1. NAME OF THE MEDICINAL PRODUCT

Veklury® 100 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 100 mg of remdesivir. After reconstitution, each vial contains 5 mg/mL of remdesivir solution.

Excipients with known effect

Each vial contains 3 g betadex sulfobutyl ether sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion (powder for concentrate).
White to off-white to yellow powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

(see section 5.1)

4.2 Posology and method of administration

Patients should be monitored when receiving remdesivir (see section 4.4).

Patients receiving remdesivir in an outpatient setting should be monitored according to local medical practice. Use under conditions where treatment of severe hypersensitivity reactions, including anaphylaxis, is possible.

Posology

Table 1: Recommended dose in adults and paediatric patients

	Given by intravenous infusion		
	Adults	**Paediatric patients (weighing at least 40 kg)**	**Paediatric patients at least 4 weeks old (weighing at least 3 kg but less than 40 kg)**
Day 1 (single loading dose)	200 mg	200 mg	5 mg/kg
Day 2 and onwards (once daily)	100 mg	100 mg	2.5 mg/kg

Table 2: Treatment duration

	Adults	**Paediatric patients (weighing at least 40 kg)**	**Paediatric patients at least 4 weeks old (weighing at least 3 kg but less than 40 kg)**
Patients with **pneumonia and requiring supplemental oxygen**	The recommended duration of treatment is **5 days**	The recommended duration of treatment is **5 days**	**Daily for up to a total of 10 days**
Patients who **do not require supplemental oxygen and are at increased risk for progressing to severe COVID-19**	The total duration of treatment should be **3 days**, starting as soon as possible after diagnosis of COVID-19 and within 7 days of the onset of symptoms.	Not applicable.	Not applicable.

Special populations

Elderly
No dose adjustment of remdesivir is required in patients over the age of 65 years (see sections 5.1 and 5.2).

Renal impairment
The pharmacokinetics of remdesivir have not been evaluated in patients with renal impairment. Patients with eGFR ≥ 30 mL/min have received remdesivir for treatment of COVID-19 with no dose adjustment. Remdesivir should not be used in patients with eGFR < 30 mL/min (see sections 4.4 and 5.2).

Hepatic impairment
The pharmacokinetics of remdesivir have not been evaluated in patients with hepatic impairment. It is not known if dosage adjustment is appropriate in patients with hepatic impairment (see sections 4.4 and 5.2).

Paediatric population
The safety and efficacy of remdesivir in children less than 4 weeks of age and weighing less than 3 kg have not yet been established. No data are available.

Immunocompromised population
The safety and efficacy of remdesivir in immunocompromised patients have not yet been established. Only limited data are available (see section 4.4).

Method of administration

For intravenous use.

Remdesivir is for administration by intravenous infusion after reconstitution and further dilution.

It must not be given as an intramuscular (IM) injection.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

Table 3: Recommended rate of infusion – for reconstituted and diluted remdesivir powder for concentrate for solution for infusion in adults and paediatric patients weighing at least 40 kg

Infusion Bag Volume	Infusion Time	Rate of Infusion
250 mL	30 min	8.33 mL/min
	60 min	4.17 mL/min
	120 min	2.08 mL/min
100 mL	30 min	3.33 mL/min
	60 min	1.67 mL/min
	120 min	0.83 mL/min

Table 4: Recommended rate of infusion – for reconstituted and diluted remdesivir powder for concentrate for solution for infusion in paediatric patients at least 4 weeks of age and weighing at least 3 kg but less than 40 kg

Infusion Bag Volume	Infusion Time	Rate of Infusion[a]
100 mL	30 min	3.33 mL/min
	60 min	1.67 mL/min
	120 min	0.83 mL/min
50 mL	30 min	1.67 mL/min
	60 min	0.83 mL/min
	120 min	0.42 mL/min
25 mL	30 min	0.83 mL/min
	60 min	0.42 mL/min
	120 min	0.21 mL/min

a Rate of infusion may be adjusted based on total volume to be infused.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hypersensitivity including infusion-related and anaphylactic reactions

Hypersensitivity reactions including infusion-related and anaphylactic reactions have been observed during and following administration of remdesivir. Signs and symptoms may include hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnoea, wheezing, angioedema, rash, nausea, vomiting, diaphoresis, and shivering. Slower infusion rates, with a maximum infusion time of up to 120 minutes, can be considered to potentially prevent these signs and symptoms. Monitor patients for hypersensitivity reactions during and following administration of remdesivir as clinically appropriate. Patients receiving remdesivir in an outpatient setting should be monitored after administration according to local medical practice. If signs and symptoms of a clinically significant hypersensitivity reaction occur, immediately discontinue administration of remdesivir and initiate appropriate treatment.

Transaminase elevations

Transaminase elevations have been observed in the remdesivir clinical trials, including in healthy volunteers and patients with COVID-19. Liver function should be determined in all patients prior to starting remdesivir and should be monitored while receiving it as clinically appropriate. No clinical studies with remdesivir have been conducted in patients with hepatic impairment. Remdesivir should only be used in patients with hepatic impairment if the potential benefit outweighs the potential risk.

- Remdesivir should not be initiated in patients with alanine aminotransferase (ALT) ≥ 5 times the upper limit of normal at baseline
- Remdesivir should be discontinued in patients who develop:
  - ALT ≥ 5 times the upper limit of normal during treatment with remdesivir. It may be restarted when ALT is < 5 times the upper limit of normal.
    OR

- ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or international normalised ratio (INR) (see sections 4.8 and 5.2).

Renal impairment

In animal studies on rats and monkeys, severe renal toxicity was observed (see section 5.3). The mechanism of this renal toxicity is not fully understood. A relevance for humans cannot be excluded.

All patients should have eGFR determined prior to starting remdesivir and while receiving it as clinically appropriate. Remdesivir should not be used in patients with eGFR < 30 mL/min.

