoV-2 severe acute respiratory syndrome coronavirus-2

SmPC summary of product characteristics

SOC standard of care

SpO2 oxygen saturation

TEAE treatment-emergent adverse event

TESAE treatment-emergent serious adverse event

US United States

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

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Gilead Sciences Ireland UC submitted to the European Medicines Agency on 22 December 2020 an application for a variation.

The following variation was requested:

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

Extension of indication to include treatment of adults with pneumonia not requiring supplemental oxygen (moderate COVID-19), based on Part A of Study GS-US-540-5774, a Phase 3, randomized, open-label, multicenter study comparing 2 RDV regimens (5 days and 10 days) versus standard of care in 584 participants with moderate COVID 19, and Study CO US 540 5776 [Adaptive COVID-19 Treatment Trial (ACTT) 1, a National Institute of Allergy and Infectious Diseases (NIAID)-sponsored Phase 3, randomized, double blind, placebo controlled, multicenter study]. As a consequence, sections 4.1 and 5.1 of the SmPC are being updated, and the Package Leaflet is updated in accordance. A revised version 1.2 of the RMP has also been submitted.

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

Information on paediatric requirements

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

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

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Janet Koenig Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	22 December 2020
Start of procedure:	20 February 2021
CHMP Rapporteur Assessment Report	22 April 2021
PRAC Rapporteur Assessment Report	29 April 2021
PRAC members comments	28 April 2021
Updated PRAC Rapporteur Assessment Report	5 May 2021
PRAC Outcome	6 May 2021
CHMP members comments	10 May 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	12 May 2021
Request for supplementary information (RSI)	20 May 2021
CHMP Rapporteur Assessment Report	17 August 2021
PRAC Rapporteur Assessment Report	19 August 2021
PRAC members comments	25 August 2021
Updated PRAC Rapporteur Assessment Report	26 August 2021
PRAC Outcome	2 September 2021
CHMP members comments	6 September 2021
ETF discussion	10 September 2021
Updated CHMP Rapporteur Assessment Report	14 September 2021
Request for supplementary information (RSI)	16 September 2021
MAH's responses submitted to the CHMP on	15 October 2021
CHMP Rapporteur Assessment Report	18 November 2021
PRAC Rapporteur Assessment Report	19 November 2021
PRAC members comments	24 November 2021
PRAC Outcome	2 December 2021
CHMP members comments	6 December 2021
MAH's responses submitted to the CHMP on	8 December 2021
ETF discussion	10 December 2021
Updated CHMP Rapporteur Assessment Report	10 December 2021
CHMP opinion	16 December 2021

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

The efficacy of antiviral agents may vary depending on whether a patient presents early or late in the course of COVID-19 (i.e., during viral pathogenesis versus after immunopathologic manifestations) {Harrington 2020}. Although research into COVID-19 continues to evolve, it is expected that the impact of antiviral agents such as RDV is likely to be greatest early in the course of COVID-19 (i.e., prior to the need for advanced respiratory support). Antivirals that limit disease progression and reduce the duration of hospitalization are likely to reduce healthcare resource utilization, particularly as COVID-19 case counts continue to grow globally.

Disease or condition

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

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

Claimed therapeutic indication

The following therapeutic indication was proposed at the time of the submission:

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

- in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen,
- in adults with pneumonia not requiring supplemental oxygen

(see section 5.1)

During the procedure the MAH proposed a modification of the above indication:

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

- adults who do not require invasive mechanical ventilation at start of treatment.
- adolescents (aged 12 to less than 18 years and weighing at least 40 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment).

(see section 5.1)

Epidemiology

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

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

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

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

As of 10 December 2020, a total of 267,865,289 confirmed cases of COVID-19 and 5,285,888 associated deaths were reported worldwide, including 98,346,191 cases in the Americas and 90,914,526 cases in Europe {World Health Organization (WHO) 2020}.

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

Biologic features, Aetiology and pathogenesis

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

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

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

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

The natural course of COVID-19 is classified into 3-stage, recognizing that COVID-19 illness exhibits 3 grades of increasing severity, which correspond with distinct clinical findings, response to therapy, and clinical outcome. Stage 1 is the early infection stage, with mild symptoms and high viral load. The second

stage is characterised by pulmonary involvement with or without hypoxia, established pulmonary disease, viral multiplication and localized inflammation in the lung. A minority of COVID-19 patients will transition into the third and most severe stage of the illness, which manifests as an extrapulmonary systemic hyperinflammation syndrome and systemic hyperinflammation.

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

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

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

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

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

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

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

Management

In the EU four vaccines against SARS-CoV-2 infection are approved.

Treatment with Dexamethasone have been proven effective and safe in the treatment of severe COVID-19. Recently, Tocilizumab has also been approved for its use in adults with COVID-19 who are receiving treatment with corticosteroid medicines and require extra oxygen or mechanical ventilation. Furthermore, remdesivir is approved for the treatment of patients with COVID-19 who require low-flow oxygen, high-flow oxygen or non-invasive mechanical ventilation at the start of therapy.

Currently, two monoclonal antibodies are approved for the treatment of mild and moderate COVID-19 infection outside the hospital setting, Ronapreve (casirivimab/imdevimab) and Regkirona (regdanvimab). Ronapreve is indicated for treating COVID-19 in adults and adolescents (from 12 years of age and weighing at least 40 kilograms) who do not require supplemental oxygen and who are at increased risk of

their disease becoming severe and can also be used for preventing COVID-19 in people aged 12 years and older weighing at least 40 kilograms. Regkirona is indicated for the treatment of adults with COVID-19 who do not require supplemental oxygen and who are also at increased risk of their disease becoming severe.

The following treatments can be used in the EU to treat COVID-19, after EMA's CHMP completed its review under Article 5(3): Dexamethasone, and recently molnupiravir. Monoclonal antibody combination casirivimab / imdevimab and monoclonal antibody regdanvimab were also previously available through art 5(3).

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

2.1.2. About the product

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

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

remdesivir is a nucleotide prodrug that is intracellularly metabolized into an analogue of adenosine triphosphate that inhibits viral RNA polymerases. remdesivir competes with the natural ATP substrate for incorporation into nascent RNA chains by the SARS-CoV 2 RNA-dependent RNA polymerase, which results in delayed chain termination during replication of the viral RNA. remdesivir triphosphate can also inhibit viral RNA synthesis following its incorporation into the template viral RNA by compromising the efficiency of incorporation of the complementary natural nucleotide. remdesivir has broad-spectrum activity against members of the coronaviruses (CoVs; eg, severe acute respiratory syndrome coronavirus-2 [SARS-CoV-2], SARS-CoV, Middle East respiratory syndrome [MERS]-CoV), filoviruses (e.g., Ebola virus, Marburg virus), and paramyxoviruses (e.g., respiratory syncytial virus [RSV], Nipah virus, Hendra virus).

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

There is no CHMP guidance on clinical trials for medicinal products for COVID-19.

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

2.1.4. General comments on compliance with GLP, GCP

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

The Danish Medicines Agency performed a national inspection at a clinical investigator site which participated in the study GS-US-540-9012. No significant or concerning issues in regard to patients safety, rights or well-being or on data integrity were reported.

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity/environmental risk assessment

No new non-clinical data have been submitted in this application, which is considered acceptable.

2.2.2. Discussion on non-clinical aspects

No new non-clinical data have been submitted in this application.

2.2.3. Conclusion on the non-clinical aspects

The extended indication does not lead to a significant increase in environmental exposure further to the use of remdesivir nor the environmentally relevant API GS-441524.

Remdesivir and the environmentally relevant API GS-441524 is not expected to pose a risk to the environment.

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

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

Overview of clinical studies:

- GS-US-540-5774: Phase 3, randomized, open-label, multicenter study comparing 2 RDV regimens (5 days and 10 days) versus standard of care (SOC) in 584 participants with moderate COVID-19 (Part A of Study GS-US-540-5774).

- NIAID ACTT-1 (CO-US-5776:(NIAID)-sponsored Phase 3, randomized, double-blind, placebo-controlled, multicentre study (Study CO-US-540-5776 [Adaptive COVID-19 Treatment Trial (ACTT)-1]. For Study CO-US-540-5776, only the subset of 138 hospitalized participants with moderate COVID-19 were considered.

- GS-US-540-9012: A Phase 3, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of remdesivir (GS-5734™) treatment of early stage COVID-19 who were at higher risk of disease progression in an outpatient setting

2.3.2. Pharmacokinetics

No new pharmacokinetic studies were submitted.

2.3.3. Pharmacodynamics

No new pharmacokinetic studies were submitted.

2.3.4. PK/PD modelling

No new PK/PD modelling data were submitted.

2.3.5. Discussion on clinical pharmacology

No new clinical pharmacology data were submitted. No data on clinical virology were submitted.

2.3.6. Conclusions on clinical pharmacology

No new clinical pharmacology data and no data on clinical virology were submitted. Hence, *in vivo* proof of concept is currently still missing. Within the currently ongoing renewal procedure, the MAH committed to provide interim virology data on studies 5774 and 5776 by May 2021. However, confidentially provided viral load data of the DisCoVeRy trial by INSERM indicate no antiviral activity of remdesivir, which is cause of concern as this data could impact the benefit/risk of remdesivir. The impact on the B/R of these antiviral data of the DisCoVeRy trial were assessed in the first renewal (please see procedure (EMEA/H/C/005622/R/0015)).

2.4. Clinical efficacy

2.4.1. Dose response studies

No additional dose response studies have been submitted.

2.4.2. Main studies

The studies supporting the clinical efficacy and safety of RDV for the treatment of moderate COVID-19 are a Phase 3, randomized, open-label, multicenter study comparing 2 RDV regimens (5 days and 10 days) versus standard of care (SOC) in 584 participants with moderate COVID-19 (Part A of Study GS-US-540-5774) and a National Institute of Allergy and Infectious Diseases (NIAID)-sponsored Phase 3, randomized, double-blind, placebo-controlled, multicentre study (Study CO-US-540-5776 [Adaptive COVID-19 Treatment Trial (ACTT)-1];

Table 1). For Study CO-US-540-5776, only the subset of 138 hospitalized participants with moderate COVID-19 were considered. Supportive safety data were provided from Part B of Study GS-US-540-5774, in which an additional 503 hospitalized participants with moderate COVID-19 received open-label RDV for up to 10 days.

Table 1: Overview of Key Studies/Programs for the extension of indication

Study	Description of Study	Data Cross-Reference	Module 2 Cross-Reference
GS-US-540-5774	Completed, Phase 3, randomized, open-label, multicenter study conducted in 2 parts: Part A, a randomized, open-label, multicenter study; Part B, a single-group, multicenter study (sponsored by Gilead)	GS-US-540-5774 Interim 2 (Final Part A) CSR and Final (Part B) CSR; {Spinner 2020}	m2.7.3, Section 2.1.3
CO-US-540-5776 (ACTT-1)	Completed part of a Phase 3, adaptive, randomized, double-blind, placebo-controlled, multicenter study to evaluate available investigational treatments for COVID-19, including RDV[a] (sponsored by NIAID)	CO-US-540-5776 Final CSR; {Beigel 2020a, Beigel 2020b}	m2.7.3, Section 2.1.1

ACTT = Adaptive COVID-19 Treatment Trial; COVID-19 = coronavirus disease 2019; CSR = clinical study report; Gilead = Gilead Sciences; NIAID = National Institute of Allergy and Infectious Diseases; RDV = remdesivir (GS-5734™)
a Subsequent to ACTT-1, ACTT progressed to Part 2 (ACTT-2), evaluating the combination of baricitinib + RDV versus placebo + RDV, and Part 3 (ACTT-3), evaluating the combination of interferonβ-1a + RDV versus placebo + RDV.

Study GS-US-540-5776 (ACTT-1)

Study GS-US-540-5776 (ACTT-1) is an adaptive, randomized, double-blinded, placebo-controlled trial to evaluate the safety and efficacy of investigational therapeutic agents in hospitalized adults diagnosed with COVID-19. The study is a multi-centre trial, conducted in approximately 60 sites globally.

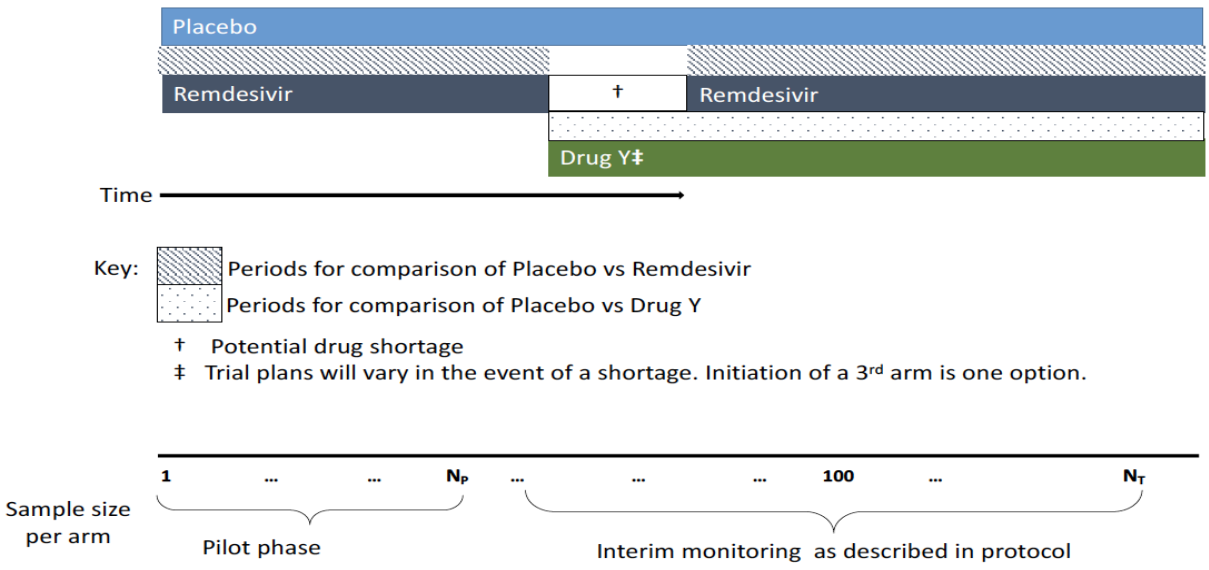


Figure 1: Schema of study design

Study participants

Main inclusion criteria

- Admitted to a hospital with symptoms suggestive of COVID-19 infection.
- Male or non-pregnant female adult ≥18 years of age at time of enrolment.
- Laboratory-confirmed SARS-CoV-2 infection as determined by PCR or other commercial or public health assay in any specimen, as documented by either of the following:
    - PCR positive in sample collected < 72 hours prior to randomization; OR
    - PCR positive in sample collected ≥ 72 hours prior to randomization, documented inability to obtain a repeat sample (e.g. due to lack of testing supplies, limited testing capacity, results taking > 24 hours, etc.). AND progressive disease suggestive of ongoing SARS-CoV-2 infection.
- Illness of any duration, and at least one of the following:
    - Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), OR
    - SpO2 ≤ 94% on room air, OR
    - Requiring supplemental oxygen, OR
    - Requiring mechanical ventilation.
- Women of childbearing potential must agree to either abstinence or use at least one primary form of contraception not including hormonal contraception from the time of screening through Day 29.

Exclusion Criteria

- ALT or AST > 5 times the upper limit of normal.
- Estimated glomerular filtration rate (eGFR) < 30 ml/min (including patients receiving haemodialysis or hemofiltration).
- Pregnancy or breast feeding.
- Anticipated discharge from the hospital or transfer to another hospital, which is not a study site within 72 hours.
- Allergy to any study medication.

Number of centres

Planned: more than 100 centres worldwide

Status (as of May 22, 2020): trial sites in total 60 sites/13 sub-sites; 45 USA, 8 Denmark, 3 Germany, 4 Greece, 1 Japan, 2 Korea, 2 Mexico, 1 Singapore, 2 Spain, 5 United Kingdom.

Treatments

Regimens

- RDV 10-day group: remdesivir administered as a 200 mg IV loading dose on Day 1, followed by a 100 mg once-daily IV maintenance dose while hospitalized for up to a 10 day total course. If a subject is no longer hospitalized, then infusions were no longer given.
- Placebo group: A matching placebo was given at an equal volume at the same schedule.

- The total course should not exceed 10 calendar days even if an infusion was missed.

Justification for Dose

- The dose of remdesivir used in this study is the same dose that was used in the Ebola clinical trials.

Formulations:

- The lyophilized formulation of remdesivir is a white to off-white or yellow, lyophilized solid containing 150 mg or 100 mg of remdesivir to be reconstituted with 29 mL or 19 mL (respectively) of sterile water for injection respectively and diluted into IV infusion fluids prior to IV infusion. Following reconstitution, each vial contains a 5 mg/mL remdesivir concentrated solution with sufficient volume to allow withdrawal of 40 mL (200 mg of remdesivir) or 20 mL (100 mg of remdesivir). In addition to the active ingredient, RDV for injection, 100 mg, contains the following inactive ingredients: betadex sulfobutyl ether sodium (SBECD), water for injection, hydrochloric acid, and sodium hydroxide. Hydrochloric acid and sodium hydroxide are used to adjust the formulation to a pH of 3.0 to 4.0.
- The supplied matching placebo lyophilized formulation, 150 mg or 100 mg equivalent, was identical in physical appearance to the active lyophilized formulation and contained the same inactive ingredients.
- Alternatively, due to limitations on placebo supplies, a matching placebo of normal saline was given at some sites at an equal volume as placebo at the same schedule. This was done in all EU/UK sites and some non-EU sites. In this case, IV bags of study treatment (both the active and the placebo) were covered by an opaque bag to mask the slight colour difference between the RDV solution and placebo to maintain the study blind.

Objectives

The primary null hypothesis being tested is that time-to-recovery does not differ between the experimental and control arms.

A key secondary endpoint is the distribution of the 8-point ordinal scale at Day 15. For this, the parameter of interest is the "common odds ratio," which quantifies the shift in the severity distribution resulting from treatment. For an efficacious treatment, an odds ratio greater than 1 quantifies an improvement in disease severity; a value of 2 indicates a bigger improvement than a value of 1.25. The null hypothesis to be tested is that the odds of improvement on the ordinal scale is the same for the placebo and experimental treatment arms (i.e., the common odds ratio is 1).

Outcomes/endpoints

Primary endpoint

The primary efficacy endpoint was time to recovery. Recovery was defined as clinical status in states 1, 2, or 3 of the 8-point ordinal scale, censored at Day 29, defined as follows:

Table 2: 8-point ordinal scale

8.	Death
7.	Hospitalized, on invasive mechanical ventilation or ECMO
6.	Hospitalized, on noninvasive ventilation or high-flow oxygen devices
5.	Hospitalized, requiring supplemental oxygen
4.	Hospitalized, not requiring supplemental oxygen—requiring ongoing medical care (COVID-19 related or otherwise)
3.	Hospitalized, not requiring supplemental oxygen—no longer requiring ongoing medical care
2.	Not hospitalized, limitation on activities and/or requiring home oxygen
1.	Not hospitalized, no limitations on activities

The time to recovery was the elapsed time (in days) from randomization to the earliest day on which a participant reached recovery.

Subgroup analyses

Subgroup analyses for the main efficacy outcomes (i.e., the primary and key secondary analyses) evaluated the treatment effect across the following subgroups:

- Geographic region:
- US sites; Non-US sites
- North American sites; Asian sites; European sites
- Duration of symptoms prior to enrolment:
    - Quartiles
    - ≤ 10 days; > 10 days
    - ≤ median; > median
- Race (White; Black/African American; Asian; Other)
- Comorbidities:
    - None; any
    - None; 1; 2 or more
    - Obese; non-obese
- Age (18 to < 40 years; 40 to 64 years; 65 years and older)
- Sex (female; male)
- Severity of disease:
    - Randomization stratification: mild-to-moderate; severe

- Actual disease severity at baseline: mild-to-moderate; severe
- Baseline ordinal scale category: 4; 5; 6; 7

Secondary Efficacy Endpoints

Key Secondary Efficacy Endpoint

The key secondary endpoint was the distribution of clinical status (8-point ordinal scale) on Day 15.

The outcome was analysed using a proportional odds model with treatment arm and disease severity as covariates for both the ITT and As Treated Populations. The treatment OR estimated from the model is presented with the p-value. Predicted individual probabilities of scale levels by treatment arm and disease severity were summarized graphically. Similar analyses were conducted by replacing disease severity with other subgroups as a covariate.

Other Secondary Efficacy Endpoints

- Ordinal outcome assessed daily while hospitalized and on Days 15, 22, and 29
- NEWS assessed daily while hospitalized and on Days 15 and 29
- Days of supplemental oxygen (if applicable)
- Days of non-invasive ventilation/high-flow oxygen (if applicable)
- Days of invasive mechanical ventilation/ECMO (if applicable)
- Days of hospitalization
- Date and cause of death (if applicable)

All secondary outcomes evaluated the treatment effect across the following subgroups:

- Duration of symptoms prior to enrolment (≤ median; > median)
- Severity of disease
  - Randomization stratification: mild-to-moderate; severe
  - Actual disease severity at baseline: mild-to-moderate; severe
  - Baseline ordinal scale category: 4; 5; 6; 7

Exploratory

To evaluate the virologic efficacy of different investigational therapeutics as compared to the control arm as assessed by:

- Percent of subjects with SARS-CoV-2 detectable in OP sample at Days 3, 5, 8, 11, 15, and 29.
- Quantitative SARS-CoV-2 virus in OP sample at Days 3, 5, 8, 11, 15, and 29.
- Development of resistance of SARS-CoV-2 in OP sample at Days 3, 5, 8, 11, 15, and 29.
- Quantitative SARS-CoV-2 virus in blood at Days 3, 5, 8, and 11.
- Qualitative and quantitative polymerase chain reaction (PCR) for SARS-CoV-2 in OP swab on Day 1; Days 3, 5, 8, and 11 (while hospitalized); and Days 15 and 29 (if attends in-person visit or still hospitalized).
- Qualitative and quantitative PCR for SARS-CoV-2 in blood on Day 1; Days 3, 5, 8, and 11 (while hospitalized).

Sample size

For the log-rank test, the two key determinants of power are the total number of events (i.e., recoveries) and the treatment-to-control ratio of the rate of recovery. For 85% power, approximately 320 recoveries are required to detect a 40% increase in the rate of recovery (θ=1.40) from remdesivir. A recovery rate ratio of 1.40 is similar to, but slightly higher than the figure of 1.31 reported in Cao, Wang, Wen et al. (2020) for a lopinavir/ritonavir trial that used time to improvement by 2 categories as primary endpoint. A total of 400 recoveries is needed for a recovery ratio of 1.35 with 85% power.

The initial sample size was projected to be 572 subjects to achieve 400 subjects with a "recovered" status (per the primary objective). The primary analysis was planned to be based on those subjects enrolled in order to 400 recoveries. An additional analysis of the moderate severity subgroup (those with baseline status of "Hospitalized, requiring supplemental oxygen" or "Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care") is also of public health importance. Hence, enrolment was permitted until the date of April 20, 2020 to ensure 400 recoveries and provide additional data about this important subgroup.

For the key secondary endpoint, a sample size can be computed using an (assumed) ordinal scale distribution for the placebo and the odds ratio representing clinical improvement. The odds ratio represents the odds of improvement in the ordinal scale for treatment relative to placebo. Five scenarios are considered for outcome probabilities in the placebo arm for sample size determination. There is significant uncertainty with these assumptions given the limited data available. A total sample size of 396 gives approximately 85% power to detect an odds ratio of 1.75 using a 2-tailed test at level α=0.05.

Randomisation

The study randomized subjects 1:1 to placebo or investigational product. Randomization was stratified by:

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

The randomization procedure is described in the MOP. The randomization is based on a variable blocked scheme to provide an approximately balanced allocation to the treatment groups during the study.

Blinding (masking)

A matching placebo or normal saline was given at an equal volume at the same schedule. If saline placebo was used, IV bags of study treatment were covered to mask the slight colour difference between the remdesivir solution and placebo to maintain the study blind.

Statistical methods

The ITT Population included all participants who were randomized. Analyses using the ITT Population were summarized by the planned treatment arm. The As Treated Population included all randomized participants who received any study treatment infusion even if the infusion was halted or slowed. Analyses using the As Treated Population were summarized by the actual treatment arm.

The primary analysis was performed on the ITT Population. The primary analysis was planned to be based on those subjects enrolled in order to achieve 400 recoveries. Unblinding of the study was planned to occur after all subjects enrolled for 400 recoveries have reached the end of study, and these visits are monitored and data is cleaned. Subsequent analysis were planned to be performed on all enrolled subjects.

For the primary and secondary outcomes analyses, stratification was based on mild-to-moderate versus severe disease at randomization. Cox models were run within each of the disease severity strata to obtain stratum-specific estimates of the treatment HR.

There was only 1 primary outcome measure. There was no planned adjustment for multiple comparisons in any secondary analyses.

For time-to-event outcomes, participants who were lost to follow-up or terminated the study prior to Day 29 and prior to observing/experiencing the event were censored at the time of their last observed assessment. Participants who died within Day 29 and prior to observing/experiencing the event were censored at Day 29. Participants who completed the study without observing/experiencing the event were censored at the day of their Day 29 visit. For the analysis of the key secondary outcome, participants who were not discharged or died by the Day 15 visit but had missing ordinal scores on the Day 15 visit were excluded from the analysis.

The primary analysis used the stratified log-rank test to compare treatment to control through Day 29 with respect to time to recovery. The primary null hypothesis being tested with a two-sided type I error rate of 5% is that time-to-recovery does not differ between the experimental and control arms. The treatment RRR estimate, CI, and p-value from the stratified log-rank test are presented. The median time to event and 95% CI were summarized by treatment arm and disease severity. Kaplan-Meier (KM) curves for each treatment arm are presented, supplemented with the RRR estimate and p-value.

Supplemental and sensitivity analyses include the following:

1) An analysis on the As Treated Population where participants who were not treated were censored at enrolment
2) An estimation of the HR using the Cox proportional hazards models. First, participants who died prior to recovering were treated as experiencing a competing risk in the Fine-Gray proportional hazards regression model. Second, a Cox model was fit with binary indicators for treatment group and disease severity [separate models for randomized stratum and actual stratum]) as well as a treatment * disease severity interaction term.
3) An analysis of subgroups
4) A "leave one out" sensitivity analysis to assess the impact of individual sites by excluding 1 site at a time
5) A sensitivity analysis for readmittance, such that participants who recovered but were later readmitted were not considered a recovery but were instead censored at 28 days.
6) A sensitivity analysis for unblinding and crossover treatment
    a) Participants who were crossover treated with RDV (per 29 April 2020 Protocol Administrative Letter) were censored at the time of RDV treatment initiation.
    b) Participants who were unblinded, regardless of whether they received crossover treatment of RDV or not, were censored at the time of unblinding.
7) An analysis in which participants who took medications of interest were treated as treatment failures and were censored at the time of medication use.

The key secondary endpoint was the distribution of clinical status (8-point ordinal scale) on Day 15. The outcome was analysed using a proportional odds model with treatment arm and disease severity as covariates for both the ITT and As Treated Populations. The hypothesis test performs a stratified test to evaluate whether the common odds ratio for treatment is equal to one (it is worth noting that, for large sample sizes, the test based on the proportional odds model is nearly the same as the Wilcoxon rank sum test). The treatment OR estimated from the model is presented with the p-value. Predicted individual probabilities of scale levels by treatment arm and disease severity were summarized graphically.

Multiple supplemental analyses of this key secondary outcome were performed to determine time to improvement by at least 1 and 2 categories in the clinical 8-point ordinal scale. The log-rank test was performed to test whether the KM curves differ between treatment arms, as well as to estimate the median improvement time and its 95% CI. Improvement rate ratio (IRR), which is identical to an HR but denotes the relative odds of improvement, and its 95% CI were estimated from a Cox proportional hazards model.

According to the protocol, sensitivity analyses were defined in the SAP to evaluate the impact of making different assumptions about missing observations.

The median time to discharge or to a NEWS of ≤ 2 and 95% CI were summarized by treatment group with the hazard ratio (HR) and log-rank p-values for both the ITT and As Treated Populations; differences in time-to-event endpoints by treatment arm were summarized with KM curves with number at risk, HR, and log-rank p-values. The mean (standard deviation) of change from baseline in NEWS was reported by treatment arm and study visit Days 3, 5, 8, 11, 15, and 29 in both the ITT and As Treated Populations.

For the secondary analyses that involved duration (i.e., days of oxygenation, non-invasive ventilation/high-flow oxygen, invasive mechanical ventilation/ECMO, and hospitalization), the total duration was the sum of all reported days, regardless of whether the days occurred consecutively or in disjointed intervals. The analyses were performed on the ITT and As Treated Populations. Median days and quartiles were presented by treatment arm.

For the secondary analyses that involved incidence of new use of respiratory support (oxygen use, non-invasive ventilation/high-flow oxygen, invasive mechanical ventilation/ECMO) among participants who were not on the modality of oxygen support under evaluation at baseline, the number of participants reporting new use, incidence rate, and 95% CI were reported by treatment arm. The analyses were performed on both the ITT and As Treated Populations. The median days and quartiles of duration of new use were reported by treatment arm.

Subgroup analyses for the efficacy outcomes evaluated the treatment effect across the following subgroups: geographic region, race, comorbidities, age, sex, duration of symptoms prior to enrolment, and severity of disease.

Originally, an interim efficacy analysis was planned after at least approximately 50% of total information was obtained. However, because of the rapid pace of enrolment, the preliminary analysis actually occurred after completion of enrolment while follow-up was still ongoing using the data cut date of 28 April 2020.

A DSMB monitored ongoing results to ensure subject well-being and safety as well as study integrity. The DSMB was asked to recommend early termination or modification only when there is clear and substantial evidence of a treatment difference.

The unblinded statistical team prepared closed reports for DSMB review and recommendations. Analyses were presented with blinded codes for treatment arms. Given the positive findings in the preliminary analysis, the results were subsequently made public and unblinded. The treating physician could have requested to be made aware of the treatment assignment of participants who had not completed Day 29

if clinically indicated (e.g., because of worsening clinical status), and participants originally in the placebo group could have been given RDV.

Results

In general, data presentations in the submitted clinical overview focussed on the 138 participants from Study CO-US-540-5776 who had a baseline ordinal score of 4 because this categorization of disease severity (i.e., using an 8-point ordinal scale based on the participant's hospitalization and oxygen support status) as the MAH considered this more clinically relevant. However, for completeness, some analyses were also presented by actual disease severity.

Participant flow

Participants were enrolled and treated at 60 main study sites in the US, Denmark, the UK, Greece, Germany, Republic of Korea, Mexico, Spain, Japan, and Singapore.

1114 participants were screened, of whom 1062 were randomised and 1048 received at least one dose of study treatment (RDV 10-day group, 531 participants; placebo group, 517 participants).

Of the 1062 patients randomised, 159 were allocated to the mild-moderate disease stratum (RDV 10-day group, 82 participants; placebo group, 77 participants). One participant in the placebo group did not receive at least one infusion.

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

The ITT Population included all participants who were randomised to the mild/moderate disease stratum (N= 159 participants (RDV 10-day group, 82 participants; placebo group, 77 participants)).

The As Treated (AsT) Population included all randomized participants who received any study treatment infusion, even if the infusion was halted or slowed (N= 158 participants (RDV 10-day group, 82 participants; placebo group, 77 participants)).

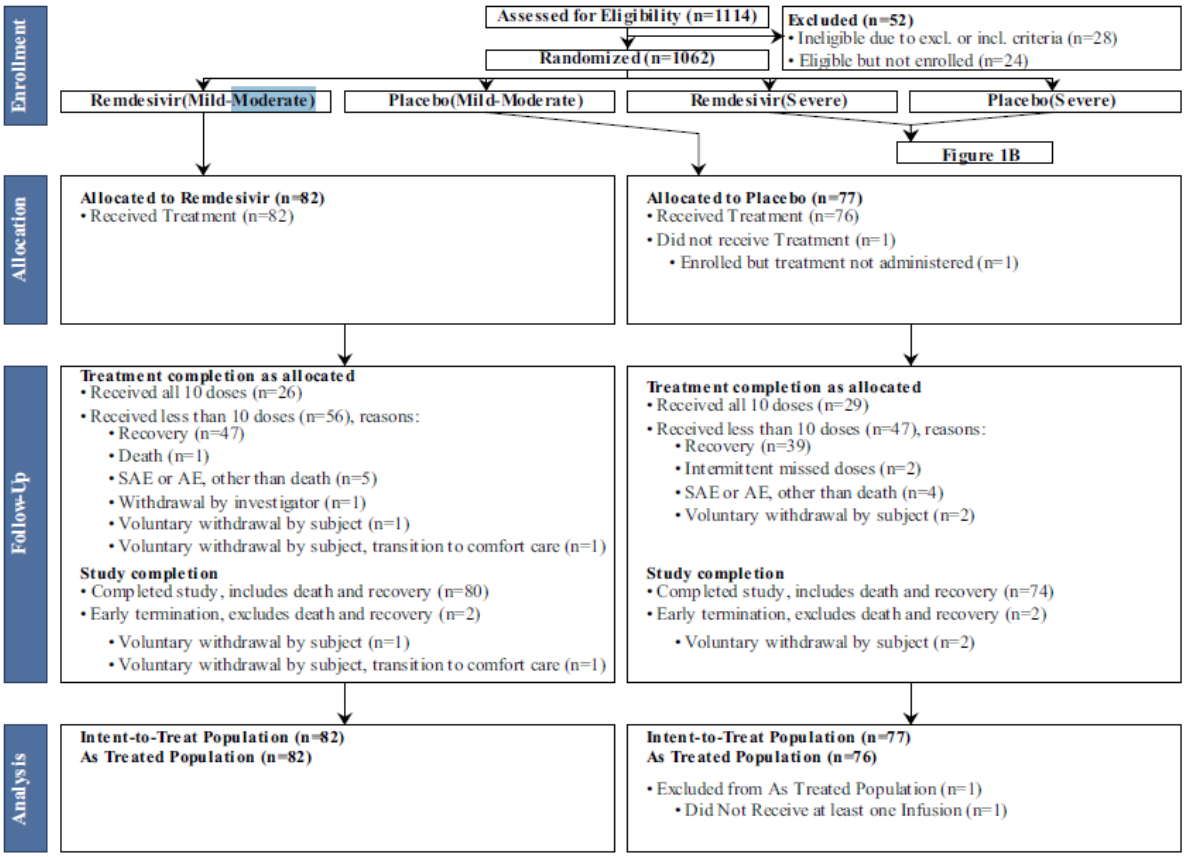


Figure 2: CO-US-540-5776: Disposition of Participants mild moderate stratum (All Screened Participants)

Recruitment

Recruitment was halted on 19 April 2020. Data cut-off date for review of preliminary results by the DSMB was 22 April 2020. Database freeze for the publication was 28th April 2020. Last patient last observation for final analysis was on 21 May 2020.

Conduct of the study

Table 3 lists the key dates relevant to the conduct of Study CO-US-540-5776.

Table 3: CO-US-540-5776: Key Dates

Event	Date
First Participant Screened	21 February 2020
First Participant Enrolled (or Randomized)	21 February 2020
Last Participant Enrolled (or Randomized)	20 April 2020
Last Participant Last Observation	21 May 2020
Database Finalization	25 June 2020
Treatment Unblinding	28 April 2020

Changes in the Conduct of the Study or Planned Analyses

Major amendments were made to the protocol. The most relevant change pertains to the primary endpoint as detailed above. The original protocol was amended twice during Study CO-US-540-5776 and there were two region/country-specific protocol amendments for the EU/UK and 2 administrative letters, as indicated in the following table:

Table 4: Protocol and Protocol Amendments

Protocol/Amendment	Date
Original Protocol (Version 1.0)	18 February 2020
Protocol Amendment 1 (Version 2.0)	01 March 2020
Protocol Amendment 2 (Version 3.0)	02 April 2020
EU/UK-Specific Amendment 1	17 March 2020
EU/UK-Specific Amendment 2	05 April 2020
Administrative Letter 1 (Letter of Amendment to clarify contraceptive requirements)	26 February 2020
Administrative Letter 2 (Administrative Letter regarding treatment of subjects in the ACTT-1 trial)	29 April 2020

Participants were enrolled under the global/regional version of the protocol or amendment that was applicable at the time of enrolment. No participant was enrolled at US sites under Version 1.0 of the protocol (dated 18 February 2020). The most important change from protocol-specified analyses are listed below.

Protocol Amendment 1 (01 March 2020)

- The sample size was increased to 440 participants.
- The ordinal scale was increased to 8 categories to address the concern that "Hospitalized not on oxygen" was in fact 2 separate categories, i.e., those participants still needing medical care and those kept in hospital solely for infection control.
- A follow-up phone call on Day 22 was added to the study procedures and schedule of assessments due to concerns that the peak illness could be missed if the condition of a participant worsened between 2 and 4 weeks of illness. This was also to address concerns regarding participants with more severe COVID-19 being discharged by Day 29.
- An inclusion criterion was added to specify that participants must have been admitted to hospital with symptoms suggestive of COVID-19 infection.
- Inclusion criterion #7 was updated to align with the contraceptive requirements for women of childbearing potential.
- The key secondary efficacy objective was revised to include a new endpoint, whereby participants who were either "hospitalized, on invasive mechanical ventilation or ECMO" or "hospitalized, on non-invasive ventilation or high-flow oxygen devices" would be analysed separately on the 8-point ordinal scale.
- In the additional secondary efficacy objectives, a new objective was added to analyse 14-day mortality to allow better assessment of short-term as well as long-term mortality.

- More detail was added to describe efficacy and virology assessments in the protocol, in order to facilitate these procedures.

Protocol Amendment 2 (02 April 2020)

- More flexibility for follow-up procedures was added.
- The sample size was changed to ensure there was a sufficient number of participants (400) who achieved a "recovered" status for the primary objective. Additionally, enrolment was permitted after 400 recoveries were observed up until midnight 20 April 2020, to provide additional data for important subgroups of interest.
- The primary endpoint was changed from an ordinal scale assessment on a given day (Day 15) to days to recovery (the best 3 categories of the ordinal scale).
- The prior primary endpoint was relabelled as the key secondary endpoint.
- Additional flexibility was added to inclusion criterion #5 to account for delays in receiving diagnostic polymerase chain reaction (PCR) results at some sites.
- In exclusion criterion #2, the lower cut-off of estimated glomerular filtration rate (eGFR) was decreased to 30 mL/minute after discussion between Gilead and the FDA.
- The DSMB oversight plan was modified, with input from the DSMB, regarding when the DSMB recommended performing interim reviews. Considering the rapid pace of enrolment, the prior plans for DSMB oversight were not practical.
- The protocol was amended to reflect the fact that the newly manufactured lot of RDV was provided in 100 mg vials and, due to a limited supply of placebo, the option of using saline with an opaque bag for the control infusion was added.
- Significant increases were observed in the use of off-label therapies for COVID-19, including many repurposed agents and therapies targeting immune response. Additional wording was added to cover these scenarios to minimize the use of additional confounding medications/concomitant therapies.
- The protocol was amended to allow exclusion of some samples (blood for PCR SARS-CoV-2, oropharyngeal (OP) swab, and blood for serum for secondary research) that had to be processed in a Biosafety Laboratory (BSL)-3 environment, due to limitations in the facilities at some sites for processing, shipping, and storage of these samples.

European Union/United Kingdom-Specific Amendment 1 (17 March 2020)

In the EU/UK, this study was conducted by sites of the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT). This protocol amendment (INSIGHT Version 1.0) was based on global Protocol Amendment 01 (01 March 2020). Region/country-specific changes in this protocol amendment were as follows:

- Exploratory objectives were revised to indicate that they would be performed with stored samples and they would require a separate consent.
- Inclusion criteria were revised, as follows:
    - To allow a LAR to agree to comply with planned procedures
    - Remove the agreement to the collection of OP swabs
- Use of matching placebo to RDV was revised to normal saline, and the maintenance of study blind by the use of a covering over intravenous (IV) bags was added.

- It was revised to specify that only participants who consent may provide research laboratory samples (global change).
- Also revised, as follows:
    - To include a total volume for safety laboratory tests only
    - To specify that only participants who consent to specimen storage would be participant to blood for serum and plasma draws (global change)
    - To update total blood volumes for a sum of blood volumes for safety laboratory tests and blood for serum and plasma
- Section 10.1.1.1 was revised, as follows:
    - The title was changed to "Optional Specimen Collection (Requires Separate Consent)"
    - "OP samples" was added as a specimen type
    - "secondary research" was revised to "future research" (global revision)

European Union/United Kingdom-Specific Amendment 2 (05 April 2020)

This protocol amendment (INSIGHT Version 2.0) was based on global Protocol Amendment 02 (02 April 2020). There were no additional region/country-specific changes in this protocol amendment.

