Emergency Use Authorization (EUA) for remdesivir, an unapproved product
Center for Drug Evaluation and Research (CDER) Review

### Identifying Information

<table>
<thead>
<tr>
<th>Application Type (EUA or Pre-EUA)</th>
<th>EUA</th>
</tr>
</thead>
<tbody>
<tr>
<td>If EUA, designate whether pre-event or intra-event EUA request.</td>
<td>EUA Application Number(s)</td>
</tr>
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</tr>
<tr>
<td>Sponsor (entity requesting EUA or pre-EUA consideration), point of contact, address, phone number, fax number, email address</td>
<td>Gilead Sciences, Inc. Attention:</td>
</tr>
<tr>
<td>333 Lakeside Drive Foster City, CA 94404</td>
<td></td>
</tr>
<tr>
<td>Manufacturer, if different from Sponsor</td>
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<tr>
<td>Submission Date(s)</td>
<td>April 16, 2020</td>
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<td>Receipt Date(s)</td>
<td>April 16, 2020</td>
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<tr>
<td>OND Division / Office</td>
<td>Division of Antivirals (DAV)/Office of Infectious Diseases (OID)</td>
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<tr>
<td>Reviewer Name(s)/Discipline(s)</td>
<td>Kirk Chan-Tack, MD/Clinical Reviewer</td>
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<tr>
<td></td>
<td>Adam Sherwat, MD/Clinical Team Leader (TL)</td>
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<tr>
<td></td>
<td>Eric Donaldson, PhD/Virology Reviewer</td>
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<tr>
<td></td>
<td>Jules O’Rear, PhD/Virology TL</td>
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<td></td>
<td>Mario Sampson, PharmD/Clinical Pharmacology (C/P) Reviewer</td>
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<td></td>
<td>Vikram Arya, PhD, FCP/C/P TL</td>
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<td>John Dubinion, PhD/Pharmacology/Toxicology (P/T) Reviewer</td>
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<td></td>
<td>Hanan Ghantous, PhD, DABT/P/T TL</td>
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<td>Erika Englund, PhD/CMC TL</td>
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<td>Daniel Rubin, PhD/Statistics Reviewer</td>
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<td>Thamban Valappil, PhD/Statistics TL</td>
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<td></td>
<td>Jeff Murray, MD, MPH/Deputy Director</td>
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<tr>
<td></td>
<td>Debra Birnkrant, MD/Director</td>
</tr>
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<td></td>
<td>John Farley, MD, MPH/Director (Acting)/OID</td>
</tr>
<tr>
<td>Integrated Review Completion Date</td>
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<td>Proprietary Name</td>
<td>N/A</td>
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<tr>
<td>Established Name/Other names used during development</td>
<td>Remdesivir (RDV)</td>
</tr>
<tr>
<td>Dosage Forms/Strengths</td>
<td>Lyophilized formulation for injection, 100 mg</td>
</tr>
<tr>
<td></td>
<td>Solution formulation for injection, 5 mg/mL</td>
</tr>
</tbody>
</table>

1 If a Pre-EUA is in existence at the time of the EUA request submission and has been assigned an EUA number, the EUA request should use the same EUA number and electronic archive file.
Therapeutic Class | Coronavirus nucleoside analog RNA polymerase inhibitor  
---|---  
Intended Use or Need for EUA | Treatment of coronavirus disease 2019 (COVID-19)  
Intended Population(s) | Adult and pediatric patients with severe COVID-19  
Product in the Strategic National Stockpile (SNS) | No  
Distributor, if other than Sponsor | Please refer to the Letter of Authorization for details  

I. EUA Determination/Declaration

On February 4, 2020, the Secretary of Health and Human Services determined pursuant to section 564 of the Federal Food, Drug, and Cosmetic (FD&C) Act that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad and that involves a novel (new) coronavirus (nCoV) first detected in Wuhan City, Hubei Province, China in 2019 (2019-nCoV). The virus is now named SARS-CoV-2, which causes the illness COVID-19.

On the basis of this determination, the Secretary of Health and Human Services declared that circumstances exist justifying the authorization of emergency use of drugs and biologics during the COVID-19 outbreak, pursuant to section 564 of the FD&C Act, subject to the terms of any authorization issued under that section.

II. Recommendations

FDA has completed the review of EUA-046. No further information is requested at this time.

Recommend EUA Issuance

The Division of Antivirals, Office of Infectious Diseases, Office of New Drugs, CDER recommends EUA issuance.

A. EUA Communications

The EUA will be issued for the treatment of suspected or laboratory confirmed coronavirus disease 2019 (COVID-19) in adults and children who are hospitalized with severe disease defined as SpO2 ≤ 94% on room air, or requiring supplemental oxygen, or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO).

B. Eligibility of the Product for an EUA
COVID-19 is a serious or life-threatening disease or condition caused by SARS-CoV-2, as specified in the declaration of emergency. There are no adequate, approved, and available alternatives to the candidate products for treating this serious or life-threatening disease. Based on the scientific evidence available to FDA, it is reasonable to believe that the known and potential benefits of RDV outweigh the known and potential risks of the drug for the treatment of suspected or laboratory confirmed COVID-19 in adults and children hospitalized with severe disease as defined above.

III. Proposed Use and Dosing of the Product Under the EUA

- Proposed use(s) under EUA: Adult and pediatric patients hospitalized with suspected or laboratory confirmed SARS-CoV-2 infection and severe clinical manifestations
- Proposed dosing regimen(s) for use under EUA
  - Adult and pediatric patients weighing ≥40 kg requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO): single intravenous (IV) loading dose of remdesivir 200 mg on Day 1 followed by 100 mg IV once-daily maintenance doses for a total of up to 10 days of dosing.
  - Adult and pediatric patients weighing ≥40 kg not requiring invasive mechanical ventilation and/or ECMO: single loading dose of remdesivir 200 mg on Day 1 followed by 100 mg IV once-daily maintenance doses for 4 days. If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days (i.e., up to a total of 10 days).
  - Pediatric patients with body weight between 3.5 kg and <40 kg requiring invasive mechanical ventilation and/or ECMO: single loading dose of remdesivir 5 mg/kg IV on Day 1 followed by 2.5 mg/kg IV once-daily maintenance doses for a total of up to 10 days of dosing.
  - Pediatric patients with body weight between 3.5 kg and <40 kg not requiring invasive mechanical ventilation and/or ECMO: single loading dose of remdesivir 5 mg/kg IV on Day 1 followed by 2.5 mg/kg IV once-daily maintenance doses for 4 days. If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days (i.e., up to a total of 10 days).
  - Pregnant or lactating patients: No change in dosing is recommended. The need for dose adjustments in these patient populations has not been established because pharmacokinetic (PK) data are not available. Dose recommendations in these populations have been based largely on risk/benefit considerations.
Other specific populations (e.g., geriatric patients, patients with renal or hepatic impairment): No change in dosing is recommended. The need for dose adjustments in the setting of renal or hepatic impairment has not been established because PK data in humans with renal or hepatic insufficiency are not available. Dose recommendations in these populations have been based largely on risk/benefit considerations.

- Rationale for dosing regimen: The dosing and duration of treatment are based on the regimen that was evaluated in the randomized, double-blinded, placebo-controlled trial conducted by NIAID (NCT04280705) and in the Gilead-sponsored open-label trial that evaluated different durations of remdesivir (NCT04292899). These trials evaluated patients with severe COVID-19.

IV. Product Information (Dose Preparation and Administration)

- IND 1 and IND 1 were referenced for this EUA. IND 1 contains the supporting CMC information.
- There are 2 formulations described in the EUA: Remdesivir for injection (100 mg) and remdesivir injection (5 mg/mL). Both of these formulations are described in IND 1.
- Preparation instructions:
  - Remdesivir for injection is reconstituted with 19 mL of sterile water for injection, and then further diluted in 0.9% saline prior to administration. Remdesivir injection is a concentrated solution which is also diluted with 0.9% saline prior to administration.
  - Remdesivir for injection is stored below 30 °C, and remdesivir injection is stored at refrigerated conditions (2 °C- 8 °C)
- Instructions for use of a delivery or dosing device: Not applicable
- Instructions for administration: Intravenous infusion.
- Instructions for handling, if applicable: The reconstituted remdesivir for injection should be used within 4 hours at room temperature, or 24 hours at refrigerated conditions.

V. Background Information on the Disease/Condition and Available Therapeutic Alternatives

- Background information on the condition
  - Coronavirus disease 2019 (COVID-19) can cause severe disease which can result in pneumonia, respiratory failure, multi-organ failure, and death.
  - Globally, according to the World Health Organization (WHO), approximately 3,090,445 confirmed cases of COVID-19 caused by the

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2 Remdesivir is not recommended in adult and pediatric patients (>28 days old) with eGFR less than 30 mL/min or in full-term neonates (>7 days to ≤28 days old) with serum creatinine greater than or equal to 1 mg/dL unless the potential benefit outweighs the potential risk.
2019 novel coronavirus (SARS-CoV-2) have been reported as of April 30, 2020, including an estimated 217,769 deaths. In the US, according to the Centers for Disease Control and Prevention (CDC), approximately 1,031,659 cases of COVID-19 have been reported with 60,057 deaths as of April 30, 2020. On March 11, 2020, the WHO declared the COVID-19 outbreak a pandemic.