Risk of reduced antiviral activity when coadministered with chloroquine or hydroxychloroquine

Coadministration of remdesivir and chloroquine phosphate or hydroxychloroquine sulphate is not recommended based on *in vitro* data demonstrating an antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of remdesivir (see sections 4.5 and 5.1)

Immunocompromised patients:

It is unclear if the treatment duration of three days is sufficient to clear the virus in immunocompromised patients, in whom prolonged viral shedding occurs. There is a potential risk of resistance development. Only limited data are available.

Excipients

Veklury contains betadex sulfobutyl ether sodium, which is renally cleared and accumulates in patients with decreased renal function, which may potentially adversely affect renal function. Therefore Veklury should not be used in patients with eGFR < 30 mL/min (see sections 4.2 and 5.2).

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Due to antagonism observed *in vitro*, concomitant use of remdesivir with chloroquine phosphate or hydroxychloroquine sulphate is not recommended.

Pharmacokinetic interactions

Effects of other medicinal products on remdesivir
In vitro, remdesivir is a substrate for esterases in plasma and tissue, drug metabolizing enzyme CYP3A4 and is a substrate for Organic Anion Transporting Polypeptides 1B1 (OATP1B1) and P-glycoprotein (P-gp) transporters. GS-704277 (a metabolite of remdesivir) is a substrate for OATP1B1 and OATP1B3.

A drug-drug interaction study was conducted with remdesivir. Table 5 summarises the pharmacokinetic effects of studied drugs on remdesivir and metabolites GS-704277 and GS-441524.

Table 5: Effect of other drugs on remdesivir and metabolites GS-704277 and GS-441524

Co-administered Drug Dose (mg)	Interaction Geometric mean change (%)	Recommendation concerning co-administration
Cyclosporin 400 single dose	remdesivir: C_{max} ↑49% AUC_{inf} ↑89% GS-704277: C_{max} ↑151% AUC_{inf} ↑197% GS-441524: C_{max} ↑17% AUC_{inf} ↔ No interactions are expected when co-administering remdesivir with inhibitors of OATP1B1/1B3 and/or P-gp.	No dose adjustment of remdesivir is required when it is co-administered with inhibitors of OATP1B1 and OATP1B3.
Carbamazepine 300 twice daily	remdesivir: C_{max} ↓13% AUC_{inf} ↓8% GS-704277: C_{max} ↔ AUC_{inf} ↔ GS-441524: C_{max} ↔ AUC_{inf} ↓17% No interactions are expected when co-administering remdesivir with strong CYP3A4 inducers or CYP3A4 inhibitors.	No dose adjustment of remdesivir is required when it is co-administered with strong CYP3A4 and/or P-gp inducers.

NOTE: Interaction study conducted in healthy volunteers.

Effects of remdesivir on other medicinal products
In vitro, remdesivir is an inhibitor of CYP3A4, UGT1A1, MATE1, OAT3, OCT1, OATP1B1 and OATP1B3. Until respective clinical data become available, the coadministration of sensitive substrates of these enzymes and/or transporters should be considered with caution. Remdesivir induced CYP1A2 and potentially CYP3A *in vitro.* Co-administration of remdesivir with CYP1A2 or CYP3A4 substrates with narrow therapeutic index may lead to loss of their efficacy.

Dexamethasone is a substrate of CYP3A4 and although remdesivir inhibits CYP3A4, due to remdesivir's rapid clearance after IV administration, remdesivir is unlikely to have a significant effect on dexamethasone exposure.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data from the use of remdesivir in pregnant women. (less than 300 pregnancy outcomes). Most of the exposures occurred in the second, third or an unknown trimester and available data do not indicate any risk.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at exposures of the major metabolite of remdesivir that were around human therapeutic exposures (see section 5.3).

Due to very limited experience, remdesivir should not be used during first trimester in pregnancy unless the clinical condition of the woman requires treatment with it. Use in the second and third trimester of pregnancy may be considered.
Use of effective contraception during treatment should be considered in women of child-bearing potential.

Breast-feeding

Remdesivir and its major metabolite are excreted into breast milk in very small amounts after intravenous administration. No clinical effect on the infant, is expected due to low breast milk transfer and poor oral bioavailability.

As the clinical experience is limited, a decision about breast-feeding during treatment should be made after a careful individual benefit-risk assessment.

Fertility

No human data on the effect of remdesivir on fertility are available. In male rats, there was no effect on mating or fertility with remdesivir treatment. In female rats, however, an impairment of fertility was observed (see section 5.3). The relevance for humans is unknown.

4.7 Effects on ability to drive and use machines

Remdesivir is predicted to have no or negligible influence on these abilities.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reaction in healthy volunteers is increased transaminases (14%). The most common adverse reaction in patients with COVID-19 is nausea (4%).

Tabulated summary of adverse reactions

The adverse reactions in Table 6 are listed below by system organ class and frequency. Frequencies are defined as follows: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); not known (cannot be estimated from the available data).

Table 6: Tabulated list of adverse reactions

Frequency	**Adverse reaction**
Immune system disorders	
Rare	hypersensitivity
Not known	anaphylactic reaction, anaphylactic shock
Nervous system disorders	
Common	headache
Cardiac disorders	
Not known	sinus bradycardia*
Gastrointestinal disorders	
Common	nausea
Hepatobiliary disorders	
Very common	transaminases increased
Skin and subcutaneous tissue disorders	
Common	rash
Investigations	
Very common	prothrombin time prolonged
Injury, poisoning and procedural complications	
Rare	infusion-related reaction

*Reported in post-marketing, usually normalised within 4 days following last remdesivir administration without additional intervention