Administrative Letter 1 (26 February 2020)

An administrative letter was issued to clarify contraceptive requirements. This included the following:

- Section 1.2: Added a urine/serum pregnancy test on Day 29 for females of childbearing potential
- Section 2.3.2: Added a statement that use of hormonal contraception with RDV was not recommended
- Section 5.1: Revised the inclusion criteria, as follows:
    - Inclusion criterion #7 should read: "Women of childbearing potential must agree to use at least one primary form of contraception not including hormonal contraception from the time of enrolment through Day 60."
    - Add inclusion criterion #8, which should read: "Male subjects with a partner of childbearing potential should use condoms from the initiation of treatment through Day 60."
- Section 8.1.1: Revised third bullet, as follows:
    - Counsel subjects to use adequate birth control methods required during the trial to avoid pregnancy.
        - Women should be counselled to use birth control methods not including hormonal contraception from the initiation of treatment to 1 month after the end of the study. Women should also be counselled to contact the study staff if there is a delayed menses (> 1 month between menstruations) in order to get pregnancy testing.
        - Males with partners of child bearing potential should be counselled to use condoms from the initiation of treatment to 1 month after the end of the study.

Administrative Letter 2 (29 April 2020)

An administrative letter was issued to notify sites that the preliminary efficacy data from the DSMB meeting on 27 April 2020 demonstrated significant efficacy for participants who received RDV and that investigators may request unblinding to treatment assignment and administer RDV to participants assigned to placebo. Furthermore, individual participants may be unblinded after study completion or death.

Protocol Deviations:

Table 5 provides a categorical summary of major protocol deviations that occurred during the study. Protocol deviations were documented during routine monitoring visits.

Table 5: CO-US-540-5776: Major Protocol Deviations (ITT Population)

	Subject–Specific Deviations		Non–Subject-Specific Deviations
Deviation Category	**RDV 10-day (N = 541)**	**Placebo (N = 521)**	**n**
Number of Major Protocol Deviations			
Blinding policy/procedure	3	2	—
Eligibility/enrollment	56	48	3
Protocol procedure/assessment	43	44	26
Treatment administration	8	8	1
Treatment administration schedule	3	4	1
Follow-up visit schedule	—	—	1
Protocol category not selected	—	—	1

Major and nonmajor deviation categories are not defined in the protocol or case report form. These major deviations were categorized by the Statistical and Data Coordinating Center Lead Project Manager and Division of Microbiology and Infectious Diseases Associate Director of Clinical Research as part of a previous United States Food and Drug Administration request.
Source: Section 15.1, Addendum Table 3 and Addendum Table 5

Table 6: Distribution of Subject Specific Major Protocol Deviations by Category, Type, Treatment Group, and Randomized Disease Severity - ITT Population

		Remdesivir (N=541)				Placebo (N=521)				All Subjects (N=1062)			
		Mild-Moderate (N=82)		Severe (N=459)		Mild-Moderate (N=77)		Severe (N=444)		Mild-Moderate (N=159)		Severe (N=903)	
Category	Deviation Type	# of Subj.	# of Dev.	# of Subj.	# of Dev.	# of Subj.	# of Dev.	# of Subj.	# of Dev.	# of Subj.	# of Dev.	# of Subj.	# of Dev.
Blinding policy/procedure	Any type	-	-	3	3	-	-	2	2	-	-	5	5
	Treatment unblinded	-	-	3	3	-	-	2	2	-	-	5	5
Eligibility/enrollment	Any type	34	35	21	21	31	31	17	17	65	66	38	38
	Did not meet inclusion criterion	-	-	3	3	-	-	4	4	-	-	7	7
	ICF not signed prior to study procedures	-	-	-	-	-	-	2	2	-	-	2	2
	Incorrect version of ICF signed	1	1	4	4	-	-	1	1	1	1	5	5
	Met exclusion criterion	-	-	1	1	-	-	1	1	-	-	2	2
	Required procedure done incorrectly	1	1	1	1	1	1	2	2	2	2	3	3
	Required procedure not conducted	1	1	1	1	-	-	-	-	1	1	1	1
	Stratification error	7	7	4	4	8	8	3	3	15	15	7	7
	Other	25	25	7	7	22	22	4	4	47	47	11	11
Protocol procedure/assessment	Any type	8	9	30	34	6	6	35	38	14	15	65	72
	Blood not collected	-	-	2	2	1	1	1	1	1	1	3	3
	ICF not signed prior to study procedures	-	-	1	1	1	1	1	1	1	1	2	2
	Incorrect version of ICF signed	-	-	-	-	1	1	2	2	1	1	2	2
	Required procedure done incorrectly	5	6	9	10	2	2	10	11	7	8	19	21
	Required procedure not conducted	1	1	6	6	-	-	5	5	1	1	11	11
	Specimen result not obtained	1	1	4	4	1	1	4	4	2	2	8	8
	Other	1	1	11	11	-	-	14	14	1	1	25	25
Treatment administration	Any type	-	-	8	8	1	1	6	7	1	1	14	15
	Missed treatment administration	-	-	1	1	1	1	1	1	1	1	2	2
	Required procedure done incorrectly	-	-	2	2	-	-	-	-	-	-	2	2
	Required procedure not conducted	-	-	1	1	-	-	-	-	-	-	1	1
	Other	-	-	4	4	-	-	5	6	-	-	9	10
Treatment administration schedule	Any type	-	-	3	3	-	-	4	4	-	-	7	7
	Missed treatment administration	-	-	2	2	-	-	2	2	-	-	4	4
	Other	-	-	1	1	-	-	2	2	-	-	3	3

N = Number of subjects enrolled.

Monitoring

The provided Monitoring plan is dated 05 June 2020 and refers to volume 3.0. The monitoring of the clinical data was done either on-site or remotely, depending on restrictions for on-site visits due to the COVID-19 pandemic.

For EU/UK sites, remote monitoring was not possible due to data protection regulations. Because most sites were also inaccessible to external monitors, qualified personnel from the site's institutions who were not otherwise involved with the study served as monitors, after training by the International Coordinating Centers or Site Coordinating Centers.

Baseline data

Of the 1048 participants who were enrolled and received any study treatment infusion, 138 participants (RDV 10-day 75; placebo 63) had a baseline ordinal score of 4 (hospitalized, not requiring supplemental oxygen - requiring ongoing medical care [COVID-19 related or otherwise]) and a total of 105 participants (RDV 10-day 55; placebo 50) had mild/moderate actual disease severity (defined as SpO2 > 94% and respiratory rate < 24 breaths/minute without supplemental oxygen).

Demographic and baseline characteristics among participants with baseline ordinal score of 4 (N = 138) are shown in the table below.

Table 7: Demographic and Baseline Characteristics for Participants with Baseline Ordinal Score of 4 (ITT Population). Taken from the Clinical Overview.

	RDV 10 Days (N = 75)	Placebo (N = 63)
Median (Q1, Q3) age, years	59.0 (48, 69)	55.0 (44, 68)
≥ 65 years, n (%)	25 (33.3%)	19 (30.2%)
Male, n (%)	52 (69.3%)	37 (58.7%)
Not Hispanic or Latino, n (%)	61 (81.3%)	46 (73.0%)
Race category, n (%)		
Asian	14 (18.7%)	18 (28.6%)
Black	14 (18.7%)	8 (12.7%)
White	41 (54.7%)	32 (50.8%)
Other	6 (8.0%)	5 (7.9%)
Median (Q1, Q3) BMI, kg/m^2	27.15 (24.4, 30.2)	26.10 (23.8, 30.6)
Median (Q1, Q3) duration of symptoms prior to enrollment, days	7.0 (5, 10)	9.0 (7, 11)
Participants with, n (%)		
No comorbidities	21 (28.0%)	22 (34.9%)
One comorbidity	19 (25.3%)	11 (17.5%)
Two or more comorbidities	35 (46.7%)	30 (47.6%)

BMI = body mass index; ITT = intent-to-treat; Q1 = first quartile; Q3 = third quartile; RDV = remdesivir (GS-5734™)
N = number of participants in the ITT Population
Source: Table req12690.16.1 and Table req12690.16.2

Table 8: Duration of symptoms prior to enrolment in patients with baseline ordinal score 4. Taken from the clinical overview.

	Remdesivir (N=75)	Placebo (N=63)
Duration of Symptoms prior to Enrollment		
First Quartile (<= 6 Days)	31 (41.3%)	13 (20.6%)
Second Quartile (7 to <= 9 Days)	25 (33.3%)	27 (42.9%)
Third Quartile (10 to <= 12 Days)	13 (17.3%)	12 (19.0%)
Fourth Quartile (13+ Days)	6 (8.0%)	11 (17.5%)
Duration of Symptoms prior to Enrollment		
<= 10	66 (88.0%)	45 (71.4%)
> 10	9 (12.0%)	18 (28.6%)

Table 9: Categorical Demographic and Baseline Characteristics by Randomized Disease Severity and Treatment Group - ITT Population. Taken from the CSR.

		Remdesivir						Placebo						All Subjects					
		Mild-Moderate (N=82)		Severe (N=459)		All Subjects (N=541)		Mild-Moderate (N=77)		Severe (N=444)		All Subjects (N=521)		Mild-Moderate (N=159)		Severe (N=903)		All Subjects (N=1062)	
Demographic Category	Characteristic	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Sex	Male	58	71	294	64	352	65	43	56	289	65	332	64	101	64	583	65	684	64
	Female	24	29	165	36	189	35	34	44	155	35	189	36	58	36	320	35	378	36
Ethnicity	Not Hispanic or Latino	63	77	319	69	382	71	63	82	310	70	373	72	126	79	629	70	755	71
	Hispanic or Latino	17	21	117	25	134	25	12	16	104	23	116	22	29	18	221	24	250	24
	Not Reported	1	1	14	3	15	3	2	3	12	3	14	3	3	2	26	3	29	3
	Unknown	1	1	9	2	10	2	-	-	18	4	18	3	1	1	27	3	28	3
Race	American Indian or Alaska Native	2	2	2	<1	4	1	1	1	2	<1	3	1	3	2	4	<1	7	1
	Asian	14	17	65	14	79	15	18	23	38	9	56	11	32	20	103	11	135	13
	Native Hawaiian or Other Pacific Islander	1	1	1	<1	2	<1	-	-	2	<1	2	<1	1	1	3	<1	4	<1
	Black or African American	17	21	92	20	109	20	15	19	102	23	117	22	32	20	194	21	226	21
	White	39	48	240	52	279	52	38	49	249	56	287	55	77	48	489	54	566	53
	Multi-Racial	2	2	-	-	2	<1	-	-	1	<1	1	<1	2	1	1	<1	3	<1
	Unknown	7	9	59	13	66	12	5	6	50	11	55	11	12	8	109	12	121	11
Geographic Region 1	US Site	56	68	371	81	427	79	48	62	362	82	410	79	104	65	733	81	837	79
	Non-US Site	26	32	88	19	114	21	29	38	82	18	111	21	55	35	170	19	225	21
Geographic Region 2	North America	57	70	374	81	431	80	50	65	366	82	416	80	107	67	740	82	847	80
	Europe	16	20	68	15	84	16	15	19	64	14	79	15	31	19	132	15	163	15
	Asia	9	11	17	4	26	5	12	16	14	3	26	5	21	13	31	3	52	5
Age (years)	<40	15	18	44	10	59	11	10	13	50	11	60	12	25	16	94	10	119	11
	40-64	42	51	253	55	295	55	44	57	220	50	264	51	86	54	473	52	559	53
	>=65	25	30	162	35	187	35	23	30	174	39	197	38	48	30	336	37	384	36
Baseline Clinical Status[a]	Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care	54	66	21	5	75	14	46	60	17	4	63	12	100	63	38	4	138	13
	Hospitalized, requiring supplemental oxygen	19	23	213	46	232	43	24	31	179	40	203	39	43	27	392	43	435	41
	Hospitalized, on non-invasive ventilation or high flow oxygen devices	8	10	87	19	95	18	3	4	95	21	98	19	11	7	182	20	193	18
	Hospitalized, on invasive mechanical ventilation or ECMO	1	1	130	28	131	24	3	4	151	34	154	30	4	3	281	31	285	27
Duration of Symptoms prior to enrollment[b]	First Quartile (<= 6 Days)	28	34	130	28	158	29	16	21	108	24	124	24	44	28	238	26	282	27
	Second Quartile (7 to <= 9 Days)	31	38	117	25	148	27	32	42	120	27	152	29	63	40	237	26	300	28
	Third Quartile (10 to <= 12 Days)	12	15	101	22	113	21	13	17	95	21	108	21	25	16	196	22	221	21
	Fourth Quartile (13+ Days)	11	13	110	24	121	22	16	21	119	27	135	26	27	17	229	25	256	24
Duration of Symptoms prior to enrollment[b]	<= 10 Days	69	84	287	63	356	66	54	70	266	60	320	61	123	77	553	61	676	64
	> 10 Days	13	16	171	37	184	34	23	30	176	40	199	38	36	23	347	38	383	36
Duration of Symptoms prior to enrollment[b]	<= Median (9 Days)	59	72	247	54	306	57	48	62	228	51	276	53	107	67	475	53	582	55
	> Median (9 Days)	23	28	211	46	234	43	29	38	214	48	243	47	52	33	425	47	477	45
Comorbidities[c]	Asthma	5	6	58	13	63	12	5	7	52	12	57	11	10	6	110	12	120	11
	Cardiac failure congestive	6	7	25	6	31	6	2	3	26	6	28	5	8	5	51	6	59	6
	Chronic kidney disease	10	12	28	6	38	7	4	5	25	6	29	6	14	9	53	6	67	6
	Chronic respiratory disease	3	4	34	8	37	7	3	4	38	9	41	8	6	4	72	8	78	7

		Remdesivir						Placebo						All Subjects					
		Mild-Moderate (N=82)		Severe (N=459)		All Subjects (N=541)		Mild-Moderate (N=77)		Severe (N=444)		All Subjects (N=521)		Mild-Moderate (N=159)		Severe (N=903)		All Subjects (N=1062)	
Demographic Category	Characteristic	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	Coronary artery disease	8	10	61	14	69	13	7	9	50	11	57	11	15	9	111	12	126	12
	Dependence on oxygen therapy	4	5	11	2	15	3	1	1	3	1	4	1	5	3	14	2	19	2
	Hypertension	41	50	228	51	269	51	34	45	230	52	264	51	75	47	458	51	533	51
	Immune system disorder	10	12	22	5	32	6	11	14	30	7	41	8	21	13	52	6	73	7
	Liver disorder	4	5	10	2	14	3	2	3	10	2	12	2	6	4	20	2	26	2
	Neoplasm malignant	10	12	33	7	43	8	7	9	30	7	37	7	17	11	63	7	80	8
	Obesity	28	34	214	48	242	46	22	29	212	48	234	45	50	32	426	48	476	45
	Type 1 diabetes mellitus	1	1	6	1	7	1	-	-	3	1	3	1	1	1	9	1	10	1
	Type 2 diabetes mellitus	22	27	142	32	164	31	20	26	138	31	158	30	42	27	280	31	322	31
Comorbidities Group 1	Any Comorbidities	64	78	371	81	435	80	52	68	370	83	422	81	116	73	741	82	857	81
	No Comorbidities	18	22	79	17	97	18	24	31	73	16	97	19	42	26	152	17	194	18
	Unknown	-	-	9	2	9	2	1	1	1	<1	2	<1	1	1	10	1	11	1
Comorbidities Group 2	No Comorbidities	18	22	79	17	97	18	24	31	73	16	97	19	42	26	152	17	194	18
	1 Comorbidity	28	34	110	24	138	26	13	17	124	28	137	26	41	26	234	26	275	26
	2 or more Comorbidities	36	44	260	57	296	55	39	51	244	55	283	54	75	47	504	56	579	55
	Unknown	-	-	10	2	10	2	1	1	3	1	4	1	1	1	13	1	14	1
Comorbidities Group 3	Obese	28	34	214	47	242	45	22	29	212	48	234	45	50	31	426	47	476	45
	Non-Obese	54	66	235	51	289	53	54	70	230	52	284	55	108	68	465	51	573	54
	Unknown	-	-	10	2	10	2	1	1	2	<1	3	1	1	1	12	1	13	1

N = Number of subjects enrolled.
[a]Baseline clinical status data was missing for 11 subjects.
[b]Duration of Symptoms prior to enrollment data was missing for 3 subjects.
[c]Percentages are based on the number of subjects with data available for the individual comorbidity.

Numbers analysed

Data from 1062 patients were analysed. According to the protocol, the primary analysis was by "intention to treat". In the as Treated (AsT) Population 1048 participants were included.

Data presentations in the submitted clinical overview focussed on the 138 participants (RDV 10-day 75; placebo 63) from Study CO-US-540-5776 who had a baseline ordinal score of 4 (hospitalized, not requiring supplemental oxygen - requiring ongoing medical care) because this categorization of disease severity (i.e., using an 8-point ordinal scale based on the participant's hospitalization and oxygen support status) as the MAH considered this more clinically relevant. For completeness, some analyses were also presented for the 105 participants (RDV 10-day 55; placebo 50) had mild/moderate actual disease severity (defined as SpO2 > 94% and respiratory rate < 24 breaths/minute without supplemental oxygen).

Outcomes and estimation

Primary outcome – Time to recovery

Time to recovery in patients with baseline ordinal score of 4 (N = 138) according to treatment group is shown in Table 10 below.

Table 10: CO-US-540-5776: Proportion of Participants with Recovery by Day 29a for Participants with Baseline Ordinal Score of 4 (ITT Population). Presented in the clinical overview.

	RDV 10 Days (N = 75)	Placebo (N = 63)
Number of recoveries	73	58
Median time to recovery (95% CI), days	5 (4, 6)	6 (4, 7)
Recovery rate ratio (95% CI)[b]	1.29 (0.91, 1.83)	

CI = confidence interval; ITT = intent-to-treat; RDV = remdesivir (GS-5734™)
a Confidence intervals have not been adjusted for multiple comparisons.
b Recovery rate ratio was calculated from the Cox model. Recovery rate ratios greater than 1 indicate a benefit with RDV.
Source: {Beigel 2020a}

Among participants in the mild/moderate actual disease severity (N = 105), median time to recovery was 5 days (95% CI: 4, 6) in the RDV 10-day group and 5 days (95% CI: 4, 7) in the placebo group (recovery rate ratio [95% CI]: 1.22 [0.82, 1.81]; {Beigel 2020b}).

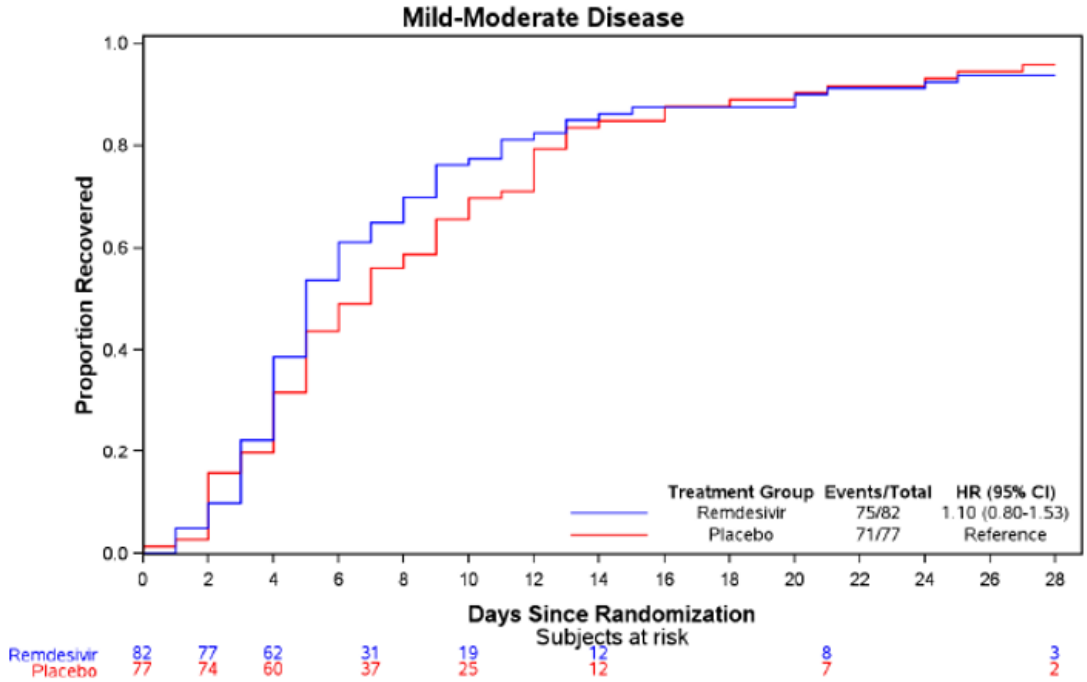


Figure 3: CO-US-540-5776: Kaplan-Meier Curves of Time to Recovery by Treatment Group in the mild moderate stratum (ITT Population).Taken from the CSR

Sensitivity Analyses of the Primary Endpoint

All pre-specified sensitivity analyses of the primary endpoint are shown below:

a) Time to Recovery by Treatment Group and Randomized Disease Severity: Fine-Gray and Interaction Modelling

Analysis using a Cox proportional hazards model, in which death prior to recovery was treated as a competing risk in the Fine-Gray proportional hazards regression model, is shown below (Table 11). Further sensitivity analyses were conducted using Cox proportional hazards models, including binary indicators for treatment group and disease severity stratum (randomized or actual severity were analysed in separate models).

Table 11: Time to Recovery by Treatment Group and Randomized Disease Severity: Fine-Gray and Interaction Modelling. Taken from the CSR.

		HR	
Model	**Disease Severity**	**Estimate**	**95% CI**
Fine-Gray	Mild/Moderate	1.10	0.82, 1.49
	Severe	1.35	1.16, 1.58
	Any Severity	1.30	1.13, 1.49
Treatment-Severity Interaction (Randomized Severity)	Mild/Moderate	1.09	0.78, 1.50
	Severe	1.34	1.14, 1.58
Treatment-Severity Interaction (Actual Severity)	Mild/Moderate	1.24	0.83, 1.83
	Severe	1.31	1.12, 1.52
P-value for the treatment by randomized disease severity interaction term is 0.2471. P-value for the treatment by actual disease severity interaction term is 0.8043.			

b) Readmittance Sensitivity Analysis – ITT Population

A sensitivity analysis examining the effect of unsustained recovery (readmittance for hospitalization) is shown in Table 12.

Table 12:Time to Recovery by Treatment Group and Randomized Disease Severity: Readmittance Sensitivity Analysis – ITT Population. Taken from the CSR.

					Median Time to Recovery		HR	
Analysis Population	**Treatment Group**	**Disease Severity**	**m**	**n**	**Estimate**	**95% CI**	**Estimate**	**95% CI**
ITT Population	Remdesivir (N=82)	Mild/Moderate	5	70	6.0	5.0, 8.0	1.05	0.75, 1.47
	Placebo (N=77)		4	67	7.0	5.0, 10.0		
	Remdesivir (N=459)	Severe	21	303	13.0	11.0, 16.0	1.26	1.07, 1.49
	Placebo (N=444)		11	270	20.0	17.0, 22.0		
	Remdesivir (N=541)	Any Severity	26	373	11.0	10.0, 13.0	1.22	1.05, 1.41
	Placebo (N=521)		15	337	16.0	14.0, 20.0		
N= Number of subjects in the specified treatment group, disease severity, and analysis population. m = Number of subjects who were readmitted. n = Number of recovered subjects. HR for the 'Any Severity' group is the ratio of the hazard of recovery in each treatment group estimated from the stratified Cox Model. The ratio is Remdesivir to Placebo. For this analysis, subjects who recovered but were subsequently readmitted were censored at 28 days.								

Key secondary outcomes

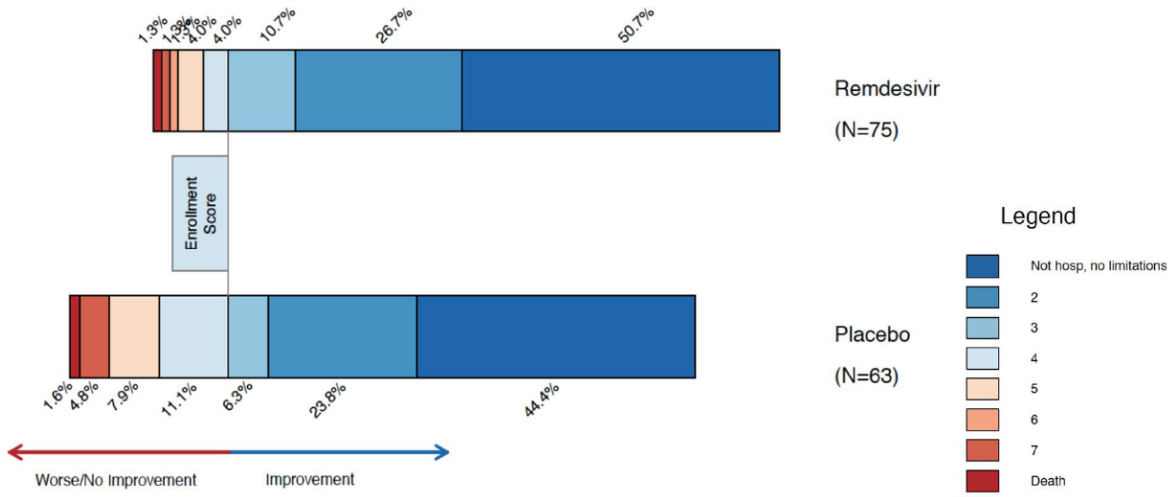
Clinical Status and odds of Improvement in Clinical Status 8-Point Ordinal Scale Category at Day 15

Clinical status scores at Day 15 are summarized by treatment group in patients with baseline ordinal scale 4 and the odds of improvement in clinical status at Day 15 are shown in the table below.

Table 13: CO-US-540-5776: Clinical Status Scores at Day 15 for Participants with Baseline Ordinal Score of 4 (ITT Population). Taken from the clinical overview.

Clinical Status Score at Day 15 (± 2 Days), n (%)	RDV 10 Days (N = 75)	Placebo (N = 63)
1	38 (50.7%)	28 (44.4%)
2	20 (26.7%)	15 (23.8%)
3	8 (10.7%)	4 (6.3%)
4	3 (4.0%)	7 (11.1%)
5	3 (4.0%)	5 (7.9%)
6	1 (1.3%)	0
7	1 (1.3%)	3 (4.8%)
8	1 (1.3%)	1 (1.6%)
Odds ratio (95% CI)[a]	1.5 (0.8, 2.7)	
P-value	0.234	

CI = confidence interval; COVID-19 = coronavirus disease 2019; ITT = intent-to-treat; RDV = remdesivir (GS-5734™)
a P-value and CI have not been adjusted for multiple comparisons.
The ordinal score at Day 15 is the participant's worst score on the ordinal scale during the previous day. Scores on the ordinal scale are as follows: 1, not hospitalized, no limitations of activities; 2, not hospitalized, limitation of activities, home oxygen requirement, or both; 3, hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection-control reasons); 4, hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (COVID-19–related or other medical conditions); 5, hospitalized, requiring any supplemental oxygen; 6, hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices; 7, hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); and 8, death. Odds ratio and p-value were calculated with the use of a proportional odds model. Odds ratio values greater than 1 indicate a benefit with RDV.
Source: {Beigel 2020a}; CO-US-540-5776 Final CSR, Section 15.1, Table 23



ECMO = extracorporeal membrane oxygenation; ITT = intent-to-treat; O_2 = oxygen
Scores on the ordinal scale are as follows: 1, not hospitalized, no limitations of activities; 2, not hospitalized, limitation of activities, home oxygen requirement, or both; 3, hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection-control reasons); 4, hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (COVID-19–related or other medical conditions); 5, hospitalized, requiring any supplemental oxygen; 6, hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices; 7, hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); and 8, death.
Source: {Beigel 2020b}

Figure 4: CO-US-540-5776: Distribution of Clinical Status at Day 15 for Participants with Baseline Ordinal Score of 4 (ITT Population). Taken from the clinical overview.

The odds of improvement in clinical status at Day 15 in the mild/moderate stratum are presented below.

Table 14: Odds Ratio for Better (Lower) Clinical Status Score at Day 15 by Treatment in the mild moderate disease stratum Using a Proportional Odds Model, remdesivir Relative to Placebo – ITT Population. Taken from the CSR.

Severity of disease (Randomization stratification: Mild-Moderate Disease)	Remdesivir (N=82)	1.2	0.7, 2.2	0.475
	Placebo (N=77)			
Severity of disease (Randomization stratification: Severe Disease)	Remdesivir (N=459)	1.6	1.3, 2.0	<0.001
	Placebo (N=444)			
Severity of disease (Actual disease severity at baseline: Mild-Moderate Disease)	Remdesivir (N=55)	1.5	0.7, 3.0	0.302
	Placebo (N=50)			

Time to Improvement by ≥ 1 Clinical Status Category

Table 15: : Time to Improvement by at Least One Clinical Status Category on the 8-Point Ordinal Scale by Treatment Group by baseline clinical status score 4– ITT population. Taken from the CSR.

				Median Time		HR	
Subgroup	Subgroup Category	Treatment Group	n	Estimate	95% CI	Estimate	95% CI
Randomized Disease Severity Stratum	Severe Disease	Remdesivir (N=450)	366	7.0	6.0, 8.0	1.26	1.08, 1.46
		Placebo (N=440)	335	10.0	8.0, 12.0		
	Mild-Moderate Disease	Remdesivir (N=82)	76	6.0	4.0, 8.0	0.99	0.72, 1.37
		Placebo (N=76)	71	6.0	5.0, 9.0		
Actual Disease Severity Stratum	Severe Disease	Remdesivir (N=477)	388	7.0	6.0, 8.0	1.23	1.06, 1.42
		Placebo (N=467)	360	9.0	8.0, 12.0		
	Mild-Moderate Disease	Remdesivir (N=55)	54	6.0	5.0, 9.0	1.11	0.74, 1.65
		Placebo (N=49)	46	7.0	5.0, 9.0		
	Baseline Clinical Status Score 4	Remdesivir (N=75)	73	6.0	5.0, 8.0	1.31	0.93, 1.86
		Placebo (N=63)	58	8.0	6.0, 10.0		

NE = Not Estimated.
N = Number of subjects in the specified subgroup category, treatment group and analysis population, with data.
n = Number of subjects with improvement.
HR is the ratio of the hazard of improvement in each treatment group estimated from the Cox model. The ratio is Remdesivir to Placebo.

Time to Improvement by ≥ 2 Clinical Status Categories

The subgroup analyses for time to improvement by ≥ 2 clinical status categories is shown in the table below.

Table 16: Time to Improvement by at Least Two Clinical Status Categories on the 8-Point Ordinal Scale by Treatment Group by baseline ordinal scale category – ITT population

				Median Time		HR	
Subgroup	Subgroup Category	Treatment Group	n	Estimate	95% CI	Estimate	95% CI
Randomized Disease Severity Stratum	Severe Disease	Remdesivir (N=459)	345	12.0	10.0, 13.0	1.34	1.15, 1.57
		Placebo (N=444)	301	15.0	13.0, 16.0		
	Mild-Moderate Disease	Remdesivir (N=82)	71	9.0	6.0, 12.0	0.98	0.71, 1.37
		Placebo (N=77)	69	11.0	7.0, 13.0		
Actual Disease Severity Stratum	Severe Disease	Remdesivir (N=486)	367	12.0	10.0, 13.0	1.32	1.13, 1.53
		Placebo (N=471)	325	14.0	13.0, 16.0		
	Mild-Moderate Disease	Remdesivir (N=55)	49	9.0	5.0, 13.0	1.02	0.68, 1.53
		Placebo (N=50)	45	9.0	6.0, 12.0		

	Baseline Clinical Status Score 4	Remdesivir (N=75)	69	7.0	5.0, 11.0	1.21	0.85, 1.72
		Placebo (N=63)	55	11.0	7.0, 12.0		

NE = Not Estimated.
N = Number of subjects in the specified subgroup category, treatment group and analysis population, with data.
n = Number of subjects with improvement.
HR is the ratio of the hazard of improvement in each treatment group estimated from the Cox model. The ratio is Remdesivir to Placebo.

Other Secondary Endpoints

Analyses for the time to Discharge or to a NEWS of ≤ 2 by Treatment Group within Subgroups for the ITT Population are shown below.

Table 17: the time to Discharge or to a NEWS of ≤ 2 by Treatment Group within Subgroups for the ITT Population

				Median Time		HR	
Subgroup	Subgroup Category	Treatment Group	n	Estimate	95% CI	Estimate	95% CI
Randomized Disease Severity Stratum	Severe Disease	Remdesivir (N=459)	340	9.0	8.0, 11.0	1.34	1.15, 1.56
		Placebo (N=444)	302	16.0	13.0, 18.0		
	Mild-Moderate Disease	Remdesivir (N=82)	75	3.0	2.0, 4.0	0.92	0.66, 1.27
		Placebo (N=77)	72	2.5	1.0, 4.0		
Actual Disease Severity Stratum	Severe Disease	Remdesivir (N=486)	361	9.0	8.0, 11.0	1.29	1.11, 1.50
		Placebo (N=471)	327	15.0	12.0, 17.0		
	Mild-Moderate Disease	Remdesivir (N=55)	54	2.0	1.0, 3.0	1.02	0.69, 1.51
		Placebo (N=50)	47	1.0	1.0, 2.0		
	Baseline Clinical Status Score 4	Remdesivir (N=75)	73	2.0	2.0, 3.0	1.09	0.77, 1.54
		Placebo (N=63)	60	1.0	1.0, 2.0		

NE = Not Estimated.
N = Number of subjects in the specified subgroup category, treatment group and analysis population, with data.
n = Number of subjects who discharged or had a NEWS of ≤ 2 prior to Day 29.
HR is the ratio of the hazard of Discharge or NEWS ≤ 2 in each treatment group estimated from the Cox model. The ratio is Remdesivir to Placebo.

Study GS-US-540-5774

Methods

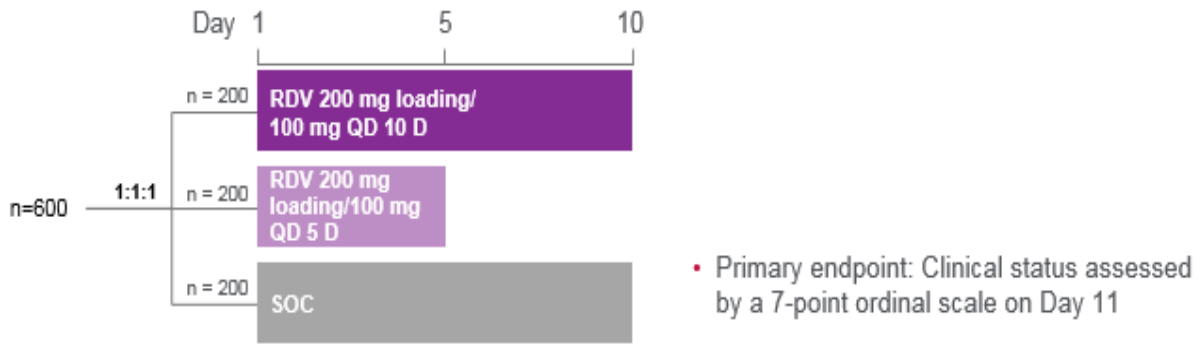
Study GS-US-540-5774 was a Phase 3 of RDV therapy in participants with moderate COVID-19. The study was conducted in two parts.

Part A of this study was a Phase 3 randomized, open-label, multi-centre study of RDV therapy in adult and adolescent patients with moderate COVID-19. Eligible participants were randomized in a 1:1:1 ratio to one of three treatment groups (Figure 5). No stratification was performed. All participants continued to receive SOC therapy according to local guidelines. Participants randomized to receive RDV received this in addition to their other care.

Part B was a single group multi-centre study of RDV in participants with moderate COVID-19 and approximately 1000 participant were to be enrolled after enrolment to Part A was completed.

The Interim 2 clinical study report (final CSR, part A) provides the final results for participants in Part A. The database freeze was 08. July 2020.

A flow chart of Part A is shown below:



Source: Slide deck on GS-US-540-5734, Part A, submitted by the Applicant on 2nd May 2020, Slide 54

Figure 5: Study 5774 – Flow chart – Part A

Study participants

Main inclusion criteria

1. Participants with SARS-CoV-2 infection confirmed by polymerase chain reaction (PCR) ≤ 4 days before randomization
2. Aged ≥ 18 years (at all sites), or aged ≥ 12 and < 18 years of age weighing ≥ 40 kg (where permitted according to local law and approved nationally and by the relevant IRB or IEC)
3. Hospitalized and requiring medical care for COVID-19
4. SpO2 > 94% on room air at screening
5. Radiographic evidence of pulmonary infiltrates

Main exclusion Criteria

1. Concurrent treatment or planned concurrent treatment with other agents with actual or possible direct acting antiviral activity against SARS-CoV-2
2. Requiring mechanical ventilation at screening
3. ALT or AST > 5 x ULN, if per local practice only ALT is routinely measured, exclusion criteria will be evaluated on ALT alone
1. Creatinine clearance < 50 mL/min using the Cockcroft-Gault formula for participants ≥ 18 years of age {Cockcroft 1976} and Schwartz Formula for participants < 18 years of age
2. Positive pregnancy test
3. Breastfeeding woman

Prior and Concomitant Drugs

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

- Traditional herbal treatments including herb sho-saiko-to (or Xiao-Shai-Hu-Tang)
- Investigational agents with putative antiviral activity for COVID-19 including approved HIV protease inhibitors such as lopinavir (LPV)/ritonavir (RTV), chloroquine, interferon, etc.

Number of centres

Initially, up to 50 centres globally, primarily in Asia were planned. The location and number of centres was amended with protocol amendment 1 to up to approximately 100 centres globally and with protocol amendment 2 (April 29, 2020) to up to approximately 160 centres globally.

Number of planned participants

Approximately 1600 patients (part A and B) were planned to be enrolled. From initially approximately 600 patients (part A) it was changed to 1600 to account for the planned enrolment of 1000 patients to Part B.

Treatments

Part A:

One loading dose of RDV 200 mg intravenous (IV; infused over 30 min where possible) on Day 1 followed by RDV 100 mg IV (infused over 30 min where possible) once daily for 5 days (treatment group 1), 10 days (treatment group 2) or continued SOC therapy (treatment group 3).

Treatment Group 1: Continued SOC therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, and 5

Treatment Group 2: continued SOC therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10

Treatment Group 3: continued SOC therapy.

Duration of treatment:

Participants in part A received study treatment with RDV for five days (treatment group 1), for 10 days (treatment group 2), no RDV (treatment group 3). If the participant was discharged, RDV treatment was stopped at that time.

Formulation:

remdesivir for injection, 100 mg, is a preservative-free, white to off-white to yellow, lyophilized solid containing 100 mg of GS-5734 that was to be reconstituted with sterile water for injection and diluted into 0.9% saline prior to administration by IV infusion.

In addition to the active ingredient, it contains the following inactive ingredients: water for injection, sulfobutylether β-cyclodextrin sodium (SBECD), hydrochloric acid, and/or sodium hydroxide. Hydrochloric acid and/or sodium hydroxide were used to adjust the formulation to a final pH of 3.0 to 4.0.

Batches used were EW1804A1-B, EW1805A1-A, EW2001A1-A and EW2002A1-A.

Objectives

The primary objective (according to the amendment on 15th March 2020) is to evaluate the efficacy of two RDV regimens (5 days vs. 10 days) compared to standard of care (SOC), with respect to clinical status assessed by a 7-point ordinal scale on Day 11.

Secondary objective was to evaluate the safety and tolerability of RDV compared to standard of care.

Outcomes/endpoints

Primary endpoint:

Clinical status assessed by a 7-point ordinal scale on Day 11.

Primary Outcome measure:

The Odds of Ratio for improvement on a 7-point Ordinal Scale on Day 11. The odds ratio represents the odds of improvement in the ordinal scale between the treatment groups. The ordinal scale is an assessment of the clinical status at a given study day. Each day, the worst (i.e., lowest ordinal) score from the previous day will be recorded, i.e., on Day 3, the lowest ordinal score from Day 2 is obtained and recorded for Day 2. The scale is as follows:

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

Secondary endpoint:

The proportion of participants with treatment emergent adverse events.

