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Veklury® (remdesivir) ACTT-1 Study

This document is in response to your request for information regarding the ACTT-1 study, which evaluated the use of Veklury® (remdesivir [RDV]) in participants hospitalized with 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

NIAID-Sponsored Study: ACTT-1

A phase 3, randomized, double-blind, placebo-controlled study evaluated the safety and efficacy of RDV in hospitalized adult participants (N=1062) with COVID-19.[1]

- The primary endpoint: Participants who received RDV had a significantly shorter median time to recovery than participants who received placebo: 10 days vs 15 days, which yielded an increased recovery rate by 29% compared to placebo (recovery rate ratio: 1.29 [95% CI: 1.12–1.49]; *P*<0.001; Table 2).[1]
- The key secondary endpoint: RDV produced 50% increased clinical improvement on the ordinal scale compared with placebo (OR: 1.5 [95% CI: 1.2–1.9]; *P*<0.001; Table 3).[1]
- SAEs were significantly lower in the RDV group than the placebo group (24.6% vs 31.6%; *P*=0.01; Table 5). No treatment-related deaths were reported, as judged by site investigators.[1]

NIAID-Sponsored Study: ACTT-1

Study Design and Demographics

A phase 3, randomized, adaptive, double-blind, placebo-controlled, multicenter study (NCT04280705) evaluated the safety and efficacy of RDV in adults hospitalized with COVID-19. The primary outcome was the time to recovery up to Day 29, defined as the first day that the participant met categories 1, 2, or 3 of this ordinal scale: 1) not hospitalized and had no limitation on activities; 2) not hospitalized and had limitation on activities and/or required supplemental O_2 at home; 3) hospitalized and did not require supplemental O_2 or ongoing medical care; 4) hospitalized and did not require supplemental O_2, but did require ongoing medical care (for COVID-19 or otherwise); 5) hospitalized and required supplemental O_2; 6) hospitalized and required NIV or high-flow O_2 devices; 7) hospitalized and required IMV or ECMO; 8) death.[1]

Participants were randomly assigned in a 1:1 ratio to receive either RDV 200 mg loading dose via IV infusion on Day 1, followed by RDV 100 mg/day via IV infusion for up to 9 days or for the duration of hospitalization (total course: up to 10 days), or placebo for the duration of hospitalization. Randomization was stratified according to the study site and disease severity.[1] Participants were enrolled from February 21, 2020 through April 19, 2020. Participants who were discharged from the hospital returned for study assessments on Days 15 and 29.[1,2]

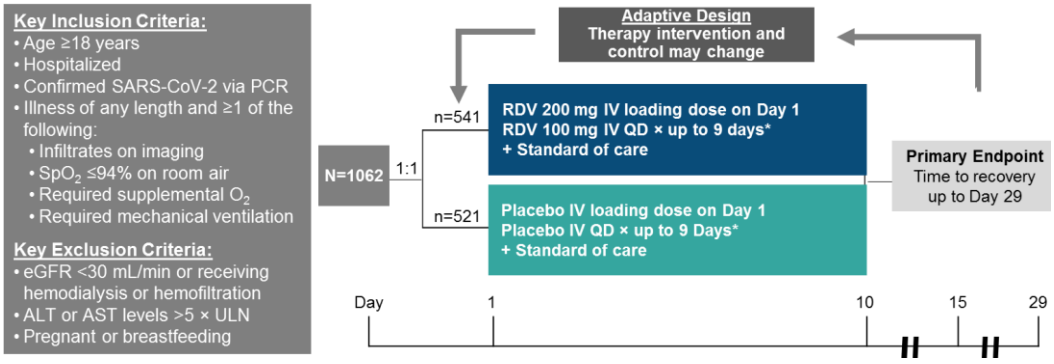

Figure 1. Study Design[1-3]

Note: Of the 1062 participants enrolled, 531 received ≥1 dose of RDV and 517 received ≥1 dose of placebo.
*Study treatment doses were given for the duration of the hospitalization up to Day 10 or until death.