Description of selected adverse reactions

Transaminases Increased
In healthy volunteer studies, increases in ALT, aspartate aminotransferase (AST) or both in subjects who received remdesivir were grade 1 (10%) or grade 2 (4%). In a randomised, double-blind, placebo-controlled clinical study of patients with COVID-19 (NIAID ACTT-1), any grade (≥ 1.25 × upper limit of normal (ULN)) laboratory abnormalities of increased AST and increased ALT occurred in 33% and 32% of patients, respectively, receiving remdesivir compared with 44% and 43% of patients, respectively, receiving placebo. Grade ≥ 3 (≥ 5.0 × ULN) laboratory abnormalities of increased AST and increased ALT occurred in 6% and

3% of patients, respectively, receiving remdesivir compared with 8% and 6% of patients, respectively, receiving placebo. In a randomised, open-label multi-centre clinical trial (Study GS-US-540-5773) in hospitalised patients with severe COVID-19 receiving remdesivir for 5 (n=200) or 10 days (n=197), any grade laboratory abnormalities of increased AST and increased ALT occurred in 40% and 42% of patients, respectively, receiving remdesivir. Grade ≥ 3 laboratory abnormalities of increased AST and increased ALT both occurred in 7% of patients receiving remdesivir. In a randomised, open-label multi-centre clinical trial (Study GS-US-540-5774) in hospitalised patients with moderate COVID-19 receiving remdesivir for 5 (n=191) or 10 days (n=193) compared to standard of care (n=200), any grade laboratory abnormalities of increased AST and increased ALT occurred in 32% and 33% of patients, respectively, receiving remdesivir, and 33% and 39% of patients, respectively, receiving standard of care. Grade ≥ 3 laboratory abnormalities of increased AST and increased ALT occurred in 2% and 3% of patients, respectively, receiving remdesivir and 6% and 8%, respectively, receiving standard of care.

Prothrombin time prolonged
In a clinical study (NIAID ACTT-1) of patients with COVID-19, the incidence of prolonged prothrombin time or INR (predominantly Grades 1-2) was higher in subjects who received remdesivir compared to placebo, with no difference observed in the incidence of bleeding events between the two groups. Prothrombin time should be monitored while receiving remdesivir as clinically appropriate.
In Study GS-US-540-9012, the incidence of increased prothrombin time or INR was similar in patients treated with remdesivir compared to placebo.

Paediatric population
The safety assessment of remdesivir in children 4 weeks of age and older and weighing at least 3 kg with COVID-19 is based on data from a Phase 2/3, open-label clinical trial (Study GS-US-540-5823) that enrolled 53 patients who were treated with remdesivir (see Section 5.1). The adverse reactions observed were consistent with those observed in clinical trials of remdesivir in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

Treatment of overdose with remdesivir should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with remdesivir.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, direct acting antivirals, ATC code: J05AB16

Mechanism of action

Remdesivir is an adenosine nucleotide prodrug that is metabolized within host cells to form the pharmacologically active nucleoside triphosphate metabolite. Remdesivir triphosphate acts as an analog of adenosine triphosphate (ATP) and 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. As an additional mechanism, remdesivir triphosphate can also inhibit viral RNA synthesis following its incorporation into the template viral RNA as a result of read-through by the viral polymerase that may occur in the presence of higher nucleotide concentrations. When

remdesivir nucleotide is present in the viral RNA template, the efficiency of incorporation of the complementary natural nucleotide is compromised, thereby inhibiting viral RNA synthesis.

Antiviral activity

Remdesivir exhibited *in vitro* activity against a clinical isolate of SARS-CoV-2 in primary human airway epithelial cells with a 50% effective concentration (EC_{50}) of 9.9 nM after 48 hours of treatment. Remdesivir inhibited the replication of SARS-CoV-2 in the continuous human lung epithelial cell lines Calu-3 and A549-hACE2 with EC_{50} values of 280 nM after 72 hours of treatment and 115 nM after 48 hours of treatment, respectively. The EC_{50} values of remdesivir against SARS-CoV-2 in Vero cells were 137 nM at 24 hours and 750 nM at 48 hours post-treatment.

The antiviral activity of remdesivir was antagonised by chloroquine phosphate in a dose-dependent manner when the two drugs were co-incubated at clinically relevant concentrations in HEp-2 cells infected with respiratory syncytial virus (RSV). Higher remdesivir EC_{50} values were observed with increasing concentrations of chloroquine phosphate. Increasing concentrations of chloroquine phosphate reduced formation of remdesivir triphosphate in A549-hACE2, HEp-2 and normal human bronchial epithelial cells.

Based on *in vitro* testing, remdesivir retained similar antiviral activity (EC_{50} fold change values below the in *vitro* susceptibility change cutoff of 2.8-fold) against clinical isolates of SARS-CoV-2 variants compared to an earlier lineage SARS-CoV-2 (lineage A) isolate, including Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), Epsilon (B.1.429), Zeta (P.2), Iota (B.1.526), Kappa (B.1.617.1), Lambda (C.37), and Omicron variants (including B.1.1.529/BA.1, BA.2, BA.2.12.1, BA.2.75, BA.4, BA.4.6, BA.5, BF.5, BF.7, BQ.1, BQ.1.1 , CH.1.1, EG.1.2, EG.5.1, FL.22, XBB, XBB.1.5, XBB.1.16, XBB.2.3.2 and XBF). For these variants, the EC_{50} fold change values ranged between 0.2 to 2.3 compared to an earlier lineage SARS-CoV-2 (lineage A) isolate. Using the SARS-CoV-2 replicon system, remdesivir retained similar antiviral activity (EC_{50} fold change values below the in vitro susceptibility change cutoff of 2.5-fold) against Omicron subvariants BA.2.86 and XBB.1.9.2 compared to the wildtype reference replicon (lineage B).

