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Veklury® (remdesivir) Treatment Initiation and Symptom Onset

This document is in response to your request for information regarding Veklury® (remdesivir [RDV]) and treatment initiation relative to the onset of COVID-19 symptoms. This response was developed according to principles of evidence-based medicine and contains data from phase 3 clinical studies.

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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

Product Labeling[1]

- Hospitalized patients: The treatment course of RDV should be initiated as soon as possible after a diagnosis of symptomatic COVID-19 has been made.
- Non-hospitalized patients: The treatment course of RDV should be initiated as soon as possible after a diagnosis of symptomatic COVID-19 has been made and within 7 days of symptom onset.

Clinical Data on RDV Initiation Relative to the Onset of COVID-19 Symptoms

In a subanalysis of ACTT-1 study, participants hospitalized with COVID-19 who received RDV ≤10 days after symptom onset had a median time to recovery of 9 days, compared with 15 days with placebo (HR, 1.37; 95% CI: 1.14–1.64). Participants who received RDV >10 days after symptom onset had a median time-to-recovery of 11 days, compared with 15 days with placebo (HR, 1.2; 95% CI: 0.94–1.52).[2,3]

In the SIMPLE study of participants hospitalized with severe COVID-19, discharge rates were higher among those who received RDV within 10 days of COVID-19 symptoms than among those who initiated RDV ≥10 days after symptom onset.[4]

In a post hoc analysis of the SIMPLE study in participants hospitalized with moderate COVID-19, no differences in improvement of clinical status scores were observed between those who received RDV with COVID-19 symptoms for ≥9 or <9 days.[5,6]

In subgroup analyses of the PINETREE study in non-hospitalized participants with COVID-19, of those treated ≤5 days after onset of symptoms 1 participant (0.5%) in the RDV group and 9 participants (4.6%) in the placebo group had a COVID-19–related hospitalization by Day 28 (HR, 0.1; 95% CI: 0.01–0.82), compared with 1 participant (1.3%) and 6 participants (6.7%) who received RDV or placebo, respectively, ≥6 days after symptom onset (HR, 0.19; 95% CI: 0.02–1.61).[7,8]

Clinical Data on RDV Initiation Relative to the Onset of COVID-19 Symptoms

NIAID-Sponsored Study: ACTT-1

Study design and baseline symptom onset

A phase 3, randomized, adaptive, double-blind, placebo-controlled, multicenter study evaluated the safety and efficacy of RDV in hospitalized adult participants diagnosed with COVID-19 who had evidence of lower respiratory tract infection. Participants received a 10-day course of RDV (200 mg IV on Day 1, followed by 100 mg IV daily for a total treatment duration of 10 days). The primary outcome measure was the time to recovery up to Day 29.[2] Participants were not excluded from the study based on the duration of their symptoms prior to enrollment.[3]

As shown in Table 1, 64% of all participants had symptoms for ≤10 days prior to enrollment, and 36% had symptoms for >10 days prior to enrollment.[3]

Table 1. ACTT-1: Duration of Symptoms Prior to Study Enrollment[3]

Duration of Symptoms Prior to Enrollment	Overall (N=1059)[a]	RDV (n=540)[a]	Placebo (n=519)[a]
Median (IQR), days	9 (6–12)	9 (6–12)	9 (7–13)
Mean ± SD, days	9.8±5.4	9.7±5.7	10±5
Minimum, maximum, days	0, 46	0, 46	1, 34
≤10 days/>10 days, n (%)	676 (64)/383 (36)	356 (66)/184 (34)	320 (61)/199 (38)
First quartile (≤6 days), n (%)	282 (27)	158 (29)	124 (24)
Second quartile (7 to ≤9 days), n (%)	300 (28)	148 (27)	152 (29)
Third quartile (10 to ≤12 days), n (%)	221 (21)	113 (21)	108 (21)
Fourth quartile (≥13 days), n (%)	256 (24)	121 (22)	135 (26)

[a]Symptom onset data were missing for 3 participants.