Secondary Outcome measure:

Proportion of participants experiencing any treatment-emergent adverse events. First dose date up to 10 days plus 30 days.

Other endpoints of interest:

- The proportion of participants with negative SARS-CoV-2 polymerase chain reaction (PCR)
- Time to clinical improvement (days): clinical improvement is defined as a ≥ 2-point improvement in clinical status (7-point ordinal scale) from Day 1
- Time to ≥ 1-point improvement (days) from baseline clinical status
- Time to recovery: defined as an improvement in clinical status from a baseline score of 2 through 5 to a score of 6 or 7, or an improvement from a baseline score of 6 to a score of 7
- Time to modified recovery: defined as an improvement in clinical status from a baseline score of 2 through 4 to a score of 5, 6, or 7, or an improvement from a baseline score of 5 to a score of 6 or 7, or an improvement from a baseline score of 6 to a score of 7
- Time to room air: defined as an improvement in clinical status from a baseline score of 2 through 4 to a score of 5, 6, or 7
- Duration of oxygen therapy (days)
- Shift in oxygen support status from baseline
- Duration of hospitalization (days)
- All-cause mortality at Day 28
- Plasma concentration of RDV and metabolites
- Part B: The proportion of participants in the Extension Treatment Group with treatment emergent adverse events

Sample size

The sample size computation is based on an assumed distribution of the 7-point ordinal scale on Day 11 for the SOC treatment group. The odds ratio represents the odds of improvement in the 7-point ordinal scale for an RDV treatment group relative to the SOC treatment group. The sample size needed to detect a given odds ratio for a 1:1 randomization using a 2-tailed test at level α is given by:

$$12\ (z_{\alpha/2} + z_{\beta})^2\ /\ \theta^2(1 - \sum_{i=1}^{7} \rho_i^3)$$

Where θ is the log odds ratio, ρ_i is the overall probability (combined over both treatment groups) of being in the width category of the ordinal outcome, and $z_{\alpha/2}$ and z_{β} are the (1-α/2)- and β-quantiles of the standard normal distribution (Whitehead 1993).

A sample size of 600 participants (200 in each group) achieves > 85% power to detect an odds ratio of 1.8 using a two-sided significance level of 0.05 for comparing each RDV group (n=200) to standard of care group (n=200). In this sample size calculation, it is assumed that the probability distribution of the ordinal scale at Day 11 for Treatment Group 3 is as follows:

1. Death, 0.5%

2. Hospitalized, on invasive mechanical ventilation or ECMO, 2.5%

3. Hospitalized, on non-invasive ventilation or high flow oxygen devices, 7%

4. Hospitalized, requiring low flow supplemental oxygen, 8%

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

(COVID-19 related or otherwise), 15%

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

(other than per protocol RDV administration), 27%

7. Not hospitalized, 40%

The sample size calculation was done using software PASS (Version 14.0).

Randomisation

Subjects who met eligibility criteria were randomized in a 1:1:1 ratio to 1 of 3 treatment groups on Day 1 using an IWRS, and assigned a subject number. Randomization was not stratified.

Assessor's comment

Randomisation is overall acceptable. It is unusual that randomization was not stratified by site, which may be explained by the large number of centres.

Blinding (masking)

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

Statistical methods

The primary analysis set for efficacy analysis is defined as the Full Analysis Set (FAS), which includes all participants who (1) are randomized into Part A of the study and (2) have received at least 1 dose of study treatment if randomized to 1 of the RDV treatment groups. Participants were grouped according to the treatment to which they were randomized.

The primary efficacy endpoint was clinical status assessed by a 7-point ordinal scale on Day 11, which was analysed using a proportional odds model. Each RDV group was compared to the SOC only group. A separate model was used for each comparison. For the primary analysis, the primary endpoint was analysed using a proportional odds model that included treatment as the independent variable.

The null hypothesis being tested was whether the odds of improvement on the ordinal scale is the same for the SOC group and either RDV group (i.e., whether the common odds ratio is equal to 1). The odds ratio and 95% confidence interval for each comparison was provided. The protocol stated that the primary endpoint will be analysed using a proportional odds model including baseline clinical status as a covariate; however, this was changed in the SAP to a proportional odds model including treatment as the independent variable (dropping baseline clinical status as a covariate).

The proportion of subjects in each category are summarized by treatment group. The validity of the proportionality assumption was evaluated. If a participant was discharged prior to Day 11, the Day 11 ordinal scale category was considered to be not hospitalized. If a participant died prior to Day 11, the Day 11 ordinal scale category was considered to be death. Every effort was made to obtain clinical status data for all subjects prior to discharge. All post-baseline days with missing ordinal scale score, from Day 2 to Day 14 and Day 28, used the previous last known clinical status.

To control for Type I error rate, the statistical significance of RDV treatment effect was assessed based on the Bonferroni method. Each hypothesis (5-day RDV vs. SOC and 10-day RDV vs. SOC) was tested at alpha level of 0.025.

As supportive analysis of the primary efficacy endpoint, the clinical status on Day 11 was compared between each RDV group (5-day or 10-day) and the SOC only group using a 2-sided Wilcoxon rank sum test. In addition, the primary endpoint was analysed using a proportional odds model including treatment as the independent variable and baseline clinical status as a nominal covariate. Due to the smaller number of participants with baseline clinical status of 3 and 6, those with baseline clinical status of 3 or 4 were combined into 1 category and those with baseline clinical status of 5 or 6 were combined into 1 category.

The change from baseline in clinical status category on Days 5, 7, 11, 14, 28 and at last available assessment was summarized by treatment group using descriptive statistics. Change from baseline was compared between the treatment groups (RDV 5-day group versus SOC only group and RDV 10-day group versus SOC only group) using a 2-sided Wilcoxon rank sum test.

The secondary endpoint of proportion of participants with treatment emergent AEs was compared between each of the RDV groups and standard of care group in Part A using a Fisher's Exact test. The point estimates of the treatment differences and the associated 95% confidence intervals are provided. Other endpoints of interest related to proportion of participants were compared between treatment groups in Part A using a chi-square test or Fisher's Exact test. Point estimates of treatment differences in percentages and 95% confidence intervals are provided.

All-cause mortality was estimated using the Kaplan-Meier product limit method with all available data. Each RDV (5-day or 10-day) group was compared to the SOC group using the log-rank test, and hazard ratios and 95% confidence intervals will be provided.

Efficacy endpoints that are measured as time to first event were compared between treatment groups using a competing risk model (with death as the competing risk). The hazard ratio and 95% confidence interval are provided. Continuous endpoints were compared between treatment groups using a Wilcoxon rank sum test or analysis of variance model.

The primary endpoint was analysed for the following participant subgroups:

- Age (years): (a) < 65 and (b) ≥ 65

- Sex at birth: (a) male and (b) female
- Oxygen support status based on the 7-point ordinal scale: (a) invasive mechanical ventilation, (b) high flow oxygen, (c) low flow oxygen, and (d) room air (See Appendix 2)
- Country: (a) USA, (b) Italy, and (c) ex-Italy

Results

Participant flow

Participants for Part A were enrolled and treated at 105 study sites in France, Germany, Hong Kong, Italy, Republic of Korea, Netherlands, Singapore, Spain, Switzerland, Taiwan, United Kingdom, and the US.

612 participants were screened, of whom 596 were randomized, and 584 received at least 1 dose of study treatment (RDV groups: RDV 5-day group, 191 participants; RDV 10-day group, 193 participants) and 200 completed the protocol-specified Day 1 visit (SOC only group) in Part A of the study (

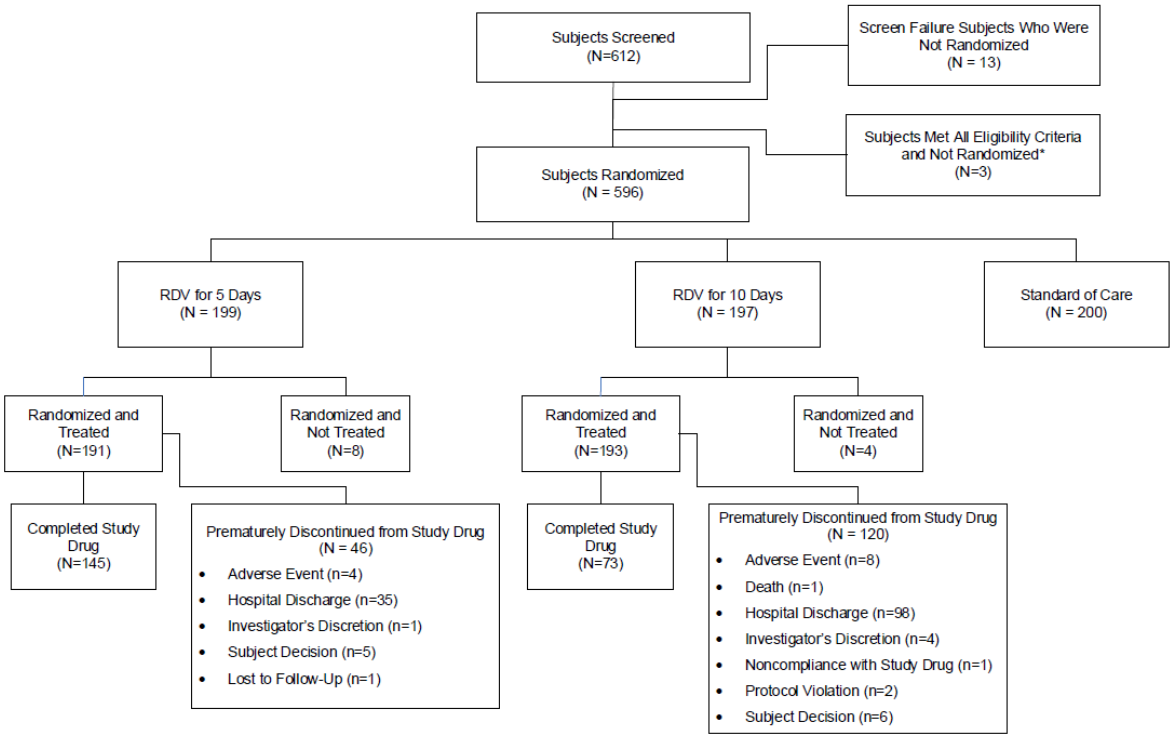
Table 18). Twelve randomized participants did not receive study treatment (3 were enrolled in violation of the study protocol, 8 withdrew consent, and 1 was withdrawn due to investigator discretion).

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

Table 18: GS-US-540-5774: Disposition of Participants (All Screened participants)

	RDV 5 Days	RDV 10 Days	SOC	Total
Subjects Screened				612
Screen Failure Subjects Who Were Not Randomized				13
Subjects Met All Eligibility Criteria and Not Randomized[a]				3
Subjects Randomized	199	197	200	596
Subjects Randomized and Never Treated	8	4	0	12
Subjects in Safety Analysis Set	191	193	200	584
Subjects in Full Analysis Set	191	193	200	584
Subjects Completed Study Drug	145 (75.9%)	73 (37.8%)	NA	218 (56.8%)
Subjects Prematurely Discontinuing Study Drug	46 (24.1%)	120 (62.2%)	NA	166 (43.2%)
Reasons for Prematurely Discontinuing Study Drug				
Adverse Event	4 (2.1%)	8 (4.1%)		12 (3.1%)
Death	0	1 (0.5%)		1 (0.3%)
Hospital Discharge	35 (18.3%)	98 (50.8%)		133 (34.6%)
Investigator's Discretion	1 (0.5%)	4 (2.1%)		5 (1.3%)
Noncompliance with Study Drug	0	1 (0.5%)		1 (0.3%)
Protocol Violation	0	2 (1.0%)		2 (0.5%)
Subject Decision	5 (2.6%)	6 (3.1%)		11 (2.9%)
Lost to Follow-Up	1 (0.5%)	0		1 (0.3%)
Subjects Completed Study	179 (93.7%)	176 (91.2%)	178 (89.0%)	533 (91.3%)
Subjects Prematurely Discontinuing from Study	12 (6.3%)	17 (8.8%)	22 (11.0%)	51 (8.7%)
Reasons for Prematurely Discontinuing from Study				
Death	2 (1.0%)	2 (1.0%)	4 (2.0%)	8 (1.4%)
Noncompliance with Study Drug	0	1 (0.5%)	0	1 (0.2%)
Protocol Violation	0	0	1 (0.5%)	1 (0.2%)
Withdrew Consent	2 (1.0%)	2 (1.0%)	5 (2.5%)	9 (1.5%)
Lost to Follow-Up	8 (4.2%)	12 (6.2%)	12 (6.0%)	32 (5.5%)

NA = not applicable
a Three subjects met all eligibility criteria and were not randomized due to withdrawal of consent.
For study drug completions and discontinuations, the denominator is the percentage of subjects in the Safety Analysis Set who received RDV study drug.
For study completions and discontinuations, the denominator is the percentage of subjects in the Safety Analysis Set.
The number of screen failures is counted by unique subject based on rescreening information entered into the eCRF.
Case report form data collected up to 08 July 2020 are included.
Screen failure subjects are the subjects who did not meet all eligibility criteria.
Source: Table 15.8.1.2



CRF data collected up to 08JUL2020 are included.
Screen failure subjects are subjects who did not meet all eligibility criteria.
*Three subjects met all eligibility criteria and were not randomized due to withdrawal of consent.
Source: Table 15.8.1.2

Recruitment

The key dates relevant to the conduct of Study GS-US-540-5774 are listed in Table 19.

While approximately 37% of the participants have been recruited in Europe, 44% come from the USA.

Conduct of the study

The key dates relevant to the conduct of Study GS-US-540-5774 are listed in Table 19.

Table 19: GS-US-540-5774: Key Dates

Event	Date
First Participant Screened	15 March 2020
First Participant Enrolled (or Randomized) for Part A	15 March 2020
Last Participant Enrolled (or Randomized) for Part A	18 April 2020
Last Participant Last Observation for the Primary Endpoint for Part A	29 April 2020
Last Participant Last Observation for this Report	20 May 2020
Database Finalization	08 July 2020

Protocol and Protocol Amendments

Changes in the Conduct of the Study or Planned Analyses

The protocol was amended 2 times during the course of Study GS-US-540-5774, as indicated in Table 20.

All participants in Part A were enrolled under the original protocol and Protocol Amendment 1.0. The primary endpoint was updated in the first protocol amendment, dated 15 March 2020. The decision to change the primary endpoint was made before enrolling any participants in the study.

Table 20: Protocol and Protocol Amendments

Protocol/Amendment	Date
Original	24 February 2020
Amendment 1 Summary of Changes	15 March 2020
Amendment 2 Summary of Changes	29 April 2020
Amendment 2	29 April 2020
Administrative Letter 1	27 February 2020
Administrative Letter 2	12 March 2020
Administrative Letter 3	03 April 2020

Protocol Deviations

A categorical summary of important protocol deviations (IPDs) that occurred during Part A of the study is provided in Table 21.

Table 21: GS-US-540-5774: Important Protocol Deviations (Full Analysis Set)

Protocol Deviation Category	RDV 5 Days (N = 191)	RDV 10 Days (N = 193)	SOC (N = 200)
Subjects with at Least 1 Important Protocol Deviation	8 (4.2%)	11 (5.7%)	16 (8.0%)
Eligibility Criteria	3 (1.6%)	6 (3.1%)	9 (4.5%)
Other	3 (1.6%)	0	6 (3.0%)
Not Withdrawn, Despite Meeting Withdrawal Criteria	2 (1.0%)	2 (1.0%)	0
Excluded Concomitant Medication	0	2 (1.0%)	1 (0.5%)
Informed Consent	0	1 (0.5%)	0
Off Schedule Procedure	1 (0.5%)	0	0
Total Number of Important Protocol Deviations	9	11	17
Eligibility Criteria	3	6	9
Other	3	0	7
Not Withdrawn, Despite Meeting Withdrawal Criteria	2	2	0
Excluded Concomitant Medication	0	2	1
Informed Consent	0	1	0
Off Schedule Procedure	1	0	0

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

Monitoring

The initial Monitoring plan is dated 01.03.2020 and was amended once on 12 June 2020 to implement protocol amendments 1 and 2. The monitoring of the clinical data was exclusively done remotely, due to the COVID-19 pandemic.

GCP-Inspections

Two investigator site inspections were conducted by the United States (US) Food and Drug Administration (FDA), one between 06 July 2020 and 20 July 2020 and one between 09 July 2020 and 17 July 2020, for Studies GS-US-540-5773 and GS US 540-5774.

A sponsor monitor inspection of Gilead Sciences in Foster City, CA, US was conducted by the FDA between 06 August 2020 and 18 August 2020 for Studies GS-US-540-5773 and GS US 540-5774.

Baseline data

Demographic and Baseline Characteristics

Demographic and baseline characteristics are shown in

Table 22 and Table 23 below. Most participants were male (61.1%), with a median age (range) of 57 (12 to 95) years; most participants were white (61.3%) and not Hispanic or Latino (81.9%). The median (Q1, Q3) body mass index was 27.1 (24.1, 31.1) kg/m2.

Overall, high-flow oxygen was required by 0.9% of participants at baseline. Low flow oxygen was required by 15.1% participants, and 84.1% of participants were breathing on room air.

Table 22: GS-US-540-5774: Demographic and Baseline Characteristics (Safety Analysis Set)

	RDV 5 Days (N = 191)	RDV 10 Days (N = 193)	SOC (N = 200)	Total (N = 584)	P-Value
Age (Years)					
N	191	193	200	584	0.7607
Mean (SD)	56 (14.6)	55 (15.5)	55 (15.1)	56 (15.1)	
Median	58	56	57	57	
Q1, Q3	48, 66	45, 66	45, 66	46, 66	
Min, Max	12, 90	20, 94	23, 95	12, 95	
Age Categories (Years)					
< 50	58 (30.4%)	67 (34.7%)	65 (32.5%)	190 (32.5%)	0.9832
≥ 50 to < 65	84 (44.0%)	74 (38.3%)	77 (38.5%)	235 (40.2%)	
≥ 65 to < 75	31 (16.2%)	26 (13.5%)	38 (19.0%)	95 (16.3%)	
≥ 75	18 (9.4%)	26 (13.5%)	20 (10.0%)	64 (11.0%)	
Sex at Birth					
Male	114 (59.7%)	118 (61.1%)	125 (62.5%)	357 (61.1%)	0.8500
Female	77 (40.3%)	75 (38.9%)	75 (37.5%)	227 (38.9%)	
Race					
American Indian or Alaska Native	2 (1.1%)	0	1 (0.6%)	3 (0.6%)	0.8317
Asian	34 (18.8%)	31 (17.6%)	37 (20.8%)	102 (19.1%)	
Black	35 (19.3%)	37 (21.0%)	27 (15.2%)	99 (18.5%)	
Native Hawaiian or Pacific Islander	1 (0.6%)	1 (0.6%)	1 (0.6%)	3 (0.6%)	
White	109 (60.2%)	107 (60.8%)	112 (62.9%)	328 (61.3%)	
Not Permitted	5	5	7	17	
Other	5	12	15	32	
Ethnicity					
Hispanic or Latino	25 (13.4%)	42 (22.6%)	34 (18.3%)	101 (18.1%)	0.0691
Not Hispanic or Latino	162 (86.6%)	144 (77.4%)	152 (81.7%)	458 (81.9%)	
Not Permitted	4	7	13	24	
- Missing -	0	0	1	1	
Baseline Body Mass Index (kg/m²)					
N	185	183	191	559	0.2380
Mean (SD)	27.8 (6.50)	28.9 (6.77)	28.2 (6.65)	28.3 (6.64)	
Median	26.7	27.6	26.7	27.1	
Q1, Q3	23.8, 30.4	24.5, 32.2	23.5, 31.1	24.1, 31.1	
Min, Max	17.2, 76.9	16.1, 63.2	15.9, 53.9	15.9, 76.9	

max = maximum; min = minimum
For race and ethnicity, "Not Permitted," "Missing," and "Other" were excluded from the percentage calculation and p-value calculation.
Not Permitted = local regulators did not allow collection of race/ethnicity information. All but 3 values of "Other' are unknown, not specified, etc.
For categorical data, p-value was from the CMH test (general association statistic for nominal data and row mean scores differ statistic for ordinal data). For continuous data, p-value was from the Kruskal-Wallis test.
Source: Table 15.8.3.1

Table 23: GS-US-540-5774: Other Baseline Characteristics (Safety Analysis Set)

	RDV 5 Days (N = 191)	RDV 10 Days (N = 193)	SOC (N = 200)	Total (N = 584)	P-Value
Clinical Status (7-Point Ordinal Scale)					
3 - Hospitalized, on noninvasive ventilation or high-flow oxygen devices[a]	2 (1.0%)	1 (0.5%)	2 (1.0%)	5 (0.9%)	0.0781
4 - Hospitalized, requiring low-flow supplemental oxygen[a]	29 (15.2%)	23 (11.9%)	36 (18.0%)	88 (15.1%)	
5 - Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care	160 (83.8%)	163 (84.5%)	160 (80.0%)	483 (82.7%)	
6 - Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care	0	6 (3.1%)	2 (1.0%)	8 (1.4%)	
Duration of Hospitalization Prior to Study Day 1 (Days)					
N	191	193	199	583	0.6273
Mean (SD)	3 (4.4)	3 (4.6)	3 (3.6)	3 (4.2)	
Median	2	2	2	2	
Q1, Q3	1, 3	1, 3	1, 3	1, 3	
Min, Max	0, 36	0, 30	0, 33	0, 36	
Duration of Symptoms Prior to Study Day 1 (Days)					
N	191	189	197	577	0.0253
Mean (SD)	9 (6.5)	8 (5.7)	9 (5.2)	9 (5.8)	
Median	8	8	9	8	
Q1, Q3	5, 11	5, 11	6, 11	5, 11	
Min, Max	1, 48	1, 40	1, 34	1, 48	
ALT (U/L)					
N	191	193	200	584	0.8702
Mean (SD)	39 (31.3)	40 (35.4)	42 (35.5)	40 (34.1)	
Median	30	28	30	29	
Q1, Q3	19, 51	21, 47	19, 49	19, 50	
Min, Max	6, 221	4, 229	5, 289	4, 289	
AST (U/L)					
N	186	187	193	566	0.9772
Mean (SD)	42 (28.2)	41 (29.5)	42 (30.9)	42 (29.5)	
Median	32	34	34	33	
Q1, Q3	25, 48	23, 48	24, 49	24, 49	
Min, Max	8, 147	9, 215	8, 229	8, 229	

	RDV 5 Days (N = 191)	RDV 10 Days (N = 193)	SOC (N = 200)	Total (N = 584)	P-Value
Baseline Oxygen Support Status					
High-Flow Oxygen	2 (1.0%)	1 (0.5%)	2 (1.0%)	5 (0.9%)	0.2070
Low-Flow Oxygen	29 (15.2%)	23 (11.9%)	36 (18.0%)	88 (15.1%)	
Room Air	160 (83.8%)	169 (87.6%)	162 (81.0%)	491 (84.1%)	

max = maximum; min = minimum

a Either enrolled under the original protocol which allowed participants to be included if they were receiving supplemental oxygen but had oxygen saturations > 94% on room air or had a requirement for supplemental oxygen develop between screening and the beginning of treatment, or were on supplemental oxygen at enrollment and were designated as representing important protocol deviations.

For Clinical Status: Category 5 includes medical care (COVID-19 related or otherwise); Category 6 excludes per-protocol RDV administration. Category 7 (Not Hospitalized) and Category 1 (Death) are not included in this table.

Baseline was the last available value recorded on or prior to dosing for RDV groups and Study Day 1 for SOC. For clinical status for SOC, baseline was the eCRF record labeled "Day 1 Predose."

For oxygen support status, p-value was from the CMH test (row mean scores differ statistic). For clinical status and continuous data, p-value was from the Kruskal-Wallis test.

Source: Table 15.8.3.2

Table 24: Relevant medical history –Safety Analysis Set

Comorbidity	**RDV for 5 Days**	**RDV for 10 days**	**SOC**
Hypertension	77 (40.3%)	73 (37.8%)	78 (39.0%)
Coronary artery disease	7 (3.7%)	4 (2.1 %)	9 (4.5%)
Atrial fibrillation	8 (4.2%)	13 (6.7%)	8 (4.0%)
Hyperlipidaemia	28 (14.7%)	39 (20.2%)	23 (11.5%)
Diabetes Type 2	17 (8.9%)	39 (9.8%)	26 (13.0%)
Asthma	17 (8.9%)	25 (13.0%)	25 (12.5%)
COPD	5 (2.6%)	5 (2.6%)	3 (1.5%)

Numbers analysed

Number of Participants (Planned and Analysed):

Approximately 1600 participants (600 participants in Part A) were planned.

Analysed (Part A):

- All Randomized Analysis Set: 596 participants (199 in the RDV 5-day group, 197 in the RDV 10-day group, and 200 in the SOC only group)
- Full Analysis Set (FAS) and Safety Analysis Set: 584 participants (191 in the RDV 5-day group, 193 in the RDV 10-day group, and 200 in the SOC only group)

Outcomes and estimation

Primary Endpoint odds of improvement at D11

The results of the clinical status assessed by a 7-point ordinal scale on Day 11 in the FAS, which was analysed using a proportional odds model is shown in Table 25. The assumption of odds proportionality was assessed using a score test for both the RDV 5 day group versus SOC and the RDV 10-day group versus SOC.

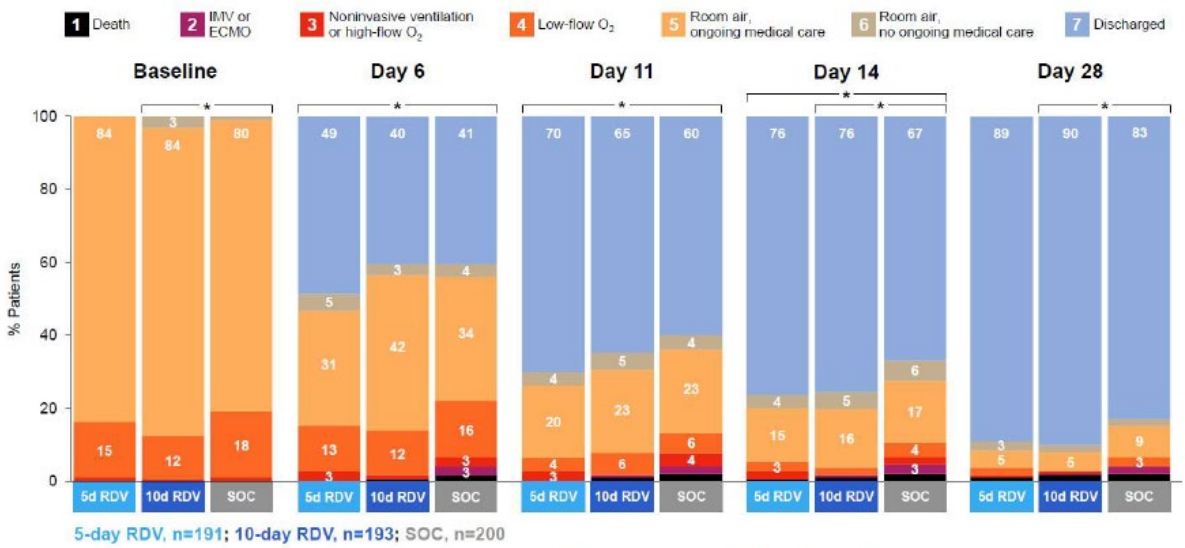
Table 25: GS-US-540-5774: Analysis of Clinical Status (7-Point Ordinal Scale) on Day 11 Using Proportional Odds (Full Analysis Set)

	Observations Included in Model	P-Value for Testing Proportionality of Odds Assumption (Score Test)	Parameter Estimate (SE)	Odds Ratio (95% CI)	P-Value
RDV 5 Days/SOC	391	0.3960	0.50 (0.210)	1.65 (1.092, 2.483)	0.0174
RDV 10 Days/SOC	393	< 0.0001	0.27 (0.203)	1.31 (0.880, 1.952)	0.1826

SE = standard error
Clinical status is based on an ordinal scale from 1 = Death to 7 = Not hospitalized.
Clinical status was derived from death, hospital discharge, and the ordinal scale as follows: 1 for all days on or after the death date; 7 for all days on or after discharged alive date; ordinal scale using the last available postbaseline record for missing assessment.
Source: Table 15.9.1.1.1

Clinical Status by Study Day

Clinical status on the 7-point ordinal scale is presented by study day and treatment group in Figure 6.



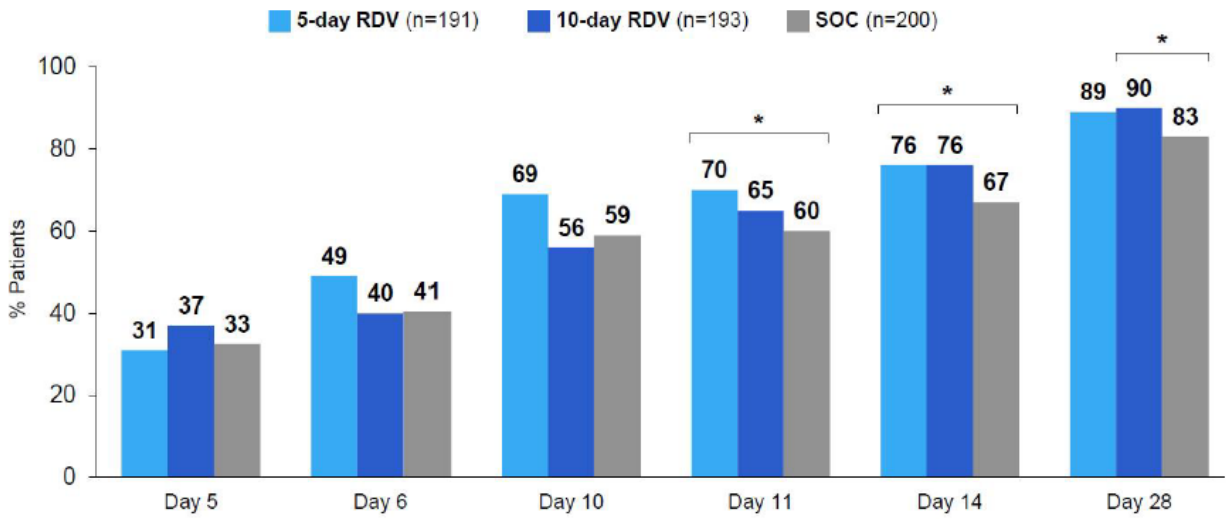
d = day(s); ECMO = extracorporeal membrane oxygenation; IMV = invasive mechanical ventilation; O_2 = oxygen; RDV = remdesivir (GS-5734™); SOC = standard of care
* $p < 0.05$.
Clinical status was derived from death, hospital discharge, and the ordinal scale as follows: 1 for all days on or after the death date; 7 for all days on or after discharged alive date; ordinal scale using the last available postbaseline record for missing assessment.
P-value was from the Wilcoxon rank sum test to compare the 5-day dosing and 10-day dosing treatment groups to SOC.
Source: GS-US-540-5774 Interim 2 (Final Part A) CSR, Table 15.9.1.2.1

Figure 6: GS-US-540-5774: Clinical Status (7-Point Ordinal Scale) by Study Day – Part A (Full Analysis Set)

Other Endpoints of Interest

Cumulative Hospital Discharge by study day

The cumulative proportion of hospital discharge is shown below.



RDV = remdesivir (GS-5734™); SOC = standard of care
* $p < 0.05$.
Clinical status was derived from death, hospital discharge, and the ordinal scale as follows: 1 for all days on or after the death date; 7 for all days on or after discharged alive date; ordinal scale using the last available postbaseline record for missing assessment.
P-value was from the Fisher exact test to compare the 5-day dosing and 10-day dosing treatment groups to SOC.
Source: GS-US-540-5774 Interim 2 (Final Part A) CSR, Table 15.9.1.2.1; Table req10683.42

Figure 7: GS-US-540-5774: Proportion of Participants with Hospital Discharge by Study Day – Part A (Full Analysis Set)

Hospitalisation (taken from the CSR):

Duration of hospitalization by treatment group for participants who were discharged alive prior to Day 28 is presented in Table 26.

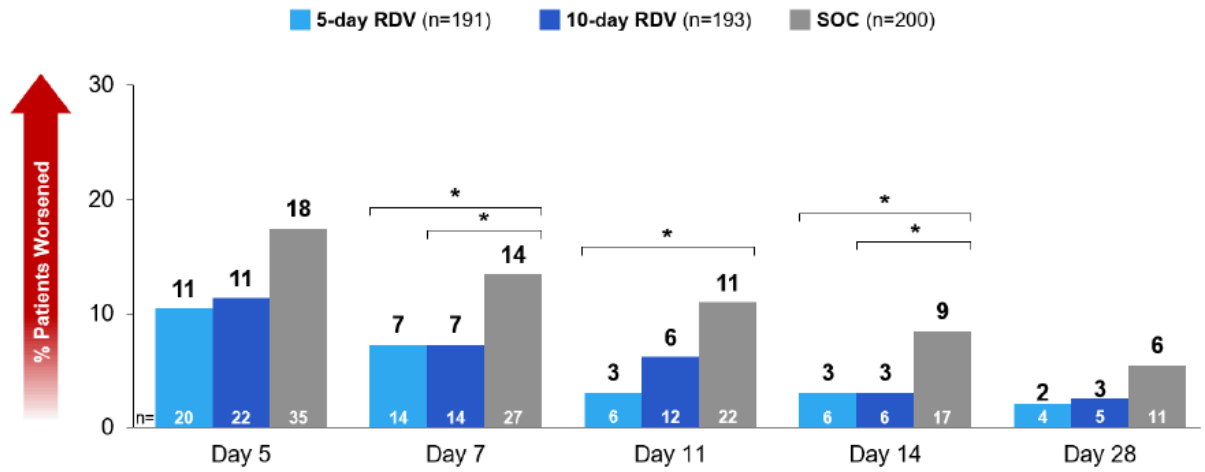
Table 26: Hospitalization Discharge Status and Duration of Hospitalization (Full Analysis Set)

	RDV 5 Days (N = 191)	RDV 10 Days (N = 193)	SOC (N = 200)	RDV 5 Days vs SOC P-Value	RDV 10 Days vs SOC P-Value
Number of Subjects Still in Hospital at Day 11	50 (26.2%)	60 (31.1%)	62 (31.0%)		
Number of Subjects Discharged Alive by Day 11	134 (70.2%)	125 (64.8%)	120 (60.0%)		
Number of Subjects Who Died on or Prior to Day 11	0	2 (1.0%)	4 (2.0%)		
Number of Subjects Who Transferred to Other Facility on or Prior to Day 11	7 (3.7%)	6 (3.1%)	14 (7.0%)		
Number of Subjects Who Were Released to Palliative Care on or Prior to Day 11	0	0	0		
Number of Subjects Still in Hospital at Day 28	15 (7.9%)	14 (7.3%)	25 (12.5%)		
Number of Subjects Discharged Alive by Day 28	164 (85.9%)	166 (86.0%)	154 (77.0%)		
Number of Subjects Who Died on or Prior to Day 28	2 (1.0%)	3 (1.6%)	4 (2.0%)		
Number of Subjects Who Transferred to Other Facility on or Prior to Day 28	11 (5.8%)	11 (5.7%)	17 (8.5%)		
Number of Subjects Who Were Released to Palliative Care on or Prior to Day 28	0	0	0		
Duration of Hospitalization from Day 1 (Days)					
N	164	166	154	0.7728	0.3324
Mean (SD)	8 (5.3)	9 (6.0)	8 (6.2)		
Median	6	7	6		
Q1, Q3	5, 9	4, 11	4, 10		
Min, Max	2, 26	1, 27	1, 28		
Total Duration of Hospitalization (Days)					
N	164	166	154	0.8019	0.3106
Mean (SD)	10 (6.6)	11 (8.6)	10 (6.6)		
Median	8	9	8		
Q1, Q3	6, 12	6, 13	6, 13		
Min, Max	3, 40	2, 57	2, 35		

max = maximum; min = minimum; vs = versus
Only subjects who were discharged alive on or prior to Day 28 are included in the duration of hospitalization descriptive statistics.
Duration of hospitalization from Day 1 = number of days from first dose for RDV groups and Study Day 1 for SOC to date discharged alive.
Total duration of hospitalization = number of days from hospital admission to date discharged alive.
Subjects who died after being discharged alive, transferred to another facility, or released to palliative care and with death date prior to the indicated day are presented in each applicable row.
P-value was from the Wilcoxon rank sum test to compare the 5-day dosing and 10-day dosing treatment groups to standard of care.

Disease Worsening

The proportion of participants with a ≥ 1-point worsening from baseline in clinical status are shown in the figure below.

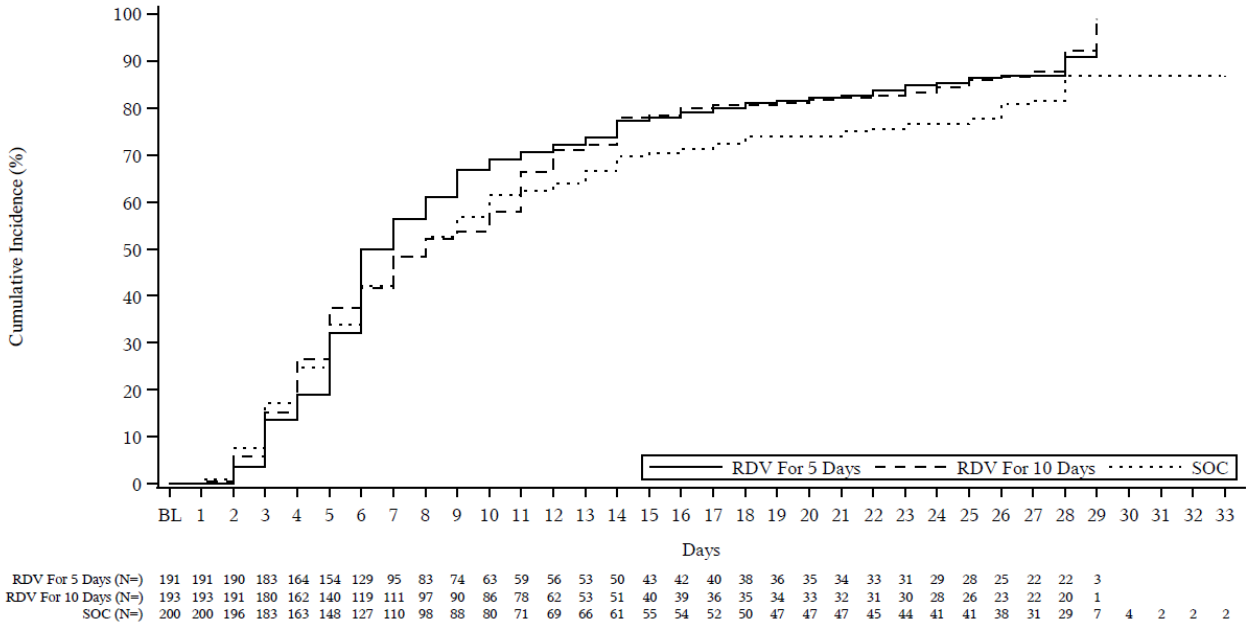


eCRF = electronic case report form; RDV = remdesivir (GS-5734™); SOC = standard of care
* $p < 0.05$.
Clinical status is based on an ordinal scale from 1 = Death to 7 = Not hospitalized.
Clinical status was derived from death, hospital discharge, and the ordinal scale as follows: 1 for all days on or after the death date; 7 for all days on or after discharged alive date; ordinal scale using the last available postbaseline record for missing assessment.
Baseline was the last available value recorded on or prior to dosing for RDV groups and eCRF record labeled "Day 1 Predose" for SOC.
P-value was from the Fisher exact test to compare the 5-day dosing and 10-day dosing treatment groups to SOC.
Source: GS-US-540-5774 Interim 2 (Final Part A) CSR, Table 15.9.1.8; Table req10683.43

Figure 8: GS-US-540-5774: Proportion of Participants with ≥ 1-Point Worsening from Baseline in Clinical Status by Study Day (Full Analysis Set)

Clinical Improvement ≥ 2-Points (taken from the CSR)

The competing risk analysis of time to ≥ 2-point improvement from baseline in clinical status on a 7-point ordinal scale by treatment group and study day is shown in Figure 9 below.



