GILEAD | Medical Information

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

A phase 3, randomized, open-label study compared the outcomes of hospitalized participants with moderate COVID-19 who received 5 or 10 days of RDV treatment and SOC with those of participants who received SoC alone for 10 days.[1,2]

- Participants in the 5-day RDV treatment group had 65% higher odds of experiencing clinical improvement than those in the SoC treatment group at Day 11 (OR, 1.65; 95% CI: 1.09–2.48; *P*=0.02).[1]
- The difference in clinical status distribution between the 10-day RDV and SoC groups was not statistically significant at Day 11 (*P*=0.18).[1]
- Rates of SAEs were numerically lower with RDV than with SoC. The most common AEs were nausea and diarrhea. No significant differences in the changes in CrCl, ALT levels, or AST levels over time were observed between participants who received RDV and those who received SOC.[1]

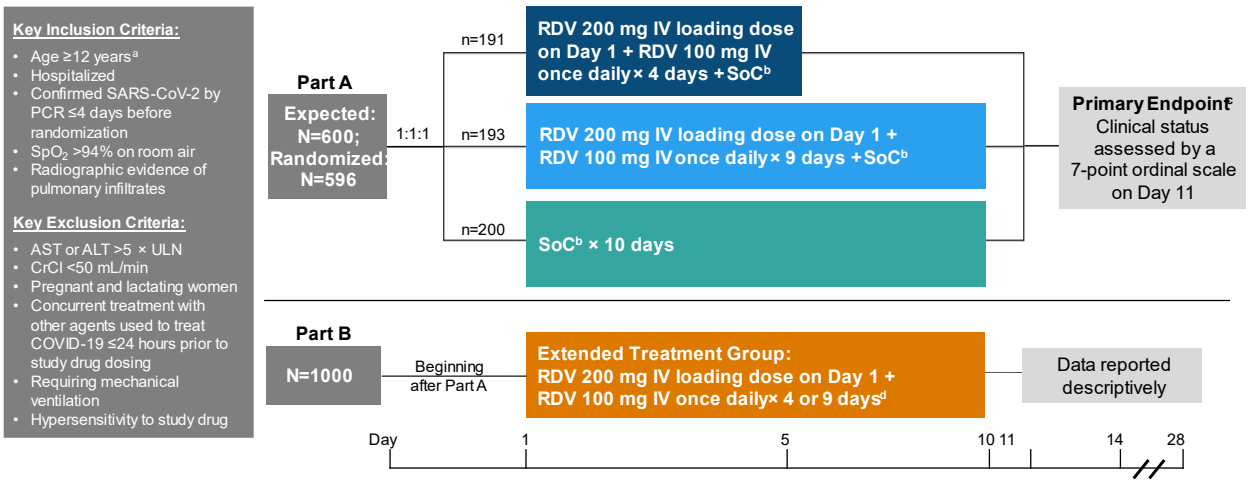
SIMPLE Study: RDV Use in Moderate COVID-19

Study Design

A phase 3, randomized, two-part (Parts A and B), open-label study compared the outcomes of hospitalized participants with moderate COVID-19 who received 5 or 10 days of RDV treatment and SoC with those of participants who received SoC alone for 10 days (Figure 1). Data from participants in Part A, conducted between March 15 and April 18, 2020, are available. The primary efficacy endpoint was the distribution of clinical status scores on a 7-point ordinal scale on Day 11 (each RDV group was compared with the SoC group using a 2-sided test [α=0.25; Bonferroni]).[1,2] The secondary endpoint was the proportion of participants with AEs throughout the study.[1]

Part A consisted of 596 participants who were randomly assigned to receive SoC therapy according to local guidelines either alone or with a 5- or 10-day course of RDV (loading dose of RDV 200 mg IV on Day 1, followed by RDV 100 mg/day IV for either 4 days or for 9 days). RDV was infused over 30 to 60 minutes.[1]

Figure 1. SIMPLE Study in Moderate COVID-19: Study Design[1,3]



Abbreviations: PCR=polymerase chain reaction; SpO_2=serum pressure O_2.
[a]Adults ≥18 years or adolescents between 12 and 18 years (weighing ≥40 kg) were included.
[b]SoC was defined by local written policies or guidelines.
[c]The primary efficacy population was composed of participants from Part A. Clinical status was assessed with a 7-point ordinal scale that includes the following categories: 1) death; 2) hospitalized and required invasive mechanical ventilation or extracorporeal membrane oxygenation; 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.
[d]In Part B, treatment may be reduced to a total of 5 days following an analysis of the data from Part A.
Note: A total of 600 participants (200 per group) was calculated in order to provide >85% power to detect an OR of 1.8 for each RDV group compared with the SoC group. Of the 596 participants who underwent randomization, 584 participants began the study.

