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Veklury® (remdesivir) SIMPLE Study in Patients With Severe COVID-19

This document is in response to your request for information on the SIMPLE study, which evaluated the use of Veklury® (remdesivir [RDV]) in hospitalized participants with severe COVID-19.

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The full indication, important safety information, and boxed warnings are available at: www.gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_pi.

Summary

SIMPLE Study: RDV Use in Severe COVID-19

A phase 3, randomized, open-label study compared the outcomes of non-mechanically ventilated participants with severe COVID-19 who received either 5 or 10 days of RDV treatment and SoC.[1]

- The 10- and 5-day RDV groups experienced similar rates of recovery (54% [106/197] and 64% [129/200], respectively) and times to recovery (11 and 10 days).[1,2]
- The mortality rate was numerically lower in the 5-day RDV group than in the 10-day RDV group (8% [12/200] and 11% [21/197], respectively).[1]
- The number of AEs and SAEs were similar in the 5-day and 10-day RDV groups. The most common AEs were nausea, worsening respiratory failure, elevated ALT level, and constipation.[1]

SIMPLE Study: RDV Use in Severe COVID-19

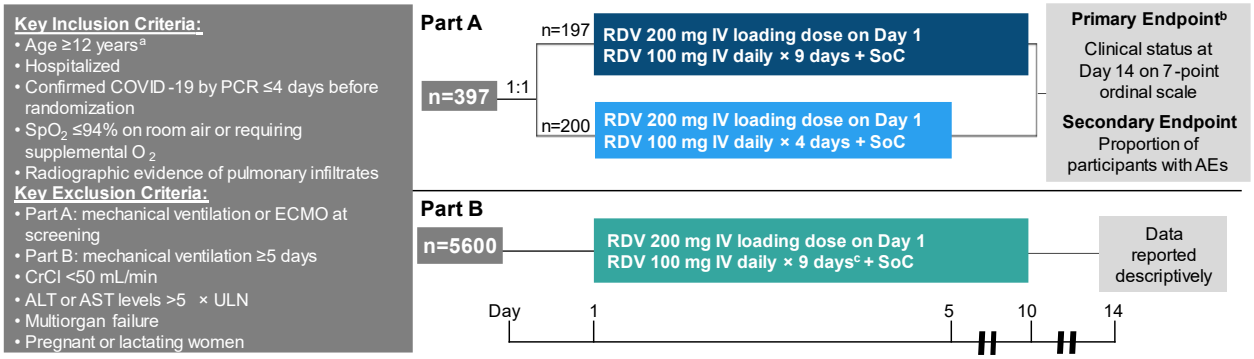
Study Design

A phase 3, randomized, two-part (Parts A and B), open-label study compared the outcomes of hospitalized participants with severe COVID-19 who received 5 or 10 days of RDV and SoC. The primary outcome was the distribution of clinical status scores on a 7-point ordinal scale on Day 14. The secondary objective was the proportion of patients who had a treatment-emergent AE or a treatment-emergent clinical laboratory abnormality.[1,2]

Part A enrolled 397 participants who were not mechanically ventilated between March 6 and March 26, 2020, and those who met all eligibility criteria were randomly assigned in a 1:1 ratio to receive RDV 200 mg IV loading dose on Day 1, followed by RDV 100 mg/day IV for either 4 days or 9 days with SoC therapy (Figure 1). Both treatment arms continued to

receive SoC therapy. The protocol did not require participants whose clinical status improved enough to be eligible for hospital discharge to complete the full course of assigned RDV treatment.[1]

Figure 1. SIMPLE Study in Severe COVID-19: Study Design[1,2]



Abbreviations: PCR=polymerase chain reaction; SpO_2=peripheral oxygen saturation; ULN=upper limit of normal.
[a]Adults ≥18 years or adolescents between 12 and 18 years weighing ≥40 kg were included.
[b]The primary efficacy population was composed of participants from Part A. Clinical status was assessed with a 7-point ordinal scale that included the following categories: 1) death; 2) hospitalized and required IMV or ECMO; 3) hospitalized and required NIV or high-flow O_2 devices; 4) hospitalized and required low-flow supplemental O_2; 5) hospitalized and did not require supplemental O_2 but required ongoing medical care (COVID-19-related or otherwise); 6) hospitalized but did not require supplemental O_2 or ongoing medical care; 7) not hospitalized.
[c]In Part B, treatment could be reduced to a total of 5 days following analysis of the data from Part A.
Note: Of the 402 participants who underwent randomization, 397 began RDV treatment.

Baseline Demographics and Participant Disposition[1]

Baseline demographics were balanced between the groups; however, significantly more participants in the 10-day RDV group were in the two highest disease severity groups, and therefore had a worse clinical status at baseline, compared with the 5-day RDV group (*P*=0.02).