Results by symptom onset

In a subanalysis, participants who received RDV ≤10 days after symptom onset had a median time to recovery of 9 days compared with 15 days with placebo (HR, 1.37; 95% CI: 1.14–1.64). Participants who received RDV >10 days after symptom onset had a median time to recovery of 11 days compared with 15 days with placebo (HR, 1.2; 95% CI: 0.94–1.52; Table 2).[2,3]

Table 2. ACTT-1: Time to Recovery by Treatment Group Relative to the Duration of Symptoms (ITT Population)[3]

Pooled Duration of Symptoms by Category	Treatment Group	n	Time to Recovery, Median (95% CI), Days	HR (95% CI)
First quartile (≤6 days)	RDV (n=158)	119	10 (7–14)	1.92 (1.41–2.6)
	Placebo (n=124)	65	24 (17–NE)	
Second quartile (7 to ≤9 days)	RDV (n=148)	110	10 (8–13)	0.99 (0.76–1.28)
	Placebo (n=152)	116	12 (9–15)	
Third quartile (10 to ≤12 days)	RDV (n=113)	86	7 (5–11)	1.45 (1.07–1.98)
	Placebo (n=108)	76	14 (9–20)	
Fourth quartile (≥13 days)	RDV (n=121)	84	12 (9–17)	1.15 (0.86–1.54)
	Placebo (n=135)	94	16 (12–19)	

Pooled Duration of Symptoms by Category	Treatment Group	n	Time to Recovery, Median (95% CI), Days	HR (95% CI)
≤10 days	RDV (n=356)	270	9 (8–11)	1.37 (1.14–1.64)
	Placebo (n=320)	212	15 (12–19)	
>10 days	RDV (n=184)	129	11 (9–13)	1.2 (0.94–1.52)
	Placebo (n=199)	139	15 (12–19)	

Abbreviation: NE=not estimable.

In a subanalysis using a proportional odds model, participants who received RDV ≤10 days after symptom onset had significantly greater odds of an improved clinical status score than those who received placebo (OR, 1.7; 95% CI: 1.3–2.2; *P*<0.001), whereas those who received RDV >10 days after symptom onset had odds of improved clinical status score that were not significant (OR, 1.3; 95% CI: 0.9–1.9; *P*=0.125).[3]

Safety results were not reported by symptom onset.[2]

SIMPLE Study: RDV in Severe COVID-19[4]

A phase 3, randomized, open-label study evaluated the safety and efficacy of 5-day or 10-day RDV dosing regimens (200 mg IV on Day 1, followed by 100 mg IV daily for a total treatment duration of 5 or 10 days) in addition to SOC in hospitalized participants with severe COVID-19. The primary endpoint was the efficacy of two RDV regimens with respect to clinical status assessed by a 7-point ordinal scale on Day 14. The median duration of symptoms before RDV initiation was 9 days in the 10-day RDV group and 8 days in the 5-day RDV group.

Discharge rates in the overall population among participants with <10 vs ≥10 days of symptoms before the first dose of RDV were as follows: 62% vs 49%, respectively.

Safety results were not reported by symptom onset.

SIMPLE Study: RDV in Moderate COVID-19

A phase 3, open-label study compared the efficacy of 5-day or 10-day RDV dosing regimens (200 mg IV on Day 1, followed by 100 mg IV daily for a total treatment duration of 5 or 10 days) with SOC in hospitalized participants with moderate COVID-19. The primary endpoint was the efficacy of two RDV regimens with respect to clinical status, assessed by a 7-point ordinal scale on Day 11. The median (IQR) duration of symptoms before RDV initiation was 8 (5–11) days in the RDV groups and 9 (6–11) days in the SOC group.[5]

Post hoc sensitivity analyses that adjusted for Day 1 clinical status score, symptom duration, imputing participants with missing status as dead, and using the ITT population had primary endpoint results similar to those for the overall population.[5] In a subgroup analysis, there were no differences in the proportions of participants with ≥1-point improvement in clinical status scores between those with COVID-19 symptoms for ≥9 days or <9 days (secondary endpoint).[5,6]

Safety results were not reported by symptom onset.[5]

PINETREE: RDV Outpatient Study

Overall study design[9,10]

A phase 3, randomized, double-blind, placebo-controlled, multicenter study evaluated the safety and efficacy of a 3-day course of RDV (200 mg IV loading dose on Day 1, followed by 100 mg IV daily for a total treatment duration of 3 days) administered in an outpatient setting

in non-hospitalized participants with baseline characteristics that increased their risk for COVID-19 disease progression. Participants were included if they had confirmed SARS-CoV-2 within 4 days of screening, had symptoms for ≤7 days, and were age ≥12 years with risk factors for progression (eg, chronic lung disease, hypertension, cerebrovascular or cardiovascular disease, diabetes mellitus, obesity, immunocompromised status, chronic kidney disease, chronic liver disease, current cancer, and sickle cell anemia) or age ≥60 years with or without preexisting risk factors.