Baseline Demographics and Participant Disposition[1]

Baseline characteristics were balanced between the three groups; however, more participants in the SoC group than in either RDV group received concomitant medications to treat COVID-19 (Table 1).

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

Key Demographics and Characteristics		5-Day RDV (n=191)	10-Day RDV (n=193)	SoC (n=200)
Age, median (IQR), years		58 (48–66)	56 (45–66)	57 (45–66)
Male, n (%)		114 (60)	118 (61)	125 (63)
Race, White/Black/Asian/other,[a] %		59/19/18/4	57/20/16/7	58/14/19/9
Hispanic/Latinx, n/N (%)		25/187 (13)	42/186 (23)	34/186 (18)
Most common coexisting conditions, n (%)	Cardiovascular disease	111 (58)	111 (58)	107 (54)
	Hypertension	82 (43)	85 (44)	81 (41)
	Diabetes	71 (37)	85 (44)	76 (38)
Duration of symptoms before RDV initiation, median (IQR), days		8 (5–11)	8 (5–11)	9 (6–11)

Key Demographics and Characteristics		5-Day RDV (n=191)	10-Day RDV (n=193)	SoC (n=200)
Baseline clinical status on the 7-point scale, n (%)	3 – Hospitalized, required NIV or high-flow O_2	2 (1)	1 (1)	2 (1)
	4 – Hospitalized, required low-flow O_2	29 (15)	23 (12)	36 (18)
	5 – Hospitalized, did not require O_2 but required medical care	160 (84)	163 (84)	160 (80)
	6 – Hospitalized, did not require O_2 or medical care[b]	0	6 (3)	2 (1)
Most common concomitant medications,[c] n (%)	Azithromycin	35 (18)	41 (21)	62 (31)
	Steroids	33 (17)	29 (15)	38 (19)
	Hydroxychloroquine/chloroquine	16 (8)	22 (11)	89 (45)

[a]Other included American Indian or Alaska Native, Native Hawaiian or Pacific Islander, Arab, unknown, and not specified.
[b]Despite not requiring medical care, some participants stayed in the hospital for quarantine or social issues.
[c]Included those taken between Day 1 and the last day of RDV or after Day 1 in the SoC group.

Seventy-six percent of participants (145/191) in the 5-day group received all 5 days of RDV treatment (median [range] doses, 5 [1–5]), and 38% of participants (73/193) in the 10-day group received all 10 days of RDV treatment (median [range] doses, 6 [1–10]). The most common reason for RDV discontinuation was hospital discharge (5-day group, 18%; 10-day group, 51%). Thirty-seven participants did not die, were not yet discharged, or did not have clinical status available for Day 11; therefore, the last available clinical status data were used for these participants.

Efficacy[1]

Participants who received 5 days of RDV had 65% higher odds of having clinical improvement than those in the SoC treatment group at Day 11 (OR, 1.65; 95% CI: 1.09–2.48; *P*=0.02). For participants in the 10-day RDV group, the clinical status distribution was not significantly different compared with the SoC group (*P*=0.18).

Table 2. SIMPLE Study in Moderate COVID-19: Efficacy Results[1,4]

Efficacy Outcomes, n (%)		5-Day RDV (n=191)	10-Day RDV (n=193)	SoC (n=200)
Clinical improvement	Day 3	26 (14)	29 (15)	33 (17)
	Day 5	61 (32)	72 (37)	66 (33)
	Day 7	106 (55)	92 (48)	94 (47)
	Day 11	134 (70)	126 (65)	121 (61)
	% difference vs SoC (95% CI)	9.7 (0.1–19.1)	4.8 (-5 to 14.4)	-
	Day 14	146 (76)	148 (77)	135 (68)
	Day 28	171 (90)	174 (90)	166 (83)
Recovery	Day 11	141 (74)	132 (68)	128 (64)
	% difference vs SoC (95% CI)	9.8 (0.3–19)	4.4 (-5 to 13.8)	-
	Day 14	153 (80)	153 (79)	145 (73)
	Day 28	175 (92)	178 (92)	170 (85)

The rates of all-cause mortality at Day 28 were not significantly different between the SoC group (2%; 95% CI: 0.1–4.1%) and the 5-day RDV group (1%; 95% CI: 0–2.6%; *P*=0.43) and the 10-day RDV group (2%; 95% CI: 0–3.6%; *P*=0.72).