Table 1. SIMPLE Study in Severe COVID-19: Select Baseline Demographics and Disease Characteristics[1]

Key Demographics and Characteristics		10-Day RDV (n=197)	5-Day RDV (n=200)
Age, median (IQR), years		62 (50–71)	61 (50–69)
Male, n (%)		133 (68)	120 (60)
Race,[a] White/Black/Asian/other, n (%)		134 (70)/23 (12)/ 25 (13)/10 (5)	142 (71)/21 (10)/ 20 (10)/17 (8)
Most common coexisting conditions, n (%)	Hypertension	98 (50)	100 (50)
	Hyperlipidemia	49 (25)	40 (20)
	Diabetes	43 (22)	47 (24)
Clinical status on the 7-point ordinal scale,[b] n (%)	2 - Required IMV or ECMO	9 (5)	4 (2)
	3 - Required NIV or high-flow O_2	60 (30)	49 (24)
	4 - Required low-flow supplemental O_2	107 (54)	113 (56)
	5 - Did not require supplemental O_2 but required medical care	21 (11)	34 (17)

Key Demographics and Characteristics	10-Day RDV (n=197)	5-Day RDV (n=200)
Duration of symptoms before RDV initiation, median (IQR), days	9 (6–12)	8 (5–11)

[a]Patient-reported race data were available for 192 participants who received 10 days of RDV and for all 200 participants who received 5 days of RDV.
[b]*P*=0.02 for 5-day vs 10-day group.

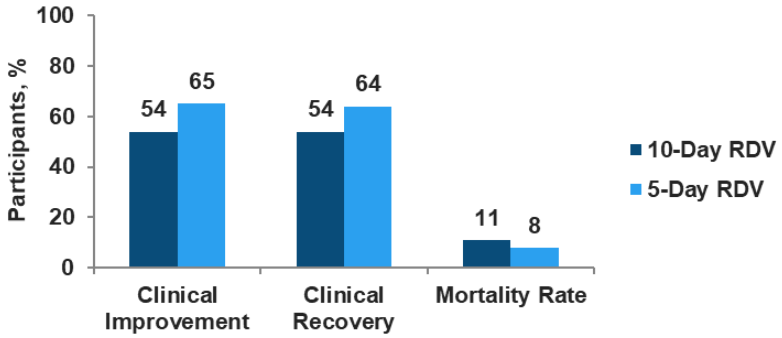
All participants who received ≥1 dose of study treatment were included in the analyses of efficacy and safety. In the 5-day group, 86% of participants (172/200) completed the course of RDV (median [IQR] duration: 5 [5–5] days); 8% (16/200) were discharged from the hospital; and 4% (9/200) discontinued RDV due to AEs. In the 10-day group, 44% of participants (86/197) completed the course of RDV (median [IQR] duration: 9 [5–10] days); 35% (68/197) were discharged from the hospital; 11% (22/197) discontinued RDV due to AEs; and 6% (12/197) died.

Efficacy[1]

The proportion of participants who had clinical improvement of ≥2 points on the 7-point ordinal scale at Day 14 was similar between the 10-day and 5-day RDV groups (54% [107/197] and 64% [129/200], respectively; Figure 2 and Table 2). After adjusting for differences in baseline disease severity, the rate of clinical improvement at Day 14 was similar between participants who received 5 days of RDV treatment and those who received 10 days of RDV treatment (odds ratio, 0.75; 95% CI: 0.51–1.12).

The mortality rate was numerically lower in the 5-day group than in the 10-day group (8% [16/200] vs 11% [21/197]). Non-significant differences between groups were observed for the rates of recovery and modified recovery.

Figure 2. SIMPLE Study in Severe COVID-19: Observed Rates of Clinical Improvement,[a] Clinical Recovery,[b] and Mortality[1]



[a]Defined as a ≥2-point improvement in ordinal scale.
[b]Defined as improvement from a baseline score of 2 to 5 to a score of 6 or 7.

Table 2. SIMPLE Study in Severe COVID-19: Efficacy Outcomes at Day 14[1,2]

Efficacy Outcomes	10-Day RDV (n=197)	5-Day RDV (n=200)	Baseline-Adjusted Difference[a] (95% CI)
Clinical improvement,[b] n (%)	107 (54)	129 (64)	-6.5% (-15.7 to 2.8)
Time to clinical improvement,[c] days	11	10	0.79 (0.61–1.01)
Clinical recovery[d] at Day 14, n (%)	106 (54)	129 (64)	-6.3 (-15.4 to 2.8)
Time to recovery,[c] median (IQR), days	11 (7 to NE)	10 (6 to 18)	0.81 (0.64–1.04)
Modified recovery[e] at Day 14, n (%)	116 (59)	140 (70)	-6.7 (-15.3 to 1.9)
Time to modified recovery,[c] days	10	9	0.82 (0.64–1.04)