	BL	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33
RDV For 5 Days (N=)	191	191	190	183	164	154	129	95	83	74	63	59	56	53	50	43	42	40	38	36	35	34	33	31	29	28	25	22	22	3				
RDV For 10 Days (N=)	193	193	191	180	162	140	119	111	97	90	86	78	62	53	51	40	39	36	35	34	33	32	31	30	28	26	23	22	20	1				
SOC (N=)	200	200	196	183	163	148	127	110	98	88	80	71	69	66	61	55	54	52	50	47	47	47	45	44	41	41	38	31	29	7	4	2	2	2

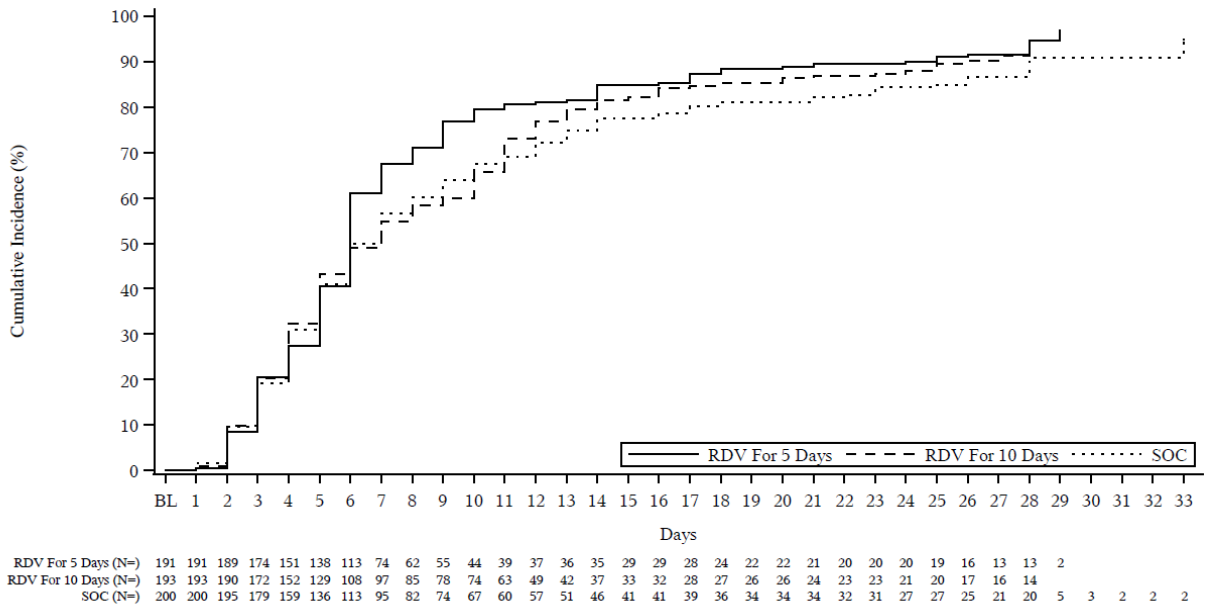
BL = Baseline.
Clinical status is based on an ordinal scale from 1 = Death to 7 = Not hospitalized.
Clinical improvement is defined as >= 2 point improvement from the baseline clinical status or discharged alive.
Subjects not achieving clinical improvement at the last assessment were censored on the day of the last clinical assessment. Subjects who died were considered to have experienced a competing event.
N represents the number of subjects at risk at the beginning of the interval.

Data Extracted: CRF Data, Lab Data: 08JUL2020
Source: .../final_part_a/version1/prog/g-cr-imp.sas v9.4 Output file: g-cr-imp2pt.pdf 14JUL2020: 7:12

Figure 9: Time to Clinical Improvement (>= 2-point Improvement) (Competing Risk Analysis) (FAS)

Clinical Improvement ≥ 1-Point (taken from the CSR)

The competing risk analysis of time to ≥ 2-point improvement from baseline in clinical status on a 7-point ordinal scale by treatment group and study day is shown in Figure 10 below.



	BL	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33
RDV For 5 Days (N=)	191	191	189	174	151	138	113	74	62	55	44	39	37	36	35	29	29	28	24	22	22	21	20	20	20	19	16	13	13	2				
RDV For 10 Days (N=)	193	193	190	172	152	129	108	97	85	78	74	63	49	42	37	33	32	28	27	26	26	24	23	23	21	20	17	16	14					
SOC (N=)	200	200	195	179	159	136	113	95	82	74	67	60	57	51	46	41	41	39	36	34	34	34	32	31	27	27	25	21	20	5	3	2	2	2

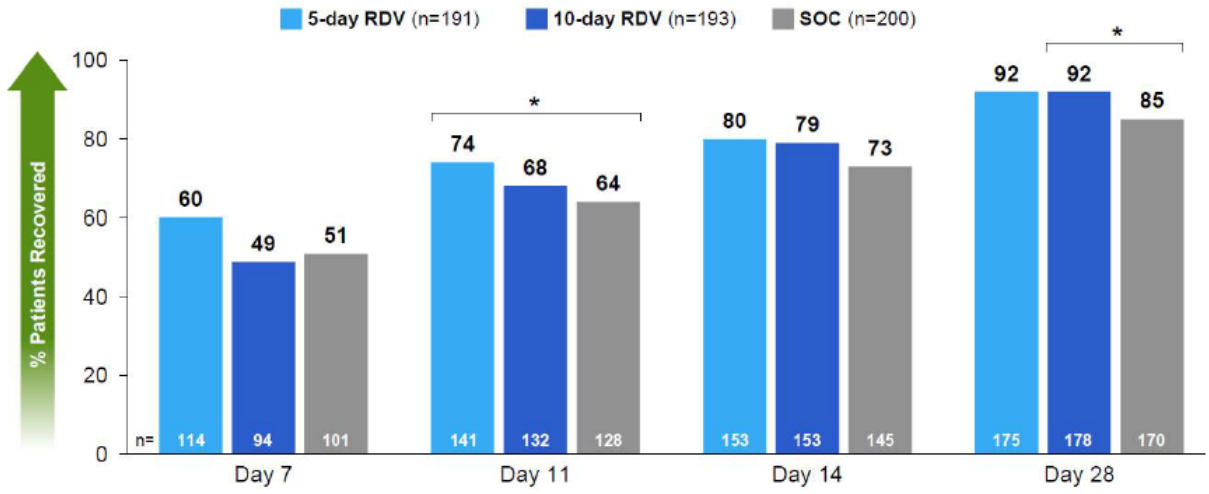
BL = Baseline.
Clinical status is based on an ordinal scale from 1 = Death to 7 = Not hospitalized.
Clinical improvement is defined as >= 1 point improvement from the baseline clinical status.
Subjects not achieving clinical improvement at the last assessment were censored on the day of the last clinical assessment. Subjects who died were considered to have experienced a competing event.
N represents the number of subjects at risk at the beginning of the interval.

Data Extracted: CRF Data, Lab Data: 08JUL2020
Source: .../final_part_a/version1/prog/g-cr-imp.sas v9.4 Output file: g-cr-imp1pt.pdf 14JUL2020: 7:12

Figure 10: Time to Clinical Improvement (>= 1-point Improvement) (Competing Risk Analysis) (FAS)

Recovery

The proportion of participants who achieved recovery is shown below.

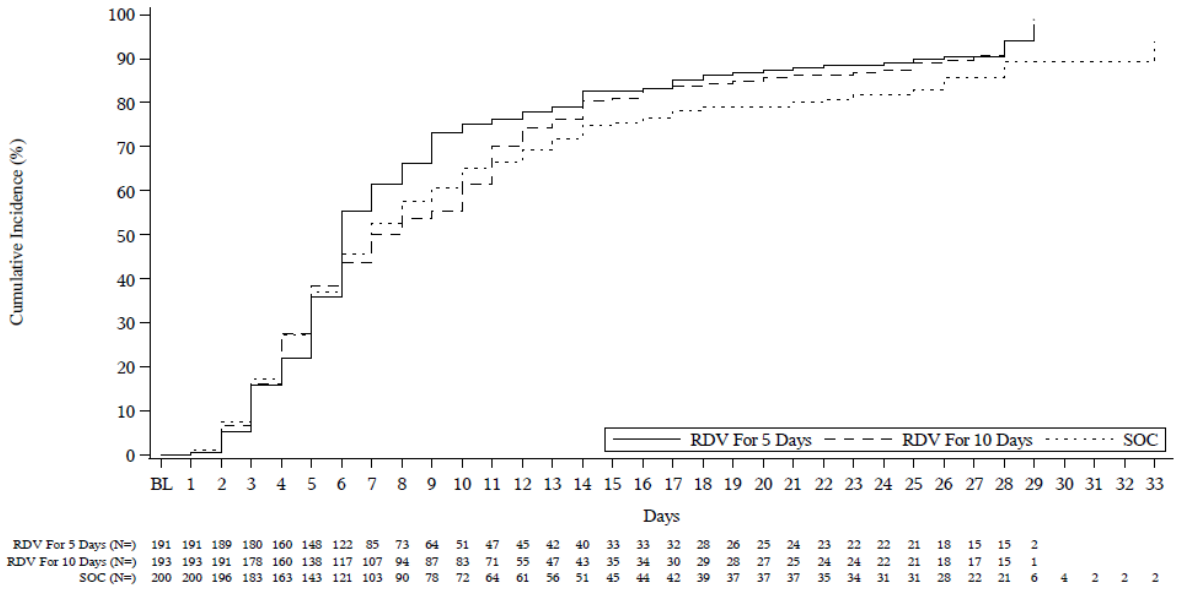


eCRF = electronic case report form; RDV = remdesivir (GS-5734™); SOC = standard of care
* $p < 0.05$.
Clinical status is based on an ordinal scale from 1 = Death to 7 = Not hospitalized. Clinical status was derived from death, hospital discharge, and the ordinal scale as follows: 1 for all days on or after the death date; 7 for all days on or after discharged alive date; ordinal scale using the last available postbaseline record for missing assessment. Baseline was the last available value recorded on or prior to dosing for RDV groups and eCRF record labeled "Day 1 Predose" for SOC. Recovery is defined as baseline score of 2 through 5 improved to 6 or 7; baseline score of 6 improved to 7.
P-value comparing the percentages of participants with recovery was from the Fisher exact test.
Source: GS-US-540-5774 Interim 2 (Final Part A) CSR, Table 15.9.2.6.4

Figure 11: GS-US-540-5774: Proportion of Participants with Recovery by Study GS-US-540-5774: Proportion of Participants with Recovery by Study Day – Part A (Full Analysis Set)

Time to Recovery (taken from the CSR)

Recovery was defined as an improvement from a baseline score of 2 through 5 to a score of 6 or 7, or an improvement from a baseline score of 6 to a score of 7. The competing risk analysis of participants in the FAS with recovery, are presented by treatment group in Figure 12.



BL = Baseline.
Clinical status is based on an ordinal scale from 1 = Death to 7 = Not hospitalized.
Recovery is defined as follows: baseline score of 2-5 improved to a score of 6 or 7; baseline score of 6 improved to a score of 7.
Subjects not achieving recovery at the last assessment were censored on the day of the last clinical assessment. Subjects who died were considered to have experienced a competing event.
N represents the number of subjects at risk at the beginning of the interval.

Data Extracted: CRF Data, Lab Data: 08JUL2020
Source: .../final_part_a/version1/prog/g-cr-imp.sas v9.4 Output file: g-cr-recover.pdf 14JUL2020: 7:12

Figure 12: Time to Recovery (Competing Risk Analysis) (FAS)

Subgroup analyses

Analysis of Clinical Status (7-Point Ordinal Scale) on Day 11 by oxygen support status (taken from the CSR)

Table 27: Analysis of Clinical Status (7-Point Ordinal Scale) on Day 11 by oxygen support status (taken from the CSR)

Subgroup	Observations Included in Model	P-Value for Testing Proportionality of Odds Assumption (Score Test)	Parameter Estimate (SE)	Odds Ratio (95% CI)	P-Value
RDV 5 Days/SOC					
Oxygen Support					
High-Flow Oxygen	4	NE	NE	NE	NE
Low-Flow Oxygen	65	< 0.0001	0.90 (0.511)	2.46 (0.906, 6.708)	0.0774
Room Air	322	0.8123	0.46 (0.234)	1.59 (1.003, 2.511)	0.0483

RDV 10 Days/SOC					
Oxygen Support					
High-Flow Oxygen	3	NE	NE	NE	NE
Low-Flow Oxygen	59	0.4457	0.91 (0.553)	2.48 (0.838, 7.334)	0.1009
Room Air	331	< 0.0001	0.14 (0.223)	1.15 (0.746, 1.786)	0.5197

NE = not evaluable due to quasi-complete separation or indistinguishable mean score predicted probabilities; SE = standard error
Clinical status is based on an ordinal scale from 1 = Death to 7 = Not hospitalized.
Clinical status was derived from death, hospital discharge, and the ordinal scale as follows: 1 for all days on or after the death date; 7 for all days on or after discharged alive date; ordinal scale using the last available postbaseline record for missing assessment.
The odds ratio (OR) and corresponding 95% confidence interval were from a proportional odds model on Day 11 clinical status with a treatment effect.
Other race includes American Indian or Alaska Native, Native Hawaiian or Pacific Islander, Not Permitted, and Other.
Not Permitted = local regulators did not allow collection of race/ethnicity information. All but 3 values of "Other" are unknown, not specified, etc.
Source: Table 15.9.1.7

Time to recovery by baseline oxygen status (taken form the CSR)

Analysis of time to recovery by baseline oxygen status for participants on high flow or low flow oxygen at baseline showed no statistically significant differences in the median (Q1, Q3) times to recovery in the RDV 5-day and RDV 10-day groups compared with those in the SOC only group (9 [6, 13]) days and 8 [5, 12] days versus 8 [6, 26] days, respectively).

For participants on room air at baseline, there were no statistically significant differences in the median (Q1, Q3) times to recovery in the RDV 5-day and RDV 10-day groups compared with those in the SOC only at baseline (6 [5, 9]) days and 7 [4, 13] days versus 7 [4, 14] days, respectively).

Virological endpoint SARS-CoV-2 RNA by RT-qPCR (Taken from the CSR)

Results for detection of SARS-CoV-2 RNA by RT-qPCR on Days 5 and 10 by treatment group are presented in Table 28.

Table 28: Proportion of Subjects with Negative SARS-COV-2 PCR on Day 5 and Day 10 (FAS)

				RDV For 5 Days vs. SOC	RDV For 10 Days vs. SOC
	RDV For 5 Days (N=191)	RDV For 10 Days (N=193)	SOC (N=200)	Difference in Percentages (95% CI)	Difference in Percentages (95% CI)
Subjects with SARS-COV-2 PCR on Day 5					
Negative	22 (38.6%)	13 (34.2%)	12 (29.3%)	9.3% (-10.3% to 28.2%)	4.9% (-16.0% to 25.8%)
95% CI	26.0% to 52.4%	19.6% to 51.4%	16.1% to 45.5%		
Positive	35 (61.4%)	25 (65.8%)	29 (70.7%)		
Equivocal	1	0	0		
- Missing -	133	155	159		
Subjects with SARS-COV-2 PCR on Day 10					
Negative	10 (34.5%)	14 (38.9%)	8 (33.3%)	1.1% (-25.1% to 27.9%)	5.6% (-20.4% to 29.9%)
95% CI	17.9% to 54.3%	23.1% to 56.5%	15.6% to 55.3%		
Positive	19 (65.5%)	22 (61.1%)	16 (66.7%)		
Equivocal	2	2	0		
- Missing -	160	155	176		

Denominator for percentages was the number of subjects with available PCR (negative or positive) results at the indicated visit.
Day 5 window is from 4 to 6 days. Day 10 window is from 9 to 11 days.
The 95% CI for percentage of subjects in each treatment group was obtained using the Clopper-Pearson Exact method.
Differences in percentage of subjects between treatment groups and 95% CI were calculated based on exact method.

Data Extracted: CRF Data, Lab Data: 08JUL2020
Source: .../final_part_a/version1/prog/t-negpcr.sas v9.4 Output file: t-negpcr.pdf 14JUL2020: 7:12 Page 1 of 1

Ancillary analyses

N/A

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 29A. Summary of Efficacy for trial NIAID-ACTT-1 trial (CO-US-540-5776) in patients with mild/moderate disease

Title: NIAID-ACTT-1 (CO-US-540-5776)		
Study identifier	CO-US-540-5776	
Design	randomized, double-blind, placebo-controlled, multicentre study	
	Duration of main phase:	28 days
	Duration of Run-in phase:	not applicable

<table>
<tr><td></td><td colspan="2">Duration of Extension phase:</td><td>not applicable</td></tr>
<tr><td>Hypothesis</td><td colspan="3">Superiority</td></tr>
<tr><td>Treatments groups</td><td colspan="2">RDV</td><td>remdesivir, i.V. for up to 10 days, (D1: 200 mg i.V, D2-9: 100 mg), N=82</td></tr>
<tr><td></td><td colspan="2">Placebo</td><td>Placebo to match and/or saline for up to 10 days (D1: 200 mg i.V, D2-9: 100 mg), N=72</td></tr>
<tr><td>Endpoints and definitions</td><td>Primary endpoint</td><td>Time to clinical recovery</td><td>The primary efficacy endpoint was time to recovery. Recovery was defined as clinical status in states 1, 2, or 3 of the 8-point ordinal scale, censored at Day 29, defined as follows:
Table 29A.1: 8-point ordinal scale
<table><tr><td>8.</td><td>Death</td></tr><tr><td>7.</td><td>Hospitalized, on invasive mechanical ventilation or ECMO</td></tr><tr><td>6.</td><td>Hospitalized, on noninvasive ventilation or high-flow oxygen d</td></tr><tr><td>5.</td><td>Hospitalized, requiring supplemental oxygen</td></tr><tr><td>4.</td><td>Hospitalized, not requiring supplemental oxygen—requiring on otherwise)</td></tr><tr><td>3.</td><td>Hospitalized, not requiring supplemental oxygen—no longer re</td></tr><tr><td>2.</td><td>Not hospitalized, limitation on activities and/or requiring home</td></tr><tr><td>1.</td><td>Not hospitalized, no limitations on activities</td></tr></table>
The time to recovery was the elapsed time (in days) from randomization to the earliest day on which a participant reached recovery.</td></tr>
<tr><td></td><td>Key Secondary endpoint</td><td>Clinical status at D15</td><td>The key secondary endpoint was the distribution of clinical status (8-point ordinal scale) on Day 15.</td></tr>
</table>

	Secondary endpoint		Ordinal outcome assessed daily while hospitalized and on Days 15, 22, and 29 NEWS assessed daily while hospitalized and on Days 15 and 29 Days of supplemental oxygen (if applicable) Days of non-invasive ventilation/high-flow oxygen (if applicable) Days of invasive mechanical ventilation/ECMO (if applicable) Days of hospitalization Date and cause of death (if applicable)
	Extraploratory endpoint	Virologic efficacy of remdesivir compared to the control arm	Percent of subjects with SARS-CoV-2 detectable in OP samples on D3, 5, 8, 11, 15 and 29 Quantitative SARS-CoV-2 virus in OP-samples at D3, 5, 8, 11, 15 and 29 Development of resistance of SARS-CoV-2 in OP-samples at D3, 5, 8, 11, 15 and 29 Quantitative SARS-CoV-2 virus in blood at D3, 5, 8 and 11 Qualitative and quantitative PCR for SARS-CoV-2 in OP-samples at D3, 5, 8, 11 (while hospitalised) and days 15 and 29 (if attends in-person visit or still hospitalised) Qualitative and quantitative PCR for SARS-CoV-2 in blood on D 1, 3, 5, 8 and 11 (while hospitalised)
Database lock	21 May 2020.		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat at Day 28 (subgroup of patients with mild/moderate disease)		
Descriptive statistics and estimate variability	Treatment group	RDV	Placebo
	Number of subject	82	77

	Time to recovery (median [95% CI])	5 (4-6)	7 (5,9)	
Effect estimate per comparison	Primary endpoint	Comparison groups	RDV vs Placebo	
		HR (95% CI)	1.10 (0.80,1.53)	
		P-value	Not provided	
	Key Secondary Endpoint	Comparison groups	RDV vs Placebo	
		Odds Ratio	1.20 (0.70,2.20)	
		P-value	0.47	
Notes	This analysis was an exploratory analysis in the subgroup of patients with mild/moderate disease. The original primary confirmatory analysis of the study was based on the overall population also including patients with severe disease.			

Table 30 B. Summary of Efficacy for trial GS-US-540-5774

Title: Simple moderate study GS-US-540-5774		
Study identifier	GS-US-540-5774	
Design		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	28 days not applicable not applicable
Hypothesis	Superiority	
Treatments groups	5-day RDV	Continued SOC therapy + IV RDV 200 mg on D1 followed by 100 mg on Day 2-5, N= 191<treatment>. <duration>, <number randomized>
	10 day RDV	Continued SOC therapy + IV RDV 200 mg on D1 followed by 100 mg on Day 2-10, <treatment>. <duration>, N= 193
	SOC	continued SOC therapy, N= 200

Endpoints and definitions	Primary endpoint	Clinical status at D 11	Clinical status assessed on a 7 point ordinal scale on D 11. 1 = death 2= hospitalised, on IMV or ECMO 3= hospitalised on NIMV or high flow oxygen 4= Hospitalized, requiring low flow supplemental oxygen 5= Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise) 6=Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care (other than per protocol RDV administration) 7= Not hospitalised
	Secondaryendpoints	Proportion of patients with treatment emergent adverse events	

	Other endpoints of interest		Proportion of participants with negative SARS-CoV-2 PCR Time to clinical improvement (days) definded as > 2 points improvement in clinical status (7-point ordinal scale) from D 1 Time to >1 point clinical improvement (days) Time to recovery: defined as an improvement in clinical status from a baseline score of 2 through 5 to a score of 6 or 7, or an improvement from a baseline score of 6 to a score of 7 Time to modified recovery: defined as an improvement in clinical status from a baseline score of 2 through 4 to a score of 5, 6, or 7, or an improvement from a baseline score of 5 to a score of 6 or 7, or an improvement from a baseline score of 6 to a score of 7 Time to room air: defined as an improvement in clinical status from a baseline score of 2 through 4 to a score of 5, 6, or 7 Duration of oxygen therapy (days) Shift in oxygen support status from baseline Duration of hospitalization (days) All-cause mortality at Day 28 Plasma concentration of RDV and metabolites
Database lock	08.July 2020		
Results and Analysis			

Analysis description	**Primary Analysis**			
Analysis population and time point description	Full analysis set (FAS) D11			
Descriptive statistics and estimate variability	Treatment group	5-Day RDV	10-Day RDV	SOC
	Number of subject	191	193	200

	Clinical status (7-point ordinal scale) at day 11			
1 - Death		0	2 (1.0%)	4 (2.0%)
2		0	1 (0.5%)	4 (2.0%)
3		5 (2.6%)	0	7 (3.5%)
4		7 (3.7%)	12 (6.2%)	11 (5.5%)
5		38 (19.9%)	44 (22.8%)	46 (23.0%)
6		7 (3.7%)	9 (4.7%)	8 (4.0%)
7 - Not Hospitalized		134 (70.2%)	125 (64.8%)	120 (60.0%)

Effect estimate per comparison	Primary endpoint	Comparison groups	5-day RDV vs SOC
		Proportional Odds Ratio (95% CI)	1.65 (1.09,2.48)
		P-value	0.017
		Comparison groups	10-day RDV vs SOC
		P-value	0.18
Notes	Bonferroni correction for multiplicity adjustment was introduced with SAP after all patients completed part A. The size of the treatment effect and the conclusion of a statistical significant difference depend critical on the method for missing data handling		

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

No analysis was provided.

Clinical studies in special populations

No such studies were provided.

Supportive studies

In response, to the concerns of the previous round that study 5774 and the NIAID ACTT-1 would not suffice to demonstrate efficacy in the applied indication, the MAH submitted with study **GS-US-540-9012 new data from the outpatient setting** in order to support the initially applied proposed extension of indication to patients with moderate disease. The proposal was that the efficacy data from study -9012

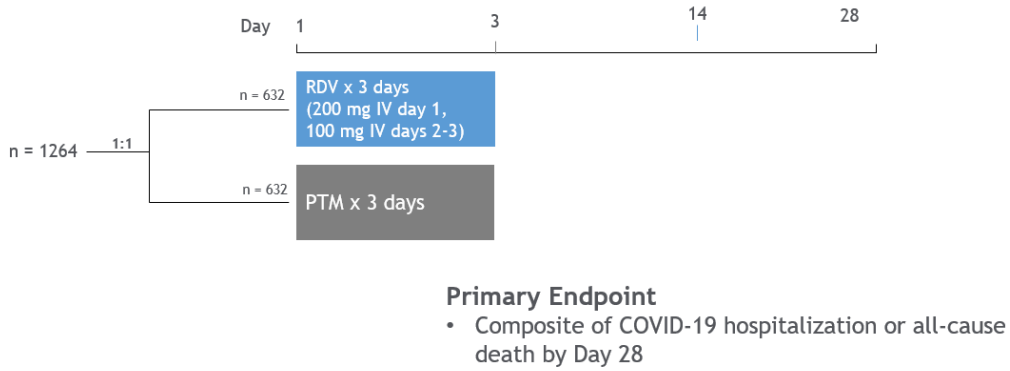
could be used to **extrapolate efficacy from the outpatient setting** to the initially applied **moderate population**, and who are at **risk** of progression to **severe disease**. Study GS-US-540-9012 was conducted in an outpatient setting, hence the enrolled population in this study does not cover the MAH's initially applied indication of patients with moderate COVID-19.

Study GS-US-540-9012

Study GS-US-540-9012 was a Phase 3, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of remdesivir (GS-5734™) treatment of early stage COVID-19 who were at increased risk of disease progression in an outpatient setting. The study was a multi-centre trial, conducted in 64 sites globally.

Eligible participants were randomized in a 1:1 ratio to one of the two treatment groups (Figure 13). Randomization was stratified by participants who resided in a skilled nursing facility, by participant's age (< 60 vs ≥ 60 years), and by region (US vs ex-US).

Participants received either study treatment with remdesivir (RDV) or Placebo to match (PTM) for 3 days and were followed up for 28 days.



Source: Information taken from the MAH's presentation on study GS-US-540-9012, EMA-Rapp and MAH meeting 8th September 2021, Slide 6

Figure 13: Scheme of GS-US-540-9012 study design

Study participants

Main inclusion criteria

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

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

   - Chronic lung disease: chronic obstructive pulmonary disease, moderate-to-severe asthma, cystic fibrosis, pulmonary fibrosis
   - Hypertension: systemic or pulmonary
   - Cardiovascular or cerebrovascular disease: coronary artery disease, congenital heart disease, heart failure, cardiomyopathy, history of stroke, atrial fibrillation, hyperlipidemia
   - Diabetes mellitus: type 1, type 2, or gestational
   - Obesity (BMI ≥ 30)

- Immunocompromised state; having a solid organ transplant, blood, or bone marrow transplant; immune deficiencies; HIV with a low CD4 cell count or not on HIV treatment; prolonged use of corticosteroids; or use of other immune weakening medicines
- Chronic mild or moderate kidney disease
- Chronic liver disease
- Current cancer
- Sickle cell disease

OR

Age ≥ 60 years, regardless of the presence of other pre-existing risk factors for progression

3. SARS-CoV-2 infection confirmed by molecular diagnostics (nucleic acid [e.g., PCR] or antigen testing) ≤ 4 days prior to screening
4. Presence of ≥ 1 symptom(s) consistent with COVID-19 for ≤ 7 days prior to randomization (such as fever, cough, fatigue, shortness of breath, sore throat, headache, myalgia/arthralgia)
5. Did not receive, require, or expect to require supplemental oxygen
6. Did not require hospitalization (hospitalization defined as ≥ 24 hours of acute care)

Main exclusion criteria

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

Prior and concomitant drugs:

Concomitant medications taken within 30 days prior to screening and up to and including 30 days after the last dose of study drug were recorded in the source documents and electronic case report forms (eCRFs).

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

- Investigational or approved agents for the SARS-CoV-2 virus including approved HIV protease inhibitors such as lopinavir/ritonavir, interferon, etc. Use of these medications for an approved indication other than SARS-CoV-2 infection was not prohibited.
- Use of hydroxychloroquine or chloroquine for any indication.
- Strong inducers of P-glycoprotein (e.g., rifampicin or herbal medications).

Number of centres

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

Treatments

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

Placebo group: Participants received PTM remdesivir on Days 1 to 3.

Duration of treatment:

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

Justification of dose and duration of treatment:

The dosing of RDV in this study, 200 mg on Day 1 and 100 mg on each of Days 2 and 3 was the initial dosing recommended by US Food and Drug Administration and approved by European Medicines Agency for adults and adolescents weighing ≤ 40 kg.

Justification of treatment duration:

In patients with severe COVID-19 who do not require mechanical ventilation, 5 days of RDV showed similar efficacy to a 10-day regimen. Similarly, 5 days treatment of RDV in participants with moderate COVID-19 was associated with a significant improvement in clinical status compared with SOC and approximately a third of participants were discharged prior to completion of 5 days RDV therapy.

In early viral infection, shorter courses of antivirals are often effective in preventing disease progression {Nicholson 2000}. As such, a shorter duration of 3 days of RDV treatment is proposed in participants with early stage COVID-19 not requiring hospitalization or oxygen supplementation with the goal of preventing disease progression.

Treatment administration:

remdesivir infusions will be administered to participants at the site under close supervision or in the participant's home by a home health service provider. Healthcare professionals administering RDV infusions should have the appropriate medication available for immediate use in case of hypersensitivity or infusion related reactions. The participant should be treated according to the SOC for management of hypersensitivity reaction or infusion related reactions. Post infusion monitoring should be done according to site or home health protocol.

Formulation:

remdesivir: remdesivir for injection, 100 mg, is a preservative-free, white to off-white to yellow, lyophilized solid containing 100 mg of GS-5734 that was to be reconstituted with sterile water for injection and diluted into 0.9% saline prior to administration by IV infusion.

In addition to the active ingredient, it contains the following inactive ingredients: water for injection, sulfobutylether β-cyclodextrin sodium (SBECD), hydrochloric acid, and/or sodium hydroxide. Hydrochloric acid and/or sodium hydroxide were used to adjust the formulation to a final pH of 3.0 to 4.0.

The batch number of the RDV 100 mg for IV injection was EW2009A1.

PTM: The supplied Placebo to match (PTM) RDV for injection was identical in physical appearance to the active lyophilized formulation and contained the same inactive ingredients.

Objectives

Primary objectives:

- To evaluate the efficacy of RDV in reducing the rate of COVID-19 related hospitalization or all-cause death in non-hospitalized participants with early stage COVID-19
- To evaluate the safety of RDV administered in an outpatient setting

Secondary objectives:

- To evaluate the efficacy of RDV in reducing the rate of COVID-19 related medically attended visits (MAVs; medical visits attended in person by the participant and a health care professional) or all-cause death in non-hospitalized participants with early stage COVID-19
- To determine the antiviral activity of RDV on SARS-CoV-2 viral load
- To assess the impact of RDV on symptom duration and severity

Exploratory objectives:

- To assess the impact of RDV on other clinical outcomes
- To evaluate the emergence of viral resistance to RDV
- To identify and assess associations of host biomarkers with disease progression and treatment response
- To assess the pharmacokinetics (PK) of RDV and its metabolites in participants with COVID-19
- To assess patient-reported outcome using the COVID-19-adapted InFLUenza Patient-Reported Outcome Plus (FLU-PRO Plus©) questionnaire and validate the questionnaire (if available)

Outcomes/endpoints

Primary endpoints:

- Composite endpoint of COVID-19 related hospitalization (defined as at least 24 hours of acute care) or all-cause death by Day 28
- Proportion of participants with treatment-emergent AEs

Secondary endpoints:

- Composite endpoint of COVID-19 related MAVs (medical visits attended in person by the participant and a health care professional) or all-cause death by Day 28
- All-cause mortality at Day 28
- Proportion of participants hospitalized by Day 28
- Composite endpoint of COVID-19 related hospitalization (defined as at least 24 hours of acute care) or all-cause death by Day 14
- Composite endpoint of COVID-19 related MAVs (medical visits attended in person by the participant and a health care professional) or all-cause death by Day 14
- Time-weighted average change in SARS-CoV-2 viral load from baseline to Day 7
- Time to alleviation (mild or absent) of baseline COVID-19 symptoms as reported on the COVID-19-adapted FLU-PRO Plus

- Proportion of participants progressing to requiring oxygen supplementation by Day 28

Exploratory endpoints:

- Time to alleviation (mild or absent) of baseline symptoms in each domain of the COVID-19-adapted FLU-PRO Plus
- Change from baseline in COVID-19-adapted FLU-PRO Plus total score and score in each domain
- Psychometric validity of COVID-19-adapted FLU-PRO Plus questionnaire
- Time-weighted average change in SARS-CoV-2 viral load from baseline to Day 14
- Time to first negative SARS-CoV-2 polymerase chain reaction (PCR)
- Proportion of participants with negative SARS-CoV-2 PCR at each study visit
- Emergence of viral resistance to RDV
- Baseline levels and change from baseline for inflammation/immune-related, acute respiratory distress syndrome (ARDS)-related and coagulation-related biomarkers
- Proportion of participants admitted to the intensive care unit by Day 28
- Proportion of participants started on mechanical ventilation by Day 28
- The plasma concentrations and PK parameters of RDV and metabolites

Sample size

A sample size of 1264 participants (632 in each group with 1:1 randomization) achieves > 90% power to detect a ratio of 0.55 (RDV to placebo) in proportion of COVID-19-related hospitalization or all-cause death, which is equal to a hazard ratio: [HR] of 0.534) using a 2-sided significance level of 0.05 assuming the overall COVID-19-related hospitalization or all-cause death rate is 9.3% (12% in the placebo group and 6.6% in the RDV IV for 3 days group) and a 5% drop out rate. The sample size provides approximately 80% power to detect a smaller treatment effect size with a ratio of 0.60 (RDV to placebo), assuming a 2-sided significance level of 0.05 and the overall COVID-19-related hospitalization or all-cause death rate is 9.6% (12% in the placebo group and 7.2% in the RDV group) and a 5% drop out rate. The proportion of patients with COVID-19-related hospitalizations or emergency department visits was 13.5% in high-risk patients (age ≥ 65 or BMI ≥ 35) who received placebo, 12% was assumed for the study to account for decrease in hospitalization rate in recent months.

Randomisation

Participants who met all randomization eligibility criteria were randomized in a 1:1 ratio to Treatment Group A or Treatment Group B and assigned a participant number. Randomization was stratified by participant residence in a skilled nursing facility, by participant's age (< 60 vs ≥ 60 years), and by region (US vs ex-US).

Blinding (masking)

During the randomized phase participants and all personnel directly involved in the conduct of the study were blinded to treatment assignment. Specified personnel may have been unblinded based on their study role. Study drug was dispensed by the study pharmacist, or designee, in a blinded fashion to the participants. The Pharmacokinetics (PK) File Administrator, or designee, in Bioanalytical Operations and/or Clinical Data Management, who facilitated the data transfer of PK files between Gilead and vendors, remained unblinded. Individuals in clinical virology performing sample selection for resistance analysis may have been unblinded. Individuals in Clinical Packaging and Labelling or Clinical Supply Management who had an unblinded Inventory Manager role in the interactive web/voice response system

(IXRS) for purposes of study drug inventory management were remained unblinded. Individuals in Global Patient Safety (GLPS) responsible for safety signal detection, IND safety reporting, and/or expedited reporting of suspected unexpected serious adverse reactions may have been unblinded to individual case data and/or group level summaries. Research and Development Quality and Compliance may also have been unblinded for purposes of supporting Quality Assurance activities and/or Regulatory Agency inspections.

Statistical methods

Statistical methods were described in the statistical analysis plan (SAP) that was based on the study protocol amendment 4 dated 14 January 2021 and the electronic case report form (eCRF). The SAP was finalised before database finalization.

Analysis sets defined the participants to be included in an analysis. Participants included in each analysis set were determined before the study blind was broken for analysis. The primary analysis set for efficacy analysis was defined as the Full Analysis Set (FAS), which included all participants who (1) were randomized into the study, and (2) received at least 1 dose of study treatment. Participants were grouped according to the treatment to which they were randomized.
A modified Full Analysis Set (mFAS) included all participants from the FAS enrolled under protocol amendment 2 or later.
The Virology Analysis Set included all participants who (1) were randomized into the study, (2) received at least 1 dose of study treatment, and (3) had positive SARS-CoV-2 viral load at baseline (result of "No SARS-CoV-2 detected" was considered negative, results of "Inconclusive," "<2228cp/mL SARSCoV2 detected" and numerical results were considered positive).

The primary endpoint of the study was the composite endpoint of COVID-19-related hospitalization (defined as at least 24 hours of acute care) or all-cause death by Day 28. The endpoint was derived by combining the available all-cause death and COVID-19-related hospitalization reported by the site. The first COVID-19-related hospitalization was used for the proportion of COVID-19-related hospitalization or all-cause death.

Null hypothesis: The HR of COVID-19-related hospitalization or all-cause death by Day 28 between the 2 treatment groups was equal to 1.

Alternative hypothesis: The HR of COVID-19-related hospitalization or all-cause death by Day 28 between the 2 treatment groups did not equal 1.

The HR of COVID-19-related hospitalization or all-cause death between the 2 treatment groups was estimated using a Cox model with stratification factors as covariates. The HR, P value, 95% CI for the HR from Cox model, and proportion of COVID-19-related hospitalization or all-cause death at Day 28 from Kaplan-Meier estimate were provided. If a participant prematurely discontinued from the study prior to Day 28 or the hospitalization status was missing, the participant was censored at the date of last contact.

A post-hoc sensitivity analysis was conducted using the following alternative approach for the primary endpoint: A CMH test including baseline stratification factors as strata for the statistical comparison between the 2 treatment groups. If a participant prematurely discontinued from the study prior to Day 28 with no event before discontinuation or the hospitalization/death status was missing, the participant was considered as with no hospitalization/death.

The primary endpoint was examined for the following participant subgroups: Region (US vs ex-US); Participant's age (< 18, ≥ 18 to < 60, ≥ 60 years); Participants who resided in a skilled nursing facility (Yes, No); Sex at birth: (a) male and (b) female; Race: (a) Asian, (b) Black, (c) White, (d) other; Baseline risk factor (Yes, No): Chronic lung disease, Hypertension, Cardiovascular or cerebrovascular disease, Diabetes mellitus, Obesity, Immunocompromised state, Chronic mild or moderate kidney

disease, Chronic liver disease, Current cancer, Sickle cell disease; Common COVID-19 symptoms at baseline: absence or presence for each of the following symptoms: stuffy or runny nose, sore throat, shortness of breath (difficulty breathing), cough, low energy or tiredness, muscle or body aches, headache, chills or shivering, feeling hot or feverish, nausea, vomit, diarrhoea, loss of smell, loss of taste.

There was no multiplicity adjustment in the final analysis. Efficacy was evaluated using the primary efficacy endpoint at the significance level of 0.05. All other efficacy endpoints were exploratory in nature and were tested using 2-sided tests at the 5% significance level without multiplicity adjustment.

The FAS was the primary analysis set for secondary endpoints. The mFAS was used for secondary endpoints of the composite endpoint of COVID-19-related MAVs or death.

The secondary endpoint of COVID-19-related hospitalization or all-cause death by Day 14, COVID-19-related MAVs or death by Day 28, and COVID-19-related MAVs or death by Day 14 was analysed using the same method as for the primary endpoint.

Number and percentage of participants progressing to requiring oxygen supplementation by Day 28 were summarised and compared between treatment groups using the Fisher exact test. Participants discontinued from the study before progressing to requiring oxygen supplementation were considered as not requiring oxygen supplementation.

Time-weighted average change in SARS-CoV-2 viral load from baseline to Day 7 was summarized by treatment groups and compared between treatment groups using an analysis of covariance (ANCOVA) model with baseline viral load as covariate; the analysis was based on the Virology Analysis Set.

For analysis of time to alleviation of symptoms and COVID-19-related hospitalisation by Day 28, proportion of hospitalised patients and patients with alleviation of symptoms was estimated using the Kaplan-Meier method and compared between the two treatment groups using a log-rank test. Hazard ratio and 2-sided 95% CI estimated using the Cox regression with baseline stratification factors as covariates were provided.