- Per the CDC (MMWR March 27, 2020 / 69(12);343-346), between February 12 and March 16, 2020, 4,226 COVID-19 cases were reported in the United States; 31% of cases, 45% of hospitalizations, 53% of ICU admissions, and 80% of deaths occurred among adults aged ≥65 years, with the highest percentage of severe outcomes among persons aged ≥85 years. These findings are similar to data from China, which indicated >80% of deaths occurred among persons aged ≥60 years (JAMA. 2020;323(13):1239-1242). These preliminary data also demonstrate that severe illness leading to hospitalization, including ICU admission and death, can occur in adults of any age with COVID-19. In contrast, persons aged ≤19 years appear to have milder COVID-19 illness, with almost no hospitalizations or deaths reported to date in the United States in this age group.

- Therapeutic alternatives for the disease/condition
  - There are currently no treatments approved by the FDA for treatment of COVID-19.
  - On March 28, 2020, FDA authorized the emergency use of chloroquine phosphate and hydroxychloroquine sulfate, pursuant to Section 564 of the Act, for treatment of adult and adolescent patients who weigh 50 kg or more hospitalized with COVID-19 when clinical trials are not available, or participation is not feasible.

VI. Related Regulatory Submission(s)

- Related NDA
  - NDA 2
    - No approved indications, dosage forms, or dosing regimen(s)
    - Approval status: Rolling review
    - Applicant: Gilead Sciences

- Related INDs
  - IND 1
    - Two ongoing, Phase 3 randomized clinical trials:
      1. Phase 3 Randomized Open-Label Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734) in in Adults and Adolescents with Moderate COVID-19 Compared to Standard of Care Treatment
      2. Phase 3 Randomized Open-Label Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734) in Adults and Adolescents with Severe COVID-19
    - Dose, duration, and route (adults): 200 mg IV loading dose on Day 1, followed by 100 mg IV daily on Days 2-5 or Days 2-10
• Cross-reference to IND 1(b)(4)
• Sponsor: Gilead Sciences

IND 1(b)(4)
• Phase 1 healthy volunteer studies:
  1. Randomized, double-blinded, placebo-controlled, single ascending dose study (3, 10, 30, 75, 150, and 225 mg IV)
  2. Randomized, blinded, placebo-controlled, multi-dose study (150 mg IV daily x 7 days; 150 mg IV daily x 14 days)
  3. Open-label, mass balance study (single, 150 mg IV dose of radiolabeled [14C]-remdesivir)
  4. Randomized, double-blinded, placebo-controlled study evaluating 200 mg IV loading dose on Day 1, followed by 4 or 9 days of 100 mg IV daily
• Completed nonclinical toxicology program supporting future NDA
• Sponsor: Gilead Sciences

IND 147,771
• Ongoing, Phase 3 randomized clinical trial: Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Adults
  • Dose, duration, and route (adults): 200 mg IV loading dose on Day 1, followed by 100 mg IV daily on Days 2-10
  • Cross-reference to IND 1(b)(4)
  • Sponsor: Division of Microbiology & Infectious Diseases, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH)

IND 147,993
  • Dose, duration, and route (adults): 200 mg IV loading dose on Day 1, followed by 100 mg IV daily on Days 2-10
  • Cross-reference to IND 1(b)(4)
  • Sponsor: US Army Medical Research and Development Command

IND 125,530
• Phase 3, Multicenter, Randomized, Controlled Safety and Efficacy Study of Investigational Therapeutics for the Treatment of Patients with Ebola Virus Disease (PALM)
  • Dose, duration, and route (adults): 200 mg IV loading dose on Day 1, followed by 100 mg IV daily on Days 2-10 (note: Sponsor stated the recommended dosing duration is 10 days, but dosing may be continued for an additional 4 days [i.e. up to Day 14] at 100 mg IV daily if virus is detectable in plasma at Day 10 of treatment)
  • Cross-reference to IND 1(b)(4)
  • Sponsor: NIAID, NIH

IND 130,621
Phase 2 double-blind, randomized, 2-phase, placebo-controlled, trial of remdesivir to assess the antiviral activity, longer-term clearance of Ebola Virus, and safety in Male Ebola Survivors with evidence of Ebola Virus persistence in semen (PREVAIL IV)

- Dose, duration, and route (adults): 100 mg IV daily x 5 days
- Cross-reference to IND 1
- Sponsor: NIAID, NIH

**Related Pre-INDs**
- Pre-IND 131,958 (Treatment of acute filovirus disease)
  - Exploratory animal data
  - No clinical studies are planned
  - Sponsor: Joint Mobile Emerging Disease Intervention Clinical Capability (JMEDICC)
- Pre-IND 1
  - Exploratory animal data
  - No clinical studies are planned
  - Sponsor: Gilead Sciences
## VII. Summary of Clinical Data

### Table 1. All Clinical Trials conducted under IND

<table>
<thead>
<tr>
<th>Study Number</th>
<th>IND</th>
<th>Type of Study (PK, Efficacy, Safety)</th>
<th>Population (N)</th>
<th>Study Design and Type of Control</th>
<th>RDV Dosing Regimens; Dosage Forms; Routes of Administration; Duration</th>
<th>Study Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol No. 20-0006</td>
<td>147,771</td>
<td>Efficacy, Safety</td>
<td>572 RDV (n=286) PBO (n=286)</td>
<td>Multicenter, Adaptive, Randomized Double-Blinded Controlled Trial on the Safety and Efficacy Study of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Adults with Laboratory Confirmed SARS CoV 2 Infection (<a href="https://clinicaltrials.gov/ct2/show/NCT04280705">https://clinicaltrials.gov/ct2/show/NCT04280705</a>)</td>
<td>200 mg IV Day 1; Followed by 100 mg IV QD Days 2-10</td>
<td>Ongoing</td>
</tr>
<tr>
<td>GS-US-540-5773</td>
<td>1 (b) (4)</td>
<td>Efficacy, Safety, PK</td>
<td>Part A (n=400) • RDV x 5 days (n=200) • RDV x 10 days (n=200)</td>
<td>Phase 3 Randomized Open-Label Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734) in Adults and Adolescents with Severe COVID-19 (<a href="https://clinicaltrials.gov/ct2/show/NCT04292899">https://clinicaltrials.gov/ct2/show/NCT04292899</a>) Part B (single arm; runs concurrently with Part A) • Part B will enroll participants on mechanical ventilation and, after enrollment to Part A is complete, Part B will enroll up to 5600 additional patients who meet enrollment criteria; Total N ~ 6000</td>
<td>200 mg IV Day 1; Followed by 100 mg IV QD Days 2-5 or Days 2-10</td>
<td>Ongoing</td>
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<tr>
<td>GS-US-540-5774</td>
<td>1 (b) (4)</td>
<td>Efficacy, Safety, PK</td>
<td>Part A (n=600) • RDV x 5 days (n=200) • RDV x 10 days (n=200) • SOC (n=200)</td>
<td>Phase 3 Randomized Open-Label Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734) in in Adults and Adolescents with Moderate COVID-19 Compared to Standard of Care Treatment (<a href="https://clinicaltrials.gov/ct2/show/NCT04292730">https://clinicaltrials.gov/ct2/show/NCT04292730</a>) Note: Part B: After Part A has enrolled, Sponsor plans to enroll up to 1000 patients to receive RDV x 10 days; Total N ~ 1600</td>
<td>200 mg IV Day 1; Followed by 100 mg IV QD Days 2-5 or Days 2-10</td>
<td>Ongoing</td>
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<tr>
<td>CO-US-399-5366a</td>
<td>125,530</td>
<td>Efficacy, Safety, PK</td>
<td>6/3 RDV (n=175) ZMapp (n=169) mAb114 (n=174) REGN (n=155)</td>
<td>Multicenter, Randomized, Controlled Safety and Efficacy Study of Investigational Therapeutics for the Treatment of Patients With Ebola Virus Disease (<a href="https://www.nejm.org/doi/full/10.1056/NEJMc1909318">N Engl J Med</a>) (up to Day 14 if detectable viremia at Day 10)</td>
<td>200 mg IV on Day 1; Followed by 100 mg IV QD Days 2-10 (up to Day 14 if detectable viremia at Day 10); RDV arm completed</td>
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<tr>
<td>CO-US-399-4006b</td>
<td>130,621</td>
<td>Efficacy, Safety, PK</td>
<td>RDV (n=19) PBO (n=19)</td>
<td>Double-Blinded randomized two-part placebo controlled Phase 2 trial of GS-5734 to assess the safety, anti-viral activity, and long-term clearance of Ebola virus in Ebola survivors with evidence of Ebola virus persistence</td>
<td>100 mg IV QD x 5 days</td>
<td>Prematurely terminated</td>
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<td>GS-US-399-1812</td>
<td>1 (b) (4)</td>
<td>Safety, PK</td>
<td>96 RDV (n=78) PBO (n=18)</td>
<td>Phase 1, Double-Blinded, Randomized, Placebo Controlled, First in Human, Single-Ascending Dose Study Evaluating the Safety, tolerability, and Pharmacokinetics of IV GS-5734 in Healthy Adults</td>
<td>3, 10, 30, 75, 150, and 225 mg IV</td>
<td>Completed</td>
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<tr>
<td>GS-US-399-1954</td>
<td>1 (b) (4)</td>
<td>Safety, PK</td>
<td>24 RDV (n=16) PBO (n=8)</td>
<td>Phase 1, Blinded, Randomized, Placebo Controlled, Multiple-Dose Study Evaluating the Safety, tolerability, and Pharmacokinetics of IV GS-5734</td>
<td>150 mg IV QD x 7 days or 14 days</td>
<td>Completed</td>
</tr>
<tr>
<td>GS-US-399-4231</td>
<td>1 (b) (4)</td>
<td>Mass balance</td>
<td>8</td>
<td>Phase 1 Open-Label Single Dose Study to Evaluate the Pharmacokinetics, Metabolism, and Excretion of GS-5734 in Healthy Subjects</td>
<td>150 mg IV single dose</td>
<td>Completed</td>
</tr>
<tr>
<td>GS-US-399-5505</td>
<td>1 (b) (4)</td>
<td>Safety, PK</td>
<td>35 RDV (n=28) PBO (n=7)</td>
<td>Phase 1, Double-Blinded, Randomized, Placebo Controlled, Multiple Dose Study Evaluating the Safety, tolerability, and Pharmacokinetics of IV Remdesivir in Healthy Volunteers</td>
<td>200 mg IV Day 1; Followed by 100 mg IV QD Days 2-5 or Days 2-10</td>
<td>Completed</td>
</tr>
</tbody>
</table>

PK, pharmacokinetic; IV, intravenous; QD, once daily; PBO, placebo; SOC, standard-of-care; aPALM, Pamoja Tulinde Maisha; bPREVAIL IV, Partnership for Research on Ebola Virus in Liberia; cPREVAIL IV was terminated due to Gilead’s interest to consider an increase in RDV dosing after the PALM results and due to slow enrollment; dOnly topline data are available at this time; eOnly topline blinded data are available at this time

Reference ID: 4601617
VIII. Human Clinical Efficacy

Randomized Controlled Clinical Trials:

Results are available from two randomized, double-blind, placebo-controlled trials that are discussed below. Patient-level data have not been submitted or reviewed for either trial.