Resistance

In Cell Culture
SARS-CoV-2 isolates with reduced susceptibility to remdesivir have been selected in cell culture. In one selection with GS-441524, the parent nucleoside of remdesivir, virus pools emerged expressing combinations of amino acid substitutions at V166A, N198S, S759A, V792I, C799F, and C799R in the viral RNA-dependent RNA polymerase, conferring EC_{50} fold-changes of 2.7 up to 10.4. When individually introduced into a wild-type recombinant virus by site-directed mutagenesis, 1.7- to 3.5-fold reduced susceptibility to remdesivir was observed. In a second selection with remdesivir using a SARS-CoV-2 isolate containing the P323L substitution in the viral polymerase, a single amino acid substitution at V166L emerged. Recombinant viruses with substitutions at P323L alone or P323L+V166L in combination exhibited 1.3- and 1.5-fold changes in remdesivir susceptibility, respectively.

Cell culture resistance profiling of remdesivir using the rodent CoV murine hepatitis virus identified two substitutions (F476L and V553L) in the viral RNA-dependent RNA polymerase at residues conserved across CoVs that conferred 5.6-fold reduced susceptibility to remdesivir. Introduction of the corresponding substitutions (F480L and V557L) into SARS-CoV resulted in 6-fold reduced susceptibility to remdesivir in cell culture and attenuated SARS-CoV pathogenesis in a mouse model. When individually introduced into a SARS-CoV-2 recombinant virus, the corresponding substitutions at F480L and V557L each conferred 2-fold reduced susceptibility to remdesivir.

In Clinical Trials
In NIAID ACTT-1 Study (CO-US-540-5776), among 61 patients with baseline and post-baseline sequencing data available, the rate of emerging substitutions in the viral RNA-dependent RNA polymerase was similar in patients treated with remdesivir compared to placebo. In 2 patients treated with remdesivir, substitutions in the RNA-dependent RNA polymerase previously identified in resistance selection experiments (V792I or C799F) and associated with low fold change in remdesivir susceptibility ($\leq$3.4-fold) were observed. No other RNA-

dependent RNA polymerase substitutions observed in patients treated with remdesivir were associated with resistance to remdesivir.

In Study GS-US-540-5773, among 19 patients treated with remdesivir who had baseline and post-baseline sequencing data available, substitutions in the viral RNA-dependent RNA polymerase (nsp12) were observed in 4 patients. The substitutions T76I, A526V, A554V and C697F were not associated with resistance to remdesivir (≤ 1.45-fold change in susceptibility). The effect of substitution E665K on susceptibility to remdesivir could not be determined due to lack of replication.

In GS-US-540-9012 Study, among 244 patients with baseline and post-baseline sequencing data available, the rate of emerging substitutions in the viral RNA-dependent RNA polymerase was similar in patients treated with remdesivir compared to placebo. In one patient treated with remdesivir, one substitution in the RNA-dependent RNA polymerase (A376V) emerged and was associated with a decrease in remdesivir susceptibility *in vitro* (12.6-fold). No other substitutions in the RNA-dependent RNA polymerase or other proteins of the replication-transcription complex observed in patients treated with remdesivir were associated with resistance to remdesivir.

In Study GS-US-540-5823, among patients with baseline and post-baseline sequencing data available, substitutions in the viral RNA-dependent RNA polymerase (A656P and G670V) were observed in one of 23 patients treated with remdesivir. The substitutions observed have not been associated with resistance to remdesivir.

Clinical efficacy and safety

Clinical trials in patients with COVID-19

NIAID ACTT-1 Study (CO-US-540-5776)
A randomised, double-blind, placebo-controlled clinical trial evaluated remdesivir 200 mg once daily for 1 day followed by remdesivir 100 mg once daily for up to 9 days (for a total of up to 10 days of intravenously administered therapy) in hospitalised adult patients with COVID-19 with evidence of lower respiratory tract involvement. The trial enrolled 1,062 hospitalised patients: 159 (15%) patients with mild/moderate disease (15% in both treatment groups) and 903 (85%) patients with severe disease (85% in both treatment groups). Mild/moderate disease was defined as SpO2 > 94% and respiratory rate < 24 breaths/minute without supplemental oxygen; severe disease was defined as SpO2 ≤ 94% on room air, a respiratory rate ≥ 24 breaths/min, and an oxygen requirement, or a requirement for mechanical ventilation. A total of 285 patients (26.8%) (n=131 received remdesivir) were on mechanical ventilation/Extracorporeal Membrane Oxygenation (ECMO). Patients were randomised 1:1, stratified by disease severity at enrolment, to receive remdesivir (n=541) or placebo (n=521), plus standard of care.

The baseline mean age was 59 years and 36% of patients were aged 65 or older. Sixty-four percent were male, 53% were White, 21% were Black, 13% were Asian. The most common comorbidities were hypertension (51%), obesity (45%) and type 2 diabetes mellitus (31%); the distribution of comorbidities was similar between the two treatment groups.

Approximately 38.4% (208/541) of the patients received a 10-day treatment course with remdesivir.

The primary clinical endpoint was time to recovery within 29 days after randomisation, defined as either discharged from hospital (with or without limitations of activity and with or without home oxygen requirements) or hospitalised but not requiring supplemental oxygen and no longer requiring ongoing medical care. The median time to recovery was 10 days in the remdesivir group compared to 15 days in the placebo group (recovery rate ratio 1.29; [95% CI 1.12 to 1.49], p < 0.001).

No difference in time to recovery was seen in the stratum of patients with mild-moderate disease at enrolment (n=159). The median time to recovery was 5 days in the remdesivir and 7 days in the placebo groups (recovery rate ratio 1.10; [95% CI 0.8 to 1.53]); the odds of improvement in the ordinal scale in the remdesivir

group at Day 15 when compared to the placebo group were as follows: odds ratio, 1.2; [95% CI 0.7 to 2.2, p = 0.562].

Among patients with severe disease at enrolment (n=903), the median time to recovery was 12 days in the remdesivir group compared to 19 days in the placebo group (recovery rate ratio, 1.34; [95% CI 1.14 to 1.58]; p < 0.001); the odds of improvement in the ordinal scale in the remdesivir group at Day 15 when compared to the placebo group were as follows: odds ratio, 1.6; [95% CI 1.3 to 2.0].