Efficacy Outcomes	10-Day RDV (n=197)	5-Day RDV (n=200)	Baseline-Adjusted Difference[a] (95% CI)
Duration of hospitalization, median (IQR), days	8 (5–10)	7 (6–10)	Not evaluated

Abbreviation: NE=not estimable.
[a]Baseline-adjusted difference values are rate differences, except for the time to clinical improvement, time to recovery, and time to modified recovery.
[b]Defined as a ≥2-point improvement in ordinal scale.
[c]The median day of 50% cumulative incidence.
[d]Defined as improvement from a baseline score of 2 to 5 to a score of 6 or 7.
[e]Defined as improvement from a baseline score of 2 to 4 to a score of 5 to 7 or improvement from a baseline score of 5 to a score of 6 or 7.

Numerically, more patients were discharged from the hospital in the 5-day group than in the 10-day group (60% [120/200] vs 52% [103/197], respectively). Discharge rates were higher in the overall population among patients with <10 days of symptoms before the first dose of RDV than among those with ≥10 days of symptoms before the first dose (62% vs 49%), respectively.

Safety[1]

The incidence of AEs was similar between groups (see Table 3). AEs of Grade 3 or higher were observed in 43% of participants in the 10-day group and 30% in the 5-day group.[1]

Table 3. SIMPLE Study in Severe COVID-19: Safety Outcomes[1]

Safety Outcomes, n (%)		10-Day RDV (n=197)	5-Day RDV (n=200)
Any AE		145 (74)	141 (70)
Most common AEs (≥5% of participants)	Acute respiratory failure	21 (11)	12 (6)
	Nausea	17 (9)	20 (10)
	ALT level increased	15 (8)	11 (6)
	Acute kidney injury	15 (8)	4 (2)
	Respiratory failure	14 (7)	7 (4)
	Constipation	13 (7)	13 (6)
	AST level increased	13 (7)	10 (5)
	Hypokalemia	12 (6)	10 (5)
	Hypotension	12 (6)	9 (4)
	Insomnia	11 (6)	10 (5)
Any SAE		68 (35)	42 (21)
Most common SAEs (≥5% of participants)	Acute respiratory failure	18 (9)	10 (5)
	Respiratory failure	10 (5)	5 (2)
AEs that led to RDV discontinuation		20 (10)	9 (4)

Most of the laboratory abnormalities were transient, and there were no significant differences in the median changes in laboratory abnormalities between treatment groups. Aminotransferase elevations led to treatment discontinuation in 3.6% of participants in the 10-day RDV group and in 2.5% of those in the 5-day RDV group. More participants in the 10-day RDV group than in the 5-day RDV group experienced Grade 4 CrCl reductions (12% vs 3%). Among the participants with Grade 4 CrCl decreases, 71% required IMV, NIPPV, or high-flow O_2 supplementation at baseline.

Table 4. SIMPLE Study in Severe COVID-19: Laboratory Abnormalities[1]

Key Laboratory Abnormalities,[a] n/N (%)		10-Day RDV (n=197)	5-Day RDV (n=200)
Any Grade ≥3 laboratory abnormality		64/191 (34)	53/195 (27)
CrCl decreased	Grade 3	13/188 (7)	13/193 (7)
	Grade 4	23/198 (12)	5/193 (3)
ALT level increased	Grade 3	11/191 (6)	8/194 (4)
	Grade 4	5/191 (3)	4/194 (2)
AST level increased	Grade 3	7/190 (4)	11/194 (6)
	Grade 4	4/190 (2)	3/194 (2)
Total bilirubin level increased	Grade 3	3/190 (2)	1/193 (1)
	Grade 4	1/190 (1)	0

[a]Graded laboratory abnormalities were defined with the grading scheme in the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Event, Version 2.1, dated July 2017.

References

1. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. *N Eng J Med.* 2020:1-11.
2. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19 [Protocol]. *N Eng J Med.* 2020.

Abbreviations

AE=adverse event
ECMO=extracorporeal membrane oxygenation
IMV=invasive mechanical ventilation
NIPPV=noninvasive positive pressure ventilation
NIV=noninvasive ventilation
O_2=oxygen
RDV=remdesivir
SAE=serious adverse event
SoC=standard of care

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Biktarvy US Prescribing Information available at: www.gilead.com/~/media/files/pdfs/medicines/hiv/biktarvy/biktarvy_pi.

Follow Up

For any additional questions, please contact Gilead Medical Information at:

☎1-866-MEDI-GSI (1-866-633-4474) or 🖱 www.askgileadmedical.com

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Please report all adverse events to:

Gilead Global Patient Safety ☎ 1-800-445-3235, option 3 or
🖱 https://www.gilead.com/utility/contact/report-an-adverse-event

FDA MedWatch Program by ☎ 1-800-FDA-1088 or ✉MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or 🖱 www.accessdata.fda.gov/scripts/medwatch

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