- An analysis report is available from a large definitive trial sponsored by the National Institute of Allergy and Infectious Disease (clinicaltrials.gov identifier NCT04280705).

Top line results are also available from a Gilead-sponsored trial that compared 5-day and 10-day remdesivir durations in patients with severe COVID-19 (clinicaltrials.gov identifier NCT04292899).

Additional results for remdesivir may become available from several other randomized clinical trials (clinicaltrials.gov identifiers NCT04252664, NCT04292730, NCT04321616, NCT04315948).

NIAID-Sponsored Trial:

This double-blind trial randomized a total of 1063 patients in a 1:1 ratio to receive remdesivir or placebo for 10 days. Remdesivir was administered intravenously at a dose of 200 mg on Day 1 followed by 100 mg on Days 2-10 in single daily infusions.

Inclusion criteria specified that patients were to be males and non-pregnant females aged ≥18 years who had laboratory-confirmed SARS-CoV-2 infection as determined by RT-PCR or other public health assay in any specimen. Patients could have illness of any duration. For inclusion, patients were to have at least one of the following: radiographic infiltrates by imaging, SpO2 ≤94% on room air, requirement for supplemental oxygen, or requirement for mechanical ventilation. Exclusion criteria disallowed patients with ALT/AST >5 times the upper limit of normal or eGFR <30 mL/min.

Patients in this trial could have either mild-to-moderate or severe COVID-19. Severe disease was defined as hospitalization requiring supplemental oxygen, non-invasive ventilation, high-flow oxygen devices, invasive mechanical ventilation, or ECMO. Randomization was stratified on this baseline classification of mild/moderate versus severe disease, as well as by study site.

The primary efficacy endpoint was time to recovery through Day 29. Recovery was defined by being in category 1, 2, or 3 in the 8-point ordinal scale listed below. Patients who died before recovering were censored in the analysis at Day 29, corresponding to failing to recover through the entire follow-up period. The time to recovery analysis was to
be based on an estimated hazard ratio from a Cox proportional hazards model, log-rank test, and comparison of median days to recovery between the remdesivir and placebo groups.

8-Point Ordinal Scale:

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

The pre-specified primary efficacy analysis was to be conducted in an intention-to-treat population of all randomized patients.

A pre-specified key secondary efficacy analysis was an analysis of the above ordinal scale at Day 15 using a proportional odds model.

Because the primary efficacy endpoint was a time to event endpoint, this trial was powered as an event driven study that would reach the final analysis after 400 patients had met recovery criteria. This was planned to provide 85% power for detecting a hazard ratio of 1.35 (on a scale where values greater than 1.00 corresponded to faster recovery in the remdesivir group). Enrollment was halted on April 20, 2020 after 1063 patients had been randomized.

The statistical analysis plan pre-specified an interim analysis to be conducted by the data and safety monitoring board (DSMB) after 200 of the 400 recoveries had been observed. This meeting was scheduled for April 27, 2020. However, due to rapid enrollment there had already been over 400 recoveries in the analysis set presented to the DSMB at this meeting. Because this exceeded the originally planned final number of recoveries in the trial, no interim adjustment to significance tests or confidence intervals was applied for the DSMB analysis. Although the trial has now reached the specified number of recoveries, follow-up of many enrolled patients through the 29 day follow-up period is still ongoing. Results presented below were communicated by NIAID to the FDA on April 28, 2020 and represent the most currently up-to-date information.

The table and figure below display results for the primary efficacy analysis of time to recovery. In the intent-to-treat population of all randomized patients, the time to recovery was significantly faster in the remdesivir group than the placebo group. Median days to recovery were 11 days in the remdesivir group versus 15 days in the placebo group. The estimated hazard ratio (on a scale with values greater than 1.00 favoring remdesivir) was
1.31 with a 95% confidence interval for the hazard ratio from 1.12 to 1.54, and a two-sided p-value <0.001. In patients with mild-to-moderate disease at baseline, there was little evidence of a difference in recovery times between remdesivir versus placebo, and both groups had a short median recovery time of only 5 days. In patients classified as having severe disease at baseline, there was significantly faster recovery in the remdesivir group (median 12 days) than the placebo group (median 18 days), with a two-sided p<0.001.

Table 2: Time to recovery by treatment group and disease severity

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Disease Severity</th>
<th>n</th>
<th>Median Time to Recovery</th>
<th>HR</th>
<th>P-value</th>
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<td></td>
<td></td>
<td>5</td>
<td>4.7</td>
<td>1.081</td>
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<tr>
<td>Remdesivir (N=62)</td>
<td>Mild/Moderate</td>
<td>52</td>
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<tr>
<td>Placebo (N=57)</td>
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<td>46</td>
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<tr>
<td>Remdesivir (N=475)</td>
<td>Severe</td>
<td>281</td>
<td>12</td>
<td>10, 14</td>
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<td>Placebo (N=463)</td>
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<td>227</td>
<td>18</td>
<td>15, 21</td>
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<td>Remdesivir (N=537)</td>
<td>Any Severity</td>
<td>333</td>
<td>11</td>
<td>9, 12</td>
<td>1.312</td>
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<tr>
<td>Placebo (N=520)</td>
<td></td>
<td>273</td>
<td>15</td>
<td>13, 19</td>
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</tr>
</tbody>
</table>

N= Number of subjects enrolled.

n = Number of recovered subjects.

HR is the hazard ratio from the stratified Cox Model

P-value calculated using the stratified log-rank test

Source: DSMB report for April 28, 2020, Table 1.

Figure 1: Stratified Kaplan-Meier plot of time to recovery/discharge
The subsequent table and figure display all-cause mortality results. Although follow-up for Day 29 all-cause mortality is still ongoing for many patients, there was a numerical trend towards lower mortality in the remdesivir group [43/538 (8.0%)] than the placebo group [60/519 (11.6%)]. The estimated hazard ratio (on a scale with values less than 1.00 favoring remdesivir) was 0.69, with a 95% confidence interval for the hazard ratio from 0.47 to 1.02, and a two-sided p-value of 0.06. These results combined patients with mild-to-moderate and severe disease at baseline. However, almost all mortality occurred in the severe disease stratum. As of the April 27, 2020 interim analysis, mortality rates in the mild-to-moderate stratum were 1/57 (<2%) for remdesivir versus 1/54 (<2%) for placebo.

Table 3: Time to death by treatment group

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment Group</strong></td>
<td>n</td>
<td>Estimate</td>
<td>95% CI</td>
<td>P-value</td>
</tr>
<tr>
<td>Remdesivir (N=538)</td>
<td>43</td>
<td></td>
<td></td>
<td>0.059</td>
</tr>
<tr>
<td>Placebo (N=519)</td>
<td>60</td>
<td>0.688</td>
<td>[0.465, 1.017]</td>
<td></td>
</tr>
</tbody>
</table>

N= Number of subjects enrolled
n = Number of deaths
HR is the hazard ratio from the Cox Model
P-value calculated using the log-rank test
The next table presents results for the key secondary efficacy analysis of the previously described ordinal scale at Day 15. An analysis from a proportional odds model estimated an odds ratio (on a scale with values greater than 1.00 favoring remdesivir) of 1.50, with a 95% confidence interval for the odds ratio from 1.14 to 1.98, and a two-sided p<0.01. In patients with mild-to-moderate disease at baseline, there were similar numbers of patients in each category between the remdesivir group and the placebo group. In patients with severe disease at baseline, the remdesivir group had a greater number of patients in categories 1 and 2 (representing hospital discharge) and fewer patients in category 8 (representing death).

Table 4: Numbers of people in the different categories of the 8-point ordinal scale at Day 15 by baseline severity and arm

<table>
<thead>
<tr>
<th>Category</th>
<th>Mild-Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Remdesivir</td>
</tr>
<tr>
<td>1 (discharged, no lim.)</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8 (death)</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Source: DSMB report for April 28, 2020, Table 8.
Overall, results from this large trial provided reliable and statistically persuasive evidence of benefit for remdesivir.

Wang et al. (2020) Trial

This double-blind trial randomized patients in a 2:1 ratio to receive remdesivir or placebo for 10 days. Remdesivir was administered intravenously at a dose of 200 mg on Day 1 followed by 100 mg on Days 2-10 in single daily infusions. A total of 237 patients out of the planned 453 patients were enrolled after February 6, 2020 prior to study termination on April 1, 2020. The study was terminated due to operational futility as the epidemic had largely ended in China.