Overall, the odds of improvement in the ordinal scale were higher in the remdesivir group at Day 15 when compared to the placebo group (odds ratio, 1.6; [95% CI 1.3 to 1.9], p < 0.001).

The 29-day mortality in the overall population was 11.6% for the remdesivir group vs 15.4% for the placebo group (hazard ratio, 0.73; [95% CI 0.52 to 1.03]; p=0.07). A post-hoc analysis of 29-day mortality by ordinal scale is reported in Table 7.

Table 7: 29-Day mortality outcomes by ordinal scale[a] at baseline—NIAID ACTT-1 trial

	Ordinal Score at Baseline			
	5		**6**	
	Requiring low-flow oxygen		**Requiring high-flow oxygen or non-invasive mechanical ventilation**	
	Remdesivir (N=232)	Placebo (N=203)	Remdesivir (N=95)	Placebo (N=98)
29-day mortality	4.1	12.8	21.8	20.6
Hazard ratio[b] (95% CI)	0.30 (0.14, 0.64)		1.02 (0.54, 1.91)	

a Not a pre-specified analysis.
b Hazard ratios for baseline ordinal score subgroups are from unstratified Cox proportional hazards models.

Study GS-US-540-5773 in Patients with Severe COVID-19
A randomised, open-label multi-centre clinical trial (Study 5773) of patients at least 12 years of age with confirmed SARS-CoV-2 infection, oxygen saturation of ≤ 94% on room air, and radiological evidence of pneumonia compared 200 patients who received remdesivir for 5 days with 197 patients who received remdesivir for 10 days. All patients received 200 mg of remdesivir on Day 1 and 100 mg once daily on subsequent days, plus standard of care. The primary endpoint was clinical status on Day 14 assessed on a 7-point ordinal scale ranging from hospital discharge to increasing levels of oxygen and ventilatory support to death.

The odds of improvement at Day 14 for patients randomized to a 10-day course of remdesivir compared with those randomized to a 5-day course was 0.67 (odds ratio); [95% CI 0.46 to 0.98]. Statistically significant imbalances in baseline clinical status were observed in this study. After adjusting for between-group differences at baseline, the odds of improvement at Day 14 was 0.75 (odds ratio); [95% CI 0.51 to 1.12]. In addition, there were no statistically significant differences in recovery rates or mortality rates in the 5-day and 10-day groups once adjusted for between group differences at baseline. All-cause 28-day mortality was 12% vs 14% in the 5- and 10-day treatment groups, respectively.

Study GS-US-540-9012 in patients with confirmed COVID-19 at increased risk for disease progression
A randomised, double-blind, placebo-controlled, multi-centre clinical trial to evaluate treatment with remdesivir in an outpatient setting in 562 patients with confirmed COVID-19 and at least one risk factor for disease progression to hospitalisation. Risk factors for disease progression were: aged ≥ 60 years, chronic lung disease, hypertension, cardiovascular or cerebrovascular disease, diabetes mellitus, obesity, immunocompromised state, chronic mild or moderate kidney disease, chronic liver disease, current cancer, or sickle cell disease. Vaccinated patients were excluded from the study.

Patients treated with remdesivir received 200 mg on Day 1 and 100 mg once daily on subsequent days for a total of 3 days of intravenously administered therapy. Patients were randomized in a 1:1 manner, stratified by residence in a skilled nursing facility (yes/no), age (< 60 vs ≥ 60 years), and region (US vs ex-US) to receive remdesivir (n=279) or placebo (n=283), plus standard of care.

At baseline, mean age was 50 years (with 30% of patients aged 60 or older); 52% were male, 80% were White, 8% were Black, 2% were Asian, 44% were Hispanic or Latino; median body mass index was 30.7 kg/m^2. The most common comorbidities were diabetes mellitus (62%), obesity (56%), and hypertension (48%). Median (Q1, Q3) duration of symptoms prior to treatment was 5 (3,6) days; median viral load was 6.3 log_{10} copies/mL at baseline. The baseline demographics and disease characteristics were balanced across the remdesivir and placebo treatment groups. Post-hoc exploratory analysis of optional biomarker samples showed 14.8% of patients were serological positive at baseline and 37.7% were serological negative (47.5% did not consent to optional biomarker collection).

The primary endpoint was the proportion of patients with COVID-19 related hospitalisation (defined as at least 24 hours of acute care) or all-cause 28-day mortality. Events (COVID-19-related hospitalisation or all-cause 28-day mortality) occurred in 2 (0.7%) patients treated with remdesivir compared to 15 (5.3%) patients concurrently randomized to placebo, demonstrating an 87% reduction in COVID-19-related hospitalisation or all-cause mortality compared to placebo (hazard ratio, 0.134 [95% CI, 0.031 to 0.586]; p=0.0076). The absolute risk reduction was 4.6% (95% CI, 1.8% to 7.5%). No deaths were observed at Day 28. Six of the 17 hospitalisation events occurred in participants with known baseline serostatus (serological positive: n=0 in remdesivir group and n=2 in placebo group; serological negative: n=2 in remdesivir group and n=2 in placebo group). Eleven of the 17 hospitalisation events occurred in participants with unknown baseline serostatus in placebo group and none in the remdesivir group. No conclusion can be made on efficacy in the subgroups stratified by serostatus due to the small number of patients with known serostatus and overall low event rates.

QT

Current non-clinical and clinical data do not suggest a risk of QT prolongation, but QT prolongation has not been fully evaluated in humans.

Paediatric population

Study GS-US-540-5823 is a single-arm, open-label study where the pharmacokinetics and safety of remdesivir in paediatric patients at least 28 days of age and weighing at least 3 kg with COVID-19 (n=53) was assessed. Efficacy endpoints were secondary and descriptively analysed and therefore these should be interpreted with caution. The study is ongoing.