Subanalysis: effect of the duration from symptom onset at treatment initiation on the efficacy of RDV

Study design[7]

A subanalysis was conducted to evaluate the effect of the time from COVID-19 symptom onset to the initiation of treatment (≤3 and >3 days; ≤5 and ≥6 days; and as a continuous variable) on the efficacy of RDV using the Cox proportional-hazards model that adjusted for treatment and stratification factors, including residence in a skilled nursing facility, age (<60 years or ≥60 years), and country of residence (US vs outside US). The median (IQR) symptom durations prior to the first study drug dose in the RDV (n=279) and placebo (n=283) groups were 5 (3–6) days and 5 (4–6) days, respectively. A total of 201/279 participants in the RDV group and 194/283 participants in the placebo group received the first infusion ≤5 days from symptom onset; the first infusion was administered ≥6 days from symptom onset in 78/279 participants in the RDV group and in 89/283 participants in the placebo group.

Results

Symptom onset was assessed as ≤3 days, ≥4 days, ≤5 days, and ≥6 days for COVID-19–related hospitalizations (Table 3), MAVs (Table 4), and symptom alleviation (Table 5).[7]

Of the participants who received RDV or placebo ≤5 days of COVID-19-related symptoms onset, 1 participant (0.5%) in the RDV group and 9 participants (4.6%) in the placebo group had a COVID-19–related hospitalization by Day 28 (HR, 0.1; 95% CI: 0.01–0.82), compared with 1 participant (1.3%) and 6 participants (6.7%) who received RDV or placebo, respectively, >5 days after symptom onset (HR, 0.19; 95% CI: 0.02–1.61; Table 3).[7]

Table 3. PINETREE Subanalysis: COVID-19–Related Hospitalizations by Symptom Onset Timeline[8]

Symptom Onset, Days	Participants With COVID-19–Related Hospitalizations, n/N (%)		HR (95% CI)
	RDV	Placebo	
≤3	0/77	5/69 (7.2)	N/A
≥4	2/202 (1)	10/214 (4.7)	0.21 (0.04–0.94)
≤5	1/201 (0.5)	9/194 (4.6)	0.1 (0.01–0.82)
≥6	1/78 (1.3)	6/89 (6.7)	0.19 (0.02–1.61)

Among participants treated ≤5 days or ≥6 days after symptom onset, RDV was associated with a lower number of COVID-19-related MAVs (Table 4) and a higher number of participants who reported symptom alleviation by Day 14 (Table 5) compared to placebo.[7]

Table 4. PINETREE Subanalysis: COVID-19–Related MAVs by Symptom Onset Timeline[8]

Symptom Onset, Days	Participants With COVID-19–Related MAVs, n/N (%)		HR (95% CI)
	RDV	Placebo	
≤3	0/77	6/69 (8.7)	N/A
≥4	4/202 (2)	15/214 (7)	0.26 (0.09–0.8)
≤5	1/201 (0.5)	14/194 (7.2)	0.07 (0.01–0.52)
≥6	3/78 (3.8)	7/89 (7.9)	0.44 (0.11–1.77)

Table 5. PINETREE Subanalysis: COVID-19 Symptom Alleviation by Day 14 Symptom Onset Timeline[8]

Symptom Onset, Days	Participants Who Reported COVID-19 Symptom Alleviation, n/N (%)		Rate Ratio (95% CI)
	RDV	Placebo	
≤3	17/41 (41)	9/40 (22)	1.99 (0.88–4.54)
≥4	44/128 (34)	24/125 (19)	1.91 (1.16–3.15)
≤5	45/123 (37)	24/120 (20)	1.9 (1.16–3.13)
≥6	16/46 (35)	9/45 (20)	2.32 (0.94–5.72)

Abbreviation: FLU-PRO=InFLUenza Patient-Reported Outcome.
Note: Includes symptom alleviation data from participants who received their first infusion within 5 days of symptom onset and completed the baseline FLU-PRO Plus questionnaire on Day 1 of study drug administration.

References

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Abbreviations

ACTT=Adaptive COVID-19 Treatment Trial
HR=hazard ratio
MAV=medically attended visit
NIAID=National Institute of Allergy and Infectious Diseases
OR=odds ratio
RDV=remdesivir
SOC=standard of care

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:

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