Inclusion criteria specified that patients were to be males and non-pregnant female patients aged ≥18 years who were RT-PCR positive for SARS-CoV-2, had pneumonia confirmed by chest imaging, had a SpO₂ ≥94% on room air or a PaO₂/FiO₂ ratio ≤300mgHg, and were within 12 days of illness onset. Exclusion criteria disallowed pregnancy or breast-feeding; hepatic cirrhosis or alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevated over 5 times the ULN; known severe renal impairment (estimated eGFR< 30 mL/min/1.73m²), or having received continuous renal replacement therapy (CRRT), hemodialysis or peritoneal dialysis; or possibility of transfer to a non-study hospital within 72 hours.

Among 255 patients who were screened, 237 patients were eligible, consented and were randomized, of whom 1 withdrew. 158 patients were assigned to receive remdesivir and 78 to placebo. In the remdesivir group, 155 (98%) received remdesivir as assigned and placebo was given to all patients in the control group. The median age of study patients was 65 years (interquartile range [IQR], 56 to 71 years) and 140 (59%) were males. The most common comorbidity was hypertension (43%), followed by diabetes (24%) and coronary heart disease (7%). Lopinavir-ritonavir was co administered in 42 (18%) patients at day 1. Most patients (82% in the remdesivir and 83% in the control group) were hospitalized for oxygen therapy at baseline but without requiring high flow or noninvasive ventilation. The median days from illness onset to randomization was 10 days (IQR 9 to 12 days), and there were more patients (60%) in the control group than in the remdesivir group (44%) who had been symptomatic for 10 days or less at the time of randomization.

The efficacy analyses were conducted in an intention-to-treat population of all randomized patients.

The primary endpoint was the time to clinical improvement. This was defined as a decline in 2 points (on a 6-point ordinal scale) or discharge. The 6-point scale included death: 6; hospitalized for ECMO and/or mechanical ventilation: 5; hospitalized for noninvasive ventilation and/or high flow oxygen therapy: 4; hospitalized for oxygen therapy (but not requiring high flow or noninvasive ventilation): 3; hospitalization but not requiring oxygen therapy: 2; discharged or having reached discharge criteria (defined as clinical recovery, i.e., normalization of pyrexia, respiratory rate [<24/minute], and SpO₂ [≥94% on room air], and relief of cough, all maintained for at least 72 hours): 1.
In the primary efficacy analysis, the median time to clinical improvement was 21 days for remdesivir versus 23 days for placebo. The hazard ratio (on a scale with values greater than 1.00 favoring remdesivir) was 1.23, with a 95% confidence interval from 0.87 to 1.75, and a two-sided p-value of 0.24 from a log-rank test. At Day 28, the proportions of patients with at least a 2-point improvement on the ordinal scale were 103/158 (65.2%) for remdesivir versus 45/78 (57.7%) for placebo, with a 7.5% difference in rates, and a 95% confidence interval for the difference from -5.7% to 20.7%. These primary efficacy results represented a numerical trend in favor of remdesivir that did not reach conventional levels of statistical significance.

Day 28 all-cause mortality rates were similar in the two treatment groups. Mortality rates were 22/158 (13.9%) for the remdesivir group versus 10/78 (12.8%) for the placebo group, with a difference in mortality rates of 1.1% and a 95% confidence interval for the difference from -8.1% to 10.3%.

The table below displays results for the ordinal scale at Day 28. The odds ratio estimated from a proportional odds model (on a scale with values greater than 1.00 favoring remdesivir) was 1.15, with a 95% confidence interval from 0.67 to 1.96.

<table>
<thead>
<tr>
<th>Ordinal scale categories</th>
<th>Remdesivir (n = 158) n (%)</th>
<th>Placebo (n = 78) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 = discharge (alive)</td>
<td>92 (58.2)</td>
<td>45 (57.7)</td>
</tr>
<tr>
<td>2 = Hospitalization, not requiring supplemental oxygen</td>
<td>14 (8.9)</td>
<td>4 (5.1)</td>
</tr>
<tr>
<td>3 = Hospitalization requiring supplemental oxygen</td>
<td>18 (11.4)</td>
<td>13 (16.7)</td>
</tr>
<tr>
<td>4 = Hospitalization requiring HFNC and/or non-IMV</td>
<td>2 (1.3)</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>5 = Hospitalization requiring ECMO and/or IMV</td>
<td>2 (1.3)</td>
<td>3 (3.8)</td>
</tr>
<tr>
<td>6 = Death</td>
<td>22 (13.9)</td>
<td>10 (12.8)</td>
</tr>
<tr>
<td>Missing</td>
<td>8 (5.1)</td>
<td>1 (1.3)</td>
</tr>
</tbody>
</table>

Source: Wang et al. (2020), Table 3.

Rates of viral clearance appeared similar between remdesivir and placebo in this trial, and viral load decreased similarly in both groups through Day 28.

Rates of adverse events were similar between treatment groups, with at least 1 adverse reported for 66% of remdesivir patients and 64% of placebo patients. However, rates of study drug discontinuation due to adverse events or serious adverse were higher for remdesivir (12% versus 5%), including 7 (5%) in the remdesivir group with respiratory failure or ARDS.
Overall, this trial was much smaller than the NIAID-sponsored trial. Consequently, there was a higher degree of uncertainty in estimating treatment effects. Meta-analysis of the two trials was not attempted, and patient-level data may be useful for standardizing endpoint definitions and follow-up periods when synthesizing trial results. Nevertheless, favorable numerical trends for remdesivir in this trial were consistent with results from the larger NIAID-sponsored trial.

**Gilead-Sponsored Trial**

This open-label trial compared 5-day and 10-day remdesivir durations for the treatment of patients with severe COVID-19. Remdesivir was administered intravenously at a dose of 200 mg on Day 1 followed by 100 mg on subsequent days. There was no placebo or standard of care group.

Inclusion criteria specified that patients were to be males and non-pregnant female patients aged ≥12 years with SARS-CoV-2 infection confirmed by RT-PCR testing, current hospitalization, radiographic evidence of pulmonary infiltrates, and SpO2 ≤94% on room air or requirement for supplemental oxygen. Exclusion criteria disallowed patients on mechanical ventilation for ≥5 days, ECMO, patients with multiorgan failure, ALT or AST >5 times the upper limit of normal, or creatinine clearance <50 mL/min.

The pre-specified primary efficacy analysis was to examine results on a 7-point ordinal scale at Day 14 using a proportional odds model. The scale was similar to that used in the NIAID-sponsored trial and Wang et al. (2020) trial, and used the following categories: 1. Death; 2. Hospitalized, on invasive mechanical ventilation or ECMO; 3. Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4. Hospitalized, requiring low flow supplemental oxygen; 5. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise); 6. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care (other than per protocol RDV administration); 7. Not hospitalized.

A total of 401 patients were randomized in a 1:1 ratio to the 5-day and 10-day remdesivir groups. The sponsor excluded 4 patients who were randomized but not treated, and the primary analysis set included 200 patients in the 5-day group and 197 patients in the 10-day group.

Baseline characteristics appeared relatively well balanced between treatment groups. In terms of demographics, patients in this trial had a median age of 61 years; 64% were male; 11% were African or African American, 12% were Asian, and 22% were Hispanic or Latino. In terms of baseline comorbidities, 22% of patients had diabetes; 22% had hyperlipidemia; 47% had hypertension; and 12% had asthma. Regarding baseline oxygen support status, 3% of patients were on invasive mechanical ventilation or ECMO; 28% had non-invasive ventilation or high flow oxygen; 55% required low flow supplemental oxygen; and 14% required ongoing medical care without supplemental oxygen.
The figure below visually displays results for the ordinal outcome from baseline through Day 14, and shows the proportion of patients in each category for the 5-day remdesivir group and the 10-day remdesivir group. The sponsor reports that the primary analysis of the proportional odds model at Day 14 yielded an estimated odds ratio (on a scale with values less than 1.00 favoring the 5-day duration) of 0.75, with a 95% confidence interval from 0.51 to 1.12. Thus, the numerical trends in this trial was towards slightly improved outcomes in the 5-day group, although this difference was not statistically significant. When assessing the best and worst categories of the scale at Day 14, the rates of discharge were 120/200 (60.0%) for the 5-day remdesivir group versus 103/197 (52.3%) for the 10-day group, while the rates of Day 14 all-cause mortality were 16/200 (8.0%) for the 5-day group versus 21/197 (10.7%) for the 10-day group.

Figure 3: Distribution of Ordinal Score Through Day 14


It is unknown whether the open-label design may have influenced healthcare resource utilization between Day 5 and Day 10 after one group had completed assigned treatment, and whether this may have impacted later results for the ordinal scale at Day 14.

Overall, results in this trial were suggestive of similar treatment effects with 5-day and 10-day regimens in this patient population, with appropriate caveats related to the open-label design.

IX. **Human Clinical Safety**

- Remdesivir (200 mg IV on Day 1, followed by 100 mg IV daily on Days 2-10) has been studied in healthy subjects and in patients with EVD.
In March 2016, IND 1 was placed on Partial Clinical Hold with dose (150 mg IV daily) and duration restrictions due to a signal of hepatotoxicity in a clinical trial.

Approximately 500 subjects have received RDV prior to the COVID-19 outbreak. To date, final study reports and patient-level data have been submitted for two completed Phase 1 studies (single ascending dose study; multi-dose study) under IND 1.