One external multidisciplinary data monitoring committee (DMC) was planned to review the progress of the study and to perform interim reviews of the efficacy (futility assessment) and safety data and to decide on sample size re-estimation. However, this DMC analysis was not performed due to the stop of study enrolment after 584 participants were randomized and prior to reaching the planned DMC analysis schedule (i.e., approximately 50% of the total 1264 planned participants completing the Day 28 assessment).

Results

Participant flow

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

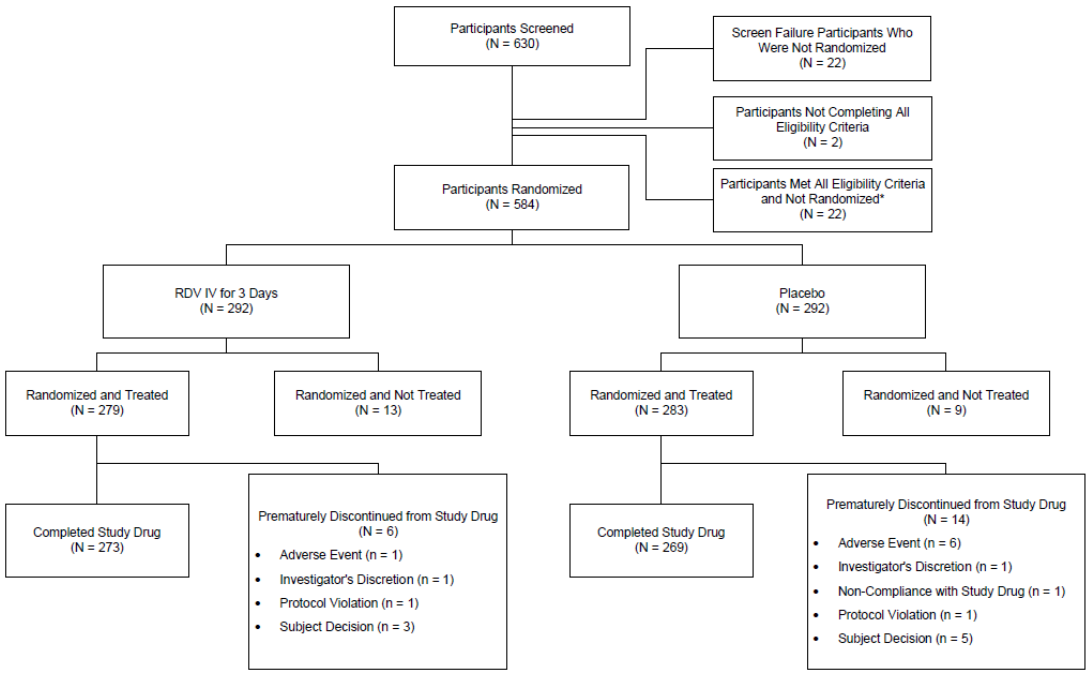
Of the 630 participants screened, a total of 584 participants were randomized, 292 to receive RDV IV for 3 days and 292 to receive placebo for 3 days. Of these, 562 participants (279 in the RDV IV for 3 days group and 283 in the placebo group) received at least one dose of study treatment (Table 30) and were included in the FAS and Safety Analysis Set. Twenty-two participants met all eligibility criteria and were not randomized due to the following reasons: withdrew consent (14); outside of visit window (3); lost to follow-up (2); other (2); and investigator's discretion (1). Twenty-two randomized participants did not receive any study treatment.

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

Table 31: Participant disposition (all screened patients) study GS-US-540-9012

Participant Disposition	RDV IV for 3 Days	Placebo	Total
Participants screened			630
Screen failure participants who were not randomized			22
Participants not completing all eligibility criteria			2
Participants met all eligibility criteria and not randomized[a]			22
Participants randomized	292	292	584
Participants randomized and never treated	13	9	22
Participants completed study drug	273 (97.8%)	269 (95.1%)	542 (96.4%)
Participants prematurely discontinuing study drug	6 (2.2%)	14 (4.9%)	20 (3.6%)
Adverse event	1 (0.4%)	6 (2.1%)	7 (1.2%)
Investigator's discretion	1 (0.4%)	1 (0.4%)	2 (0.4%)
Noncompliance with study drug	0	1 (0.4%)	1 (0.2%)
Protocol violation	1 (0.4%)	1 (0.4%)	2 (0.4%)
Participant decision	3 (1.1%)	5 (1.8%)	8 (1.4%)
Participants completed study	266 (95.3%)	272 (96.1%)	538 (95.7%)
Participants prematurely discontinuing from study	13 (4.7%)	11 (3.9%)	24 (4.3%)
Adverse event	0	3 (1.1%)	3 (0.5%)
Investigator's discretion	0	1 (0.4%)	1 (0.2%)
Protocol violation	1 (0.4%)	1 (0.4%)	2 (0.4%)
Withdrew consent	5 (1.8%)	4 (1.4%)	9 (1.6%)
Lost to follow-up	7 (2.5%)	2 (0.7%)	9 (1.6%)

eCRF = electronic case report form; IV = intravenous; RDV = remdesivir (GS-5734™)
The denominator for percentage is the number of participants in the Safety Analysis Set.
The number of screen failures was counted by unique participant based on rescreening information entered into the eCRF.
Screen failure participants were the participants who did not meet all eligibility criteria.
a Among 22 participants who met all eligibility criteria and were not randomized, the reasons (N) were: withdrew consent (14); lost to follow-up (2); investigator's discretion (1); outside of visit window (3); other (2).
Source: Table 15.8.1.2



IV = intravenous; RDV = remdesivir (GS-5734™)
Screen failures were participants who did not meet all eligibility criteria.
* Among 22 participants who met all eligibility criteria and were not randomized, the reasons (N) were: withdrew consent (14); lost to follow-up (2); investigator's discretion (1); outside of visit window (3); other (2).
Source: Figure 15.8.1

Figure 14: GS-US-540-9012: Participant Flow (All Screened Participants)

Recruitment

The key dates relevant to the conduct of Study GS-US-540-9012 are listed in Table 31
Participants were enrolled and treated across 64 centers in the US, Denmark, Spain, and the UK. While approximately only 5% of the participants have been recruited in Europe (including UK), 95% come from the USA.

Conduct of the study

Table 31 lists the key dates relevant to the conduct of Study GS-US-540-9012.

Table 32: Key dates study GS-US-540-9012

Event	Date
First participant screened	18 September 2020
First participant enrolled/randomized	18 September 2020
Last participant enrolled/randomized	08 April 2021
Last participant last visit for the primary endpoint and for this report	06 May 2021
Database finalization	13 August 2021
Treatment unblinding	13 August 2021

Protocol and Protocol Amendments

Changes in the Conduct of the Study or Planned Analyses

The protocol was amended four times during the conduct of study GS-US-540-9012, as indicated in Table 32. In addition, two country specific amendments were done.

Table 33: Protocol and Protocol Amendments

Protocol/Amendment	Date
Original	21 July 2020
Amendment 1 Summary of Changes	11 August 2020
Amendment 1.1 (United Kingdom) Summary of Changes	07 October 2020
Amendment 1.1 (Germany) Summary of Changes	14 October 2020
Amendment 2 Summary of Changes	06 November 2020
Amendment 3 Summary of Changes	12 November 2020
Amendment 4 Summary of Changes	14 January 2021
Amendment 4	14 January 2021

The most important change from protocol-specified analyses are listed below.

Amendment 1:

- Increased the number of planned study centers to 150
- Removed restriction on percentage of participants that may be enrolled from skilled nursing facilities
- Decreased minimum age to include adolescent participants ages ≥ 12
- Modified inclusion and exclusion criteria
- Added sputum samples for SARS-CoV-2 qRT-PCR viral load testing and possible resistance testing

Amendment 2:

- Updates to endpoints in the study made in response to evolving treatment paradigms and understanding of COVID-19
- Clarification and/or update of inclusion and exclusion criteria

Amendment 3:

- The secondary endpoint of time to alleviation of COVID-19 symptoms was returned back to secondary from exploratory after further consideration.

Amendment 4:

- Update to primary and secondary study objectives to align with updated study endpoints
- Update to primary and secondary study endpoints to address US regulatory agency comments
- Update to exclusion criterion #3 to clarify exclusion of COVID-19 vaccines
- Update to statistical methods

Changes from planned analyses:

The interim DMC analysis was not performed due to the stop of enrolment on 08 April 2021 after less than 50% of the participants were randomized. The reasons for stopping enrolment were administrative in nature, including rapidly declining COVID-19 case rates, increasing availability of single-infusion monoclonal antibodies as an alternative to placebo, and increasing vaccination rates among high-risk patients during the study.

Additionally, the subgroup analysis of the primary endpoint by baseline risk factor was revised to reflect that for participants with risk factors other than current cancer, the risk factors may not have been ongoing in the medical history.

The following post hoc analyses were conducted:

- Time to alleviation of baseline COVID-19 symptoms on COVID-19-adapted FLU-PRO Plus Questionnaire in participants who had baseline data defined as data on or prior to the first dosing date
- All-cause hospitalization by Day 28
- Subgroup analysis of the primary endpoint by ethnicity (Hispanic or Latino vs not Hispanic or Latino)
- Overall summaries of TEAEs and TEAEs by preferred term for participants less than 18 years of age to provide safety summaries for adolescent participants in the study

Protocol deviation

Table 33 provides a summary of important protocol deviations that occurred during the study.

Table 34: GS-US-540-9012: Important Protocol Deviations (Safety Analysis Set)

Protocol Deviation, n (%)[a]	RDV IV for 3 Days (N = 279)	Placebo (N = 283)
Participants with at least 1 important protocol deviation	11 (3.9%)	12 (4.2%)
Eligibility criteria	3 (1.1%)	5 (1.8%)
Other	4 (1.4%)	3 (1.1%)
Informed consent	3 (1.1%)	2 (0.7%)
Wrong treatment or incorrect dose	0	2 (0.7%)
Excluded concomitant medication	1 (0.4%)	0
Missing data	1 (0.4%)	0
Total number of important protocol deviations	13	13
Eligibility criteria	4	6
Other	4	3
Informed consent	3	2
Wrong treatment or incorrect dose	0	2
Excluded concomitant medication	1	0
Missing data	1	0

IV = intravenous; RDV = remdesivir (GS-5734™)
Participants with multiple protocol deviations were counted only once in each protocol deviation category.
For number of important protocol deviations, participants with multiple deviations were counted multiple times in each protocol deviation category.
Source: Table 15.8.2

Monitoring

The MAH and the monitoring contract research organization (CRO) PPD (Wilmington, NC, USA) monitored the study sites, including the data recorded in the eCRFs. The monitoring of the clinical data was exclusively done remotely, due to the COVID-19 pandemic. Source data verification was not performed. The study monitor(s) performed a CRF review where only the information recorded in EDC and available electronically was reviewed. No comparison to source documents at the sites were performed.

GCP inspection

One investigator site inspection was conducted by the Danish Medicines Agency between the 30 Jun - 02 July 2021.

Baseline data

Demographic and Baseline Characteristics

Demographic and baseline characteristics are shown in the table below.

Table 35: GS-US-540-9012: Demographic and Baseline Characteristics (Safety Analysis Set)

Characteristic	RDV IV for 3 Days (N = 279)	Placebo (N = 283)	Total (N = 562)
Age (years)			
N	279	283	562
Mean (SD)	50 (15.3)	51 (14.8)	50 (15.1)
Median	51	52	52
Q1, Q3	38, 61	41, 62	40, 61
Min, max	13, 89	14, 98	13, 98
Age category (years), n (%)			
< 18	3 (1.1%)	5 (1.8%)	8 (1.4%)
≥ 18 to < 60	193 (69.2%)	191 (67.5%)	384 (68.3%)
≥ 60	83 (29.7%)	87 (30.7%)	170 (30.2%)
Sex at birth, n (%)			
Male	148 (53.0%)	145 (51.2%)	293 (52.1%)
Female	131 (47.0%)	138 (48.8%)	269 (47.9%)
Race, n (%)			
American Indian or Alaska Native	15 (5.5%)	21 (7.6%)	36 (6.6%)
Asian	6 (2.2%)	7 (2.5%)	13 (2.4%)
Black	20 (7.3%)	22 (8.0%)	42 (7.7%)
Native Hawaiian or Pacific Islander	1 (0.4%)	0	1 (0.2%)
White	228 (83.5%)	224 (81.2%)	452 (82.3%)
Other	3 (1.1%)	2 (0.7%)	5 (0.9%)
Not permitted	6	7	13
Race category, n (%)			

Characteristic	RDV IV for 3 Days (N = 279)	Placebo (N = 283)	Total (N = 562)
Asian	6 (2.2%)	7 (2.5%)	13 (2.3%)
Black	20 (7.2%)	22 (7.8%)	42 (7.5%)
White	228 (81.7%)	224 (79.2%)	452 (80.4%)
Other[a]	25 (9.0%)	30 (10.6%)	55 (9.8%)
Ethnicity, n (%)			
Hispanic or Latino	123 (45.7%)	112 (41.5%)	235 (43.6%)
Not Hispanic or Latino	146 (54.3%)	158 (58.5%)	304 (56.4%)
Not permitted	10	13	23
Baseline weight (kg)			
N	279	283	562
Mean (SD)	90.0 (21.53)	88.4 (19.62)	89.2 (20.59)
Median	87.7	85.5	86.8
Q1, Q3	73.5, 102.8	74.8, 99.8	74.3, 101.6
Min, max	46.3, 173.2	46.0, 170.1	46.0, 173.2
Baseline body mass index (kg/m^2)			
N	276	283	559
Mean (SD)	31.2 (6.72)	30.8 (5.75)	31.0 (6.24)
Median	30.7	30.5	30.7
Q1, Q3	26.2, 34.4	26.7, 33.8	26.5, 34.2
Min, max	15.2, 57.9	18.8, 52.6	15.2, 57.9

IV = intravenous; max = maximum; min = minimum; RDV = remdesivir (GS-5734™); Q1 = first quartile; Q3 = third quartile
For race and ethnicity, "Not Permitted" was excluded from the percentage calculation and *P* value calculation.
Not Permitted = local regulators did not allow collection of race/ethnicity information.
a For race category, "Other" included American Indian or Alaska Native, Native Hawaiian or Pacific Islander, Other, and Not Permitted.
Source: Table 15.8.3.1.1

Demographic characteristics by resident of a skilled nursing facility and a by comparison of patients receiving RDV in a home setting and outpatient setting were provided.

Other Baseline Characteristics

Other baseline characteristics are presented by group in the table below.

Table 36: GS-US-540-9012: Other Baseline Characteristics (Safety Analysis Set)

Characteristic	RDV IV for 3 Days (N = 279)	Placebo (N = 283)	Total (N = 562)
Baseline risk factor: chronic lung disease, n (%)			
Yes	67 (24.0%)	68 (24.0%)	135 (24.0%)
No	212 (76.0%)	215 (76.0%)	427 (76.0%)
Baseline risk factor: hypertension, n (%)			
Yes	138 (49.5%)	130 (45.9%)	268 (47.7%)
No	141 (50.5%)	153 (54.1%)	294 (52.3%)
Baseline risk factor: cardiovascular or cerebrovascular disease, n (%)			
Yes	20 (7.2%)	24 (8.5%)	44 (7.8%)
No	259 (92.8%)	259 (91.5%)	518 (92.2%)
Baseline risk factor: diabetes mellitus, n (%)			
Yes	173 (62.0%)	173 (61.1%)	346 (61.6%)
No	106 (38.0%)	110 (38.9%)	216 (38.4%)
Baseline risk factor: obesity, n (%)			
Yes	154 (55.8%)	156 (55.1%)	310 (55.5%)
No	122 (44.2%)	127 (44.9%)	249 (44.5%)
Baseline risk factor: immunocompromised state, n (%)			
Yes	14 (5.0%)	9 (3.2%)	23 (4.1%)
No	265 (95.0%)	274 (96.8%)	539 (95.9%)
Baseline risk factor: chronic mild/moderate kidney disease, n (%)			
Yes	7 (2.5%)	11 (3.9%)	18 (3.2%)
No	272 (97.5%)	272 (96.1%)	544 (96.8%)
Baseline risk factor: chronic liver disease, n (%)			
Yes	1 (0.4%)	1 (0.4%)	2 (0.4%)
No	278 (99.6%)	282 (99.6%)	560 (99.6%)
Baseline risk factor: current cancer, n (%)			
Yes	12 (4.3%)	18 (6.4%)	30 (5.3%)
No	267 (95.7%)	265 (93.6%)	532 (94.7%)
Baseline risk factor: sickle cell disease, n (%)			
Yes	0	0	0
No	279 (100.0%)	283 (100.0%)	562 (100.0%)
Duration of symptoms prior to first dose of study drug (days)			
N	279	283	562
Mean (SD)	5 (1.9)	5 (1.9)	5 (1.9)
Median	5	5	5
Q1, Q3	3, 6	4, 6	3, 6
Min, max	0, 18	0, 13	0, 18
Duration from SARS-CoV-2 nucleic acid/antigen confirmation to first dose of study drug (days)			
N	279	283	562
Mean (SD)	2 (1.5)	3 (1.5)	3 (1.5)
Median	2	3	2
Q1, Q3	1, 3	1, 4	1, 4
Min, max	0, 6	0, 7	0, 7
ALT (U/L)			
N	278	281	559
Mean (SD)	34 (23.8)	36 (29.9)	35 (27.0)

Characteristic	RDV IV for 3 Days (N = 279)	Placebo (N = 283)	Total (N = 562)
Median	27	27	27
Q1, Q3	19, 39	18, 41	18, 40
Min, max	5, 170	8, 210	5, 210
AST (U/L)			
N	277	281	558
Mean (SD)	29 (16.6)	30 (19.2)	30 (17.9)
Median	24	24	24
Q1, Q3	20, 34	20, 34	20, 34
Min, max	7, 128	10, 191	7, 191
Respiration rate (breaths/min)			
N	278	279	557
Mean (SD)	17 (2.6)	17 (2.2)	17 (2.4)
Median	17	17	17
Q1, Q3	16, 18	16, 18	16, 18
Min, max	10, 32	12, 25	10, 32
SARS-CoV-2 viral load - nasopharyngeal (log_{10} copies/mL)			
N	240	238	478
Mean (SD)	5.95 (1.962)	5.92 (1.987)	5.94 (1.973)
Median	6.22	6.26	6.26
Q1, Q3	4.25, 7.50	4.08, 7.56	4.14, 7.55
Min, max	2.87, 10.56	2.87, 9.99	2.87, 10.56
SARS-CoV-2 viral load – nasopharyngeal categories (log_{10} copies/mL)			
< 6.26 (median)	121 (50.4%)	118 (49.6%)	239 (50.0%)
≥ 6.26 (median)	119 (49.6%)	120 (50.4%)	239 (50.0%)
Missing	39	45	84

ALT = alanine aminotransferase; AST = aspartate aminotransferase; IV = intravenous; max = maximum; min = minimum; RDV = remdesivir (GS-5734™); Q1 = first quartile; Q3 = third quartile; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2
Participants with results of "No SARS-CoV-2 Detected" were included in the SARS-CoV-2 Viral Load summaries for Safety Analysis Set.
Source: Table 15.8.3.2.1

The overall baseline COVID-19 Symptoms severity according to the COVID−19 Adapted FLU-PRO Plus Questionnaire is shown in the table below.

Table 37: GS-US-540-9012: Overall Baseline COVID-19 Symptoms according to the COVID−19 Adapted FLU-PRO Plus Questionnaire (Safety Analysis Set)

	RDV IV for 3 Days (N = 279)	Placebo (N = 283)	Total (N = 562)
Overall, how severe were your symptoms today, n (%)			
N	66	61	127
0 = No symptoms today	2 (3%)	0	2 (1.6%)
1 = Mild	25 (37.9%)	24 (39.3%)	49 (38.6%)
2 = Moderate	35 (53.0%)	29 (47.5%)	64 (50.4%)
3 = Severe	3 (4.5%)	7 (11.5%)	10 (7.9%)
4 = Very severe	1 (1.5%)	1 (1.6%)	2 (1.6%)
In general, how would you rate your physical health today, n (%)			
N	66	61	127
0 = Poor	15 (22.7%)	14 (23.0%)	29 (22.8%)
1 = Fair	33 (50.0%)	29 (47.5%)	62 (48.8%)
2 = Good	16 (24.2%)	14 (23.0%)	30 (23.6%)
3 = Very good	2 (3.0%)	4 (6.6%)	6 (4.7%)
4 = Excellent	0	0	0
Have you returned to your usual activities today, n (%)			
N	66	61	127
0 = No	60 (90.9%)	58 (95.1%)	118 (92.9%)
1 = Yes	6 (9.1%)	3 (4.9%)	9 (7.1%)

COVID-19 = coronavirus disease 2019; FLU-PRO = InFLUenza Patient-Reported Outcome; IV = intravenous; RDV = remdesivir (GS-5734™)
Source: Table 15.8.3.2.5

Numbers analysed

Data from 562 patients were analysed (FAS). According to the protocol, the FAS ITT-population was the primary analysis set.

Table 38: GS-US-540-9012: Analysis Sets (All Randomized Analysis Set)

Analysis Set, n (%)	RDV IV for 3 Days	Placebo	Total
All Randomized Analysis Set	292	292	584
Safety Analysis Set	279 (95.5%)	283 (96.9%)	562 (96.2%)
Full Analysis Set (FAS)	279 (95.5%)	283 (96.9%)	562 (96.2%)
Modified Full Analysis Set (mFAS)	246 (84.2%)	252 (86.3%)	498 (85.3%)
Virology Analysis Set	217 (74.3%)	214 (73.3%)	431 (73.8%)
Remdesivir PK Analysis Set	148 (50.7%)	0	148 (25.3%)
GS-704277 PK Analysis Set	148 (50.7%)	0	148 (25.3%)
GS-441524 PK Analysis Set	148 (50.7%)	0	148 (25.3%)
Remdesivir Intensive PK Analysis Set	7 (2.4%)	0	7 (1.2%)
GS-704277 Intensive PK Analysis Set	7 (2.4%)	0	7 (1.2%)
GS-441524 Intensive PK Analysis Set	7 (2.4%)	0	7 (1.2%)

IV = intravenous; PK = pharmacokinetic; RDV = remdesivir (GS-5734™)
The denominator for percentage was the number of participants in the All Randomized Analysis Set.
Participants in the Safety Analysis Set were summarized according to actual treatment received.
Source: Table 15.8.4

Outcomes and estimation

Primary Efficacy Endpoint:

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

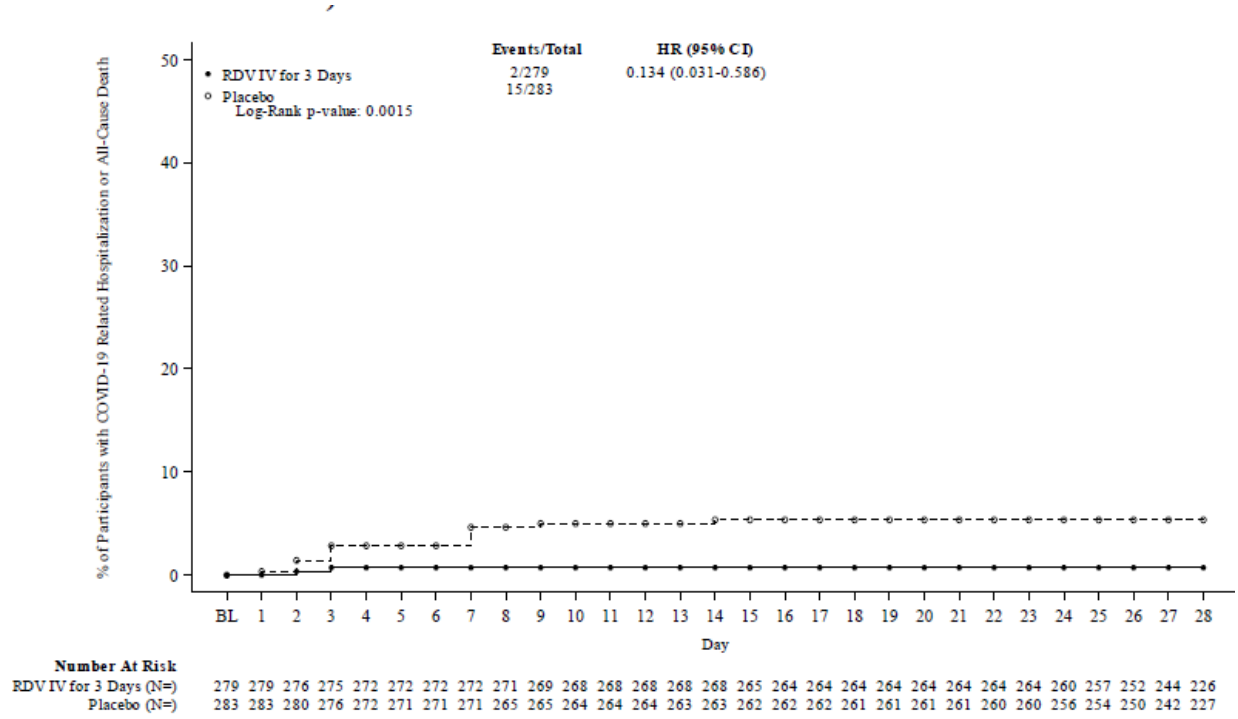
The analysis of the proportion of COVID-19-related hospitalization or all-cause death by day 28 is shown in the table below.

Table 39: Analysis of Proportion of COVID-19-related Hospitalization or All-Cause Death by Day 28 Using Cox Model with Covariates (Full Analysis Set)

	RDV IV for 3 Days (N = 279)	Placebo (N = 283)
Total participants with COVID-19-related hospitalization or all-cause death, n (%)	2 (0.7%)	15 (5.4%)
Hazard ratio for RDV vs placebo	0.134	
95% CI for hazard ratio	(0.031, 0.586)	
P value for hazard ratio	0.0076	

COVID-19 = coronavirus disease 2019; IV = intravenous; RDV = remdesivir (GS-5734™)
Proportion of COVID-19-related hospitalization or all-cause death by Day 28 from Kaplan-Meier estimate.
Hazard ratio, 2-sided 95% CI and *P* value were estimated using the Cox regression with baseline stratification factors as covariates.
Hazard ratio was adjusted for baseline stratification factors.
Source: Table 15.9.1.1

Kaplan-Meier estimate of time to COVID-19-related hospitalization or all-cause death (FAS) is shown in the figure below.



BL = baseline; COVID-19 = coronavirus disease 2019; IV = intravenous; RDV = remdesivir (GS-5734™)
Participants who did not die or whose hospitalization status were no or missing were censored at last study day or Day 28, whichever was earlier.
N represents the number of participants at risk at the beginning of the interval.
P value was based on stratified log-rank test with baseline stratification factor as strata.
Source: Figure 15.9.1.1

Figure 15: Kaplan-Meier estimate of time to COVID-19-related Hospitalization or All-Cause Death (Full Analysis Set)

Secondary efficacy endpoints:

Composite endpoint of COVID-19-related MAVs or all-cause death by day 28

The analysis of proportion of COVID-19-related MAVs or All-Cause death by Day 28 using Cox Model with Covariates (Modified Full Analysis Set) is shown below.

Table 40: Analysis of proportion of COVID-19-related MAVs or All-Cause death by Day 28 using Cox Model with Covariates (Modified Full Analysis Set)

	RDV IV for 3 Days (N = 246)	Placebo (N = 252)
Total participants with COVID-19 related MAVs or all-cause death, n (%)	4 (1.7%)	21 (8.5%)
Hazard ratio for RDV vs placebo	0.191	
95% CI for hazard ratio	(0.065, 0.555)	
P value for hazard ratio	0.0024	

COVID-19 = coronavirus disease 2019; IV = intravenous; MAV = medically-attended visit; RDV = remdesivir (GS-5734™)
Proportion of COVID-19-related MAVs or all-cause death by Day 28 from Kaplan-Meier estimate.
Hazard ratio, 2-sided 95% CI and *P* value were estimated using the Cox regression with baseline stratification factors as covariates.
Hazard ratio was adjusted for baseline stratification factors.
Source: Table 15.9.2.2

All-Cause mortality by day 28

No participant in either treatment group had all-cause mortality by Day 28.

Proportion of participants hospitalized by Day 28

Two of the 279 patients (0.7%) in the remdesivir group and 15 of the 283 patients (5.4%) in the placebo group were hospitalizations by Day 28 due to COVID-19 (P = 0.0015; Kaplan-Meier estimate; stratified log-rank test using FAS).

Composite endpoint of COVID-19-related hospitalization or all-cause death by Day 14

Results of the composite endpoint of COVID-19-related hospitalization or all-cause death by Day 14 for the FAS is shown in the table below.

Table 41: composite endpoint of COVID-19-related hospitalization or all-cause death by Day 14 for the FAS

	RDV IV for 3 Days (N = 279)	Placebo (N = 283)
Total participants with COVID-19 related hospitalization or all-cause death, n (%)	2 (0.7%)	15 (5.4%)
Hazard ratio for RDV vs placebo	0.134	
95% CI for hazard ratio	(0.031, 0.586)	
P value for hazard ratio	0.0076	

COVID-19 = coronavirus disease 2019; IV = intravenous; RDV = remdesivir (GS-5734™)
Proportion of COVID-19-related hospitalization or all-cause death by Day 14 from Kaplan-Meier estimate.
Hazard ratio, 2-sided 95% CI and *P* value were estimated using the Cox regression with baseline stratification factors as covariates.
Hazard ratio was adjusted for baseline stratification factors.
Source: Table 15.9.2.1

Composite endpoint of COVID-19-related MAVs or all-cause death by day 14

Results of the composite endpoint of COVID-19-related MAVs or all-cause death by Day 14 for the mFAS are shown below.

Table 42: Composite endpoint of COVID-19-related MAVs or all-cause death by Day 14 (mFAS)

	RDV IV for 3 Days (N = 246)	Placebo (N = 252)
Total participants with COVID-19 related MAVs or all-cause death, n (%)	2 (0.8%)	20 (8.0%)
Hazard ratio for RDV vs placebo	0.100	
95% CI for hazard ratio	(0.023, 0.430)	
P value for hazard ratio	0.0019	

COVID-19 = coronavirus disease 2019; IV = intravenous; MAV = medically-attended visit; RDV = remdesivir (GS-5734™)
Proportion of COVID-19-related MAVs or all-cause death by Day 14 from Kaplan-Meier estimate.
Hazard ratio, 2-sided 95% CI and *P* value were estimated using the Cox regression with baseline stratification factors as covariates.
Hazard ratio was adjusted for baseline stratification factors.
Source: Table 15.9.2.3

Time-weighted average change from baseline to Day 7 (DAVG7) in SARS-CoV-2 viral load

Time-Weighted average change from baseline to Day 7 (DAVG7) in nasopharyngeal SARS-CoV-2 viral load for the Virology Analysis Set is shown in Table 42 and the mean change from Baseline in nasopharyngeal SARS-CoV-2 viral load by Visit for the virology Analysis Set is shown in the figure below.

Table 43: Time-Weighted average change from baseline to Day 7 (DAVG7) in nasopharyngeal SARS-CoV-2 viral load for the Virology Analysis Set

	RDV IV for 3 Days (N = 217)	**Placebo (N = 214)**
Time-weighted average change from baseline to Day 7 (log_{10} copies/mL)		
N	211	208
Mean (SD)	−1.24 (1.123)	−1.14 (1.099)
Median	−1.15	−1.11
Q1, Q3	−2.01, −0.54	−1.82, −0.41
Min, max	−4.60, 1.96	−3.56, 2.81
LS mean (SE)	−1.22 (0.06)	−1.16 (0.06)
95% CI	(−1.35, −1.10)	(−1.28, −1.03)
Difference by Day 7 (log_{10} copies/mL)		
LS mean (SE)	0.07 (0.09)	
95% CI	(−0.10, 0.24)	
P value	0.4318	

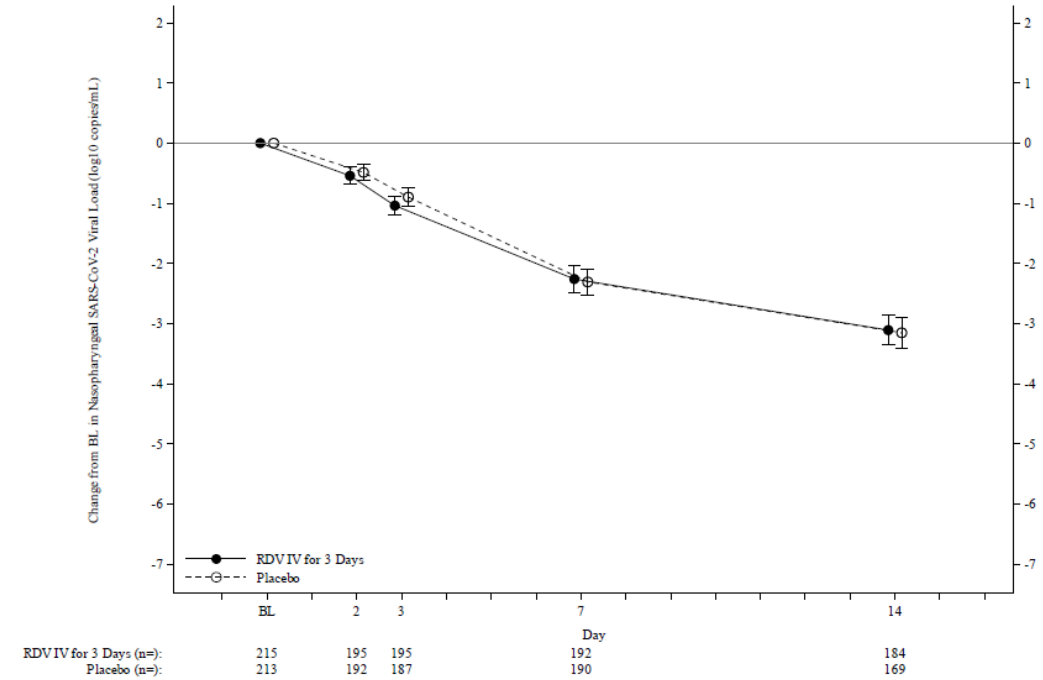
ANCOVA = analysis of covariance; $DAVG_7$ = time-weighted average change from baseline to Study Day 7; IV = intravenously; LS = least squares; max = maximum; min = minimum; RDV = remdesivir (GS-5734™); SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

The $DAVG_7$ in SARS-CoV-2 viral load (log_{10} copies/mL) was defined as the time-weighted average between the first postbaseline value through the last available value up to Day 7 minus the baseline value in SARS-CoV-2 viral load (log_{10} copies/mL). $DAVG_7$ was calculated using the trapezoidal rule and the AUC.

For participants with data through days prior to Day 7, the time-weighted average change used data up to last available time point. If there was no postbaseline data, the participant was excluded from the analysis.

LS Mean (SE), 95% CI, and *P* value were from an ANCOVA model with baseline viral load as a covariate.

Source: Table 15.9.2.10



BL = baseline; IV = intravenous; RDV = remdesivir (GS-5734™); SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2
Source: Figure 15.9.5

Figure 16: Mean (95% CI) Change from Baseline in nasopharyngeal SARS-CoV-2 viral load by Visit (Virology Analysis Set)

Time to alleviation of baseline COVID-19 symptoms on COVID-19-adapted FLU-PRO Plus Questionnaire

Overall, 126 participants (i.e., 22% of the treated population; 66 participants in the RDV IV for 3 days group and 60 participants in the placebo group) had baseline COVID-19-adapted FLU-PRO Plus questionnaire data documented prior to the first dosing time.

Kaplan-Meier estimate of time to alleviation (Mild or Absent) for those patients for whom baseline symptoms in COVID-19 Adapted FLU-PRO Questionnaire data was available is shown in the figure below.

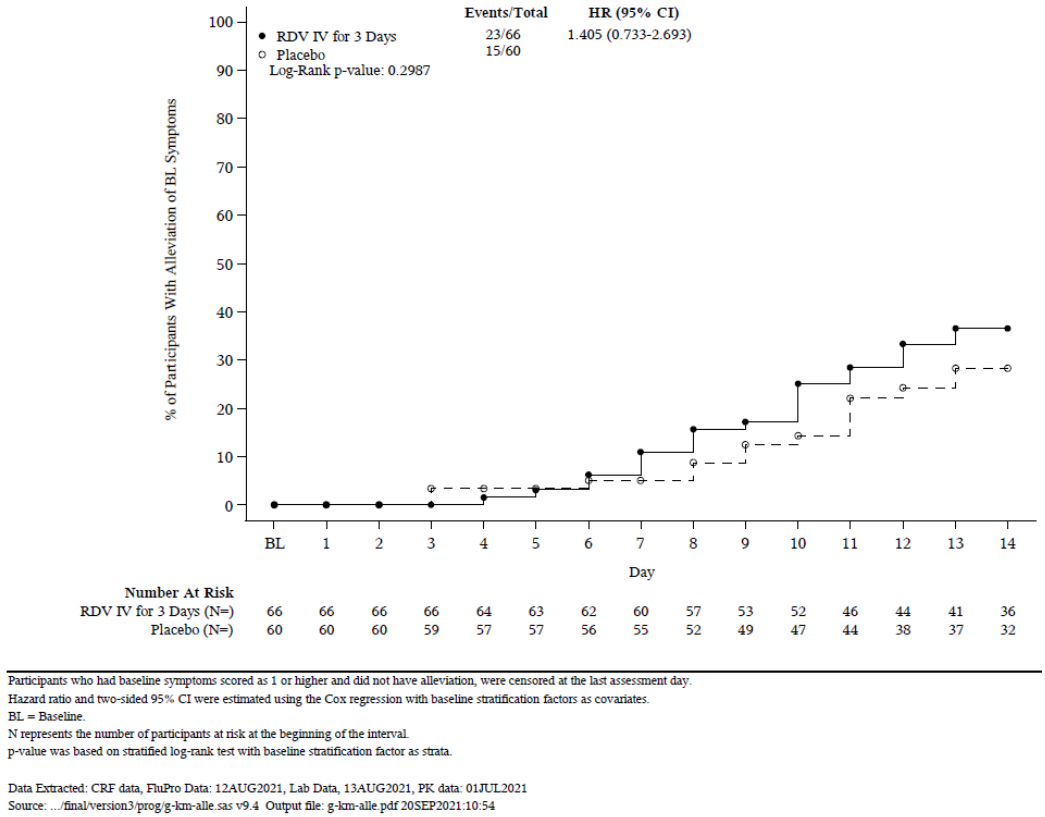


Figure 17: Kaplan-Meier Estimate of Time to Alleviation (Mild or Absent) of Baseline Symptoms in COVID-19 Adapted FLU-PRO Questionnaire (FAS)

Proportion of participants with worsening after alleviation of baseline COVID-19 symptoms on COVID-19-adapted FLU-PRO Plus questionnaire

The proportion of participants with worsening after alleviation (mild or absent) of baseline COVID-19 symptoms was reported in 7 of 23 participants (30.4%) in the RDV IV for 3 days group and 5 of 15 participants (13.3%) in the placebo group.

Proportion of participants requiring oxygen supplementation by day 28

The proportion of participants requiring oxygen supplementation as reported at each study visit by Day 28 or prior to study discontinuation was 1 of 279 participants (0.4%) in the RDV IV for 3 days group and 5 of 283 participants (1.8%) in the placebo group (P = 0.2163). One additional participant in the placebo group required mechanical ventilation at Day 16.

Ancillary analyses

Subgroup analyses of composite endpoint of COVID-19-related hospitalization or all-cause death by Day 28

Region

In the US, COVID-19-related hospitalizations or all-cause death by Day 28 were reported for 2 of 264 participants (0.8%) in the RDV IV for 3 days group and 12 of 267 participants (4.6%) in the placebo group (HR: 0.170; 95% CI: 0.038 to 0.758, based on Cox regression; P = 0.0202; Cox model using FAS).

In the Ex-US, there were only 15 participants enrolled in the RDV IV for 3 days group and 16 participants enrolled in the placebo group, of whom 3 participants (18.8%) in the placebo group had COVID-19-related hospitalization or all-cause death by Day 28.

Age

COVID-19-related hospitalizations or all-cause death by Day 28 in participants ≥ 60 years of age were reported for 1 of 83 participants (1.2%) in the RDV IV for 3 days group and 9 of 87 participants (10.3%) in the placebo group (HR: 0.109; 95% CI: 0.014 to 0.863, based on Cox regression; P = 0.0358; Cox model using FAS).