Patients weighing ≥ 40 kg received 200 mg of remdesivir on Day 1 followed by remdesivir 100 mg once daily on subsequent days (i.e., the adult dose); patients weighing ≥ 3 kg to < 40 kg received remdesivir 5 mg/kg on Day 1 followed by remdesivir 2.5 mg/kg once daily on subsequent days. Median (range) exposure to remdesivir was 5 (1, 10) days.

At baseline, median age was 7 years (range: 0.1 to 17 years); 57% were female; median weight was 24.6 kg (range: 4 kg to 192 kg). A total of 19 patients (37%) were obese (BMI-for-age ≥ 95^{th} percentile); 7 (58%), 2 (17%), 3 (27%), 3 (27%), and 4 (80%) patients in Cohorts 1, 2, 3, 4 and 8 respectively. A total of 12 patients (23%) were on invasive mechanical ventilation (score of 2 in a 7-point ordinal scale), 18 (34%) were on non-invasive ventilation or high-flow oxygen (score of 3); 10 (19%) were on low-flow oxygen (score of 4); and 13 (25%) were on room air (score of 5), at baseline. The overall median (Q1, Q3) duration of symptoms and hospitalisation prior to first dose of remdesivir was 5 (3, 7) days and 1 (1, 3) day, respectively.

In the overall population of the study, the median (Q1, Q3) change from baseline in clinical status (assessed on a 7-point ordinal scale ranging from death [score of 1] to hospital discharge [score of 7]) was +2.0 (1.0, 4.0) points on Day 10. Among those with an ordinal score of ≤ 5 points at baseline, the proportion who had a ≥ 2-point improvement in clinical status on Day 10 was 75.0% (39/52); median (Q1, Q3) time to recovery was 7 (5, 16) days. Overall, 60% of patients were discharged by Day 10. Most patients 92% (49/53) received at least 1 concomitant medication other than remdesivir for the treatment of COVID-19 including immune modulator and anti-inflammatory agents. Three patients died during the study.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of remdesivir have been investigated in healthy volunteers and patients with COVID-19.

Absorption

The pharmacokinetic properties of remdesivir and the predominant circulating metabolite GS-441524 have been evaluated in healthy adult subjects. Following intravenous administration of remdesivir adult dosage regimen, peak plasma concentration was observed at end of infusion, regardless of dose level, and declined rapidly thereafter with a half-life of approximately 1 hour. Peak plasma concentrations of GS-441524 were observed at 1.5 to 2.0 hours post start of a 30 minutes infusion.

Distribution

Remdesivir is approximately 93% bound to human plasma proteins (ex-vivo data) with free fraction ranging from 6.4% to 7.4%. The binding is independent of drug concentration over the range of 1 to 10 μM, with no evidence for saturation of remdesivir binding. After a single 150 mg dose of [^{14}C]-remdesivir in healthy subjects, the blood to plasma ratio of [^{14}C]-radioactivity was approximately 0.68 at 15 minutes from start of infusion, increased over time reaching ratio of 1.0 at 5 hours, indicating differential distribution of remdesivir and its metabolites to plasma or cellular components of blood.

Biotransformation

Remdesivir is extensively metabolized to the pharmacologically active nucleoside analog triphosphate GS-443902 (formed intracellularly). The metabolic activation pathway involves hydrolysis by esterases, which leads to the formation of the intermediate metabolite, GS-704277. In the liver, carboxylesterase 1 and cathepsin A are the esterases responsible for 80% and 10% of remdesivir metabolism, respectively. Phosphoramidate cleavage followed by phosphorylation forms the active triphosphate, GS-443902. Dephosphorylation of all phosphorylated metabolites can result in the formation of nucleoside metabolite GS-441524 that itself is not efficiently re-phosphorylated. Decyanation of remdesivir and/or its metabolites, followed by subsequent rhodanese mediated conversion generates thiocyanate anion. The levels of thiocyanate detected following administration of 100 mg and 200 mg remdesivir were observed to be significantly below endogenous levels in human plasma.

Elimination

Following a single 150 mg IV dose of [^{14}C]-remdesivir, mean total recovery of the dose was 92%, consisting of approximately 74% and 18% recovered in urine and feces, respectively. The majority of the remdesivir dose recovered in urine was GS-441524 (49%), while 10% was recovered as remdesivir. These data indicate that renal clearance is the major elimination pathway for GS-441524. The median terminal half-lives of remdesivir and GS-441524 were approximately 1 and 27 hours, respectively.

Pharmacokinetics of remdesivir and metabolites in adults with COVID-19

Pharmacokinetic exposures for remdesivir and its metabolites in adults with COVID-19 are provided in Table 8.

Table 8: Multiple dose PK parameters[a] of remdesivir and metabolites (GS-441524 and GS-704277) following IV administration of remdesivir 100 mg to adults with COVID-19

Parameters Mean[b] (95%CI)	Remdesivir	GS-441524	GS-704277
C_{max} (ng/mL)	2700 (2440, 2990)	143 (135, 152)	198 (180, 218)
AUC_{tau} (ng•h/mL)	1710 (1480, 1980)	2410 (2250, 2580)	392 (348, 442)
C_{tau}(ng/mL)	ND	61.5 (56.5, 66.8)	ND

CI=Confidence Interval; ND=Not detectable (at 24 hours post-dose)
a. Population PK estimates for 30-minute IV infusion of remdesivir for 3 days (Study GS-US-540-9012, n=147).
b. Geometric mean estimates

Other special populations

Gender, race and age
Based on gender, race and age, pharmacokinetic differences on the exposures of remdesivir were evaluated using population pharmacokinetic analysis. Gender and race did not affect the pharmacokinetics of remdesivir and its metabolites (GS-704277 and GS-441524). Pharmacokinetic exposures of the GS-441524 metabolite were modestly increased in hospitalised COVID-19 patients ≥ 60 years of age, however no dose adjustment is needed in these patients.
Pregnancy
In CO-US-540-5961 (IMPAACT 2032) study, mean exposures (AUC_{tau}, C_{max}, and C_{tau}) of remdesivir and its metabolites (GS-441524 and GS-704277) were comparable between pregnant and non-pregnant women of child-bearing potential.