**Safety overview and summary**
- In March 2016, IND 1 was placed on Partial Clinical Hold with dose (150 mg IV daily) and duration restrictions due to a signal of hepatotoxicity in a clinical trial.
- Safety results from the multi-dose study (Study GS-US-399-1954) demonstrated Grade 1-2 transaminase elevations in 2 of 8 healthy subjects in the 7-day cohort and 6 of 8 subjects in the 14-day cohort.
  - Alanine Aminotransferase (ALT) elevations were up to 10 times the subjects' baseline values.
  - The onset of these adverse events (AEs) occurred as early as day 5 in subjects.
  - One subject in the 7-day cohort was symptomatic with nausea, vomiting and anorexia concurrent with transaminitis leading to study drug discontinuation.
  - The mechanism of hepatotoxicity is currently unknown.
- In July 2019, the Partial Clinical Hold was modified to allow for the conduct of healthy volunteer Study GS-US-399-5505. FDA made the following modifications to the clinical hold parameters:
  - Single dose studies of RDV in healthy subjects (i.e., subjects with normal renal, hepatic, cardiac function, etc.) will be permitted. The dose may not exceed 200 mg IV.
  - Multiple dose studies in healthy subjects using doses ≤ 100 mg/day IV will be permitted.
  - A single loading dose ≤ 200 mg IV in multiple dose studies in healthy subjects will be permitted.
  - Single dose clinical studies to assess the impact of renal or hepatic impairment on pharmacokinetics will be permitted. The dose may not exceed 200 mg IV.
  - Clinical studies will be permitted in patients exposed to Ebola, with EVD, or in survivors of EVD who have evidence of persistent viral shedding (e.g., documented in semen or vaginal fluid) and/or post-Ebola syndrome.
  - The safety monitoring/risk mitigation plan for all protocols must adequately address the risk of hepatotoxicity.
  - The Investigator’s Brochure for RDV and Informed Consent Forms for all protocols must clearly describe the hepatic safety profile of the drug, including the safety findings from Study GS-US-399-1954.
- The Sponsor’s EUA request cites the Investigator’s Brochure which contains a brief summary of the findings from the PALM RCT that was conducted under IND 125,530. The publication with the PALM RCT results (N Engl J Med, 2019 Dec 12;381(24):2293-2303) is also cited.

Reference ID: 4601617
- Overall mortality at Day 28: RDV 53.1%, Z-Mapp 49.7%, mAb114 35.1%, REGN 33.5%.
- Of a total of 175 RDV recipients, Sponsor stated that 9 serious adverse events (SAEs) were assessed by the site investigator as not related to underlying EVD. Of these, an event of hypotension, which occurred during administration of the loading dose and led to fatal cardiac arrest, was considered related to RDV.
  - The Medwatch report for this SAE with fatal outcome has been submitted and reviewed. The Review Division agrees with the causality assessment.
- The final PALM study report has not been submitted to the Sponsor’s INDs (e.g. IND 1 or IND 1).
  - Safety data from trials in EVD are difficult to evaluate as hepatic injury is common in EVD. However, the Review Division has received safety reports from use in patients with EVD for Grade 4 transaminase elevations.
  - The Sponsor’s EUA request cites the Investigator’s Brochure which contains a brief summary of the findings from the prematurely terminated PREVAIL IV RCT that was conducted under IND 130,621.
    - Of a total of 38 subjects, the Sponsor stated that there were no SAEs. The Sponsor noted that the study allowed for blinded dose reductions for transaminase elevations and that dose reductions occurred in one RDV recipient and in 5 placebo recipients, respectively.
    - The final study report has not been submitted to the Sponsor’s INDs (e.g. IND 1 or IND 1).
  - A hepatic safety signal is the dose-limiting toxicity for RDV, and has resulted in discontinuations due to toxicity. Of note, transaminase elevations have been reported in patients with COVID-19 which may complicate the safety assessment. However, the Review Division has received safety reports from use in patients with COVID-19 for transaminase elevations up to 20 times the upper limit of normal with evidence of positive dechallenge.
  - Infusion-related reactions have been observed during and/or have been temporally associated with administration of RDV, and have resulted in discontinuations due to toxicity. Signs and symptoms may include hypotension, nausea, vomiting, diaphoresis, shivering.
  - A publication (Wang et al., 2020, Lancet, https://doi.org/10.1016/S0140-6736(20)31022-9) is available from a randomized, double-blinded, placebo-controlled trial conducted under Chinese regulatory authority in patients hospitalized with severe COVID-19 (clinicaltrials.gov identifier NCT04257656). In this trial, patients were randomized 2:1 to receive RDV or placebo (PBO). A total of 158 patients received RDV and 78 patients received PBO.
    - All-cause mortality at Day 28: RDV 14% vs. PBO 13%
    - Subjects who reported AEs: RDV 65% vs. PBO 64%
- Discontinuations due to AEs: RDV 12% vs. PBO 5%
  - The Sponsor provided a slide deck with a brief summary of the findings from the randomized portion of the Sponsor’s open-label trial in adults and adolescents with severe COVID-19. A total of 200 patients received a 5-day course of RDV (i.e. RDV₅) and 197 patients received a 10-day course of RDV (i.e. RDV₁₀). This open-label trial does not have a standard-of-care group. Follow-up to Day 28 is still ongoing.
- All-cause mortality at Day 14: RDV₅ 8% vs. RDV₁₀ 11%
- The Sponsor did not provide the timeframe for the following all-cause safety findings that were provided:
  - Death: RDV₅ 10% vs. RDV₁₀ 13%
  - Serious adverse events: RDV₅ 21% vs. RDV₁₀ 35%
  - Subjects who reported AEs: RDV₅ 71% vs. RDV₁₀ 74%
  - Subjects who reported Grade 3 AEs or higher: RDV₅ 31% vs. RDV₁₀ 43%
  - Discontinuations due to AEs: RDV₅ 5% vs. RDV₁₀ 10%
  - ALT elevations:
    - Grade 3: RDV₅ 4% vs. RDV₁₀ 6%
    - Grade 4: RDV₅ 2% vs. RDV₁₀ 3%
  - AST elevations:
    - Grade 3: RDV₅ 6% vs. RDV₁₀ 4%
    - Grade 4: RDV₅ 2% vs. RDV₁₀ 4%
  - Creatinine elevations:
    - Grade 3: RDV₅ 3% vs. RDV₁₀ 4%
    - Grade 4: RDV₅ 2% vs. RDV₁₀ 12%

The Warnings/Precautions section of the Fact Sheets will provide wording that clearly describes the hepatotoxicity safety signal and infusion related reactions that have been observed for remdesivir.

X. Specific Populations

- Safety and pharmacokinetic (PK) data are not available in pediatrics, geriatrics, pregnant women, lactating women, patients with renal insufficiency, or patients with hepatic insufficiency. The need for dose adjustments in these populations has not been established because PK data in these populations are not available. Dose recommendations in these populations have been based largely on risk/benefit considerations.
- Under IND 1⁴ (proposed indication: treatment of EVD), a pediatric dosing regimen based on Physiologically-Based Pharmacokinetic (PBPK) Modeling was provided and children were included in the PALM RCT which studied RDV (among other agents) for the treatment of EVD.
- Nonclinical reproductive and development toxicity program has not identified any risks to pregnant females or embryos exposed via lactation.
Juvenile toxicity studies are not warranted as there is no relevant safety concerns in the adult nonclinical program.

XI. Human Clinical Pharmacology

Absorption, Metabolism, Distribution, and Excretion

- Remdesivir is a prodrug that is metabolized to metabolites GS-704277 and GS-441524
- GS-441524 is a nucleoside analog that is intracellularly phosphorylated to the active nucleoside triphosphate GS-443902
- Carboxylesterase 1 is thought to primarily metabolize remdesivir. However, remdesivir is also a substrate of CYP2C8, CYP2D6, and CYP3A4.
- Remdesivir is a substrate of transporters P-gp and OATP1B1
- In a human mass balance study, 74% of the dose was recovered from urine
- Mean half-lives of remdesivir, GS-441524 and GS-443902 are 1.0 hours, 27 hours and 43 hours

Drug Interactions

Based on in vitro studies, remdesivir and metabolites have the following effects on drug metabolizing enzymes and transporters.
- Remdesivir is a weak inhibitor of CYP1A2, CYP2C9, CYP2C19, and CYP2D6, and an inhibitor of CYP3A4. Remdesivir is an inhibitor of transporters BSEP-, MRP4- and NTCP.
- GS-704277 is an inhibitor of transporters MRP2 and NTCP
- GS-441524 is an inhibitor of transporter NTCP

After IV administration, metabolites are more abundant than remdesivir in plasma.

No human drug interaction studies have been conducted.

Pharmacokinetics

Single and multiple dose pharmacokinetics (PK) of remdesivir and metabolites were evaluated in healthy adults after IV administration (Table 6, Table 7). PK has not been evaluated in subjects with COVID-19 or in specific populations (pediatrics, elderly, renal impairment, hepatic impairment, pregnant women, lactating women, etc).