Table 1. Baseline Demographics and Disease Characteristics[1,3]

Key Demographics and Characteristics		Overall N=1062	RDV n=541	Placebo n=521
Age, mean (SD), years		58.9 (15)	58.6 (14.6)	59.2 (15.4)
Male, n (%)		684 (64.4)	352 (65.1)	332 (63.7)
Key coexisting conditions	Hypertension, n/N (%)	533/1051 (50.7)	269/532 (50.6)	264/519 (50.9)
	Obesity, n/N (%)	476/1049 (45.4)	242/531 (45.6)	234/518 (45.2)
	Type 2 diabetes mellitus, n/N (%)	322/1051 (30.6)	164/532 (30.8)	158/519 (30.4)
Duration of symptoms prior to enrollment, ≤10 days/>10 days, %		64/36	66/34	61/38
Time from symptom onset to randomization, median (IQR), days		9 (6–12)	9 (6–12)	9 (7–13)
Mild/moderate disease,[a] n		105[b]	55	50
Severe disease,[a] n		957[b]	486	471
Baseline score on ordinal scale	4 - Hospitalized, did not require supplemental O_2 but required ongoing medical care, n (%)	138 (13)	75 (13.9)	63 (12.1)
	5 - Hospitalized, required supplemental O_2, n (%)	435 (41)	232 (42.9)	203 (39)
	6 - Hospitalized, required NIV or high-flow O_2 devices, n (%)	193 (18.2)	95 (17.6)	98 (18.8)
	7 - Hospitalized, received IMV or ECMO, n (%)	285 (26.8)	131 (24.2)	154 (29.6)
	Missing baseline score, n (%)	11 (1)	8 (1.5)	3 (0.6)

[a]Mild/moderate disease was defined as SpO_2 >94% and respiratory rate <24 breaths/minute and no requirement for supplemental O_2. Severe disease was defined as requirement for mechanical ventilation or supplemental O_2, SpO_2 ≤94% on room air, or respiratory rate ≥24 breaths/minute.
[b]54 of the 159 participants who were initially categorized as having mild/moderate COVID-19 were reassessed as having severe disease.
After reassessment of baseline status: 105 participants were determined to have mild/moderate disease, 957 participants had severe disease.

Results

This ITT population included a total of 1062 participants who were randomly assigned to receive either RDV (n=541) or placebo (n=521). Of the 531 participants who received ≥1 dose of RDV, 208 participants received 10 doses, and 323 participants received <10 doses. Of the 323 participants who received <10 doses of RDV, 223 participants recovered, 52 participants discontinued RDV due to AEs or SAEs (other than death), 15 participants died, 18 participants missed doses, 10 participants withdrew consent, 4 participants were withdrawn by the investigator, and 1 participant was transferred to another hospital. In the placebo group, 291 participants received <10 doses, and of those, 158 recovered, 19 died, 26 missed doses, 70 discontinued due to an AE or SAE (other than death), 14 withdrew consent, 1 was found to be ineligible after enrollment, 1 was withdrawn by the investigator, 1 was transferred to another hospital, and 1 had a protocol deviation.[1]

Primary endpoint

Participants who received RDV had a significantly shorter median time to recovery than participants who received placebo: 10 days vs 15 days, which yielded an increased recovery rate by 29% compared to placebo (recovery rate ratio: 1.29 [95% CI: 1.12–1.49]; *P*<0.001).[1,3]

Table 2. Recovery: Overall and According to Disease Severity (ITT)[1,3]

Treatment Outcomes	Overall		Mild/Moderate Disease		Severe Disease	
	RDV n=541	Placebo n=521	RDV n=55	Placebo n=50	RDV n=486	Placebo n=471
Recovery, n	399	352	54	46	345	306
Time to recovery, median (95% CI), days	10 (9–11)	15 (13–18)	5 (4–6)	5 (4–7)	11 (10–14)	18 (15–20)
Recovery rate ratio[a] (95% CI)	1.29 (1.12–1.49); *P*<0.001		1.22 (0.82–1.81)		1.31 (1.12–1.52)	

Note: *P*-values and CIs were not adjusted for multiple comparisons. *P*-values were calculated with a stratified log-rank test (by disease severity). [a]Recovery rate ratios >1 showed an RDV treatment benefit and were calculated with a stratified Cox model.