No statistically significant effect was seen in participants ≥ 18 to < 60 years of age. COVID-19-related hospitalizations or all-cause death by Day 28 were reported for 1 of 193 participants (0.5%) in the RDV IV for 3 days group and 6 of 191 participants (3.2%) in the placebo group (P = 0.0924).

Skilled Nursing Facility

Only 15 participants were residents of a skilled nursing facility, of whom none had COVID−19−related hospitalization or all-cause death by Day 28.

Race

No statistically significant between-group differences were observed for the primary efficacy endpoint in the race subgroups.

Sex

COVID-19-related hospitalizations or all-cause death by Day 28 in male patients were reported for 1 of 148 participants (0.7%) in the RDV group and 9 of 145 participants (6.4%) in the placebo group (HR: 0.107; 95% CI: 0.014 to 0.844, based on Cox regression; P = 0.0339; Cox model using FAS).

For female participants, COVID-19-related hospitalizations or all-cause death by Day 28 were reported for 1 of 131 participants (0.8%) in the RDV IV for 3 days group and 6 of 138 participants (4.3%) in the placebo group (P = 0.1038).

Baseline risk factors

The following subgroups treated with RDV IV for 3 days had statistically significant reductions in the primary endpoint compared with placebo: hypertension, diabetes mellitus, and obesity.

Table 44: GS-US-540-9012: Analysis of proportion of COVID-19 related hospitalisation or all-cause death by day 28 using Cox model with covariate by baseline risk factor (FAS)

	Yes		No	
Baseline Risk Factor	**RDV IV for 3 Days**	**Placebo**	**RDV IV for 3 Days**	**Placebo**
Chronic lung disease (N)	67	68	212	215
Total participants with COVID-19 related HO or all-cause death, n (%)	0	4 (5.9%)	2 (1.0%)	11 (5.2%)
Hazard ratio (95% CI) for RDV vs placebo	NA (0.000, NA)		0.182 (0.040, 0.822)	
P value for hazard ratio	0.9968		0.0267	
Hypertension (N)	138	130	141	153
Total participants with COVID-19 related HO or all-cause death, n (%)	2 (1.5%)	10 (7.8%)	0	5 (3.3%)
Hazard ratio (95% CI) for RDV vs placebo	0.165 (0.036, 0.760)		NA (0.000, NA)	
P value for hazard ratio	0.0208		0.9947	
Cardiovascular or cerebrovascular disease (N)	20	24	259	259
Total participants with COVID-19 related HO or all-cause death, n (%)	0	2 (8.3%)	2 (0.8%)	13 (5.1%)
Hazard ratio (95% CI) for RDV vs placebo	NA (0.000, NA)		0.162 (0.037, 0.719)	
P value for hazard ratio	0.9978		0.0167	
Diabetes mellitus (N)	173	173	106	110
Total participants with COVID-19 related HO or all-cause death, n (%)	2 (1.2%)	14 (8.2%)	0	1 (0.9%)
Hazard ratio (95% CI) for RDV vs placebo	0.142 (0.032, 0.627)		NA (0.000, NA)	
P value for hazard ratio	0.0099		0.9990	
Obesity (N)	154	156	122	127
Total participants with COVID-19 related HO or all-cause death, n (%)	1 (0.7%)	9 (5.8%)	1 (0.8%)	6 (4.8%)
Hazard ratio (95% CI) for RDV vs placebo	0.112 (0.014, 0.882)		0.184 (0.022, 1.527)	
P value for hazard ratio	0.0376		0.1168	
Immunocompromised state (N)	14	9	265	274
Total participants with COVID-19 related HO or all-cause death, n (%)	0	0	2 (0.8%)	15 (5.5%)
Hazard ratio (95% CI) for RDV vs placebo	NA (NA)		0.138 (0.032, 0.605)	
P value for hazard ratio	NA		0.0086	
Chronic mild or moderate kidney disease (N)	7	11	272	272
Total participants with COVID-19 related HO or all-cause death, n (%)	1 (14.3%)	1 (9.1%)	1 (0.4%)	14 (5.2%)
Hazard ratio (95% CI) for RDV vs placebo	1.414 (0.088, 22.637)		0.070 (0.009, 0.536)	
P value for hazard ratio	0.8065		0.0104	
Current cancer (N)	12	18	267	265
Total participants with COVID-19 related HO or all-cause death, n (%)	0	2 (11.1%)	2 (0.8%)	13 (5.0%)
Hazard ratio (95% CI) for RDV vs placebo	NA (0.000, NA)		0.150 (0.034, 0.666)	
P value for hazard ratio	0.9979		0.0126	

COVID-19 = coronavirus disease 2019; HO = hospitalization; IV = intravenous; NA = not applicable; RDV = remdesivir (GS-5734™)
Proportion of COVID-19-related hospitalization or all-cause death by Day 28 from Kaplan-Meier estimate.
Hazard ratio, 2-sided 95% CI, and *P* value were estimated using the Cox regression with baseline stratification factors as covariates.
Hazard ratio was adjusted for baseline stratification factors.
Source: Table 15.9.1.7

Common COVID-19 symptoms at baseline

One event of COVID-19-related hospitalization or all-cause death by Day 28 in each treatment group was reported in participants with common COVID-19 symptoms at baseline (i.e., absence or presence of stuffy/runny nose, sore throat, shortness of breath, cough, low energy/tiredness, muscle/body aches, headache, chills or shivering, feeling hot/feverish, nausea, diarrhoea, or smell).

Ethnicity

A post hoc analysis of the primary endpoint by ethnicity was conducted. In non-Hispanic or Latino participants, COVID-19-related hospitalization or all-cause death by Day 28 was reported for 2 of 146 participants (1.4%) in the RDV group and 8 of 158 participants (5.1%) in the placebo group (P = 0.0876; Cox model using FAS).

For Hispanic or Latino participants, COVID-19-related hospitalization or all-cause death by Day 28 was reported for none of the 123 participants in the RDV group and 6 of 112 participants (5.4%) in the placebo group (P = 0.9938).

Subgroup analyses for non-residents of a skilled nursing facility by healthcare setting

The subgroup efficacy analyses for non-residents of a skilled nursing facility by healthcare setting (home healthcare [participants who were treated at home] and outpatient facility [participants who were treated in an outpatient facility]) are shown below.

Table 45: Subgroup efficacy analysis by healthcare setting (FAS; Non-resident of Skilled Nursing Facility)

	Home Healthcare		Outpatient Facility	
	RDV IV for 3 Days	Placebo	RDV IV for 3 Days	Placebo
COVID-19 related hospitalization or all-cause death by Day 28 (N)	44	49	227	228
Total participants with COVID-19-related hospitalization or all-cause death, n (%)	1 (2.3%)	2 (4.1%)	1 (0.4%)	13 (5.7%)
Proportion of participants with COVID-19-related hospitalization or all-cause death from Kaplan-Meier estimate, %	2.3%	4.1%	0.4%	5.8%
Hazard ratio (95% CI) for RDV vs placebo	0.628 (0.057, 6.958)		0.078 (0.010, 0.600)	
P value for hazard ratio	0.7048		0.0142	
COVID-19 related MAVs or all-cause death by Day 28 (N)	31	44	207	203
Total participants with COVID-19-related MAVs or all-cause death, n (%)	0	3 (6.8%)	4 (1.9%)	18 (8.9%)
Proportion of participants with COVID-19-related MAVs or all-cause death from Kaplan-Meier estimate, %	0	6.8%	2.0%	9.0%
Hazard ratio (95% CI) for RDV vs placebo	NA (0.000, NA)		0.210 (0.071, 0.622)	
P value for hazard ratio	0.9973		0.0048	
All-cause hospitalization by Day 28 (N)	44	49	227	228
Total participants with COVID-19-related hospitalization, n (%)	1 (2.3%)	2 (4.1%)	4 (1.8%)	16 (7.0%)
Proportion of participants with COVID-19-related hospitalization from Kaplan-Meier estimate, %	2.3%	4.1%	1.8%	7.2%
Hazard ratio (95% CI) for RDV vs placebo	0.628 (0.057, 6.958)		0.249 (0.083, 0.746)	
P value for hazard ratio	0.7048		0.0130	

CI = confidence interval; COVID-19 = coronavirus disease 2019; IV = intravenous; MAV = medically-attended visit; NA = not applicable; RDV = remdesivir
Proportion of COVID-19-related hospitalizations or all-cause death by Day 28, COVID-19-related MAVs or all-cause death by Day 28, and all-cause hospitalizations by Day 28 from Kaplan-Meier estimate.
COVID-19-related MAV analyses were conducted using the modified Full Analysis Set.
One resident of a skilled nursing facility who had 1 dose of study treatment at home is included in the home healthcare subgroup.
Hazard ratio, 2-sided 95% CI, and *P* value were estimated using the Cox regression with baseline stratification factors as covariates.
Hazard ratio was adjusted for baseline stratification factors.
Source: Tables req13202.12 through req13202.14

Exploratory Efficacy Endpoints

Time to alleviation of baseline symptoms in each domain of the COVID-19-adapted FLU-PRO Plus questionnaire

The time to alleviation (mild or absent) of baseline COVID-19 symptoms through Day 14 on the COVID-19-adapted FLU-PRO Plus questionnaire was presented for the nose, throat, eyes, chest/respiratory, gastrointestinal, body/systemic, and sense domains. No significant effect between the treatment group was observed.

Change from baseline in COVID-19-adapted FLU-PRO Plus questionnaire total score and score in each domain

A similar mean decrease from baseline in total score of the COVID-19-adapted FLU-PRO Plus questionnaire through Day 14, in both treatment groups.

Time-weighted average change from baseline to Day 14 (DAVG14) in SARS-CoV-2 viral load

No statistically significant difference between the RDV group and the placebo group for DAVG14 in nasopharyngeal SARS-CoV-2 viral load was seen (least-squares [LS] mean difference 0.07 log10 copies/mL, 95% CI: −0.10 to 0.23).

Time to negative SARS-CoV-2 PCR

The Median (Q1, Q3) time to negative SARS-CoV-2 PCR (viral load) was 15 days in both treatment groups (RDV: 15.0 (14.0, 19.0); Placebo: 15.0 (14.0, 45.0); p = 0.1062; Kaplan-Meier estimate using Virology Analysis Set).

Proportion of participants with negative SARS-CoV-2 PCR at each study visit

At day 7, 31 of 201 participants (15.4%) in the RDV group and 25 of 195 participants (12.8%) in the placebo group at had a negative nasopharyngeal SARS-CoV-2 PCR (viral load) (P = 0.4744; Fisher exact test using Virology Analysis Set). At day 14, 85 of 191 participants (44.5%) in the RDV IV for 3 days group and 67 of 178 participants (37.6%) in the placebo group had a negative SARS-CoV-2 PCR (P = 0.2043).

Change from baseline in SARS-CoV-2 viral load

Mean changes from baseline in nasopharyngeal SARS-CoV-2 viral load were similar between the treatment groups at all time points. At Day 14, the mean (SD) change from baseline was −3.11 (1.713) log10 copies/mL in the RDV IV for 3 days group and −3.15 (1.741) log10 copies/mL in the placebo group.

Proportion of Participants on Mechanical Ventilation by Day 28

One participant in the placebo group required mechanical ventilation at Day 16; this participant died at Day 59.

Proportion of participants with COVID-19-related MAVs by Day 28

COVID-19-related MAVs by Day 28 were reported for 4 of 246 participants (1.7%) in the remdesivir IV for 3 days group and 21 of 252 participants (8.5%) in the placebo group (P = 0.0006; Kaplan-Meier estimate using mFAS)**.**

All-cause hospitalization by Day 28

A post hoc analysis evaluating all-cause hospitalization by Day 28 was conducted for the FAS population.

All-cause hospitalization by Day 28 was reported for 5 of 279 participants (1.8%) in the remdesivir IV for 3 days group and 18 of 283 participants (6.5%) in the placebo group (P = 0.0116; Cox model using FAS), resulting in a 72% reduction in all-cause hospitalization by Day 28 with RDV compared with placebo.

Virologic resistance analysis

The virologic resistance analysis will be conducted based on the Virology Analysis Plan and will be provided as a separate report (PAM)**.**

PHARMACOKINETIC AND PHARMACODYNAMIC EVALUATION

Due to limited intensive PK results (i.e., in 7 evaluable participants), PK data will be analysed using population PK modelling and will be summarized in a separate report.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Study GS-US-540-5774:

The GS-US-540-5774 study is a randomized, open-label, multi-centre study of two RDV regimens (5-days and 10 days) versus standard of care (SOC) therapy in 584 adult and adolescent patients with moderate COVID-19. The primary endpoint was clinical status at D11. The analysis population included 584 patients (5-day: 191 patients; 10 day: 193 patients, SOC: 200 patients).

In total, 16% of the enrolled study participants did not have mild/moderate disease at baseline. According to the MAH this was due to the rapidly deteriorating clinical status from the screening visit or for breathing comfort. Nevertheless, to adequately reflect efficacy in the applied indication a sensitivity analysis excluding patients who had any type of oxygen support at baseline were requested.

There were considerable concerns about the GCP-compliant conduct of study GS-US-540-5774. The design and outcomes of the study is prone to serious criticism, due to essential methodological deficiencies and the open-label design with an endpoint allowing for a considerable degree of subjectivity. The last version of the SAP was finalized late while the study was ongoing (perhaps in knowledge of the data). Central elements of the statistical analysis were changed in the SAP, including the primary analysis, the strategy for adjustment for multiplicity and the method for handling missing data, questioning the statistical significance reported. In particular, the method for handling missing data proved to be critical for the conclusions from the analysis regarding statistical significance and size of the treatment effect, whereby the LOCF analysis that was specified as primary in the SAP is prone to bias and not considered conservative.

In addition, the high amount of important protocol deviations, issues related to the monitoring plan and the change of the exclusion criteria late during the study course perhaps in knowledge of several deviations related to the specific exclusion criteria question the GCP-compliance and integrity of this study and may have biased the study results. Based on these findings, a GCP-inspection of study GS-US-540-5774 was considered warranted in case a positive benefit/risk of RDV in patients with mild/moderate disease is decided by CHMP**.** However, as CHMP concluded that study GS-US-540-5774 does not provide robust statistical evidence of clinical efficacy and prevents any conclusion on the benefit of remdesivir in mild/moderate disease, due to essential methodological deficiencies a GCP inspection was no longer considered necessary.

NIAID-ACTT-1 study (GS-US-540-5776):

The NIAID-ACTT-1 (GS-US 540 5776) study is a randomised, double-blinded and placebo-controlled study conducted in hospitalised patients with COVID-19, with evidence of lower respiratory tract involvement. Treatment with remdesivir/placebo was for up to 10 days. The primary endpoint was the time to recovery (defined as no longer being hospitalised or being hospitalised but no longer requiring medical care). The analysis population included 1062 patients (541 in the remdesivir group and 521 in the placebo group). In addition, 159 patients were stratified to the mild/moderate disease stratum and included in the respective analyses.

According to the final CSR of the NIAID study, incorrect numbers of patients with mild/moderate disease (105 instead of 159) and baseline ordinal score of 4 (138 instead of 100) were used in the clinical efficacy analyses provided in the clinical overview submitted for this procedure. This could have impacted the outcome of the presented data. Hence, new analyses were requested. The reason for the divergent numbers is considered related to the high number of mis-randomisation (patients randomised to the severe disease stratum, but had an ordinal score of 4), which was accounted for in hindsight. Therefore,

the data presentation for patients randomised to the mild/moderate disease stratum who had baseline ordinal scale of 4 is considered the important one.

There are considerable concerns about the GCP compliant conduct of the NIAID-ACTT-1 study with potential impact on the integrity of the study data. These concerns are related to the data management and statistics, to contracts and responsibility and to the DSMB and primary endpoint. Data managements and statistics issues identified related to changes in statistical methods/endpoints during and after the study, in particular changes made prior to breaking the blind and/or unscheduled statistical analysis. The complex organisational and administrative structure might have contributed to potentially heterogenic data that might compromise the quality of data and the reliability of the results. Furthermore, study design issues and potentially inadequate measures to prevent unblinding were identified concerning traceability of when, how and by whom and based on what data primary endpoint adjustments and changes were decided.

However, as CHMP concluded again that the mild/moderate stratum in study GS-US-540-5776 was too small to be able to show any significant evidence of clinical efficacy in the mild/moderate stratum independently, a GCP inspection was no longer considered necessary.

Study GS-US-540-9012

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

Study GS-US-540-9012 was conducted in an outpatient setting, hence the enrolled population does not cover the indication initially applied for in this procedure, i.e. patients with moderate COVID-19. Furthermore, a different treatment duration was used in study 9012, compared to studies 5774 and the NIAID ACTT-1 trial, i.e. three days of remdesivir treatment instead of the approved five days to up to ten days. Further justification of the shorter treatment duration was requested. Based on the lack of comparative data between the different treatment durations, the lack of antiviral activity and the missing virology data to support the shorter 3-day treatment duration hamper a conclusion if the shorter treatment duration is sufficient, especially in immunocompromised patients with prolonged viral shedding. Therefore, a warning should be included in section 4.4 of the SmPC.

remdesivir infusion in study 9012 was administered to the participants either at the clinical study site, at the participant’s home by a home health service provider or at skilled nursing facilities. However, no information on the administration of IV remdesivir in the different outpatient settings was provided. In order to understand the potential risk and benefits of remdesivir infusion in the different settings further information was requested. In view of the observed rates of adverse events and high rate of important protocol deviations in the outpatient setting, additional wording in the product information concerning the monitoring of patients receiving remdesivir infusion in the outpatient setting is considered necessary and therefore this is added in section 4.2.

No vaccinated patients were enrolled in study 9012.

As observed in other pivotal studies investigating antivirals, the serostatus at baseline could be important factor for response. Information on serostatus at baseline was requested. However, no information on the

baseline serostatus is currently available. The lack of data should be stated in section 4.4 of the SmPC until further data becomes available.

The Danish Medicines agency inspected one clinical site in Denmark and no significant issues in regard to patients' safety, rights or well-being or on data integrity have been reported.

Essential data including the monitoring plan and the study drug administration protocol were submitted upon request.

The study was initially designed to enrol approximately 1264 participants with confirmed symptomatic COVID-19 infection who were at risk for disease progression. However, enrolment was halted on 08 April 2021 after 584 participants (292 in the RDV IV for 3 days group and 292 in the placebo group) were randomized. The reasons for stopping enrolment were administrative, including rapidly declining COVID-19 case rates, increasing availability of single-infusion monoclonal antibodies as an alternative to placebo, and increasing vaccination rates among high-risk patients during the study. The planned interim database lock and subsequent DMC review was not conducted. Double-blind was according to MAH maintained until data finalization, and therefore the alpha value of 0.05 remained valid for final data interpretation. As the study was still full blinded when it was decided to stop enrolment pre-maturely, it can still be interpreted in a confirmatory way. The SAP was finalised one after database lock, which was on 13 August 2021. The SAP is dated 3 months after the last observation for the primary endpoint, which is quite long.

Efficacy data and additional analyses

Study GS-US-540-5774:

Study GS-US-5774 failed to show superiority of the 10-day RDV treatment compared to SOC, and also to 5-day RDV. On the contrary, the data indicate 5 days may be more beneficial than 10 days.

For the primary endpoint clinical status at Day 11, a statistically significant difference in the distribution in clinical status at Day 11 for participants receiving a 5-day course of RDV compared with those receiving SOC alone was found (p=0.017). Although the proportional odds model is a suitable approach for testing the null hypothesis of a difference between distributions of clinical status at day 11, the resulting odds ratio is difficult to interpret in terms of clinical relevance. However, it seems uncertain whether the observed difference can be considered convincing enough to discount for a potential bias due to essential methodological deficiencies, the study being open label and the outcome encompassing a considerable degree of subjectivity. In an open-label study the only meaningful objective endpoint would be mortality, which is, however, in view of the patient population not feasible, as it would require a very large sample size to power the study accordingly. Notwithstanding the degree of subjectivity, in a pandemic situation another meaningful endpoint with respect to health system resources could be the length of the hospital stay. However, the results do not indicate a positive effect of RDV here (5-day RDV: 8 days, 10-day RDV: 9 days; SOC: 8 days).

As long as there is no plausible reason why a 10-day course of RDV leads to worse outcomes than a 5-day course, the failure to show a significant difference of the 10-day course vs SOC also means that there is no "internal replication", raising additional concerns on the internal validity of the finding for the 5-day RDV course. Especially, when considering that imbalances concerning a shorter duration of symptom onset in favour of the 10-Day group where seen. Thereby, it needs also to be considered that 62% of patients in the 10-day RDV group actually discontinued treatment before 10 days. Potential baseline imbalances do not account for this finding, as results between the two RDV groups do not differ for any of the reported endpoints on day 11**.**

Furthermore, as the proportion of missing data was larger for the SOC group than the RDV 5-day group (n=19, 9.5% vs n=9, 4.7%), the last assessment carried forward approach that was applied for missing

data according to SAP may be anti-conservative (as patients tend to improve with time in this patient population).

The analysis excluding patients with missing data, which was the analysis specified in the protocol, did not find a statistically significant difference (and this is not only explained by loss of power due to a smaller sample size but by distributions being more similar). The MAH conducted additional sensitivity analyses with alternative missing data imputation methods with a MAR or MNAR assumption. These show substantially lower treatment effects in terms of OR (1.26 instead of 1.65) and p-values of ~0.04 that are not statistically significant according to the Bonferroni-corrected significance level of 0.025 (in contrast to the applicant's claim that handling of missing data has a minimal influence). Therefore, the conclusion of a statistical significance in favour of 5-day RDV vs SOC is critically dependent on the way missing data are handled. This is a critical issue as the SAP was seemingly finalized after all patients had completed part A of this open-label study. Even if the issue of conflicting definitions of missing data handling in the SAP and the protocol would be ignored and the SAP-defined analysis would be accepted as primary, the finding of a statistically significant difference of 5-day RDV vs SOC and the treatment effect estimate cannot be considered as robust.

For the interpretation of the findings for secondary outcomes, it needs to be taken into account that a large number of secondary endpoints was analyzed without any hierarchy such that claims regarding 'significance' of single outcomes need to be interpreted with care. In addition, for the endpoints regarding the improvement/worsening of 1 or 2 points on the ordinal scale, it should be considered that these are generally difficult to interpret because differences between categories of the scale are not interpretable, i.e. an improvement/worsening of 1 (or 2 points) has a different meaning depending on the baseline category. Moreover, improvements by 1 point on the ordinal scale particularly in categories 4 to 7 are of very questionable clinical relevance.

The provided post-hoc analysis of proportions of participants with disease worsening, cumulative hospital discharge and recovery are considered to be of no added value, due to the post-hoc potentially data-driven nature of the analyses (i.e. no type-1 error control) and the inconsistent outcomes at different study days.

Importantly, final CSR data did not demonstrate a statistically significant effect of RDV on duration of hospitalization (5-day RDV: 8 days, 10-day RDV: 9 days; SOC: 8 days), time to clinical improvement ≥ 2-Points (5-day RDV: 6 [5,14]) days, 10-day RDV: 8 [4, 14] days, SOC: 8 [5, 22] days), time to clinical improvement ≥ 1-Point (5-day RDV: 6 [4, 9] days, 10-day RDV: 7 [4, 12] days; SOC 7 [4, 14] days) or time to recovery (5-day RDV: 6 [5, 10] days, 10-day RDV: 8 [4, 13] days SOC: 7 [4, 15] days).

Furthermore, final CSR analysis of time to recovery by oxygen support at baseline no beneficial effect of RDV on the median (Q1, Q3) times to recovery in the RDV 5-day and RDV 10 day groups compared with those in the SOC only group was observed, neither for participants on high-flow or low-flow oxygen at baseline, nor for participants on room air. Hence, data do not point to an effect of RDV on time to recovery based on oxygen support at baseline. In addition, subgroup analysis by baseline oxygen support status did not show any meaningful effect between the two treatment groups on clinical status at Day 11. No differences in median time to clinical recovery or for hospital discharge were seen in patients with different oxygen support status. However, it has to be noted that the number of patients requiring oxygen support at baseline was low in study 5774 (N=57). Hence, this data should be interpreted with caution. However, these finding seem to support the currently approved indication and the finding in ACTT-1 and suggests that patients with baseline ordinal scale 5 benefit most from treatment and do not indicate a benefit of remdesivir in patients with mild/moderate disease who do not require supplemental oxygen.

In addition, the study failed to show an antiviral effect of remdesivir, which is of concern, since, as yet, in-vivo proof-of-concept related to the remdesivir mechanism of action is missing.

In conclusion, study 5774 cannot be regarded to provide a confirmatory proof of efficacy of remdesivir in patients with mild/moderate disease. Due to essential methodological deficiencies, the efficacy analyses of study GS-US-540-5774 do not provide robust statistical evidence of a positive effect of a 5-day remdesivir treatment course and prevent any conclusion on the benefit of remdesivir in patients with mild/moderate disease.

NIAID-ACTT-1 trial (CO-US-5776):

Overall, as already concluded in the initial assessment of the NIAID data during the CMA procedure, no beneficial effect of remdesivir was seen in patients with mild/moderate disease, neither for the primary endpoint nor for any of the analysed secondary endpoints. However, it has to be noted that the study was not powered to show statistically differences in the mild/moderate disease strata.

No difference in time to recovery, the primary endpoint of the NIAID study, was seen, neither in the mild/moderate nor in the subset of patients with baseline ordinal score of 4.

In the mild/moderate disease stratum recoveries/discharges were observed relatively fast after beginning of treatment in both treatment groups, with almost all patients recovered/discharged until day 15. No major differences are observable between the KM curves for the treatment groups, indicating frequent recovery in patients with mild/moderate disease is seen, independent of treatment. However, sample size of this subgroup was too small to draw any definitive conclusions.

For all pre-specifed sensitivity analyses of the primary efficacy analyses, no effect of remdesivir on time to recovery was seen in the mild/moderate population, consistent with the primary efficacy analyses.

The sensitivity analysis examining the effect of unsustained recovery (readmittance for hospitalization) showed no statistically significant benefit for the remdesivir 10-day group compared to the placebo group in the mild/moderate disease stratum, consistent with the analysis of the primary endpoint (RDV: 6 days [95% CI: 5, 8] Placebo: 7 days [95% CI: 5, 10]; RRR 1.05; 95% CI: 0.75, 1.47)). It remains unclear, if all patients returned to the study sites, when they were in need of medical care. Four patients deteriorated after achieving an ordinal score of 3. However, it remains unclear, if these patients were randomised to the mild/moderate disease stratum and had baseline ordinal score of 4.

Overall, no statistically significant effect of remdesivir was seen in patients with mild/moderate COVID-19 in any of the analysed secondary endpoints.

The key secondary endpoint was the primary endpoint according to the original protocol. Results were consistent with the analysis for the primary endpoint. No statistically significant effect of remdesivir on the odds of improvement in clinical status at Day 15 determined by a proportional odds model were seen, neither for patients with baseline ordinal score 4 (OR for improvement, 1.5; 95% CI: 0.8, 2.7; p = 0.234), nor for patients in the mild/moderate disease stratum (OR for improvement, 1.2; 95% CI: 0.7, 2.2; p = 0.475).

Sub-group analyses in the ITT Population showed no effect of remdesivir on time to clinical improvement by ≥ 1 or ≥ 2 clinical status categories, neither for patients with baseline ordinal score 4, nor for patients in the mild/moderate disease stratum.

Sub-group analyses in the ITT Population showed no effect of remdesivir on time to discharge or to NEWS ≤ 2 in the in the RDV group compared to placebo, neither for patients with baseline ordinal score 4, nor for patients in the mild/moderate disease stratum.

In conclusion, the NIAID-ACTT-1 study failed to demonstrate efficacy of remdesivir in patients with mild/moderate COVID-19.

Study GS-US-540-9012

Study GS-US-540-9012 showed superiority of remdesivir treatment compared to placebo in reducing COVID-19 related hospitalisation and all-cause death in high-risk, non-hospitalised and unvaccinated COVID-19 patients.

For the primary endpoint, treatment with remdesivir for 3 days resulted in an 87% relative risk reduction in COVID-19 related hospitalisation and all-cause death by day 28 compared to placebo. The corresponding estimate of the absolute risk reduction was 4.6% (95% CI, 1.8%, 7.5%) and the number needed to treat (NNT) is 22 patients (95% CI, 14, 56). COVID-19 related hospitalisation by day 28 were reported for 2 of the 279 (0.7%) remdesivir treated patients, compared 15 of the 283 (5.4%) placebo treated patients (p=0.0076). No death was reported in either treatment group by day 28. It is of note that the proportion of hospitalisations in the placebo group proved to be substantially lower than assumed for sample size calculation (5.4% instead of 12%). Results from the sensitivity analyses of the primary endpoint using the CMH analysis confirmed the results of the primary efficacy endpoint (p=0.0015).

Based on the primary efficacy analyses, it can be concluded that remdesivir treatment is effective in preventing disease progression in high-risk, non-hospitalised and unvaccinated patients.

However, for the primary analysis, patients were censored at last contact, which implies the assumption that censoring was non-informative. This assumption appears to be questionable as the hospitalisation risk may well be different for patients who discontinued the study. The number of patients who discontinued the study was low and sensitivity analyses assuming patients with missing data were not hospitalised were provided. However, given the overall small number of events in the primary analysis, single additional events could have a major impact on conclusions and treatment effect estimates. Therefore, last known health status of patients with last contact before day 28 was requested. Nineteen patients (12 in RDV-group, 7 patients in placebo group) were event-free at withdrawal, whereby for at least five of the patients who were lost to follow-up information was available until day 14 or later. Given these low numbers, although no final information on last health status is available yet for all drop-outs, relevant impact on the results and conclusions can be reasonably excluded.

For the primary endpoint and secondary time to event endpoints, absolute risk of an event was provided as Kaplan-Meier estimate by treatment group, while the treatment effect was expressed as hazard ratio (HR). As hospitalization/death was a rare event, the HR can indeed be interpreted as the relative risk for this endpoint. However, the relevance of a relative risk reduction cannot be assessed without additional information such that it should always be complemented by an estimate of the absolute risk reduction. This was provided upon request.

Furthermore, as observed in other pivotal studies investigating antivirals the serostatus at baseline could be an important factor for response. Therefore, serostatus at baseline and (if data is available) a sensitivity analysis of the primary and secondary efficacy endpoint based on baseline serostatus was requested. However, no information on the baseline serostatus is currently available. Thus, the impact of baseline serostatus on remdesivir efficacy in patients not requiring supplemental oxygen at increased risk for severe disease progression remains unclear. The MAH expects that post hoc analyses of the primary and secondary efficacy endpoints stratified by baseline serostatus will be available in Q1 2022 (PAM). Until this data becomes available, the lack of data on baseline serostatus should be included in section 4.4 of the SmPC.

A subgroup analysis of the primary endpoint for patients with symptom onset <5 days and ≥ 5 days was requested in order to inform about timing of treatment initiation. Due to the small number of events (< 5 days 0 vs 8 [5.8%], ≥ 5 days 2 [1.5%] vs. 7 [5.0%]), robust subgroup analysis was not possible. However, as the risk reduction seems to be lower in patients having symptom onset ≥5 days and in line with the inclusion criteria of study 9012, a recommendation that treatment in adults who do not require

supplemental oxygen and who are at increased risk of progressing to severe COVID-19 should be initiated as soon as possible after diagnosis of COVID-19 and within 7 days after symptom onset in section 4.2 of the SmPC is considered necessary.

It is of note, that the treatment difference in hospitalisation and death rates between remdesivir and placebo was mainly driven by patients who received remdesivir in an outpatient facility. Patients in a skilled nursing facility (SNF) or home healthcare setting were older, had a longer symptom duration prior to study drug start and a higher viral load compared to patients in the outpatient facility. Based on this, it is surprising, that no COVID-19 related hospitalisation or death occurred in residents of SNF and only three events were reported in the home healthcare setting (RDV: 1 and Placebo:2) compared to 14 events (RDV: 1 and Placebo 13) in patients treated at the outpatient facility. No statistically significant effect of remdesivir treatment was seen in patients in the home healthcare setting. This could point to a potential need of closer medical monitoring of patients, receiving remdesivir in an outpatient facility. However, the numbers of patients in the SNF (N=15) and home healthcare (N=93) were smaller than in the outpatient facility group (N=455), and consequently event rates were small. Hence, it is difficult to draw any meaningful conclusions. Further information on this issue was requested. In view of the observed higher rates of adverse events and high rate of important protocol deviations in the outpatient setting, additional wording in the product information concerning the monitoring of patients receiving remdesivir infusion in the outpatient setting is considered necessary.

Results of the composite endpoint of COVID-19-related hospitalisation or all-cause death by Day 14 were the same as those of the primary endpoint (P = 0.0076; Cox model using FAS). Notably, in both treatment groups no additional hospitalisation occurred after Day 14, potentially reflecting natural recovery rates in the majority of patients.

For the secondary endpoint remdesivir treatment was associated with an 81% relative risk reduction of COVID-19 related medical attendance visits (MVA) or all-cause death by day 28 compared to placebo. COVID-19 related MVA by day 28 were reported for 4 of the 246 (1.7%) remdesivir treated patients, compared 21 of the 252 (8.5%) placebo treated patients (p=0.0076). It has to be noted that for the secondary endpoint of COVID-19 related Medical attendance Visits (MAV) or all-cause death by Day 28 the mFAS was used, as MAVs were included as efficacy endpoint with protocol amendment 2. Hence, MAVs were started to be documented with amendment 2 and thus only patients enrolled under protocol amendment 2 could be used for this analysis.

COVID-19-related MAVs or all-cause death by Day 14 were reported for 2 of 246 participants (0.8%) in the RDV IV for 3 days group and 20 of 252 participants (8.0%) in the placebo group (P = 0.0019; Cox model using mFAS). Notably, two additional COVID-19 MAVs in the remdesivir group and one in the placebo group were reported after Day 14.

Based on currently available data on the natural course of COVID-19, it is anticipated that the window of opportunity for an antiviral, such as remdesivir is early in the disease course. The benefit of earlier treatment with antivirals refers to their potential to reduce viral load in times when viral replication is high, i.e. early during the COVID-19 disease course, and thereby avoiding clinical deterioration. However, study 9012 failed to show an antiviral effect of remdesivir in the outpatient setting. This is of concern, since, as yet, all conducted studies with remdesivir failed to demonstrate the *in-vivo* proof of concept related to remdesivir mechanism of action. This is surprising, considering that in other antiviral treatment trials for COVID-19 *in vivo* proof of concept (reduction of viral load) by nasopharyngeal swab samples was demonstrated. In view of the apparent lack of *in vivo* antiviral activity/proof of concept, a discussion of the benefit of earlier treatment with remdesivir and the place of remdesivir in the landscape of COVID-19 disease course and therapies was requested. No new information concerning the lack of proof of concept was provided, beside those that have already been assessed before without convincing evidence, i.e. the limitations of the non-human primate model, the lack of PCR to distinguish from or quantify infectious

and non-infectious SARS-CoV-2 virions. In conclusion, what remains is that an *in vivo* proof of concept of the antiviral effect of remdesivir is missing. None of the conducted remdesivir studies did show any effect on viral load reduction or time to a negative SARS-CoV-2 PCR test. This is of particular concern, as other treatment options available or under clinical development, prone to the same limitations of nasopharyngeal swap sampling and analyses of SARS-CoV-2 RNA by RT-PCR, did show an effect on viral load. While this effect might not have been strongly correlate with a clinical benefit, they did show a reduction of viral load, which was not shown for remdesivir.

No significant effect on alleviation (mild or absent) of baseline COVID-19 symptoms through Day 14 was seen. Alleviation of symptoms were reported by 23 of 66 participants in the RDV IV for 3 days group and 15 of 60 participants in the placebo group (hazard ratio [HR]: 1.405; 95% CI: 0.733 to 2.693, based on Cox regression; overall P = 0.2987, Kaplan-Meier estimate, stratified log-rank test). Interestingly, more patients in the RDV group (7/23 (30%)) had worsening of COVID-19 symptoms after alleviation of baseline COVID-19 symptoms, compared to 13% (5/15) in the placebo group. Hence, it seems that alleviation of symptoms is less sustained in patients treated with remdesivir compared to those treated with placebo. However, as only for 22% of the patients baseline FLU-PRO questionnaire data is available and because of the self-reported nature, the relevance of this data is considered limited.

No statistically significant effect in the proportion of participants requiring oxygen supplementation by Day 28 or prior to study discontinuation was seen. The severity of the cases of hospitalisation was similar in both groups. The proportion of participants requiring oxygen supplementation reported at each study visit by Day 28 or prior to study discontinuation was 1 of 279 participants (0.4%) in the RDV IV for 3 days group and 5 of 283 participants (1.8%) in the placebo group (P = 0.2163). Only one additional participant in the placebo group required mechanical ventilation at Day 16.

No vaccinated patients were enrolled in study 9012, which should be reflected in section 5.1 of the SmPC. Hence, it remains unclear, if the magnitude of benefit of remdesivir documented in study 9012 in unvaccinated patients is applicable to a population comprising vaccinated and/or naturally primed seropositive subjects.

In the presented subgroup analyses, effects in favour of remdesivir were observed for US-patients, patients > 60 years of age, male patients, patients with hypertension, diabetes mellitus and obesity. Furthermore, subgroup analysis of the primary efficacy endpoint by presence of one, two, three and four risk factors showed a consistent treatment effect in favour of remdesivir. However, due to the small number of events, robust subgroup analysis was not possible such that the consistency of the effect across subgroups cannot be assessed. Hence, the presented data are of limited value but at least reassuring.

Only an interim virology report (PC-540-2031) for study GS-US-540-9012 was provided. This interim report included only a subset of SARS-CoV-2 sequencing analyses of virus from patients who progressed to COVID-19 related hospitalisation or all-cause death. Due to the small numbers of events in the remdesivir group (N=2) and the fact that for none of those patients baseline and post-baseline values are available, this report is of limited value, as no information on the emergence of substitutions following treatment with remdesivir could be obtained. The MAH committed to provide the final virology report in the first half of 2022, which will include sequencing analyses for participants with viral load above LLOD on Day 14, and a phenotypic analysis for clinical isolated with treatment emergent amino acid substitutions in nsp12 compared to their baseline samples **(PAM).**

Additional expert consultation

There was no additional expert consultation.

Assessment of paediatric data on clinical efficacy

No paediatric data on clinical efficacy is currently available.

2.4.4. Conclusions on the clinical efficacy

At the time of the CMA the CHMP concluded that no beneficial effect of remdesivir was demonstrated in the stratum of mild/moderately ill patients in the NIAID trial and that an effect cannot be inferred from study-5774. In the previous round of this procedure, CHMP concluded that study GS-US-540-5774 does not provide robust statistical evidence of clinical efficacy in the moderate population, due to essential methodological deficiencies. Hence, for the moderate population there was no robust statistical evidence of clinical efficacy available. In response, to the previous round, the MAH submitted with study GS-US-540-9012 new data from the outpatient setting in order to support the initially applied proposed extension of indication to patients with moderate COVID-19. The proposal was that the data from study -9012 could be used to extrapolate efficacy data from the outpatient setting in patients who are at increased risk of progression to severe disease to the moderate population, including those not requiring supplemental oxygen.

Based on the primary efficacy analyses of study GS-US-540-9012, it can be concluded that remdesivir treatment is effective in preventing disease progression in high-risk, non-hospitalised and unvaccinated patients.

However, based on currently available data on the natural course of COVID-19, it is anticipated that the window of opportunity for an antiviral, such as remdesivir is early in the disease course. The benefit of earlier treatment with antivirals refers to their potential to reduce viral load in times when viral replication is high, i.e. early during the COVID-19 disease course, and thereby avoiding clinical deterioration. However, all conducted studies with remdesivir failed to demonstrate the *in-vivo* proof-of-concept related to the remdesivir's mechanism of action. This is surprising, considering that in other antiviral treatment *trials in vivo* proof of concept by nasopharyngeal swab samples was demonstrated. In view of the apparent lack of *in vivo* antiviral activity/proof of concept, the benefit of earlier treatment with remdesivir and the place of remdesivir in the landscape of COVID-19 disease course and therapies remains unclear.