Table 6. Mean (CV%) multiple dose pharmacokinetics of remdesivir and metabolites in healthy adults administered intravenous remdesivir 200 mg over 30 minutes on day 1 and 100 mg daily on days 2-5 or days 2-10.a

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Matrix</th>
<th>N</th>
<th>$C_{\text{max}}$ (ng/mL)</th>
<th>$T_{\text{max}}$ (h)</th>
<th>$\text{AUC}_{0-24h}$ (ng*h/mL)</th>
<th>$C_{24h}$ (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remdesivir</td>
<td>Plasma</td>
<td>26</td>
<td>2229 (19)</td>
<td>0.68 (0.25, 0.75)</td>
<td>1585 (17)</td>
<td>Not detectableb</td>
</tr>
</tbody>
</table>
Table 7. Mean (CV%) multiple dose pharmacokinetics of GS-443902 in peripheral blood mononuclear cells in healthy adults administered intravenous remdesivir 200 mg over 30 minutes on day 1 and 100 mg daily on days 2-5 or days 2-10.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Matrix</th>
<th>N</th>
<th>$C_{\text{max}}$ (µmol)</th>
<th>$T_{\text{max}}$ (h)</th>
<th>AUC\textsubscript{0-24h} (µmol*h)</th>
<th>C\textsubscript{24h} (µmol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS-443902</td>
<td>PBMC</td>
<td>26</td>
<td>14.6 (41)</td>
<td>6.0 (1.0, 12.0)</td>
<td>240 (25)</td>
<td>10.2 (50)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Multiple dose PK parameters are combined from the five day and 10 day dosing cohorts.

XII. Nonclinical Data to Support Safety

- Nonclinical safety studies were conducted in rats and cynomolgus monkeys for 2 weeks.
- The kidney was identified as the target organ of toxicity. Findings included increased serum creatinine, proteinuria, increased kidney weight, and proximal tubular epithelial necrosis.
- Additional adverse effects were noted on appetite, body weight gain, and (increased) respiration rate.
- Renal toxic effects of GS-5734 in monkeys were not different than the vehicle control, 12% sulfobutylether-β-cyclodextrin (SBEDC). It is important to note that SBEDC is a known renal toxicant deemed safe for use in patients > 32kg (250 mg/kg/day by EMA).
- SBEDC exposure in infants <2 (<40 kg) were supported by DMF #14364.
- GS-5734 was not assessed as a potential mutagen or clastogen.
- In vitro examinations also showed little to no potential of cytotoxicity or mitochondrial toxicity of GS-5734 or its major metabolites.
- A complete reproductive and development toxicity program has not identified any risks for pregnant mothers or their off-spring.
- The nonclinical program is complete and sufficient to support authorization of an EUA for use of GS-5734.

XIII. Nonclinical Data to Support Efficacy

- Remdesivir is a nucleotide prodrug that is intracellularly metabolized into its active form GS-441524, which is an analog of adenosine triphosphate that inhibits viral RNA synthesis.
- The GS-441524 adenosine nucleotide analog is incorporated into the nascent RNA chain by the coronavirus viral RNA polymerase (nsp12) and evades proofreading by the coronavirus exoribonuclease, resulting in a decrease in coronavirus RNA production. It is currently unknown whether it terminates RNA chains or causes mutations in them (Agostini et al., 2018).
Remdesivir exhibited antiviral activity against several human RNA viruses including, SARS-CoV and Middle East Respiratory Syndrome (MERS) CoV, Ebola virus, Marburg virus, Junin virus, and Lassa fever virus.

Remdesivir exhibited cell culture antiviral activity against a clinical isolate of SARS-CoV-2 in primary human airway epithelial (HAE) cells with a 50% effective concentration (EC$_{50}$) of 0.0099 µM after 48 hours of treatment (PC-540-2003).

The EC$_{50}$ values of remdesivir against the SARS-CoV-2 grown in Vero cells has been reported to be 0.14 µM at 24 hours and 0.75 µM at 48 hours post-treatment (PC-540-2001).

An EC$_{50}$ value of 0.77 µM in Vero cells has been reported for RDV against SARS-CoV-2 by the Wuhan Institute of Virology (Wang et al., 2020).

Remdesivir inhibited a recombinant chimeric virus expressing the RdRp gene (nsp12) of SARS-CoV-2 in a backbone of SARS-CoV with a fluorescent reporter protein in Huh7 cells with an EC$_{50}$ value 0.003 µM (PC-540-2002).

Cell culture antiviral assessments against other human and animal coronaviruses are summarized below:

- Remdesivir and GS-466547 (an opposite diastereomer) were tested in cell culture antiviral activity assessments against SARS-CoV and MERS-CoV. Remdesivir and GS-466547 inhibited replication of MERS-CoV in Vero E6 cells with mean EC$_{50}$ values of 0.52 and 0.42 µM, respectively. No cytotoxicity was observed at 10 µM, the highest concentration tested, indicating selective inhibition of virus replication with selectivity indices of >19 and >24, respectively.

- GS-466547 inhibited SARS-CoV and MERS-CoV replication in human airway epithelial (HAE) cultures as measured by the reduction in the expression of a fluorescent reporter protein at compound concentrations ranging from 0.1 to 1.1 µM.

- The activity of remdesivir against SARS-CoV and MERS-CoV was assessed using recombinant viruses expressing a fluorescent reporter protein in a continuous human lung epithelial cell line, 2B4 (Calu-3; MERS-CoV only) and primary HAE cells (SARS-CoV and MERS-CoV). Remdesivir inhibited MERS-CoV replication in Calu-3 cells, with a mean EC$_{50}$ value of 0.025 µM (Sheahan et al., 2017). In HAE cells, remdesivir inhibited both SARS-CoV and MERS-CoV replication with EC$_{50}$ values of 0.069 and 0.074 µM, respectively. In both HAE and Calu-3 cells, no cytotoxicity was observed at 10 µM of remdesivir, the highest concentration tested, indicating that remdesivir has selectivity indices >100 in these cell culture systems (Sheahan et al., 2017).

- Remdesivir showed cell culture antiviral activity against human betacoronavirus OC43 and alphacoronavirus 229E as well as the animal betacoronavirus murine hepatitis virus and the genetically divergent porcine deltacoronavirus with submicromolar EC$_{50}$ values ranging from
Remdesivir inhibited the replication of SARS-CoV-2 and SARS-CoV with EC\textsubscript{50} values of 0.0099 \mu M and 0.0066 \mu M, respectively, in HAE cells after 48 hours of treatment. No cytotoxicity has been observed for remdesivir in HAE cells at concentrations up to 10 \mu M (CC\textsubscript{50} value >10 \mu M) (PC-540-2003). The dose response curve of RDV against SARS-CoV-2 exhibited a shallow dose-dependent increase in inhibition compared to the response against SARS-CoV, indicating that RDV may be more active against SARS-CoV. Alternatively, there could be a lag in formation of the active diphosphate partially overcome by higher concentrations due to slow uptake by the cells, slow metabolism of the prodrug to the monophosphate, or a slow phosphorylation step.

The development of resistance to RDV in coronaviruses has been assessed by cell culture passaging of murine hepatitis virus (MHV), a coronavirus, in the presence of the remdesivir parent nucleoside, GS-441524. After 23 passages, two substitutions were selected in the nsp12 polymerase at residues conserved across coronaviruses: F476L and V553L.

Compared to wild-type virus, recombinant MHV containing the F476L substitution showed 2.4-fold reduced susceptibility to RDV, and MHV containing the V553L substitution demonstrated 5-fold reduced susceptibility, while the double mutant conferred 5.6-fold reduced susceptibility to RDV in cell culture. The potential relevance of this finding to SARS-CoV-2 is unknown.

There are no directly relevant animal studies showing that remdesivir inhibits SARS-CoV-2 or improves outcomes in an animal model to date using a treatment paradigm.

In a non-lethal non-human primate model of SARS-CoV-2 pathogenesis under a post-exposure prophylaxis paradigm that initiated treatment 12 hours after challenge with SARS-CoV-2, administration of a loading dose of 10 mg/kg remdesivir, followed by a 5 mg/kg dose 12 hours after the loading dose, and then a daily maintenance dose of 5 mg/kg for 5 additional days delivered as a slow intravenous bolus injection resulted in a marginal clinical benefit during SARS-CoV-2 infection in rhesus macaques. There were a number of limitations to this study, including the lack of an adequately characterized and validated model, use of a non-lethal model that cannot be used to assess mortality or severe respiratory disease, and lack of clarity related to the optimal route and dose of the viral challenge. Additionally, there were differences in RDV prodrug and metabolite exposures between infected NHPs, healthy NHPs, and healthy humans that further impede extrapolation of these results to humans with COVID-19.

In a non-lethal mouse model of SARS-CoV pathogenesis, administration of 25 mg/kg remdesivir subcutaneously twice daily beginning 1 day before or 1 day...
after SARS-CoV inoculation resulted in reduced lung viral load and improved clinical signs of disease and lung function (Sheahan et al., 2017).

- In a mouse model of MERS-CoV pathogenesis, administration of 25 mg/kg remdesivir subcutaneously twice daily beginning 1 day before or 1 day after MERS-CoV inoculation improved pulmonary function and reduced lung viral loads and lung pathology (Sheahan et al., 2020). Of note, this mouse model was not uniformly lethal at the challenge doses used in these studies, which resulted in 50% mortality by Day 6. Treatment with RDV did not improve survival.

- In MERS-CoV-infected rhesus monkeys, administration of remdesivir at 10 mg/kg or 5 mg/kg once daily for 7 days using IV bolus injection beginning 1 day prior to MERS-CoV inoculation resulted in a reduction of clinical scores, clinical signs of respiratory disease, and viral RNA levels compared to vehicle-treated animals (De Witt et al., 2020).

XIV. Supply Information

- Two vials are needed for the first day of treatment, and one vial is needed subsequently for treatment.
- The product availability as of (b)(4) is provided below. Gilead has been providing regular updates regarding the available product as additional product has been manufactured.