After adjustment for baseline ordinal score, the overall treatment-effect estimate was similar to the result for the primary outcome (recovery rate ratio: 1.26; 95% CI: 1.09–1.46). The recovery rate ratio was significantly higher for participants who had a baseline ordinal score of 5 and received RDV than for those who received placebo (1.45 [95% CI: 1.18–1.79]).[1]

The benefit of RDV was observed when treatment was initiated earlier in the illness. In a sub-analysis, for participants who received RDV ≤10 days after symptom onset, the recovery rate ratio was 1.37 (95% CI: 1.14–1.64), whereas for participants who received RDV >10 days after symptom onset, the recovery rate ratio was 1.2 (95% CI: 0.94–1.52).[1,3]

Secondary Endpoints

Using a proportional odds model at the Day 15 visit, participants who received RDV had a 50% increased rate of clinical improvement in ordinal score than those who received placebo (key secondary endpoint; OR: 1.5 [95% CI: 1.2–1.9]; *P*<0.001; Table 3).[1,3]

Table 3. Day 15 (±2 Days) Clinical Status Scores[a] by Treatment Group (ITT)[1]

Clinical Status Scores	RDV n=541	Placebo n=521
1 – Not hospitalized, no limitation on activities, n (%)	157 (29)	115 (22.1)
2 – Not hospitalized, limitation on activities, n (%)	117 (21.6)	102 (19.6)
3 – Hospitalized, did not require supplemental O_2 or ongoing medical care, n (%)	14 (2.6)	8 (1.5)
4 – Hospitalized, did not require supplemental O_2 but required ongoing medical care, n (%)	38 (7)	33 (6.3)
5 – Hospitalized, required supplemental O_2, n (%)	58 (10.7)	60 (11.5)
6 – Hospitalized, required NIV or high-flow O_2 devices, n (%)	28 (5.2)	24 (4.6)
7 – Hospitalized, received IMV or ECMO, n (%)	95 (17.60	121 (23.2)
8 – Death,[b] n (%)	34 (6.3)	58 (11.10
OR (95% CI)	1.5 (1.2–1.9); *P*<0.001	

Note: *P*-values and CIs were not adjusted for multiple comparisons. The OR and *P*-value were calculated with a proportional odds model (adjusted for disease severity), and an OR >1 indicated an RDV treatment benefit. [a]The recorded score was the participant's worst score from the previous day. [b]Four participants were included in this table as having ordinal scale scores of 8 (death) because they died 15 days after randomization; however, their deaths were not included in the Day 15 mortality data.

RDV-treated participants had less disease progression than those in the placebo group, with lower rates of new O_2 supplementation (36% [27/75] vs 44% [28/63]; difference: -8 [95% CI: -24 to 8]), new high flow O_2 or NIV (17% [52/307] vs 24% [64/266]; difference: -7 [95% CI: -14 to -1]), and new IMV/ECMO (13% [52/402] vs 23% [82/364]; difference: -10 [95% CI: -15 to -4]) among participants who were not receiving them at baseline.[1]

Mortality[1]

The mortality rate by Day 15 was significantly lower in the RDV group than the placebo group (6.7% vs 11.9%; HR: 0.55 [95% CI: 0.36 to 0.83]). The mortality rate by Day 29 was numerically lower in those who received RDV than in those who received placebo (11.4% vs 15.2%); this difference did not reach significance (Table 4). The ACTT-1 study was not powered to evaluate a difference in mortality in the overall population.

Table 4. Overall Mortality (ITT)[1,3]

Mortality Data		RDV n=541	Placebo n=521
Mortality through Day 14[a]	Deaths by Day 15, n	35	61
	Kaplan-Meier estimate by Day 15, % (95% CI)	6.7 (4.8–9.2)	11.9 (9.4–15)
	HR[b] (95% CI)	0.55 (0.36–0.83)	
Mortality over the entire study period[a]	Deaths by Day 29, n	59	77
	Kaplan-Meier estimate by Day 29, % (95% CI)	11.4 (9–14.5)	15.2 (12.3–18.6)
	HR[b] (95% CI)	0.73 (0.52–1.03); *P*=0.07	

Note: P-values and CIs were not adjusted for multiple comparisons. [a]Mortality through Day 14 included data from all participants who were still alive on Day 14 post enrollment, with data censored on Day 15, and mortality

over the entire study period censored data from participants who had completed follow-up alive at Day 28 after enrollment. [b]HRs were calculated using a stratified Cox model, HRs <1 indicated a treatment benefit with RDV.