Paediatric patients
Population pharmacokinetic models for remdesivir and its circulating metabolites (GS-704277 and GS-441524), developed using pooled data from studies in healthy subjects and in adult and paediatric patients with COVID-19, were used to predict pharmacokinetic exposures in 50 paediatric patients aged ≥ 28 days to < 18 years and weighing ≥ 3 kg (Study GS-US-540-5823) (Table 9). Geometric mean exposures (AUC_{tau}, C_{max} and C_{tau}) for these patients at the doses administered were higher for remdesivir (44% to 147%), GS-441524 (-21% to 25%), and GS-704277 (7% to 91%) as compared to those in adult hospitalised patients with COVID-19. The increases were not considered clinically significant.

Table 9: Pharmacokinetic parameters[a] estimate of steady-state plasma remdesivir, GS-441524 and GS-704277 in paediatric and adult hospitalised COVID-19 patients

Parameters Mean[b]	Paediatric patients					Adult hospitalised patients (N=277)
	Cohort 1	Cohort 8	Cohort 2	Cohort 3	Cohort 4	
	12 to <18 Years and Weighing ≥40 kg (N=12)	<12 Years and Weighing ≥40 kg (N=5)	28 Days to <18 Years and Weighing 20 to <40 kg (N=12)	28 Days to <18 Years and Weighing 12 to <20 kg (N=11)	28 Days to <18 Years and Weighing 3 to <12 kg (N=10)	
Remdesivir						
C_{max} (ng/mL)	3910	3920	5680	5530	4900	2650
AUC_{tau} (h•ng/mL)	2470	2280	3500	3910	2930	1590
GS-441524						
C_{max} (ng/mL)	197	162	181	158	202	170
AUC_{tau} (h•ng/mL)	3460	2640	2870	2400	2770	3060
C_{tau} (ng/mL)	98.3	76.2	73.8	69.4	78.4	78.4
GS-704277						
C_{max} (ng/mL)	307	278	423	444	390	233
AUC_{tau} (h•ng/mL)	815	537	754	734	691	501

a PK parameters were simulated using PopPK modeling with 0.5 hour of duration for remdesivir infusions.
b Geometric mean estimates.

Paediatric hospitalised patients are from Study GS-US-540-5823; patients received 200 mg on Day 1 followed by remdesivir 100 mg once daily on subsequent days (Cohort 1 and 8), or 5 mg/kg on Day 1 followed by remdesivir 2.5 mg/kg once daily on subsequent days (Cohort 2-4) for a total treatment duration of up to 10 days.
Adult hospitalised patients are from Study CO-US-540-5844 (a phase 3 randomised study to evaluate the safety and antiviral activity of remdesivir in patients with severe COVID-19); patients received 200 mg on Day 1 followed by remdesivir 100 mg once daily on subsequent days (10 days total treatment duration).

Renal impairment
The pharmacokinetics of remdesivir and GS-441524 in renal impairment have not been evaluated. Remdesivir is not cleared unchanged in urine to any substantial extent, but its main metabolite GS-441524 is renally cleared and the metabolite levels in plasma may theoretically increase in patients with impaired renal function. The excipient betadex sulfobutyl ether sodium is renally cleared and accumulates in patients with decreased renal function. Veklury should not be used in patients with eGFR < 30 mL/min.

Hepatic impairment
The pharmacokinetics of remdesivir and GS-441524 in hepatic impairment have not been evaluated. The role of the liver in the metabolism of remdesivir is unknown.

Hospitalisation
Pharmacokinetic exposures for remdesivir in hospitalised patients with severe COVID-19 pneumonia were generally within the range of the exposures in non-hospitalised patients. The GS-704277 and GS-441524 metabolite levels were modestly increased.
Interactions
Remdesivir inhibited CYP3A4 *in vitro* (see section 4.5). At physiologically relevant concentrations (steady-state), remdesivir or its metabolites GS-441524 and GS-704277 did not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, and 2D6 *in vitro.* Remdesivir is not a time-dependent inhibitor of CYP450 enzymes *in vitro*.

Remdesivir induced CYP1A2 and potentially CYP3A4, but not CYP2B6 *in vitro* (see section 4.5).

In vitro data indicates no clinically relevant inhibition of UGT1A3, 1A4, 1A6, 1A9 or 2B7 by remdesivir or its metabolites GS-441524 and GS-704277. Remdesivir, but not its metabolites, inhibited UGT1A1 *in vitro*.

For GS-441524 and GS-704277, the only enzyme for which metabolism could be detected was UGT1A3.

Remdesivir inhibited OAT3, MATE1, OCT1, OATP1B1 and OATP1B3 *in vitro* (see section 4.5).
At physiologically relevant concentrations, remdesivir and its metabolites did not inhibit P-gp and BCRP *in vitro.*

5.3 Preclinical safety data

Toxicology

Following intravenous administration (slow bolus) of remdesivir to rhesus monkeys and rats, severe renal toxicity occurred after short treatment durations. In male rhesus monkeys at dosage levels of 5, 10, and 20 mg/kg/day for 7 days resulted, at all dose levels, in increased mean urea nitrogen and increased mean creatinine, renal tubular atrophy, and basophilia and casts, and an unscheduled death of one animal at the 20 mg/kg/day dose level. In rats, dosage levels of >3 mg/kg/day for up to 4 weeks resulted in findings indicative of kidney injury and/or dysfunction. Systemic exposures (AUC) of the predominant circulating metabolite of remdesivir (GS-441524) were 0.1 times (monkeys at 5 mg/kg/day) and 0.3 times (rats at 3 mg/kg/day) the exposure in humans following intravenous administration at the recommended human dose (RHD).

Carcinogenesis

Long-term animal studies to evaluate the carcinogenic potential of remdesivir have not been performed.