Table 8: Current Supply of Remdesivir Drug Substance and Drug Product

<table>
<thead>
<tr>
<th>Product</th>
<th>Quantity Currently Available</th>
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XV. Chemistry, Manufacturing, and Controls Information

- The CMC information for both remdesivir injection and remdesivir for injection is included in IND 1 (b)(4).
- Both remdesivir formulations contain sulfobutylether-β-cyclodextrin sodium salt (SBECED), and hydrochloric acid and/or sodium hydroxide for pH adjustment.

XVI. Manufacturing Site Inspections

Drug Substance and Drug Product Manufacturing, Release Testing and Labeling Sites for Remdesivir Under EUA
XVII. Clinical Trial Site Inspections

- Site inspections have not been performed to date.
XVIII. Animal Study Site Inspections (Efficacy and PK/PD)

- Site Inspections have not been performed to date.

XIX. Recommendations From Treatment Guidelines and Other Sources

- The Centers for Disease Control (CDC) notes that there are no drugs or other therapeutics approved by the US Food and Drug Administration to prevent or treat COVID-19 ([https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html; April 25, 2020). CDC notes that RDV is an investigational drug and is available via clinical trials and via expanded access.
- The Infectious Diseases Society of America (IDSA) Guidelines on the Treatment and Management of Patients with COVID-19 Infection ([https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management; April 11, 2020) notes that RDV is an investigational drug and states that, because RCTs for RDV have not been completed, formalized recommendations will be made once the entire body of evidence for RDV is available. IDSA advocates that patients should be recruited into ongoing trials, which would provide much needed evidence on the efficacy and safety of various candidate drugs for COVID-19.
- The NIH COVID-19 Treatment Guidelines ([covid19treatmentguidelines.nih.gov; April 21, 2020) state that, at present, no drug has been proven to be safe and effective for treating COVID-19. NIH notes that this document will be updated in real-time as clinical trial data become available.

XX. Risk-Benefit Assessment and Recommendations for Emergency Use

RDV is a direct acting antiviral drug that inhibits viral RNA synthesis. It is an investigational drug and is not currently approved for any indication.

RDV has activity in cell culture against SARS-CoV, MERS-CoV, and SARS-CoV-2, and has activity in animal models of SARS-CoV-2, SARS-CoV, and MERS-CoV. Preliminary data from a study of RDV in non-human primates (NHPs) with SARS-CoV-2 suggests proof-of-concept antiviral activity for post-exposure prophylaxis in an NHP animal model.

The safety of remdesivir has been evaluated in healthy subjects, in patients with Ebola Virus Disease (EVD), and in patients with COVID-19. A hepatic safety signal manifested as transaminase elevations was demonstrated in a Phase 1 multi-dose trial in healthy subjects. Safety data from trials in EVD are difficult to evaluate as hepatic injury is common in EVD; similarly, transaminase elevations have been reported to occur in some patients with COVID-19. However, transaminase elevations up to 20 times the upper limit of normal with positive de-challenge, have been reported in patients receiving RDV for the
treatment of COVID-19. Careful monitoring of hepatic laboratory indices will be recommended in all patients to guide treatment decisions.

The effectiveness of remdesivir for the treatment of COVID-19 in hospitalized patients was evaluated in a randomized, double-blinded, placebo-controlled trial conducted by NIAID under US IND. This trial randomized a total of 1063 patients in a 1:1 ratio to receive remdesivir or placebo for 10 days. The primary efficacy endpoint was time to recovery through Day 29. Topline efficacy data was provided by NIAID. In the intent-to-treat population of all randomized patients, the time to recovery was significantly faster in the remdesivir group than the placebo group. Median days to recovery was 11 days in the remdesivir group versus 15 days in the placebo group (two-sided p-value <0.001). There was an interaction observed by baseline disease severity. In patients with mild-to-moderate disease at baseline, there was little evidence of a difference in recovery times between remdesivir versus placebo, and both groups had a short median recovery time of only 5 days. In patients classified as having severe disease at baseline, there was significantly faster recovery in the remdesivir group (median 12 days) than the placebo group (median 18 days), with a two-sided p<0.001. Although follow-up for Day 29 all-cause mortality is still ongoing for many patients, there was a numerical trend towards lower mortality in the remdesivir group [43/538 (8.0%)] than the placebo group [60/519 (11.6%)], with a two-sided p-value of 0.06. Overall, results from this large trial provided reliable and statistically persuasive evidence of benefit for remdesivir.

Data are also available from the Wang et al. (2020) publication of a randomized, double-blinded, placebo-controlled trial conducted under Chinese regulatory authority in patients hospitalized with severe COVID-19. This trial enrolled 237 patients out of the planned 453 patients prior to study termination due to operational futility. Due to the small sample size, there was a higher degree of uncertainty in estimating treatment effects. Nevertheless, favorable numerical trends for remdesivir in this trial were qualitatively consistent with results from the larger NIAID-sponsored trial.

Topline results were also available from a randomized, open-label trial sponsored by Gilead that compared 5-day and 10-day remdesivir durations for the treatment of patients with severe COVID-19. A total of 401 patients were randomized in a 1:1 ratio to the 5-day and 10-day remdesivir groups. Only 3% of patients required mechanical ventilation at baseline. The prespecified primary efficacy analysis was to examine results on a 7-point ordinal scale at Day 14 using a proportional odds model. Primary analysis results of the proportional odds model at Day 14 yielded an estimated odds ratio (on a scale with values less than 1.00 favoring the 5-day duration) of 0.75, with a 95% confidence interval from 0.51 to 1.12. Thus, the numerical trends in this trial was towards slightly improved outcomes in the 5-day group, although this difference was not statistically significant. When assessing the best and worst
categories of the scale at Day 14, the rates of discharge were 120/200 (60.0%) for the 5-day remdesivir group versus 103/197 (52.3%) for the 10-day group, while the rates of Day 14 all-cause mortality were 16/200 (8.0%) for the 5-day group versus 21/197 (10.7%) for the 10-day group. These results are suggestive of a similar treatment effect with 5-day and 10-day regimens in this population, with appropriate caveats related to the open-label trial design.

Observational data was also provided in support of the treatment of COVID-19 in hospitalized patients with RDV. The Sponsor conducted non-randomized comparisons between patients in their remdesivir compassionate use dataset and patients from an electronic medical records (EMR) dataset and published literature. However, due to limitations and uncertainties, the existing non-randomized human efficacy data do not provide reliable evidence that remdesivir has a beneficial effect for the treatment of COVID-19.

Based on the scientific evidence available to FDA, it is reasonable to believe that the known and potential benefits of RDV outweigh the known and potential risks of the drug for the treatment of patients hospitalized with severe COVID-19. Therefore, the Review Division and the Office of Infectious Diseases recommends issuance of an EUA for RDV for the treatment of patients hospitalized with severe COVID-19.

The most robust clinical data were generated by the NIAID-sponsored trial which studied a 10-day treatment regimen in all patients; however, the preliminary results of Gilead’s open-label trial studying 5 versus 10 days of treatment did not demonstrate a clear difference in outcomes among patients, albeit with too few patients requiring mechanical ventilation or ECMO to yield meaningful comparative information for those populations. Based on the similar treatment effect demonstrated for a 5-day versus 10-day course of remdesivir in severely ill patients not requiring mechanical ventilation or ECMO, and in order to ensure adequate drug supply for the US population, a treatment regimen that includes a 10-day treatment course for patients requiring mechanical ventilation or ECMO and a 5-day course in other patients hospitalized with severe COVID-19 will be authorized. Patients who receive a 5-day treatment course but do not demonstrate clinical improvement will be eligible to continue to receive RDV for an additional 5 days.

XXI. Considerations for Adverse Event (AE) Monitoring

This product will either be used in clinical trials or in clinical practice. If used in clinical trials done under IND, FDA IND safety reporting regulations will apply. In the setting of a pandemic where practicing physicians will have many competing priorities, adverse event reporting under this EUA will be streamlined through the MEDWATCH system.
The prescribing health care provider and/or the provider’s designee will be responsible for reporting medication errors and adverse events (death, serious adverse events*) considered to be potentially related to remdesivir occurring during Remdesivir treatment within 7 calendar days from the onset of the event. The reports should include unique identifiers and the words “Remdesivir Treatment under Emergency Use Authorization (EUA).”

XXII. Mandatory and Discretionary Requirements for Use of the Product Under the EUA

1. Treatment of coronavirus disease 2019 (COVID-19) in patients hospitalized with severe disease. Severe disease is defined as patients with an oxygen saturation (SpO2) ≤ 94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation.

2. As the health care provider, communicate to your patient or parent/caregiver information consistent with the “Fact Sheet for Patients and Parents/Caregivers” prior to the patient receiving remdesivir. Health care providers (to the extent practicable given the circumstances of the emergency) must document in the patient’s medical record that the patient/caregiver has been:
   a. Given the Fact Sheet for Patients and Parents/Caregivers,
   b. Informed of alternatives to receiving authorized remdesivir, and
   c. Informed that: Remdesivir is an unapproved drug which is authorized for the unapproved use under this Emergency Use Authorization.

3. The prescribing health care provider and/or the provider’s designee are/is to provide responses to requests from FDA for information about adverse events and medication errors following receipt of remdesivir.

4. The prescribing health care provider and/or the provider’s designee are/is responsible for reporting medication errors and adverse events (death, serious adverse events*) considered to be potentially related to remdesivir occurring during remdesivir treatment within 7 calendar days from the onset of the event. The reports should include unique identifiers and the words “Remdesivir treatment under Emergency Use Authorization (EUA).” in the description section of the report (see Section XXI above).