Safety Results[1]

Significantly lower rates of SAEs were reported by participants in the RDV group than the placebo group (24.6% vs 31.6%; *P*=0.01), and a lower incidence of Grade 3 or 4 AEs occurred in the RDV group than the placebo group (51% vs 57%; *P*=0.058). No treatment-related deaths were reported, as judged by site investigators.

Table 5. Safety Results (As-Treated Population)[1,3]

Safety Parameters		RDV n=532	Placebo n=516
Any AE, n (%)		305 (57)	323 (63)
Treatment-related AEs, n (%)		41 (8)	47 (9)
Grade 3 or 4 AEs, n (%)		273 (51)[a]	205 (57)[a]
Study discontinuation due to an AE, n (%)		45 (8)	59 (11)
Treatment discontinuation due to an AE, n (%)		57 (11)	77 (15)
Most common AEs (occurred in ≥5% of participants in either group)	GFR decreased,[b] n (%)	55 (10.3)	74 (14.3)
	Hemoglobin decreased, n (%)	48 (9)	62 (12)
	Lymphocyte count decreased, n (%)	44 (8.3)	54 (10.5)
	Anemia, n (%)	42 (7.9)	52 (10.1)
	Blood glucose increased, n (%)	39 (7.3)	27 (5.2)
	Pyrexia, n (%)	38 (7.1)	32 (6.2)
	Hyperglycemia, n (%)	34 (6.4)	34 (6.6)
	Blood creatinine increased,[b] n (%)	31 (5.8)	36 (7)
	AST increased,[c] n (%)	18 (3.4)	33 (6.4)
	Lymphopenia, n (%)	13 (2.4)	30 (5.8)
Any SAEs, n (%)		131 (24.6)[d]	163 (31.6)[d]
Treatment-related SAEs, n (%)		2 (<1)	3 (1)
Most common SAEs (occurred in ≥10 participants in either group)	Respiratory failure, n (%)	39 (7.3)	66 (12.8)
	Cardiac arrest, n (%)	10 (1.9)	7 (1.4)
	Acute respiratory failure, n (%)	8 (1.5)	14 (2.7)
	Septic shock, n (%)	8 (1.5)	15 (2.9)
	Acute kidney injury,[e] n (%)	7 (1.3)	12 (2.3)
	Respiratory distress, n (%)	6 (1.1)	11 (2.1)

[a]*P*=0.058; calculated using 2-sided Barnard's Exact Test. [b]The total number of participants with GFR decreased, blood creatinine increased, acute kidney injury (data not shown), or creatinine renal clearance decreased (data not shown) was 85 in RDV and 105 in placebo groups. [c]The total number of participants with AST increased, ALT increased (data not shown), or transaminases increased (data not shown) was 32 in RDV group and 55 in placebo group. [d]*P*=0.01; calculated using 2-sided Barnard's Exact Test. [e]The total number of participants with acute kidney injury, renal failure (data not shown), or GFR decreased (data not shown) was 14 in the RDV group and 17 in the placebo group.

References

1. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 — Final Report. *N Engl J Med.* 2020;383(19):1813-1826.
2. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 — Final Report [Protocol]. *N Engl J Med.* 2020.
3. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 — Final Report [Supplementary Appendix]. *N Engl J Med.* 2020.

Abbreviations

ACTT-1=Adaptive COVID-19 Treatment Trial-1
AE=adverse event
COVID-19=coronavirus disease 2019
ECMO=extracorporeal membrane oxygenation
HR=hazard ratio
IMV=invasive mechanical ventilation
IQR=interquartile range
NIAID=National Institute of Allergy and Infectious Diseases
NIV=noninvasive ventilation
O_2=oxygen
OR=odds ratio
RDV=remdesivir
SAE=serious adverse event
SpO_2=peripheral capillary O_2 saturation

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

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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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