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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 Study

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]

- Participants who received RDV had a shorter median time to recovery than participants who received placebo (10 days vs 15 days, respectively), with an increased recovery rate of 29% compared with placebo (recovery rate ratio, 1.29; 95% CI: 1.12–1.49; *P*<0.001; Table 2).
- RDV treatment resulted in a 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).
- SAEs were significantly lower in the RDV group than the placebo group (24.6% vs 31.6%, respectively; *P*=0.01; Table 5). No treatment-related deaths were reported.

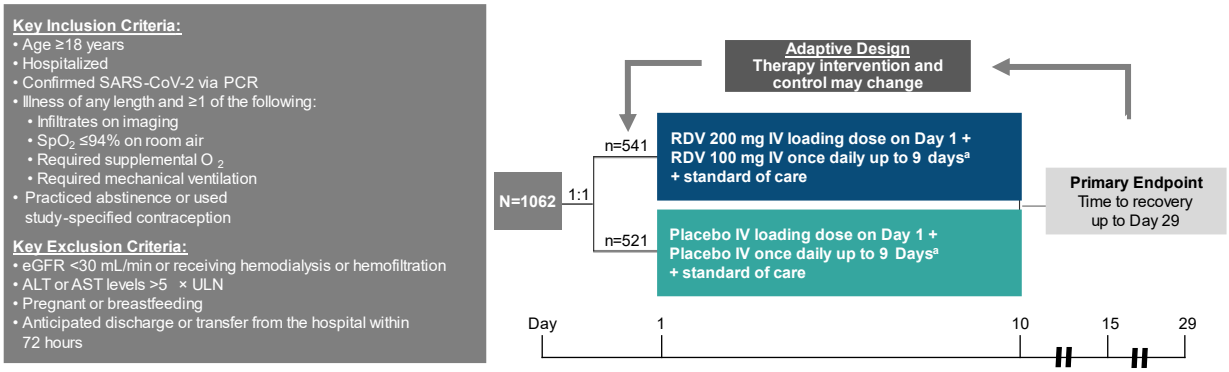
NIAID-Sponsored Study: ACTT-1 Study

Study Design and Demographics

A phase 3, randomized, adaptive, double-blind, placebo-controlled, multicenter study evaluated the safety and efficacy of RDV in adults hospitalized with COVID-19 (N=1062). 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 the following 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 (1:1) to receive either IV RDV 200 mg loading dose Day 1, followed by IV RDV 100 mg/day for up to 9 days or for the duration of hospitalization for 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. ACTT-1: Study Design[1-3]



Abbreviations: PCR=polymerase chain reaction; ULN=upper limit or normal.
[a]Study treatment doses were given for the duration of the hospitalization up to Day 10 or until death.
Note: Of the 1062 participants enrolled, 531 received ≥1 dose of RDV and 517 received ≥1 dose of placebo.

Table 1. ACTT-1: Baseline Demographics and Disease Characteristics (ITT)[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, n/N (%)	Hypertension	533/1051 (50.7)	269/532 (50.6)	264/519 (50.9)
	Obesity	476/1049 (45.4)	242/531 (45.6)	234/518 (45.2)
	Type 2 diabetes mellitus	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, n (%)	4 - Hospitalized, did not require supplemental O_2 but required ongoing medical care	138 (13)	75 (13.9)	63 (12.1)
	5 - Hospitalized, required supplemental O_2	435 (41)	232 (42.9)	203 (39)
	6 - Hospitalized, required NIV or high-flow O_2 devices	193 (18.2)	95 (17.6)	98 (18.8)
	7 - Hospitalized, received IMV or ECMO	285 (26.8)	131 (24.2)	154 (29.6)
	Missing baseline score	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]Overall, 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, and 957 participants had severe disease.

Results

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 recovered, 52 discontinued RDV due to AEs or SAEs other than death, 18 missed doses, 15 died, 10 withdrew consent, 4 were withdrawn by the investigator, and 1 was transferred to another hospital. In the placebo group, 291 participants received <10 doses; of those participants, 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, respectively), with an increased recovery rate of 29% compared with placebo (recovery rate ratio, 1.29; 95% CI: 1.12–1.49; *P*<0.001).[1,3]

Table 2. ACTT-1: Overall Recovery and Recovery 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)	

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

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 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 subanalysis, the recovery rate ratio (95% CI) for participants who received RDV ≤10 days after symptom onset was 1.37 (1.14–1.64), compared with a recovery rate ratio of 1.2 (0.94–1.52) in participants who received RDV >10 days after symptom onset.[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. ACTT-1: 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)

Clinical Status Scores	RDV n=541	Placebo n=521
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 (17.6)	121 (23.2)
8 – Death,[b] n (%)	34 (6.3)	58 (11.1)
OR (95% CI)	1.5 (1.2–1.9); *P*<0.001	

[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.
Note: *P*-value and CI 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.

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], respectively; 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).[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%, respectively; HR, 0.55; 95% CI: 0.36–0.83). The mortality rate by Day 29 was numerically lower in the RDV group than in the placebo group (11.4% vs 15.2%, respectively); however, this difference did not reach statistical significance (Table 4). The study was not powered to evaluate a difference in mortality in the overall population.

Table 4. ACTT-1: 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	

[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. Mortality over the entire study period censored data from participants who completed follow-up alive at Day 28 after enrollment.
[b]HRs were calculated using a stratified Cox model, with HRs <1 indicating a treatment benefit with RDV.
Note: *P*-value and CIs were not adjusted for multiple comparisons.

Safety Results[1]

There were significantly lower rates of SAEs in the RDV group than the placebo group (24.6% vs 31.6%, respectively; *P*=0.01) and a lower incidence of Grade 3 or 4 AEs in the RDV group than the placebo group (51% vs 57%; *P*=0.058). No treatment-related deaths were reported.

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

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

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

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
ECMO=extracorporeal membrane oxygenation
HR=hazard ratio
IMV=invasive mechanical ventilation
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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