• Submit adverse event reports to FDA MedWatch using one of the following methods:
  • Complete and submit the report online:
    • www.fda.gov/medwatch/report.htm, or
  • By using a postage-paid Form FDA 3500 (available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf) and returning by mail (MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787), or by fax (1-800-FDA-0178), or
  • Call 1-800-FDA-1088 to request a reporting form
  • Submitted reports should state “Remdesivir Treatment under EUA”.

Reference ID: 4601617
*Serious Adverse Events are defined as:
• death;
• a life-threatening adverse event;
• inpatient hospitalization or prolongation of existing hospitalization;
• a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;

Additional requirements for reporting of patient outcomes, in addition to safety, may be required as a condition of use under this EUA.

XXIII. Information to Be Conveyed to Health Care Providers and Recipients of the Product

- Fact Sheet for Health Care Providers (See Section XXVI. Appendices)
- Fact Sheet for Patients and Parents/Caregivers (See Section XXVI. Appendices)

XXIV. Outstanding Issues/Data Gaps
Not applicable

XXV. References

- References are included in the relevant sections of this review, where applicable.

XXVI. Appendices

Appendix I. Fact Sheet for Health Care Providers

Appendix II. Fact Sheet for Patients and Parent/Caregivers

Appendix III: Observational Data

Observational data are available based on 163 patients treated with remdesivir in a compassionate use program. The sponsor has conducted non-randomized comparisons between patients in this remdesivir compassionate use dataset and patients from an electronic medical records dataset. In addition, the sponsor has compared outcomes in the compassionate use program to the published literature. Patient-level data were not submitted or reviewed for these analyses.

The 163 patients in the compassionate use program were dosed with remdesivir between January 26, 2020 and March 14, 2020. Patients were to be treated with an initial intravenous loading dose of remdesivir 200 mg once daily for one day followed by a
maintenance intravenous dose of remdesivir 100 mg once daily for up to 9 days, for a total of up to 10 days of therapy. The sponsor has summarized patient characteristics in this compassionate use program as follows:

The mean treatment duration was 9 days; median follow-up time from first dose of remdesivir was 15 days (range 4-44 days). Patients had a mean age of 61 years (range 23-86 years); 33 (20%) were aged <50 years; 37 (23%) were aged 50-60 years; 41 (25%) were aged 60-70 years; and 52 (32%) were aged ≥70 years; 33 patients (20%) were female. At baseline, 104 patients (64%) were receiving invasive methods of oxygen support: 98 (60%) were receiving invasive mechanical ventilation; 6 (4%) were receiving extracorporeal membrane oxygenation (ECMO). A total of 58 (36%) patients were receiving one of the following noninvasive methods of oxygen support: noninvasive positive pressure ventilation (NIPPV) (N=16, 10%); high-flow O2 (N=8, 5%); supplemental O2 (N=31, 19%); or room air, O2 saturation <94% (N=3, 2%). Mean duration of symptoms prior to treatment with remdesivir was 13 days (range 10-16 days). Reported comorbidities included hypertension (N=45, 28%), diabetes (N=32, 20%); hyperlipidemia (N=22, 13%); history of malignancy (N=13, 8%); cardiac disease (N=19; 12%); and respiratory disease (N=24, 15%).

The overall mortality rate in the remdesivir compassionate use dataset was 33/163 (20.2%), while 49/163 (30.1%) patients were discharged.

The mortality rate substantially differed between patients in Italy [22/84 (26.2%)] and patients outside Italy [11/79 (13.9%)].

The table below summarizes post-baseline oxygen support status according to baseline status. The majority of patients were on invasive ventilation at baseline, and approximately two thirds of these patients either had died or remained on invasive ventilation at follow-up.

Table 10: The sponsor’s summary of last reported overall status by baseline oxygen support status for 163 patients in the remdesivir compassionate use program.

<table>
<thead>
<tr>
<th>Post-treatment Oxygen Support Status</th>
<th>Invasive n=104</th>
<th>Noninvasive n=24</th>
<th>Suppl Air n=31</th>
<th>Room Air O2 sat &lt;94% n=3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive</td>
<td>27 (26)</td>
<td>5 (21)</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Noninvasive</td>
<td>39 (38)</td>
<td>5 (21)</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Suppl air</td>
<td>8 (8)</td>
<td>4 (12)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Room air</td>
<td>6 (6)</td>
<td>1 (12)</td>
<td>3 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Discharge</td>
<td>12 (12)</td>
<td>9 (38)</td>
<td>24 (77)</td>
<td>3 (100)</td>
</tr>
<tr>
<td>Improvement</td>
<td>38 (37)</td>
<td>10 (42)</td>
<td>26 (84)</td>
<td>3 (100)</td>
</tr>
</tbody>
</table>

Source: EUA Request, page 53.
The sponsor compared outcomes in the remdesivir compassionate use program to outcomes from electronic medical records, and provided the following summary of the TriNetX dataset used for this comparison (“efficacy-comparison.pdf”, available at

We used real-world data from TriNetX to identify adults hospitalized for COVID-19 between Jan 20 and March 30, 2020. TriNetX is a global research network that provides access to linked electronic medical record (EMR) data for approximately 68 million patients in 56 large health care organizations predominately in the United States. TriNetX provided an anonymized dataset of electronic medical records (diagnoses, procedures, medications, laboratory values, genomic information) from patients hospitalized with COVID-19. No protected health information was received, and no study-specific activities were performed in retrospective analyses. Participating organizations include a mix of hospital, primary care, and specialty treatment providers across diverse geographies, age groups, and socioeconomic status. Outcomes extracted from the EMR included requirement for invasive ventilation, length of hospital stay, and hospital mortality.

COVID-19 was diagnosed in patients hospitalized after the first COVID-19 index patient was diagnosed in the US on 20th January 2020 on the basis of the following ICD-10 codes:

- B97.29 (other coronavirus as the causes of diseases classified elsewhere),
- B34.2 (coronavirus infection, unspecified), and
- U07.1 (2019-nCoV acute respiratory disease [WHO])

Patients were excluded from the cohort if they had the ICD-9 code 079.89 (other specific viral infections), or if they were concurrently enrolled in a clinical trial, to minimize the possibility that patients exposed to investigational RDV would be included. The study period included available patient data from 20 January 2020 to 30 March 2020.

The sponsor included a total of 153 patients diagnosed with COVID-19 in the TriNetX cohort in its analyses. The mortality rate in this cohort was only 11/153 (7.2%), which was lower than the previously discussed 20% mortality rate in remdesivir compassionate use dataset. However, this may have reflected a less severe patient population, as only 9% of patients in the TriNetX cohort were invasively ventilated at baseline compared with 64% in the remdesivir compassionate use program. In addition, only 50% of patients in the TriNetX cohort were male compared with 80% in the compassionate use dataset. To adjust for confounding due to baseline differences the sponsor performed the following analyses:

Poisson regression was used to generate incidence rates and incidence rate ratios (IRRs), adjusted by age, sex and ventilation invasive status at baseline (yes/no) as the base model. In addition, a propensity score was computed as a patient’s probability of receiving a specific treatment conditional on the observed baseline covariates (age, gender, and baseline ventilation status). This score was included as a regressor in a second model. In the final model, inverse probability treatment weighting (IPTW) with
Stabilized weights was used in conjunction with Poisson regression models to quantify comparative differences between the TriNetX analysis set and the CU study analysis set. The IPTW approach maximizes homogeneity between cohorts and minimizes the impact of treatment-selection bias.

The figure below shows that the sponsor’s estimated rate ratios for mortality favored remdesivir after adjusting for age, sex, and ventilation status using Poisson regression, adjusting for propensity scores, or inverse weighting by propensity scores. These rate ratios reached nominal statistical significance after the sponsor excluded Italian patients from the analyses.

Figure 4: The sponsor’s comparison of incidence rate ratios for mortality between 163 patients in the remdesivir compassionate use program and 153 patients in the TriNetX cohort.

![Rate Ratio Table](source)

Source: “efficacy-cu summary.pdf”, Slide 16, Available at [link]

In addition to the TriNetX comparison, the sponsor has compared outcomes in the remdesivir compassionate use program to outcomes in the published literature. The figure below from the sponsor displays that the remdesivir mortality rate was generally lower than published mortality rates for patients with severe disease at baseline.

Figure 5: The sponsor’s summary of a systematic literature review for mortality in patients with severe COVID-19 at baseline.
There are limitations and uncertainties in the analyses based on the remdesivir compassionate program. As comparisons were not randomized there was likely confounding, meaning systematic differences in prognostic baseline characteristics between patients in the remdesivir compassionate use dataset, patients in the TriNetX cohort, and patients from the published literature. Statistical adjustment for age, sex, and ventilation status in the TriNetX comparisons was unlikely to fully correct for confounding, and the modeling did not adjust for other potentially relevant variables such as comorbidities. It was also unclear whether background conditions (e.g., hospital resource constraints) and background standards of care were similar between patients in the remdesivir compassionate use program and external datasets. Further, the follow-up time for mortality assessments was not standardized between different datasets, and the median follow-up time of 15 days in the remdesivir compassionate use dataset was relatively short, which may have biased mortality comparisons in favor of remdesivir. It was also unclear whether there was immortal time bias in the remdesivir compassionate use program through exclusion of patients who died before receiving the first dose of remdesivir.

Due to these limitations, assessments of human clinical efficacy should be based on the randomized controlled trials rather than the compassionate use program.
## EUA Approvals

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<td>Office of Infectious Diseases (OID)</td>
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<td>OID/Division of Antivirals (DAV)</td>
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<td>Jeffrey Murray, MD, MPH</td>
<td>OID/DAV</td>
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CHRISTINE KIM
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Signatory for this review is listed on page 36.