Safety

There was a significant difference in rates of AEs observed between the 10-day RDV group and the SoC group (Table 3). Through Day 28, the reported deaths in all three treatment

groups occurred in participants aged ≥64 years and were deemed unrelated to RDV treatment.[1]

One renal-related SAE of acute kidney injury occurred in the SoC group, and no renal-related SAEs occurred in either RDV treatment group. No significant differences in the changes in CrCl, ALT levels, or AST levels over time were observed between participants who received RDV and those who received SoC.[4]

Table 3. SIMPLE Study in Moderate COVID-19: Safety Outcomes[1,4]

Safety Outcomes		5-Day RDV (n=191)	10-Day RDV (n=193)	SoC (n=200)
Any AE, n (%)		98 (51)	113 (59)	93 (47)
% difference vs SoC (95% CI); *P*-value		4.8 (-5.2 to 14.7); 0.36	12 (1.6–21.8); 0.02	-
Most common AEs (≥5% of participants in any group), n (%)	Nausea	19 (10)	18 (9)	6 (3)
	Diarrhea	12 (6)	10 (5)	14 (7)
	Hypokalemia	10 (5)	13 (7)	4 (2)
	Headache	10 (5)	10 (5)	5 (3)
Any renal-related AE, n (%)		3 (2)	4 (2)	4 (2)
Renal-related AEs by preferred term, n (%)	Acute kidney injury	1 (1)	1 (1)	2 (1)
	CrCl decreased	1 (1)	0	0
	GFR decreased	1 (1)	0	0
	Blood creatinine increased	0	2 (1)	2 (1)
	Urine output decreased	0	1 (1)	0
Grade ≥3 AE, n (%)		20 (10)	24 (12)	24 (12)
Any SAE, n (%)		9 (5)	10 (5)	18 (9)
% difference vs SoC (95% CI); *P*-value		-4.3 (-9.7 to 0.9); 0.11	-3.8 (-9.3 to 1.4); 0.17	-
Discontinuation of RDV due to AEs, n (%)		4 (2)	8 (4)	N/A
Deaths up to Day 28, n (%)		2 (1)[a]	3 (2)[b]	4 (2)[c]

[a]Deaths were due to respiratory failure and acute respiratory distress syndrome with worsening lung compliance (each, n=1). Each participant was on room air at baseline.
[b]Deaths were due to COVID-19 pneumonia, bloodstream infection, and ascending thoracic aortic aneurysm; acute hypoxic respiratory failure; and complete heart block (each, n=1). Each participant was on room air at baseline.
[c]Deaths were due to COVID-19 (n=3) and cardiac arrest (n=1; participant was on bi-level positive airway pressure and was likely hypoxic). Each participant required low-flow O_2 at baseline.

Table 4. SIMPLE Study in Moderate COVID-19: Select Laboratory Abnormalities[1,4]

Safety Outcomes, n/N (%)		5-Day RDV (n=191)	10-Day RDV (n=193)	SoC (n=200)
Any grade laboratory abnormality		131/180 (73)	128/179 (72)	136/186 (73)
Grade 3		18/180 (10)	25/179 (14)	25/186 (13)
Grade 4		5/180 (3)	4/179 (2)	9/186 (5)
ALT level increase	Any grade	61/179 (34)	57/177 (32)	71/182 (39)
	Grade 3 (>5 to 10 × ULN)	4/179 (2)	6/177 (3)	11/182 (6)
	Grade 4 (>10 × ULN)	0	0	3 (2)

Safety Outcomes, n/N (%)		5-Day RDV (n=191)	10-Day RDV (n=193)	SoC (n=200)
CrCl decrease	Any grade	26/178 (15)	45/176 (26)	55/183 (30)
	Grade 3[a]	4/178 (2)	7/176 (4)	9/183 (5)
	Grade 4[b]	0	2/176 (1)	5/183 (3)

[a]Defined as a CrCl of 30 to <60 mL/min or a decrease of 30% to <50% from baseline.
[b]Defined as a CrCl <30 mL/min, decrease of ≥50% from baseline, or need for dialysis.

References

1. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. *JAMA.* 2020;324(11):1048-1057. https://jamanetwork.com/journals/jama/fullarticle/2769871
2. ClinicalTrials.gov. Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Moderate Coronavirus Disease (COVID-19) Compared to Standard of Care Treatment. ClinicalTrials.gov Identifier: NCT04292730. Last Updated: 26 January, 2021. 2020.
3. Gilead Sciences Inc. *Clinical Study Protocol. A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants with Moderate COVID-19 Compared to Standard of Care Treatment. Protocol ID: GS-US-540-5775.* 2020.
4. Criner G, Ahn MY, Huhn G, et al. Safety of Remdesivir vs Standard of Care in Patients With Moderate COVID-19 [Poster 561]. Paper presented at: IDWeek Virtual; 21-25 October, 2020.

Abbreviations

AE=adverse event
NIV=non-invasive ventilation
O_2=oxygen
OR=odds ratio
RDV=remdesivir
SAE=serious adverse event
SoC=standard of care
ULN=upper limit of normal

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Veklury US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_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

Adverse Event Reporting

Please report all adverse events to:

Gilead Global Patient Safety ☎ 1-800-445-3235, option 3 or
🖱 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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