Overall, the submitted efficacy data of study 9012 demonstrated a beneficial effect of remdesivir in preventing disease progression in high-risk, non-hospitalised and unvaccinated COVID-19 patients. Subgroup analysis indicate consistent effects in favour of remdesivir for US-patients, patients > 60 years of age, male patients, patients with hypertension, diabetes mellitus and obesity. However, due to the small number of events, robust subgroup analysis was not possible such that the consistency of the effect across subgroups cannot be assessed. As no vaccinated patients were enrolled in study 9012, which should be reflected in section 5.1 of the SmPC, it remains unclear, if the magnitude of benefit of remdesivir documented in study 9012 in unvaccinated patients is applicable to a population comprising vaccinated and/or naturally primed seropositive subjects. Furthermore, the impact of the baseline serostatus on the efficacy outcome remains currently unclear. Finally, it is currently unclear, if remdesivir retains its antiviral activity against the emerging Omicron variant, therefore in addition to the ongoing SOB number 12 " In order to understand the antiviral activity of remdesivir on currently circulating (B.1.1.7; B.1.135; B.1.1.28, B1.617 and P.1) and upcoming variants of concern and clinical isolates with substitutions P323L, A97V and A547V in the RdRp, as well as the genotypic and phenotypic resistance profile of remdesivir, the MAH should submit a full virology report, due by January 2022" , an enhancement of the pharmacovigilance activities to monitor the variants is requested (see RMP and Pharmacovigilance sections below). In view of the provided subgroup analysis with symptom onset < 5 days and ≥ 5 days and in line with the inclusion criteria of study 9012, a recommendation to initiate treatment within 7 days of symptom onset is considered necessary.

The provided data of study GS-US-540-9012 is considered sufficient to conclude on a positive B/R in patients with COVID-19, who do not require supplemental oxygen and at increased risk for disease progression. However, there are several PAMs requested to address the efficacy of remdesivir in seropositive/seronegative patients, the full virology analysis to support the 3-day treatment course and the *in vitro* analyses of the antiviral activity of remdesivir against the Omicron variant. The current lack of the respective data warrants a reflection in the SmPC. Furthermore, in view of the observed rates of adverse events and high rate of important protocol deviations in the outpatient setting, additional wording in the product information concerning the monitoring of patients receiving remdesivir infusion in the outpatient setting is considered necessary.

The following measures are considered necessary to address issues related to efficacy:

- The MAH should submit post hoc analyses of the primary and secondary efficacy endpoints stratified by baseline serostatus that will be available in Q1 2022.
- The MAH committed to provide the final virology report in the first half of 2022, which will include sequencing analyses for participants with viral load above LLOD on Day 14, and a phenotypic analysis for clinical isolated with treatment emergent amino acid substitutions in nsp12 compared to their baseline samples .

Note: The antiviral activity against variants should be also further characterised. However, this is covered by SOB number 12 and therefore, there is no need to create a new measure for this issue. The pharmacovigilance plan is also updated.

2.5. Clinical safety

Introduction

Safety data are presented from Part A of Study GS-US-540-5774, which required participants to have SpO_2 > 94% on room air at screening, and from the subset of participants in Study CO-US-540-5776 who had a baseline ordinal score of 4 (hospitalized, not requiring supplemental oxygen - requiring ongoing medical care [COVID-19 related or otherwise]. Supportive safety data are provided from Part B of Study GS-US-540-5774, which required participants to have SpO_2 > 94% on room air at screening.

Patient exposure

This overview of the safety of RDV in participants with moderate COVID-19 is based on data from 962 participants who received at least 1 dose of RDV. The dosing regimen of RDV used across the pivotal Phase 3 studies was RDV 200 mg on Day 1, followed by RDV 100 mg/day for up to 9 days (up to 10 days total).

Study GS-US-540-5774 – Part A

A Phase 3 randomized study to evaluate the safety and antiviral activity of RDV (GS-5734™) in participants with moderate COVID-19 compared to standard of care treatment.

Patient exposure

Table 46: GS-US-540-5774: Exposure to Study Treatment (Safety Analysis Set)

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

max = maximum; min = minimum
Source: Table 15.11.1.1

Adverse events

Overall Summary of Adverse Events

In the table below an overall summary of AEs is provided.

Table 47: GS-US 540 5774: Overall Summary of Adverse Events – Part A (Safety Analysis Set)

				RDV 5 Days vs SOC		RDV 10 Days vs SOC	
	RDV 5 Days (N = 191)	RDV 10 Days (N = 193)	SOC (N = 200)	P-Value	Difference in Percentages (95% CI)	P-Value	Difference in Percentages (95% CI)
Subjects Experiencing Any Treatment-Emergent Adverse Event	98 (51.3%)	113 (58.5%)	93 (46.5%)	0.3633	4.8% (−5.2% to 14.7%)	0.0201	12.0% (1.6% to 21.8%)
95% CI	44.0% to 58.6%	51.3% to 65.6%	39.4% to 53.7%				
Subjects Experiencing Any Grade 3 or Higher Treatment-Emergent Adverse Event	20 (10.5%)	24 (12.4%)	24 (12.0%)	0.7492	−1.5% (−8.1% to 5.1%)	1.0000	0.4% (−6.2% to 7.1%)
95% CI	6.5% to 15.7%	8.1% to 17.9%	7.8% to 17.3%				

	RDV 5 Days (N = 191)	RDV 10 Days (N = 193)	SOC (N = 200)	RDV 5 Days vs SOC		RDV 10 Days vs SOC	
				P-Value	Difference in Percentages (95% CI)	P-Value	Difference in Percentages (95% CI)
Subjects Experiencing Any Treatment-Emergent Study Drug-Related Adverse Event	36 (18.8%)	25 (13.0%)	NA	NA	NA	NA	NA
95% CI	13.6% to 25.1%	8.6% to 18.5%	NA				
Subjects Experiencing Any Grade 3 or Higher Treatment-Emergent Study Drug-Related Adverse Event	6 (3.1%)	5 (2.6%)	NA	NA	NA	NA	NA
95% CI	1.2% to 6.7%	0.8% to 5.9%	NA				
Subjects Experiencing Any Treatment-Emergent Serious Adverse Event	9 (4.7%)	10 (5.2%)	18 (9.0%)	0.1118	−4.3% (−9.7% to 0.9%)	0.1710	−3.8% (−9.3% to 1.4%)
95% CI	2.2% to 8.8%	2.5% to 9.3%	5.4% to 13.9%				
Subjects Experiencing Any Treatment-Emergent Study Drug-Related Serious Adverse Event	1 (0.5%)	0	NA	NA	NA	NA	NA
95% CI	0.0% to 2.9%	0.0% to 1.9%	NA				
Subjects Experiencing Any Treatment-Emergent Adverse Event Leading to Premature Study Drug Discontinuation	4 (2.1%)	8 (4.1%)	NA	NA	NA	NA	NA
95% CI	0.6% to 5.3%	1.8% to 8.0%	NA				
Subjects who had Treatment-Emergent Death	2 (1.0%)	3 (1.6%)	4 (2.0%)	0.6856	−1.0% (−4.1% to 2.0%)	1.0000	−0.4% (−3.7% to 2.8%)
95% CI	0.1% to 3.7%	0.3% to 4.5%	0.5% to 5.0%				

MedDRA = Medical Dictionary for Regulatory Activities; NA = not applicable; RDV = remdesivir (GS-5734™); SOC = standard of care
Adverse events were coded using MedDRA 22.1.
Severity grades were defined by Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 July 2017.
The 95% CI for percentage of subjects in each treatment group was obtained using the Clopper-Pearson exact method.
The differences in percentages between treatment groups and 95% CI were calculated based on the exact method.
P-value was from the Fisher exact test to compare each RDV group and the SOC group.
Source: GS-US-540-5774 Interim 2 (Final Part A) CSR, Table 15.11.2.1.1.1

Common Adverse Events

The incidence and types of common AEs were generally similar among the treatment groups, with the exception of a higher frequency of nausea in the RDV 5-day and 10-day groups compared with the SOC only group (RDV 5-day group 9.9%, 19 participants; RDV 10-day group 9.3%, 18 participants; SOC only group 3.0%, 6 participants).

Table 48: GS US 540 5774: Adverse Events by Preferred Term Reported for ≥ 2% of Participants in Any Treatment Group – Part A (Safety Analysis Set)

	RDV 5 Days (N = 191)	RDV 10 Days (N = 193)	SOC (N = 200)
Number of Subjects Experiencing Any Treatment-Emergent Adverse Event	98 (51.3%)	113 (58.5%)	93 (46.5%)
Number of Subjects Experiencing Any Treatment-Emergent Adverse Event by Preferred Term			
Nausea	19 (9.9%)	18 (9.3%)	6 (3.0%)
Diarrhoea	12 (6.3%)	10 (5.2%)	14 (7.0%)
Hypokalaemia	10 (5.2%)	13 (6.7%)	4 (2.0%)
Headache	10 (5.2%)	10 (5.2%)	5 (2.5%)
Constipation	8 (4.2%)	5 (2.6%)	9 (4.5%)
Alanine aminotransferase increased	8 (4.2%)	7 (3.6%)	5 (2.5%)
Phlebitis	7 (3.7%)	7 (3.6%)	5 (2.5%)
Insomnia	7 (3.7%)	3 (1.6%)	7 (3.5%)
Pyrexia	2 (1.0%)	8 (4.1%)	7 (3.5%)
Rash	7 (3.7%)	4 (2.1%)	6 (3.0%)
Aspartate aminotransferase increased	5 (2.6%)	6 (3.1%)	5 (2.5%)
Hypotension	6 (3.1%)	6 (3.1%)	1 (0.5%)
Vomiting	5 (2.6%)	5 (2.6%)	3 (1.5%)
Hypertransaminasaemia	3 (1.6%)	6 (3.1%)	3 (1.5%)
Hypocalcaemia	6 (3.1%)	6 (3.1%)	0
Anaemia	3 (1.6%)	3 (1.6%)	4 (2.0%)
Dyspnoea	4 (2.1%)	5 (2.6%)	1 (0.5%)
Acute respiratory failure	1 (0.5%)	2 (1.0%)	5 (2.5%)
Chest pain	1 (0.5%)	6 (3.1%)	1 (0.5%)
Cough	2 (1.0%)	1 (0.5%)	5 (2.5%)
Transaminases increased	3 (1.6%)	4 (2.1%)	0

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; RDV = remdesivir (GS-5734™); SOC = standard of care
Adverse events were coded using MedDRA 22.1.
Preferred terms are presented by descending order of the total frequencies.
Multiple AEs were counted only once per subject per preferred term.
Source: GS-US-540-5774 Interim 2 (Final Part A) CSR, Table 15.11.2.1.3

AEs related to study drug

Adverse events considered related to study treatment were reported in a higher percentage of participants in the RDV 5-day group (18.8%, 36 participants) compared with the RDV 10-day group (13.0%, 25 participants).

The most commonly reported AEs considered related to study treatment in each treatment group were as follows:

- RDV 5-day group — nausea (6.8%, 13 participants), ALT increased (3.7%, 7 participants), and AST increased and rash (each 2.6%, 5 participants)
- RDV 10-day group — nausea (3.6%, 7 participants) and ALT increased, AST increased, and hypertransaminasemia (each 2.1%, 4 participants)

Serious adverse event

Serious adverse events were reported in lower percentages of participants in the RDV treatment groups (RDV 5-day group 4.7%, 9 of 191 participants; RDV 10-day group 5.2%, 10 of 193 participants) compared with the SOC only group (9.0%, 18 of 200 participants) (Table 48).

Table 49: GS-US-540-5774: Serious Adverse Events by Preferred Term for ≥ 1% of Participants in Any Treatment Group – Part A (Safety Analysis Set)

	RDV 5 Days (N = 191)	**RDV 10 Days (N = 193)**	**SOC (N = 200)**
Number of Subjects Experiencing Any Treatment-Emergent SAE	9 (4.7%)	10 (5.2%)	18 (9.0%)
Number of Subjects Experiencing Any Treatment-Emergent SAE by Preferred Term			
Acute respiratory failure	0	1 (0.5%)	5 (2.5%)
Respiratory distress	0	2 (1.0%)	2 (1.0%)
Respiratory failure	1 (0.5%)	0	2 (1.0%)
Cardiac arrest	0	0	2 (1.0%)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; RDV = remdesivir (GS-5734™); SAE = serious adverse event; SOC = standard of care
Adverse events were coded using MedDRA 22.1.
Preferred terms are presented by descending order of the total frequencies.
Multiple AEs were counted only once per subject per preferred term.
Source: GS-US-540-5774 Interim 2 (Final Part A) CSR, Table 15.11.4.5

SAEs related to study drug

The only SAE considered related to study treatment was an SAE of heart rate decreased, which was reported in 1 participant (0.5%) in the RDV 5-day group; this SAE led to premature discontinuation of study treatment and resolved the same day (GS-US-540-5774 Interim 2 [Final Part A] CSR, Table 15.11.4.9 and Listing 16.2.7.7).

Deaths

A similar percentage of deaths was reported in each treatment group (RDV 5-day group 1.0%, 2 of 191 participants; RDV 10-day group 1.6%, 3 of 193 participants; SOC only group 2.0%, 4 of 200 participants) and GS-US-540-5774 Interim 2 [Final Part A] CSR, Listing 16.2.7.4).

Laboratory findings

The majority of participants in each treatment group had at least 1 laboratory abnormality (RDV 5-day group 72.8%, 131 of 180 participants; RDV 10-day group 71.5%, 128 of 179 participants; SOC only group 73.1%, 136 of 186 participants) (GS-US-540-5774 Interim 2 [Final Part A] CSR, Table 15.11.6.4.1).

The majority of the reported laboratory abnormalities were Grade 1 or 2. The incidence of all graded individual laboratory abnormalities was generally similar among the treatment groups with the exception of decreased CLcr, for which there was at least a 2-fold difference in the incidence between the RDV 5-day group and SOC only group (RDV 5-day group 14.6%, 26 of 178 participants; SOC only group 30.1%, 55 of 183 participants).

Grade 3 or 4 laboratory abnormalities were reported in a similar percentage of participants in each treatment group, as follows: RDV 5-day group 12.8%, 23 participants; RDV 10-day group 16.2%, 29 participants; SOC only group 18.3%, 34 participants (Table 49).

The most common Grade 3 or 4 laboratory abnormality in the RDV 5 day group was hyperglycaemia (3.9%, 7 of 180 participants). The most common Grade 3 or 4 laboratory abnormality in the RDV 10 day group was decreased CLcr (5.1%, 9 of 176 participants). The most common Grade 3 or 4 laboratory abnormalities in the SOC only group were increased ALT (7.7%, 14 of 182 participants) and decreased CLcr (7.7%, 14 of 183 participants).

Table 50: GS-US-540-5774: Grade 3 or 4 Laboratory Abnormalities – Part A (Safety Analysis Set)

	RDV 5 Days (N = 191)	**RDV 10 Days (N = 193)**	**SOC (N = 200)**
Maximum Treatment-Emergent Toxicity Grade	180	179	186
Grade 3	18 (10.0%)	25 (14.0%)	25 (13.4%)
Grade 4	5 (2.8%)	4 (2.2%)	9 (4.8%)
Grade 3 or 4	23 (12.8%)	29 (16.2%)	34 (18.3%)
Hematology			
Hemoglobin (Decreased)	179	178	184
Grade 3	4 (2.2%)	2 (1.1%)	9 (4.9%)
Grade 4	2 (1.1%)	0	2 (1.1%)
Grade 3 or 4	6 (3.4%)	2 (1.1%)	11 (6.0%)
Platelets (Decreased)	179	178	184
Grade 3	1 (0.6%)	0	0
Grade 4	3 (1.7%)	0	0
Grade 3 or 4	4 (2.2%)	0	0
WBC (Decreased)	179	178	184
Grade 3	1 (0.6%)	3 (1.7%)	2 (1.1%)
Grade 4	1 (0.6%)	1 (0.6%)	0
Grade 3 or 4	2 (1.1%)	4 (2.2%)	2 (1.1%)
Chemistry			
ALT (Increased)	179	177	182
Grade 3	4 (2.2%)	6 (3.4%)	11 (6.0%)
Grade 4	0	0	3 (1.6%)
Grade 3 or 4	4 (2.2%)	6 (3.4%)	14 (7.7%)
AST (Increased)	177	175	182
Grade 3	3 (1.7%)	2 (1.1%)	6 (3.3%)
Grade 4	1 (0.6%)	0	5 (2.7%)
Grade 3 or 4	4 (2.3%)	2 (1.1%)	11 (6.0%)
Creatinine (Increased)	180	179	184
Grade 3	1 (0.6%)	3 (1.7%)	4 (2.2%)
Grade 4	0	1 (0.6%)	5 (2.7%)
Grade 3 or 4	1 (0.6%)	4 (2.2%)	9 (4.9%)

	RDV 5 Days (N = 191)	RDV 10 Days (N = 193)	SOC (N = 200)
Serum Glucose (Hyperglycemia)	180	177	181
Grade 3	7 (3.9%)	5 (2.8%)	4 (2.2%)
Grade 4	0	0	0
Grade 3 or 4	7 (3.9%)	5 (2.8%)	4 (2.2%)
Total Bilirubin (Hyperbilirubinemia)	177	176	181
Grade 3	1 (0.6%)	3 (1.7%)	1 (0.6%)
Grade 4	0	1 (0.6%)	1 (0.6%)
Grade 3 or 4	1 (0.6%)	4 (2.3%)	2 (1.1%)
Creatinine Clearance (Decreased)	178	176	183
Grade 3	4 (2.2%)	7 (4.0%)	9 (4.9%)
Grade 4	0	2 (1.1%)	5 (2.7%)
Grade 3 or 4	4 (2.2%)	9 (5.1%)	14 (7.7%)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; RDV = remdesivir (GS-5734™); SOC = standard of care; WBC = white blood cell
The denominator for percentage is the number of subjects in the Safety Analysis Set with at least 1 postbaseline value for the test under evaluation, specified in each laboratory test row.
Subjects were counted once for the maximum postbaseline severity for each laboratory test under evaluation.
Severity grades were defined by Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 July 2017.
Creatinine clearance is from Cockcroft-Gault.
Source: GS-US-540-5774 Interim 2 (Final Part A) CSR, Table 15.11.6.4.2

Safety in special populations

Summaries of overall AEs are presented by age group (< 65 years or ≥ 65 years), sex (male or female), and race in GS-US-540-5774 Interim 2 (Final Part A) CSR, Tables 15.11.2.1.1.2, 15.11.2.1.1.3, and 15.11.2.1.1.5, respectively. Summaries of AEs by system organ class and PT are presented by age group, sex, and race in GS-US-540-5774 Interim 2 (Final Part A) CSR, Tables 15.11.2.1.2.1, 15.11.2.1.2.2, and 15.11.2.1.2.4, respectively. Higher rates of AEs, Grade 3 or higher AEs, and SAEs were reported in older participants (≥ 65 years) compared with younger participants (< 65 years) across all treatment groups. Higher rates of AEs were reported in the RDV treatment groups compared with the SOC only group in participants aged < 65 years, but there were no meaningful differences among the treatment groups in participants aged ≥ 65 years. There were no meaningful differences identified in the other subpopulations among the treatment groups.

Summaries of AEs by system organ class and PT by baseline CLcr (≥ 90 mL/min, 60 to < 90 mL/min, and 30 to < 60 mL/min) are presented in Table req10643.9. Summaries of laboratory abnormalities by baseline CLcr are presented in Table req10643.10. In general, higher rates of AEs were reported in participants with baseline CLcr 30 to < 60 mL/min and 60 to < 90 mL/min than those with CLcr ≥ 90 mL/min. In general, laboratory abnormalities were reported more frequently in participants treated with RDV with baseline CLcr 30 to < 60 mL/min than those with CLcr ≥ 90 mL/min or 60 to < 90 mL/min. However, the small number of participants in the 30 to < 60 mL/min subgroup make it difficult to draw any meaningful conclusions.

Summaries of overall AEs are presented by baseline oxygen status (high flow oxygen, low flow oxygen, or room air) in GS-US-540-5774 Interim 2 (Final Part A) CSR, Table 15.11.2.1.1.4. Summaries of AEs by system organ class and PT are presented by baseline oxygen support status in GS US 540 5774 Final (Part B) CSR, Table 15.11.2.1.2.3. There were no meaningful differences identified in this subpopulation across all treatment groups.

Safety related to drug-drug interactions and other interactions

No information has been provided.

Discontinuation due to adverse events

Study treatment discontinuation was recorded only for the RDV groups. Adverse events leading to study treatment discontinuation were reported in 2.1% (4 of 191 participants) in the RDV 5-day group and 4.1% (8 of 193 participants) in the RDV-10 day group (see table below)

Table 51: GS-US-540-5774: Adverse Events Leading to Discontinuation of Study Treatment by System Organ Class and Preferred Term – Part A (Safety Analysis Set)

	RDV 5 Days (N = 191)	**RDV 10 Days (N = 193)**
Number of Subjects Experiencing Any Treatment-Emergent AE Leading to Premature Study Drug Discontinuation	4 (2.1%)	8 (4.1%)
Number of Subjects Experiencing Any Treatment-Emergent AE Leading to Premature Study Drug Discontinuation by System Organ Class and Preferred Term		
Hepatobiliary disorders	0	1 (0.5%)
Hypertransaminasemia	0	1 (0.5%)
Investigations	2 (1.0%)	5 (2.6%)
Alanine aminotransferase increased	1 (0.5%)	3 (1.6%)
Aspartate aminotransferase increased	0	2 (1.0%)
Blood alkaline phosphatase increased	0	1 (0.5%)
Blood bilirubin increased	0	1 (0.5%)
Heart rate decreased	1 (0.5%)	0
Transaminases increased	0	1 (0.5%)
Respiratory, thoracic and mediastinal disorders	0	1 (0.5%)
Acute respiratory failure	0	1 (0.5%)
Skin and subcutaneous tissue disorders	2 (1.0%)	0
Rash	2 (1.0%)	0
Vascular disorders	0	1 (0.5%)
Hypotension	0	1 (0.5%)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; RDV = remdesivir (GS-5734™)
Adverse events were coded using MedDRA 22.1.
System organ classes are presented alphabetically and preferred terms are presented by descending order of the total frequencies.
Multiple AEs were counted only once per subject for each system organ class and preferred term.
Source: GS-US-540-5774 Interim 2 (Final Part A) CSR, Table 15.11.5.1

Study GS-US-540-5776 – subgroup analysis of participants with baseline ordinal score of 4

remdesivir was well tolerated in participants with baseline ordinal score of 4 (N = 138), as demonstrated by the similarity in incidence between the RDV 10-day group and the placebo group in Grade 3 or higher AEs and SAEs. The majority of AEs were consistent with the signs and symptoms of underlying COVID-19.

Adverse events

Overall Summary of Adverse Events

Among participants with baseline ordinal score of 4 (N = 138), the incidence of any AE was 34.7% in the RDV 10-day group and 28.6% in the placebo group (see table below).

Table 52: CO-US-540-5776: Overall Summary of Adverse Events for Participants with Baseline Ordinal Score of 4 (As Treated Population)

Participants with	RDV 10 Days (N = 75)	Placebo (N = 63)
Any TEAE	26 (34.7%)	18 (28.6%)
Any study drug-related TEAE	4 (5.3%)	2 (3.2%)
Any TESAE	9 (12.0%)	10 (15.9%)
Any TEAE leading to discontinuation of study drug	3 (4.0%)	2 (3.2%)

MedDRA = Medical Dictionary for Regulatory Activities; RDV = remdesivir (GS-5734™); TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event
Adverse events were coded using MedDRA 23.0.
Ordinal score 4 = hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise).
N = Number of participants in the As Treated Population.
Source: Table req12690.12.1

Common Adverse Events

Table 53: CO-US-540-5776: Adverse Events by Preferred Term Reported for ≥ 4% of Participants in Either Treatment Group with Baseline Ordinal Score of 4 (As Treated Population)

Participants with	RDV 10 Days (N = 75)	Placebo (N = 63)
Haemoglobin decreased	5 (6.7%)	3 (4.8%)
Acute respiratory failure	1 (1.3%)	4 (6.3%)
Alanine aminotransferase increased	2 (2.7%)	3 (4.8%)
Dyspnoea	3 (4.0%)	2 (3.2%)
Glomerular filtration rate decreased	3 (4.0%)	2 (3.2%)
Prothrombin time prolonged	4 (5.3%)	1 (1.6%)

MedDRA = Medical Dictionary for Regulatory Activities; RDV = remdesivir (GS-5734™)
Adverse events were coded using MedDRA 23.0.
Multiple adverse events were counted only once per participant per preferred term.
Preferred terms are presented by descending order of the total frequencies.
Ordinal score 4 = hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise).
N = Number of participants in the As Treated Population.
Source: Table req12690.12.5

Serious adverse event/deaths

By Day 29, deaths were reported in similar percentages of participants in the RDV 10-day group and the placebo group (RDV 10-day 4.2% [3 of 72 participants with known mortality status at Day 29]; placebo

5.1% [3 of 59 participants with known mortality status at Day 29]; hazard ratio [95% CI]: 0.82 [0.17, 4.07].

Serious AEs were reported in 12.0% (9 participants) in the RDV 10-day group and 15.9% (10 participants) in the placebo group.

Discontinuation due to adverse events

Adverse events leading to discontinuation of study treatment were reported in similar percentages of participants in the RDV 10-day group and the placebo group (RDV 10-day 4.0% [3 participants]; placebo 3.2% [2 participants].

Hepatic safety

Among participants with baseline ordinal score of 4, the incidence of hepatic AEs was generally similar between the RDV 10-day group and placebo group. Study treatment-related hepatic AEs occurred in 5.3% (4 participants) in the RDV 10-day group and 1.6% (1 participant) in the placebo group.

In general, among participants with baseline ordinal score of 4, the incidence of hepatic AEs (by preferred term) was similar between the RDV 10-day group and the placebo group. Prothrombin time prolonged occurred in 5.3% (4 participants) in the RDV 10-day group and 1.6% (1 participant) in the placebo group. A description of the imbalance of prothrombin time/INR laboratory abnormalities from this study, noting no difference between treatment groups in the incidence of bleeding events, has been proposed to be added to the SmPC as part of the CMA renewal.

Renal safety

Among participants with baseline ordinal score of 4, the incidence of renal AEs was generally similar between the RDV 10-day group and the placebo group. In general, among participants with baseline ordinal score of 4, the incidence of renal AEs (by preferred term) was similar between the RDV 10-day group and the placebo group.

Study GS-US-540-5774 - Part B (supportive data)

A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of RDV (GS-5734™) in Participants with Moderate COVID-19 Compared to Standard of Care Treatment

Part B enrolled participants meeting eligibility criteria (Extension Treatment Group) after enrolment to Part A was complete. In Part B, up to an additional approximately 1000 participants who met all the eligibility criteria were assigned to receive the following:

Extension Treatment Group: continued SOC therapy together with IV RDV 200 mg on Day 1 followed by IV RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10

Exposure

Table 54: GS-US-540-5774: Exposure to Study Treatment (Expanded RDV-Treated Analysis Set)

	Extension Treatment Group (N = 503)
Number of Doses Received	
N	503
Mean (SD)	6 (3.0)
Median	6
Q1, Q3	4, 10
Min, Max	1, 11
Number of Doses Received	
1 Dose	19 (3.8%)
2 Doses	31 (6.2%)
3 Doses	52 (10.3%)
4 Doses	54 (10.7%)
5 Doses	93 (18.5%)
6 Doses	41 (8.2%)
7 Doses	27 (5.4%)
8 Doses	17 (3.4%)
9 Doses	10 (2.0%)
10 Doses	158 (31.4%)
11 Doses	1 (0.2%)

max = maximum; min = minimum
One participant received 11 doses of study drug by mistake.
Source: Table 15.11.1

Adverse events

Overall Summary of Adverse Events

In Table 54 an overall summary of AEs from Part B is provided.

Table 55: GS-US-540-5774: Overall Summary of Adverse Events – Part B (Expanded RDV-Treated Analysis Set)

	Extension Treatment Group (N = 503)
Subjects Experiencing Any Treatment-Emergent Adverse Event	282 (56.1%)
Subjects Experiencing Any Grade 3 or Higher Treatment-Emergent Adverse Event	68 (13.5%)
Subjects Experiencing Any Treatment-Emergent Study Drug-Related Adverse Event	83 (16.5%)
Subjects Experiencing Any Grade 3 or Higher Treatment-Emergent Study Drug-Related Adverse Event	10 (2.0%)
Subjects Experiencing Any Treatment-Emergent Serious Adverse Event	40 (8.0%)
Subjects Experiencing Any Treatment-Emergent Study Drug-Related Serious Adverse Event	1 (0.2%)

	Extension Treatment Group (N = 503)
Subjects Experiencing Any Treatment-Emergent Adverse Event Leading to Premature Study Drug Discontinuation	15 (3.0%)
Subjects who had Treatment-Emergent Death	13 (2.6%)

MedDRA = Medical Dictionary for Regulatory Activities; RDV = remdesivir (GS-5734™)
Adverse events were coded using MedDRA 22.1.
Severity grades were defined by Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 July 2017.
Treatment-emergent death refers to deaths that occurred between the first dose date and the last dose date plus 30 days (inclusive).
Source: GS-US-540-5774 Final (Part B) CSR, Table 15.11.2.1.1.1

Common Adverse Events

The most common AEs were nausea (8.2%, 41 participants), diarrhoea (5.6%, 28 participants), and headache (5.4%, 27 participants) (see table below)

GS-US-540-5774 Final (Part B) CSR, Table req10737.9 presents AEs by PT for adolescent participants in the Expanded RDV-Treated Analysis Set. No AE was reported in > 1 adolescent participant.

Table 56: GS US 540 5774: Adverse Events by Preferred Term Reported for ≥ 2% of Participants in Any Treatment Group – Part B (Expanded RDV Treated Analysis Set)

	Extension Treatment Group (N = 503)
Number of Subjects Experiencing Any Treatment-Emergent Adverse Event	282 (56.1%)
Number of Subjects Experiencing Any Treatment-Emergent Adverse Event by Preferred Term	
Nausea	41 (8.2%)
Diarrhoea	28 (5.6%)
Headache	27 (5.4%)
Constipation	26 (5.2%)
Pyrexia	24 (4.8%)
Hypokalaemia	23 (4.6%)
Alanine aminotransferase increased	18 (3.6%)
Aspartate aminotransferase increased	16 (3.2%)
Transaminases increased	16 (3.2%)
Phlebitis	13 (2.6%)
Vomiting	13 (2.6%)
Anxiety	12 (2.4%)
Insomnia	12 (2.4%)
Hyperglycaemia	11 (2.2%)
Urinary tract infection	11 (2.2%)
Asthenia	10 (2.0%)
Rash	10 (2.0%)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; RDV = remdesivir (GS-5734™)
Adverse events were coded using MedDRA 22.1.
Preferred terms are presented by descending order of the total frequencies.
Multiple AEs were counted only once per participant per preferred term.
Source: GS-US-540-5774 Final (Part B) CSR, Table 15.11.2.1.3

AEs related to study drug

Adverse events considered related to study treatment were reported in 16.5% of participants (83 of 503 participants). The most commonly reported AEs considered related to study treatment were nausea (4.0%, 20 participants), ALT increased (3.4%, 17 participants), AST increased (2.8%, 14 participants), and transaminases increased (2.0%, 10 participants) (GS US-540-5774 Final [Part B] CSR, Table 15.11.2.3.1.2).

Serious adverse event

Serious adverse events were reported for 40 participants (8.0%). No SAE was reported in > 1% of participants (GS US-540-5774 Final [Part B] CSR, Table 15.11.4.5).

SAEs related to study drug

The only SAE considered related to study treatment was an SAE of hypotension in 1 participant (0.2%); this SAE led to premature discontinuation of study treatment and resolved 2 days after onset (GS US-540-5774 Final [Part B] CSR, Table 15.11.4.9 and Listing 16.2.7.7).

Deaths

A total of 13 treatment-emergent deaths were reported during Part B of the study (Table 19 and GS US-540-5774 Final [Part B] CSR, Listing 16.2.7.4).

Laboratory findings

The majority of participants had at least 1 laboratory abnormality (72.9%, 349 of 479 participants) (GS-US-540-5774 Final [Part B] CSR, Table 15.11.6.4.1). The majority of the reported laboratory abnormalities were Grade 1 or 2 in severity. Grade 3 or 4 laboratory abnormalities were reported for 83 participants (17.3%) (Table 56).

The most common Grade 3 or 4 laboratory abnormality was decreased CLcr (6.4%, 30 participants). No adolescent participant had a Grade 3 or 4 laboratory abnormality for estimated glomerular filtration rate calculated using the Schwartz equation (GS-US-540-5774 Final [Part B] CSR, Listing 16.2.8.4).

Table 57: GS-US-540-5774: Grade 3 or 4 Laboratory Abnormalities – Part B (Expanded RDV-Treated Analysis Set)

	Extension Treatment Group (N = 503)
Maximum Treatment-Emergent Toxicity Grade	479
Grade 3	73 (15.2%)
Grade 4	10 (2.1%)
Grade 3 or 4	83 (17.3%)
Hematology	
Hemoglobin (Decreased)	476
Grade 3	20 (4.2%)
Grade 4	2 (0.4%)
Grade 3 or 4	22 (4.6%)

	Extension Treatment Group (N = 503)
Platelets (Decreased)	476
Grade 3	5 (1.1%)
Grade 4	4 (0.8%)
Grade 3 or 4	9 (1.9%)
WBC (Decreased)	476
Grade 3	8 (1.7%)
Grade 4	2 (0.4%)
Grade 3 or 4	10 (2.1%)
Chemistry	
ALT (Increased)	471
Grade 3	10 (2.1%)
Grade 4	0
Grade 3 or 4	10 (2.1%)
AST (Increased)	469
Grade 3	4 (0.9%)
Grade 4	0
Grade 3 or 4	4 (0.9%)
Creatinine (Increased)	478
Grade 3	11 (2.3%)
Grade 4	5 (1.0%)
Grade 3 or 4	16 (3.3%)
Creatinine Clearance (Decreased)	468
Grade 3	26 (5.6%)
Grade 4	4 (0.9%)
Grade 3 or 4	30 (6.4%)
Serum Glucose (Hyperglycemia)	477
Grade 3	19 (4.0%)
Grade 4	0
Grade 3 or 4	19 (4.0%)
Serum Glucose (Hypoglycemia)	477
Grade 3	1 (0.2%)
Grade 4	0
Grade 3 or 4	1 (0.2%)
Total Bilirubin (Hyperbilirubinemia)	470
Grade 3	0
Grade 4	0
Grade 3 or 4	0

ALT = alanine aminotransferase; AST = aspartate aminotransferase; RDV = remdesivir (GS-5734™); WBC = white blood cell
The denominator for percentage is the number of participants in the Expanded RDV-Treated Analysis Set with at least 1 postbaseline value for the test under evaluation, specified in each laboratory test row.
Participants were counted once for the maximum postbaseline severity for each laboratory test under evaluation.
Severity grades were defined by Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 July 2017.
Creatinine clearance is from Cockcroft-Gault.
Source: GS-US-540-5774 Final (Part B) CSR, Table 15.11.6.4.2

Safety in special populations

Summaries of overall AEs are presented by age group (< 65 years or ≥ 65 years), sex (male or female), race (Asian, black, white, or other), baseline oxygen support status (low-flow oxygen or room air), and region (North America, Europe, Asia) in GS-US-540-5774 Final (Part B) CSR, Tables 15.11.2.1.1.2 to 15.11.2.1.1.4. Summaries of AEs by system organ class and PT are presented by age group, sex, race, baseline oxygen support status, and region in GS US 540 5774 Final (Part B) CSR, Tables 15.11.2.1.2.1 to 15.11.2.1.2.4. Higher rates of Grade 3 or higher AEs, and SAEs were reported in older participants (≥ 65 years) compared with younger participants (< 65 years). There were no meaningful differences identified in the subpopulations for AEs by system organ class and PT.

Summaries of overall AEs are presented by baseline oxygen support status (low-flow oxygen or room air) and region (North America, Europe, Asia) in GS-US-540-5774 Final (Part B) CSR, Tables 15.11.2.1.1.5 and 15.11.2.1.1.6, respectively. Summaries of AEs by system organ class and PT are presented by baseline oxygen support status and region in GS US 540 5774 Final (Part B) CSR, Tables 15.11.2.1.2.4 and 15.11.2.1.2.5, respectively. Higher rates of treatment emergent death were reported in participants who had low-flow oxygen (5.8%, 3 of 52 participants) in comparison with participants who were on room air (2.2%, 10 of 451 participants). There were no meaningful differences identified in the other subpopulations. There were no meaningful differences identified in the subpopulations for AEs by system organ class and PT.

Safety related to drug-drug interactions and other interactions

No information has been provided.

Discontinuation due to adverse events

Adverse events that led to premature discontinuation of study treatment were reported for 15 participants (3.0%) (GS US-540-5774 Final [Part B] CSR, Table 15.11.5.1). Adverse events that led to premature study treatment discontinuation in > 1 participant were ALT increased (0.6%, 3 participants), AST increased, transaminases increased, and hypotension (each 0.4%, 2 participants). Elevations in ALT were protocol-defined discontinuation criteria (Any elevations in ALT > 5 x upper limit of normal (ULN); or ALT > 3 x ULN and total bilirubin > 2 x ULN, confirmed by immediate repeat testing).

Study GS-US-540-9012 (safety summary):

In Study GS-US-540-9012, AEs were reported in 42.3% (118 patients) of the patients in the RDV 3-day group and 46.3% (93 patients) in the Placebo group. In 12.2% (34 patients) in the RDV 3-day group and 8.8% (25 patients) in the Placebo group AEs were considered related to study treatment. SAEs were reported less frequently in the RDV 3-day group (1.8%, 5 patients) compared to the Placebo group (6.7 %, 19 patients). None of these SAEs were considered related to study drug. In 2 patients (0.7%) in the RDV 3-day group and 5 patients (1.8%) in the Placebo group adverse events were reported that led to premature discontinuation of study treatment.

The most commonly reported AEs in the RDV 3-day group were nausea 10.8% (30 patients), headache (5.7%, 16 patients), diarrhoea (3.9%, 11 patients), cough and fatigue (each 3.6%, 10 patients). In the Placebo group, the most commonly reported AEs were nausea (7.4%, 21 patients), cough (6.4%, 18 patients), headache (6.0%, 17 patients) and dyspnoea (5.3%, 17 patients). The rates of commonly reported AEs were comparable between treatment groups. Only for the AE nausea more cases were reported in the RDV 3-day group.

The rate of adverse events considered related to study treatment was higher in the RDV 3-day group (12.2%, 34 patients) compared to the Placebo group (8.8%, 25 patients). The difference was mainly driven by a higher rate of cases with nausea (6.5% vs. 3.5%) and headache (1.1% vs. 0%) in the RDV 3-day group which are known adverse reactions listed in the SmPC of Veklury. Most adverse events considered related to study treatment were reported as single cases and no signal could be identified based on these cases.

Cases of creatinine increased and creatinine clearance decreased occurred more frequently in the RDV 3-day group compared to the Placebo group (Grade 3 and 4 creatinine increased: 2.9% (8 patients) vs. 1.1% (3 patients); Grade 3 and 4 creatinine clearance decreased: 5.6% (15 patients) vs. 1.9% (5 patients)). This difference was was not considered to be clinically meaningful as the median baseline creatinine clearance was near the ULN in this group (124 mL/min), and minimal median changes from baseline to Day 14 were observed. Furthermore, most decreases in creatinine clearance occurred while creatinine was within normal range, occurred after completion of RDV therapy, and resolved on follow-up where data were available. In addition, no renal AEs were observed during the study.

When comparing safety data of Study GS-US-540-9012 with data from Study GS-US-540-5774 and subgroup analysis of participants with baseline ordinal score of 4 of Study GS-US-540-5776 the reported safety profile is broadly comparable. No new safety signal could be identified.

Post marketing experience

See PSUR and Renewal Assessment.

2.5.1. Discussion on clinical safety

Overall, 962 patients with moderate COVID-19 have received at least one dose of RDV for up to ten days (the maximal proposed duration) within randomised clinical trials in COVID-19.

The assessment of the available data from individual Phase 2/3 studies in patients with moderate COVID-19 came to the following observations:

GS-US-540-5774 – Part A:

Overall, AEs were reported in 51.3% (98 of 191 patients) of patients in the RDV 5-day group, 58.5% (113 of 193 patients) in the RDV 10-day group and 46% (93 of 200 patients) in the SOC group. Rates of Grade 3 or higher treatment-emergent AEs were comparable between treatment groups (RDV 5-day group 10.5%, RDV 10-day group 12.4%, SOC 12.0%). SAEs were reported more frequently in the SOC group (9.0%, 18 patients) compared to the RDV 5-day group (4.7 %, 9 patients) and RDV 10-day group (5.2%, 10 patients).