Mutagenesis

Remdesivir was not genotoxic in a battery of assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes, and *in vivo* rat micronucleus assays.

Reproductive toxicity

In female rats, decreases in corpora lutea, numbers of implantation sites, and viable embryos, were seen when remdesivir was administered intravenously daily at a systemically toxic dose (10 mg/kg/day) 14 days prior to mating and during conception; exposures of the predominant circulating metabolite (GS-441524) were 1.3 times the exposure in humans at the RHD. There were no effects on female reproductive performance (mating, fertility, and conception) at this dose level.

In rats and rabbits, remdesivir demonstrated no adverse effect on embryofoetal development when administered to pregnant animals at systemic exposures (AUC) of the predominant circulating metabolite of remdesivir (GS-441524) that were up to 4 times the exposure in humans at the RHD.

In rats, there were no adverse effects on pre- and post-natal development at systemic exposures (AUC) of the predominant circulating metabolite of remdesivir (GS-441524) that were similar to the exposure in humans at the RHD.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Betadex sulfobutyl ether sodium
Hydrochloric acid (to adjust pH) (E507)
Sodium hydroxide (to adjust pH) (E524)

6.2 Incompatibilities

This medicinal product must not be mixed or administered simultaneously with other medicinal products in the same dedicated line except those mentioned in section 6.6.

6.3 Shelf life

Unopened vials
The expiry date of the product is indicated on the packaging materials.

Reconstituted and diluted solution for infusion
After reconstitution dilute immediately.

Store diluted remdesivir solution for infusion up to 24 hours at room temperature (20°C to 25°C) or 48 hours in a refrigerator (2°C – 8°C). Dilute within the same day as administration.

6.4 Special precautions for storage

No special storage conditions are required. It is recommended to store the medicinal product at room temperature.
For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I clear glass vial, an elastomeric closure, and an aluminium overseal with a flip-off cap.

Pack size: 1 vial

6.6 Special precautions for disposal and other handling

Prepare solution for infusion under aseptic conditions and on the same day as administration. Remdesivir should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. Should either be observed, the solution should be discarded and fresh solution prepared.

Remdesivir must be reconstituted with 19 mL sterile water for injections and diluted in sodium chloride 9 mg/mL (0.9%) solution for injection before being administered via intravenous infusion over 30 to 120 minutes.

Preparation of remdesivir solution for infusion

Reconstitution
Remove the required number of single-use vial(s) from storage. For each vial:

- Aseptically reconstitute remdesivir powder for concentrate for solution for infusion by addition of 19 mL of sterile water for injections using a suitably sized syringe and needle per vial, and insert the needle in the centre of the vial stopper.
  - Discard the vial if a vacuum does not pull the sterile water for injections into the vial.
- Only use **sterile water** for injection to reconstitute remdesivir powder.
- Immediately shake the vial for 30 seconds.
- Allow the contents of the vial to settle for 2 to 3 minutes. A clear solution should result.
- If the contents of the vial are not completely dissolved, shake the vial again for 30 seconds and allow the contents to settle for 2 to 3 minutes. Repeat this procedure as necessary until the contents of the vial are completely dissolved.
- Inspect the vial to ensure the container closure is free from defects and the solution is free of particulate matter.
- Dilute immediately after reconstitution.

Dilution
Care should be taken to prevent inadvertent microbial contamination. As there is no preservative or bacteriostatic agent present in this product, aseptic technique must be used in preparation of the final parenteral solution. It is recommended to administer immediately after preparation when possible.

Adults and paediatric patients (weighing at least 40 kg)

- Using Table 10, determine the volume of sodium chloride 9 mg/mL (0.9%) solution for injection to withdraw from the infusion bag.

Table 10: Recommended dilution instructions – Reconstituted remdesivir powder for concentrate for solution for infusion

Remdesivir dose	Sodium chloride 9 mg/mL (0.9%) infusion bag volume to be used	Volume to be withdrawn and discarded from sodium chloride 9 mg/mL (0.9%) infusion bag	Required volume of reconstituted remdesivir
200 mg (2 vials)	250 mL	40 mL	2 × 20 mL
	100 mL	40 mL	2 × 20 mL
100 mg (1 vial)	250 mL	20 mL	20 mL
	100 mL	20 mL	20 mL

NOTE: 100 mL should be reserved for patients with severe fluid restriction, e.g. with ARDS or renal failure.

- Withdraw and discard the required volume of sodium chloride 9 mg/mL from the bag using an appropriately sized syringe and needle per Table 10.
- Withdraw the required volume of reconstituted remdesivir using an appropriately sized syringe per Table 10. Discard any unused portion remaining in the remdesivir vial.
- Transfer the required volume of reconstituted remdesivir to the selected infusion bag.

- Gently invert the bag 20 times to mix the solution in the bag. Do not shake.
- The prepared solution is stable for 24 hours at room temperature (20°C to 25°C) or 48 hours in the refrigerator (2°C to 8°C).

Paediatric patients (at least 4 weeks of age and weighing 3 kg to less than 40 kg)
- Further dilute the 100 mg/20 mL (5 mg/mL) remdesivir concentrate to a fixed concentration of 1.25 mg/mL using 0.9% sodium chloride.
- The total required infusion volume of the 1.25 mg/mL remdesivir solution for infusion is calculated from the paediatric weight-based dosing regimens of 5 mg/kg for the Loading Dose and 2.5 mg/kg for each Maintenance Dose.
- Small 0.9% sodium chloride infusion bags (e.g., 25, 50, or 100 mL) or an appropriately sized syringe should be used for paediatric dosing. The recommended dose is administered via IV infusion in a total volume dependent on the dose to yield the target remdesivir concentration of 1.25 mg/mL.
- A syringe may be used for delivering volumes <50 mL.

After infusion is complete, flush with at least 30 mL of sodium chloride 9 mg/mL.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

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8. REGISTRATION HOLDER

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