In 18.8% (36 patients) in the RDV 5-day group and 13.0% (25 patients) in the RDV 10-day group AEs were considered related to study treatment. In 2.1% (4 patients) and 4.1% (8 patients) in the RDV 5-day and RDV 10-day group adverse events were reported that led to premature discontinuation of study treatment. Due to the study design (randomized, open-label, comparison to SOC), no information about rates of study drug-related AEs, study drug-related SAEs and premature study drug discontinuation from the SOC group are available.

The most commonly reported AEs in the RDV 5-day group were nausea (9.9%, 19 of 191 patients), diarrhoea (6.3%, 12 patients), hypokalaemia and headache (each 5.2%, 10 patients). In the RDV 10-day group, the most commonly reported AEs were nausea (9.3%, 18 of 193 patients), hypokalaemia (6.7%, 13 patients), diarrhoea and headache (each 5.2%, 10 patients). In the SOC only group the most commonly reported AEs were diarrhoea (7.0%, 14 of 200 patients), constipation (4.5%, 9 patients), and

insomnia and pyrexia (each 3.5%, 7 patients). Except for nausea, hypokalaemia and transaminases increased rates of AEs by PTs are comparable between treatment groups.

The rate of adverse events considered related to study treatment was higher in RDV 5-day group (18.8%, 36 patients) compared to RDV 10-day group (13.0%, 7 patients). ADR Nausea was reported more frequently in the RDV 5-day group (6.8%, 13 patients) compared to the RDV 10-day group (3.6%, 7 patients). Other ADRs were comparable between RDV groups.

Due to the study design (randomized, open-label, comparison to SOC), no information about rates of study drug-related AEs from the SOC group is available.

Slightly more patients in the RDV 10-day group discontinued RDV treatment (4.1%, 8 patients) compared to RDV 5-day group (2.1%, 4 patients).

GS-US-540-5774 – Part B:

AEs were reported in 56.1% of the patients. Grade 3 or higher treatment-emergent AEs were reported in 13.5% of the patients. SAEs were recorded in 8.0% of cases. In 16.5% of the patients AEs were considered related to study treatment. In 3.0% of the patients events were reported that led to premature discontinuation of study treatment.

The most commonly reported AEs were nausea (8.2%, 41 patients), diarrhoea (5.6%, 28 patients), and headache (5.4%, 27 patients). The rates of AEs, SAEs, adverse events considered related to study treatment, laboratory abnormalities as well as the rate of AEs that led to premature discontinuation of study treatment were comparable to Part A.

CO-US-540-5776 – patients with baseline ordinal score of 4:

Overall, AEs were reported in 34.7% (26 of 75 patients) in the RDV 10-day group and 28.6% (18 of 63 patients) in the Placebo group. SAEs were reported more frequently in the Placebo group (15.9%) compared to the RDV 10-day group (12.0 %).

In 5.3% (4 patients) in the RDV 10-day group and 3.2% (2 patients) in the Placebo group AEs were considered related to study treatment. In 4.0% (3 patients) and 3.2% (2 patients) in the RDV 10-day and Placebo group adverse events were reported that led to premature discontinuation of study treatment.

Overall, rates of AEs and study drug-related AEs are considerably lower compared to study 5774, whereas rates of SAEs are higher in study 5776.

The most commonly reported AEs in the RDV 10-day group were haemoglobin decreased (6.7%, 5 of 75 patients), prothrombin time prolonged (5.3%, 4 patients), and dyspnea and glomerular filtration rate decreased (each 4%, 3 patients). In the Placebo group, the most commonly reported AEs were acute respiratory failure (6.3%, 4 of 63 patients), haemoglobin decreased (4.8%, 3 patients), and alanine aminotransferase increased (4.8%, 3 patients).

Adverse events leading to discontinuation of study treatment were reported in similar percentages of participants in the RDV 10-day group and the placebo group (RDV 10-day 4.0% [3 participants]; placebo 3.2% [2 participants].

Safety data of patients randomised to the mild/moderate stratum were not provided by the MAH in this procedure but were assessed within the initial CMA procedure. Overall, RDV was in general well tolerated in studies with moderate COVID-19 patients, with less than 5% of patients discontinuing due to AE’s in the studies.

No new safety signal could be identified based on data provided.

2.5.2. Conclusions on clinical safety

RDV was well tolerated in studies with moderate CoVID-19 patients. No new safety signal could be identified based on data provided.

2.5.3. PSUR cycle

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

No changes of the PSUR cycle are proposed. The second PSUR should be submitted in line with the EURD list (i.e. until 15th July 2021, with the DLP in 6th May 2021).

2.5.4. Direct Healthcare Professional Communication

N/A

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

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

The PRAC considered that the risk management plan version 3.0 is acceptable.

The CHMP endorsed this advice without changes.

Safety concerns

Summary of Safety Concerns

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

Pharmacovigilance plan

New routine pharmacovigilance activities

Monitoring of data on treatment failure due to emerging variants

As part of the enhanced signal detection activities for the duration of the COVID-19 pandemic, data on treatment failure due to emerging variants will be monitored from all available data sources, including but not limited to:

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

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

Ongoing and Planned Additional Pharmacovigilance Activities

Activity (Status)	Summary of Objectives	Safety Concerns Addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
remdesivir pregnancy safety report (Ongoing)	To provide information on pregnant women and birth outcomes with the use of RDV during pregnancy from postmarketing sources and the	Safety in pregnancy	Submission of report	Yearly, within the PSUR

Activity (Status)	Summary of Objectives	Safety Concerns Addressed	Milestones	Due dates
	compassionate use program (IN-US-540-5755) and expanded access program (GS-US-540-5821).			
GS-US-540-5912 A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study Evaluating the Efficacy and Safety of remdesivir in Participants with Severely Reduced Kidney Function who are Hospitalized for COVID-19 (Ongoing)	To evaluate the safety and tolerability of RDV in participants with severely reduced kidney function who are hospitalized for COVID-19	Safety in patients with severe renal impairment	Submission of study report	31 January 2023
GS-US-540-9014 A Phase 1 Open-Label, Adaptive, Single-Dose Study to Evaluate the Pharmacokinetics of remdesivir and its Metabolite(s) in Subjects with Normal Hepatic Function and Hepatic Impairment (Ongoing)	To evaluate the pharmacokinetics of RDV and its metabolite(s) in subjects with hepatic impairment	Safety in patients with hepatic impairment	Submission of study report	31 July 2022
GS-US-540-9015 A Phase 1 Open-Label, Parallel-Group, Single-Dose Study to Evaluate the Pharmacokinetics of remdesivir and Metabolites in Participants with Normal Renal Function and Renal Impairment (Ongoing)	To evaluate the pharmacokinetics of RDV and its metabolite(s) in subjects with renal impairment	Safety in patients with severe renal impairment	Submission of study report	30 November 2022
Study of the PK and safety of RDV in pregnant women (IMPAACT 2032)	To evaluate the pharmacokinetics and safety of remdesivir in pregnant individuals with coronavirus	Safety in pregnancy	Submission of study report	31 December 2022

Activity (Status)	Summary of Objectives	Safety Concerns Addressed	Milestones	Due dates
(Ongoing)	disease 2019 (COVID-19).			

Risk minimisation measures

Summary table of Pharmacovigilance Activities and Risk Minimisation activities by safety concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important identified risk(s)		
None		
Important potential risk(s)		
None		
Missing information		
Safety in patients with hepatic impairment	Routine risk minimization measures: SmPC section 4.2, 4.4, 4.8 and 5.2 PL section 2	Additional pharmacovigilance activities: Study GS-US-540-9014 (Phase 1 study in subjects with hepatic impairment) Submission of study report: 31 July 2022
Safety in patients with severe renal impairment	Routine risk minimization measures: SmPC section 4.2, 4.4 and 5.2 PL section 2	Additional pharmacovigilance activities: Study GS-US-540-9015 (Phase 1 study in subjects with renal impairment) Submission of study report: 30 November 2022 Study GS-US-540-5912 (Phase 3 study in patients with severely reduced kidney function who are hospitalized for COVID-19) Submission of study report: 31 January 2023

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Safety in pregnant and lactating women	Routine risk minimization measures: SmPC section 4.6 PL section 2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Postmarketing pregnancy report form Postmarketing pregnancy outcome report form Additional pharmacovigilance activities: remdesivir pregnancy safety report Submission of report: Yearly, within the PSUR Study of the PK and safety of RDV in pregnant women (IMPAACT 2032) Submission of study report: 31 December 2022

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

- In line with the European Commission guideline on the readability of the labelling and package leaflets of medicinal products for human use (Rev.1, 12 January 2009), evidence from tests on similar package leaflets may be used where appropriate. The updates to the PIL in this variation consequential to the extension of indication are limited and do not impact the design and layout of information, concept and style of writing, key messages for safety, route of administration, dose posology, layout of critical safety sections or complexity of language.

- A full user testing report was provided within the ongoing procedure EMEA/H/C/005622/REC/022.1. Although a CHMP opinion is still awaited, the Rapporteur's conclusion was that the updated PIL meets the requirements of Article 59(3).

2.7.2. Additional monitoring

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

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

2.7.3. Quick Response (QR) code

The review of the QR code request submitted by the MAH is presented in a separate attachment to this report (checklist available for download here).

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

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

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

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

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

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

3.1.2. Available therapies and unmet medical need

In the EU four vaccines against SARS-CoV-2 infection are approved.

Treatment with dexamethasone has been proven effective and safe in the treatment of severe COVID-19 disease. Recently, tocilizumab has been approved for the treatment of adults with COVID-19 who are receiving treatment with corticosteroid medicines by mouth or injection and require extra oxygen or mechanical ventilation. Furthermore, remdesivir is approved for the treatment of patients with COVID-19 who require low-flow oxygen, high-flow oxygen or non-invasive mechanical ventilation at the start of therapy.

Currently, two monoclonal antibodies are approved for the treatment of mild and moderate COVID-19 infection outside the hospital setting, Ronapreve (casirivimab/imdevimab) and Regkirona (regdanvimab).

Ronapreve is indicated for treating COVID-19 in adults and adolescents (from 12 years of age and weighing at least 40 kilograms) who do not require supplemental oxygen and who are at increased risk of their disease becoming severe and can also be used for preventing COVID-19 in people aged 12 years and older weighing at least 40 kilograms. Regkirona, is indicated for the treatment of adults with COVID-19 who do not require supplemental oxygen and who are also at increased risk of their disease becoming severe.

The following treatments can be used in the EU to treat COVID-19 after EMA's CHMP completed its review under Article 5(3): dexamethasone and recently molnupiravir. Monoclonal antibodies such as bamlanivimab / etesevimab or sotrovimab are also available under art 5(3).

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

There is a high medical need for an effective agent for treatment of COVID-19.

3.1.3. Main clinical studies

There are three studies supporting the clinical efficacy and safety of RDV for the treatment of moderate COVID-19:

GS-US-540-5774

Phase 3, randomized, open-label, multicenter study comparing 2 RDV regimens (5 days and 10 days) versus standard of care (SOC) in 584 participants with moderate COVID-19 (Part A of Study GS-US-540-5774).

NIAID ACTT-1 (CO-US-5776):

(NIAID)-sponsored Phase 3, randomized, double-blind, placebo-controlled, multicentre study (Study CO-US-540-5776 [Adaptive COVID-19 Treatment Trial (ACTT)-1]. For Study CO-US-540-5776, only the subset of 138 hospitalized participants with moderate COVID-19 were considered.

GS-US-540-9012:

A Phase 3, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of remdesivir (GS-5734™) treatment of early stage COVID-19 who were at higher risk of disease progression in an outpatient setting. Treatment with remdesivir/placebo was administered for three days. Study GS-US-540-9012 was conducted in an outpatient setting, hence the enrolled population does not cover the applied indication of patients with moderate COVID-19. The study was submitted, in order to extrapolate efficacy data from the outpatient setting in patients who are at increased risk of progression to severe disease to the moderate population, including those patients not requiring supplemental oxygen.

Supportive safety data were provided from Part B of Study GS-US-540-5774, in which an additional 503 hospitalized participants with moderate COVID-19 received open-label RDV for up to 10 days.

3.2. Favourable effects

Study GS-US-540-5774 is a randomised, open-label study comparing 5-day remdesivir with SOC and 10-day remdesivir with SOC in patients with “moderate” COVID-19”. The study was conducted in two parts. In Part A, eligible participants are randomized in a 1:1:1 ratio to either 5-day and 10-day remdesivir durations or SOC. The pre-specified primary efficacy analysis was to examine results on a 7-point ordinal scale at Day 11 using a proportional odds model. The Day 11 primary analysis included 584 patients, 191

patients in the 5-day treatment group, 193 patients in the 10-day treatment group and 200 patients in the SOC-arm.

Based on the LOCF-analysis treatment with remdesivir for 5 days resulted in significantly greater improvements in clinical status at Day 11 compared with SOC alone (OR, 1.65; 95% CI 1.09 to 2.48; p = 0.0174). Treatment with remdesivir for 10 days did not result in significantly greater improvements in clinical status at Day 11 compared with SOC alone (OR, 1.31; 95% CI, 0.88 to 1.95; p = 0.1826).

The pivotal NIAID-ACTT1 (GS-US 540 5776) study is a randomised, double-blinded and placebo-controlled study conducted in hospitalised patients with COVID-19, with evidence of lower respiratory tract involvement. Treatment with remdesivir/placebo was for up to 10 days. The primary endpoint was the time to recovery (defined as no longer being hospitalised or being hospitalised but no longer requiring medical care). The analysis population included 1062 patients (541 in the remdesivir group and 521 in the placebo group). As already evaluated in the procedure EMEA/H/C/005622/0000 and lately in the EMEA/H/C/005622/II/0012, remdesivir showed efficacy in patients with a baseline ordinal score of 5. These assessment led to the current indication of RDV for the treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or non-invasive ventilation at start of treatment). In total, 159 patients were stratified to the mild/moderate disease stratum and included in the respective analyses to support the applied indication., Analyses based on baseline ordinal score of 4 included 138 patients.

In the stratum of patients with mild/moderate disease, no difference in time to recovery was seen in the stratum of "mild-moderate disease".

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

Study GS-US-540-9012 showed superiority of remdesivir treatment compared to placebo in reducing COVID-19 related hospitalisation and all-cause death in high-risk, non-hospitalised and unvaccinated COVID-19 patients.

Treatment with remdesivir for 3 days resulted in an 87% relative risk reduction in COVID-19 related hospitalisation and all-cause death by day 28 compared to placebo. The corresponding absolute risk reduction was 4.6% (95% CI, 1.8%, 7.5%) and the number needed to treat (NNT) is 22 patients (95% CI, 14, 56). COVID-19 related hospitalisation by day 28 were reported for 2 of the 279 (0.7%) remdesivir treated patients, compared 15 of the 283 (5.4%) placebo treated patients (p=0.0076). No death was reported in either treatment group by day 28.

In the presented subgroup analyses, effects in favour of remdesivir were observed for US-patients, patients > 60 years of age, male patients, patients with hypertension, diabetes mellitus and obesity. Subgroup analysis of the primary efficacy endpoint by presence of one, two, three and four risk factors showed a consistent treatment effects in favour of remdesivir.

3.3. Uncertainties and limitations about favourable effects

There is a lack of data supporting a beneficial effect of remdesivir in patients with mild/moderate disease.

The design and outcomes of the 5774 study is prone to serious limitations, due to essential methodological deficiencies including the changing of central elements of the statistical analysis SAP during the conduct of the open-label study with an endpoint allowing for a considerable degree of subjectivity.

Study GS-US-5774 failed to show superiority of the 10-day remdesivir treatment compared to SOC. On the contrary, the data indicate 5 days may be more beneficial than 10 days.

The observed statistically significant effect in the 5-day remdesivir group cannot be considered robust enough due to the essential methodological deficiencies and the open label design of the study.

Secondary endpoints were analysed without any hierarchy such that any interpretation regarding the 'significance' of single outcomes should be interpreted with care. Efficacy data failed to demonstrate a statistically significant effect of remdesivir on the duration of hospitalisation (5-day RDV: 8 days, 10-day RDV: 9 days; SOC: 8 days), time to clinical improvement ≥ 2-Points (5-day RDV: 6 [5,14]) days, 10-day RDV: 8 [4, 14] days, SOC: 8 [5, 22] days), time to clinical improvement ≥ 1-Point (5-day RDV: 6 [4, 9] days, 10-day RDV: 7 [4, 12] days; SOC 7 [4, 14] days) or time to recovery (5-day RDV: 6 [5, 10] days, 10-day RDV: 8 [4, 13] days SOC: 7 [4, 15] days).

The provided post-hoc analysis related to the proportions of participants with disease worsening, cumulative hospital discharge and recovery are considered to be of no added value, due to the post-hoc potentially data-driven nature of the analyses (i.e. no type-1 error control) and the inconsistent outcomes at different study days.

Time to recovery by oxygen support at baseline showed no beneficial effect of remdesivir on the median (Q1, Q3) times to recovery in the remdesivir 5-day and remdesivir 10 day groups compared with those in the SOC only group was observed, neither for participants on high-flow or low-flow oxygen at baseline, nor for participants on room air.

Subgroup analysis by baseline oxygen support status did not show any meaningful effect between the two treatment groups on clinical status at Day 11.

No differences in median time to clinical recovery or for hospital discharge were seen in patients with different oxygen support status.

Study 5774 failed to show an antiviral effect of remdesivir, which is of concern, since, as yet, in-vivo proof-of-concept related to the remdesivir's mechanism of action is missing.

The NIAID study failed to demonstrate a beneficial effect of remdesivir in patients with mild/moderate disease, neither for the primary endpoint nor for any of the analysed secondary endpoints. However, it has to be noted that the study was not powered to show statistically significant differences in the respective disease strata.

No difference on the time to recovery, the primary endpoint of the NIAID study, was seen, neither in the mild/moderate nor in the subset of patients with baseline ordinal score of 4.

For all pre-specified sensitivity analyses of the primary efficacy analyses, no effect of remdesivir on time to recovery was seen in the mild/moderate population, consistent with the primary efficacy analyses.

In the sensitivity analysis examining the effect of unsustained recovery (readmittance for hospitalization) no statistically significant benefit for the remdesivir 10-day group compared to the placebo group in the

mild/moderate disease stratum, consistent with the analysis of the primary endpoint (RDV: 6 days [95% CI: 5, 8] Placebo: 7 days [95% CI: 5, 10]; RRR 1.05; 95% CI: 0.75, 1.47)).

No statistically significant effect of remdesivir on the odds of improvement in clinical status at Day 15 determined by a proportional odds model were seen, neither for patients with baseline ordinal score 4 (OR for improvement, 1.5; 95% CI: 0.8, 2.7; p = 0.234), nor for patients in the mild/moderate disease stratum (OR for improvement, 1.2; 95% CI: 0.7, 2.2; p = 0.475).

Sub-group analyses in the ITT Population showed no effect of remdesivir on time to clinical improvement by ≥ 1 or ≥ 2 clinical status categories, neither for patients with baseline ordinal score 4, nor for patients in the mild/moderate disease stratum

Sub-group analyses in the ITT Population showed no effect of remdesivir on time to discharge or to NEWS ≤ 2 in the in the RDV group compared to placebo, neither for patients with baseline ordinal score 4, nor for patients in the mild/moderate disease stratum.

The strategy of blinding was inconsistent due to change from placebo to match to normal saline as placebo and was thus not consequently kept the same throughout the study, which might have biased the blinding and thus the integrity of the study.

Sample size of patients with mild/moderate disease in the NIAID trial is small.

Study GS-US-540-9012

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

Study 9012 failed to show an antiviral effect of remdesivir, which is of concern, since, as yet, *in-vivo* proof-of-concept related to remdesivir's mechanism of action is missing.

Study 9012 failed to show an effect of remdesivir on alleviation of baseline COVID-19 symptoms.

No statistically significant effect in the proportion of participants requiring oxygen supplementation by Day 28 or prior to study discontinuation was seen. The severity of the cases of hospitalisation was similar in both groups.

No information on the baseline serostatus was provide. Thus, the impact of baseline serostatus on remdesivir efficacy in patients not requiring supplemental oxygen at risk for severe disease progression remains unclear but will be further address in a future PAM.

In the presented subgroup analyses, effects in favour of remdesivir were observed for US-patients, patients > 60 years of age, male patients, patients with hypertension, diabetes mellitus and obesity. Subgroup analysis of the primary efficacy endpoint by presence of one, two, three and four risk factors showed a consistent treatment effects in favour of remdesivir. However, due to the small number of events, robust subgroup analysis was not possible such that the consistency of the effect across subgroups cannot be assessed.

The submitted data provide no clear picture on the duration of therapy. Study 5774 failed to show an advantage of the longer treatment. They may even be indicative of detrimental effect of longer use. However, less than 50% of the patients in each of these studies received a full 10-day treatment course. While the pivotal NIAID ACTT1-study was designed to prove efficacy of a 10-day treatment course, factually only one third of the patients received a full treatment course. The observed effect in the 5-day RDV group of study 5774 cannot be regarded as statistically robust, due to methodological limitations that rendered study 5774 as not statistically robust. Based on these data it was anticipated that rather a 5-day treatment course appears generally indicated.

A different treatment duration was used in study 9012, compared to studies 5774 and the NIAID ACTT-1 trial, i.e. three days of remdesivir treatment instead of the approved five days to up to ten days. The lack of comparative data between the different treatment durations, the lack of antiviral activity, the potential risk of development of resistance due to the shorter treatment duration and the lack of scientific data supporting the shorter treatment duration currently hamper the assessment of the shorter treatment duration, especially in immunocompromised patients.

The virology report of study 9012 is currently missing but will be submitted.

Another uncertainty is the present lack of in-vivo proof of concept of anti SARS-CoV-2 activity. All to date conducted remdesivir studies failed to demonstrate an antiviral effect of remdesivir on viral load in patients with mild/moderate or severe COVID-19. In view of the apparent lack of *in vivo* antiviral activity/proof of concept, the benefit of earlier treatment with remdesivir and the place of remdesivir in the landscape of COVID-19 disease course and therapies remains unclear.

A further uncertainty is the unknown resistance profile of remdesivir.

3.4. Unfavourable effects

Overall, 962 patients with moderate COVID-19 have received RDV for up to ten days (the maximal proposed duration) within randomised clinical trials in COVID-19. Furthermore, 279 patients were investigated in an outpatient setting in participants with confirmed coronavirus disease 2019 (COVID-19) who were at risk for disease progression.

In Gilead Moderate Simple trial GS-US-540-5774 – Part A the most commonly reported AEs in the RDV 5 days group were nausea (9.9%, 19 patients), diarrhoea (6.3%, 12 patients), hypokalaemia and headache (each 5.2%, 10 patients). In the RDV 10 days group, the most commonly reported AEs were nausea (9.3%, 18 of 193 patients), hypokalaemia (6.7%, 13 patients), diarrhoea and headache (each 5.2%, 10 patients). Except for nausea, hypokalaemia and transaminases increased rates of AEs by PTs are comparable between RDV and SOC groups. The rate of adverse events considered related to study treatment was higher in RDV 5 days group (18.8%, 36 patients) compared to RDV 10 days group (13.0%, 7 patients). ADR Nausea was reported more frequently in the RDV 5 days group (6.8%, 13 patients) compared to the RDV 10 days group (3.6%, 7 patients). Other ADRs were comparable between RDV groups.

In Gilead Moderate Simple trial GS-US-540-5774 – Part B reported rates of AEs, SAEs, ADRs and treatment discontinuation are comparable to the safety data from Part A.

The most commonly reported AEs were nausea (8.2%, 41 patients), diarrhoea (5.6%, 28 patients), and headache (5.4%, 27 patients). The rates of AEs, SAEs, adverse events considered related to study treatment, laboratory abnormalities as well as the rate of AEs that led to premature discontinuation of study treatment were comparable to Part A.

In patients with baseline ordinal score of 4 in study CO-US-540-5776 AEs were reported in 34.7% (26 of 75 patients) in the RDV 10-day group and 28.6% (18 of 63 patients) in the Placebo group. SAEs were reported more frequently in the Placebo group (15.9%) compared to the RDV 10-day group (12.0 %).

In 5.3% (4 patients) in the RDV 10-day group and 3.2% (2 patients) in the Placebo group AEs were considered related to study treatment. In 4.0% (3 patients) and 3.2% (2 patients) in the RDV 10-day and Placebo group adverse events were reported that led to premature discontinuation of study treatment.

Overall, rates of AEs and study drug-related AEs are considerably lower compared to study 5774, whereas rates of SAEs are higher in study 5776.

The most commonly reported AEs in the RDV 10-day group were haemoglobin decreased (6.7%, 5 of 75 patients), prothrombin time prolonged (5.3%, 4 patients), and dyspnoea and glomerular filtration rate decreased (each 4%, 3 patients). In the Placebo group, the most commonly reported AEs were acute respiratory failure (6.3%, 4 of 63 patients), haemoglobin decreased (4.8%, 3 patients), and alanine aminotransferase increased (4.8%, 3 patients).

Adverse events leading to discontinuation of study treatment were reported in similar percentages of participants in the RDV 10-day group and the placebo group (RDV 10-day 4.0% [3 participants]; placebo 3.2% [2 participants].

In Study GS-US-540-9012, AEs were reported in 42.3% (118 patients) of the patients in the RDV 3-day group and 46.3% (93 patients) in the Placebo group. In 12.2% (34 patients) in the RDV 3-day group and 8.8% (25 patients) in the Placebo group AEs were considered related to study treatment. SAEs were reported less frequently in the RDV 3-day group (1.8%, 5 patients) compared to the Placebo group (6.7 %, 19 patients). None of these SAEs were considered related to study drug. In 2 patients (0.7%) in the RDV 3-day group and 5 patients (1.8%) in the Placebo group adverse events were reported that led to premature discontinuation of study treatment.

The most commonly reported AEs in the RDV 3-day group were nausea 10.8% (30 patients), headache (5.7%, 16 patients), diarrhoea (3.9%, 11 patients), cough and fatigue (each 3.6%, 10 patients). In the Placebo group, the most commonly reported AEs were nausea (7.4%, 21 patients), cough (6.4%, 18 patients), headache (6.0%, 17 patients) and dyspnoea (5.3%, 17 patients). The rates of commonly reported AEs were comparable between treatment groups. Only for the AE nausea more cases were reported in the RDV 3-day group (see more details in the safety section).

Overall, taking the preclinical finding of severe renal toxicity in animal studies on rats and monkeys into account, cases with Grade 3 or 4 creatinine increased and creatinine clearance decreased should be further closely monitored and discussed in upcoming PSURs.

When comparing safety data of Study GS-US-540-9012 with data from Study GS-US-540-5774 and subgroup analysis of participants with baseline ordinal score of 4 of Study GS-US-540-5776 the reported safety profile is broadly comparable. No new safety signal could be identified.

Overall, remdesivir was in general well tolerated in studies with moderate COVID-19 patients, with less than 5% of patients discontinuing due to AE's in the studies.

3.5. Uncertainties and limitations about unfavourable effects

remdesivir was in general well tolerated in studies with moderate COVID-19 patients. No further uncertainties were identified.

3.6. Effects Table

Table 58 Effects Table for Veklury for the treatment of coronavirus disease 2019 (COVID-19) in adults with pneumonia not requiring supplemental oxygen.

Effect	Short description	Unit	RDV	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Clinical status at D11	Clinical status on a 7-point ordinal scale at D11	Odds of improvement	RDV 5 days: OR: 1.65; 95% CI 1.09 to 2.48; p = 0.0174		**SoE:** RDV 5 days: OR: 1.65; 95% CI 1.09 to 2.48; **p = 0.01745**	(1)

Effect	Short description	Unit	RDV	Control	Uncertainties / Strength of evidence	References
			RDV 10 days: OR: 1.31; 95% CI, 0.88 to 1.95; p = 0.1826		**Unc:** RDV 10 days: OR: 1.31; 95% CI, 0.88 to 1.95; **p = 0.1826** **Unc:** Statistically significance in favour of 5-day RDV vs SOC is **critically dependent on the way missing data** were handled. **Unc:** Statistically significant difference of 5-day RDV vs SOC **not robust**, Alternative analyses (observed case, missing at random or missing not at random based imputation) showed no statistical significant difference of 5 days RDV vs SoC. **Unc:** No plausible reason why a 10-day course of RDV leads to worse outcomes than a 5-day course **Unc:** Failure to show a significant difference of the 10-day course vs SOC means there is **no "internal replication",** raising concerns on the **internal validity** of the finding for the 5-day RDV course	
Recovery	Days of recovery	Median time [95%CI]	RDV-5-day: 8 [5, 9] RDV-10-day: 9 [4, 11]	8 [4,10]	**Unc:** Median TTR **did not significantly differ** between RDV and placebo for the stratum of **patients with mild/moderate disease**.	(1)
Recovery	Days of recovery	Median time [95%CI]	5 [4, 6]	7 [5, 9]	**Unc:** Median TTR **did not differ** between RDV and placebo for the stratum of **patients with mild/moderate disease**.	(2)
Clinical status at D15	Clinical status on a 8-point ordinal scale at day 15	Odds of improvement	OR: 1.2; 95% CI: 0.7, 2.2; p = 0.475		**Unc:** OR **did not differ** between RDV and placebo for the stratum of **patients with mild/moderate disease**.	(2)
Antiviral effect		c/ml	N/A		**Unc:** Lack of *in vivo* data that demonstrate antiviral effect (POC) **Unc:** Lack of antiviral effect based on interim viral load data presented from the NIAID-ACTT1 study. **Unc:** Available data from study -5774 do not show any apparent antiviral effect of RDV.	(1,2)
Unfavourable Effects						
Important potential risk	Hepatotoxicity fo RDVNephrotoxicity of RDV and SBECD Hypersensitivity including Infusion-Related Reaction				**SoE:** Hepato and nephrotoxicity**:** overall**,** no difference in frequency compared to placebo **Unc:** Lack of data	(1,2)

Abbreviations: RRR: Recovery Rate Ratio, LD: loading dose, MD maintenance dose, IV: intravenous RDV: remdesivir, PBO: Placebo, POC: Proof of concept, OR: Odds Ratio; HR: Hazard Ratio, IMV: invasive mechanical ventilation, ECMO: extracorporeal membrane oxygenation, TTR: Time to Recovery, SoC: Standard of Care

Notes: (1) Study Simple Moderate (GS-US-540-5774), (2) Study NIAID-ACTT1 (GS-US 540 5776)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

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

For the primary endpoint clinical status at Day 11, a statistically significant difference in the distribution in clinical status at Day 11 for participants receiving a 5-day course of remdesivir compared with those receiving SOC alone was found (p=0.017). However, the observed difference cannot be considered robust enough due to the identified methodological deficiencies of study 5774, the open label design and the outcome encompassing a considerable degree of subjectivity, and the conclusion of a statistical significant difference critically depends on the method for missing data handling.

As already concluded in the initial assessment of the NIAID-ACTT-1 efficacy data during the CMA procedure, the mild/moderate stratum was too small to be able to show any effect independently.

Hence, for the moderate population there was no robust statistical evidence of clinical efficacy available.

However, the submitted study GS-US-540-9012 showed superiority of remdesivir treatment compared to placebo in reducing COVID-19 related hospitalisation and all-cause death in high-risk, non-hospitalised and unvaccinated COVID-19 patients. With the exception of eight patients, all enrolled participants had at least one risk factor. The most common baseline risk factors were diabetes mellitus (62%), obesity (56%) and hypertension (48%) and were equally distributed across treatment arms. 30% of the enrolled patients were >60 year of age. Based on available virology data, none of the participants was infected with the Delta variant.

For the primary endpoint, treatment with remdesivir for 3 days resulted in an 87% reduction in COVID-19 related hospitalisation and all-cause death by day 28 compared to placebo. The corresponding absolute risk reduction was 4.6% (95% CI, 1.8%, 7.5%) and the number needed to treat (NNT) is 22 patients (95% CI, 14, 56). COVID-19 related hospitalisation by day 28 were reported for 2 of the 279 (0.7%) remdesivir treated patients, compared 15 of the 283 (5.4%) placebo treated patients (p=0.0076). No death was reported in either treatment group by day 28.

In the presented subgroup analyses, effects in favour of remdesivir were observed for US-patients, patients > 60 years of age, male patients, patients with hypertension, diabetes mellitus and obesity. Subgroup analysis of the primary efficacy endpoint by presence of one, two, three and four risk factors showed a consistent treatment effects in favour of remdesivir. However, due to the small number of events, robust subgroup analysis was not possible such that the consistency of the effect across subgroups cannot be assessed.

Opposed to this, no effect on viral load and alleviation of baseline COVID-19 symptoms was seen in study 9012. Furthermore, study 9012 failed to show an effect of remdesivir on alleviation of baseline COVID-19 symptoms. In addition, no statistically significant effect in the proportion of participants requiring oxygen supplementation by Day 28 or prior to study discontinuation was seen. The severity of the cases of hospitalization was similar in both groups.

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

No information on the baseline serostatus was provide. Thus, the impact of baseline serostatus on remdesivir efficacy in patients not requiring supplemental oxygen at risk for severe disease progression remains unclear. To address this uncertainty further data shall be provided by the company.

In the presented subgroup of the primary endpoint in patients with symptom onset < 5 days and ≥ 5 days no robust analyses could be made due to the small number of events (< 5 days RDV: 0 vs Placebo: 8 [5.8%] cases of hospitalisation, ≥ 5 days RDV 2 [1.5%] vs. Placebo: 7 [5.0%] cases of hospitalisation or death). However, based on the subgroup analyses and in view of the inclusion criteria of study 9012, it should be recommended that treatment should be initiated within seven days of symptom onset.

The submitted data provide no clear picture on the duration of therapy. At the time of CMA that a treatment duration of 5 days up to at least ten day. A different treatment duration was used in study 9012, compared to studies 5774 and the NIAID ACTT-1 trial, i.e. three days of remdesivir treatment instead of the approved five days to up to ten days. The lack of comparative data between the different treatment durations, the lack of antiviral activity, the potential risk of development of resistance due to the shorter treatment duration and the lack of scientific data supporting the shorter treatment duration currently hamper the assessment of the shorter treatment duration, especially in immunocompromised patients.

Another uncertainty is the present lack of *in-vivo* proof of concept of anti SARS-CoV-2 activity. All to date conducted remdesivir studies failed to demonstrate an antiviral effect of remdesivir on viral load in patients with mild/moderate or severe COVID-19. In view of the apparent lack of *in vivo* antiviral activity/proof of concept, the benefit of earlier treatment with remdesivir and the place of remdesivir in the landscape of COVID-19 disease course and therapies remains unclear.

Remdesivir was in general well tolerated in studies with moderate COVID-19 patients. No further uncertainties were identified.

3.7.2. Balance of benefits and risks

Remdesivir was given a 'conditional marketing authorisation' in the EU on 3 July 2020 for the treatment of COVID-19 in adults and adolescents from 12 years of age with pneumonia who require supplemental oxygen (oxygen via nasal cannula, non-invasive ventilation or high flow oxygen devices, IMV or ECMO).

At the time of the CMA the CHMP already concluded that no beneficial effect of remdesivir was demonstrated in mild/moderately ill patients. No new additional efficacy data were submitted in the first rounds of this procedure.

In the previous round of this procedure, CHMP concluded that study GS-US-540-5774 does not provide robust statistical evidence of clinical efficacy and prevents any conclusion on the benefit of remdesivir in mild/moderate disease, due to essential methodological deficiencies. Furthermore, in study NIAID ACTT-1 the mild/moderate stratum was too small to be able to show any effect independently. Hence, for the moderate population there was no robust statistical evidence of clinical efficacy available. Interim viral load data of the NIAID-ACTT-1 trial that have recently been submitted and are currently under assessment (EMEA/H/C/005622/REC/033) do not indicate an antiviral effect of remdesivir on viral load. Hence, *in vivo* proof of concept for remdesivir has not been demonstrated.

In response, to the previous round, the MAH submitted with study GS-US-540-9012 new data from the outpatient setting in order to support the initially applied proposed extension of indication to patients with moderate disease. The proposal was that the efficacy data from study 9012 could be used to extrapolate efficacy from the outpatient setting in patients at increased risk of progression to severe disease to the initially applied moderate population.

Based on the primary efficacy analyses of study GS-US-540-9012, it can be concluded that remdesivir treatment is effective in preventing disease progression in high-risk, non-hospitalised and unvaccinated patients.

However, based on currently available data on the natural course of COVID-19, it is anticipated that the window of opportunity for an antiviral, such as remdesivir is early in the disease course. The benefit of earlier treatment with antivirals refers to their potential to reduce viral load in times when viral replication is high, i.e. early during the COVID-19 disease course, and thereby avoiding clinical deterioration. However, all conducted studies with remdesivir failed to demonstrate the *in-vivo* proof-of-concept related to remdesivir's mechanism of action. This is surprising, considering that in other antiviral treatment trials *in vivo* proof of concept by nasopharyngeal swab samples was demonstrated. In view of the apparent lack of *in vivo* antiviral activity/proof of concept, the benefit of earlier treatment with remdesivir and the place of remdesivir in the landscape of COVID-19 disease course and therapies remains unclear.

Overall, the submitted efficacy data of study 9012 demonstrated a beneficial effect of remdesivir in preventing disease progression in high-risk, non-hospitalised and unvaccinated COVID-19 patients. Subgroup analysis indicate consistent effects in favour of remdesivir for US-patients, patients > 60 years of age, male patients, patients with hypertension, diabetes mellitus and obesity. Subgroup analysis of the primary efficacy endpoint by presence of one, two, three and four risk factors showed a consistent treatment effects in favour of remdesivir. However, due to the small number of events, robust subgroup analysis was not possible such that the consistency of the effect across subgroups cannot be assessed. As no vaccinated patients were enrolled in study 9012, which should be reflected in section 5.1 of the SmPC, it remains unclear, if the magnitude of benefit of remdesivir documented in study 9012 in unvaccinated patients is applicable to a population comprising vaccinated and/or naturally primed seropositive subjects. Furthermore, the impact of the baseline serostatus on the efficacy outcome remains currently unclear. In addition, it is currently unclear, if remdesivir retains its antiviral activity against the emerging Omicron variant. In view of the provided subgroup analysis with symptom onset < 5 days and ≥ 5 days and in line with the inclusion criteria of study 9012, a recommendation to initiate treatment within 7 days of symptom onset is considered necessary.

The provided data of study GS-US-540-9012 is considered sufficient to conclude on a positive B/R in patients with COVID-19, who do not require supplemental oxygen and at increased risk for disease progression. However, the MAH has been requested to address post-authorisation the efficacy of remdesivir in seropositive/seronegative patients, the virology analysis to support the 3-day treatment course and the *in vitro* analyses of the antiviral activity of remdesivir against the Omicron variant. The current lack of the respective data warrant a reflection in the SmPC. Furthermore, in view of the observed rates of adverse events and high rate of important protocol deviations in the outpatient setting, additional wording the product information concerning the monitoring of patients receiving remdesivir infusion in the outpatient setting in is considered necessary.

3.7.3. Additional considerations on the benefit-risk balance

Clinical data of the Solidarity trial and the DisCoVeRy trial do not indicate a beneficial effect of remdesivir in the treatment of patients with COVID-19 independent of disease severity. Of particular interest are the viral load data that were evaluated in the DisCoVeRy trial that do not indicate an antiviral activity of remdesivir, neither in the overall population, nor in the moderate disease stratum (see procedure EMEA/H/C/005622/LEG/031).

3.8. Conclusions

The provided data of study GS-US-540-9012 is considered sufficient to demonstrate efficacy in adult patients who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.

The MAH committed to provide the requested missing data as PAMs.

The benefit/risk balance of Veklury considered positive.

The following measures are considered necessary to address issues related to efficacy:

- The MAH should submit a post hoc analyses of the primary and secondary efficacy endpoint stratified by baseline serostatus that will be available in Q1 2022.
- The MAH committed to provide the final virology report in the first half of 2022, which will include sequencing analyses for participants with viral load above LLOD on Day 14, and a phenotypic analysis for clinical isolated with treatment emergent amino acid substitutions in nsp12 compared to their baseline samples .

Note: The antiviral activity against variants should be also further characterised. However, this is covered by SOB number 12 and therefore, there is no need to create a new measure for this issue. The pharmacovigilance plan is also updated.

4. Recommendations

Outcome

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

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

Extension of indication to include treatment of adults who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19; as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. An update of the Risk Management Plan (RMP) (Version 3.0) has been also submitted.

Amendments to the marketing authorisation

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