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Veklury® (remdesivir) Outpatient PINETREE Study

This document summarizes available information regarding the outpatient Veklury® (remdesivir [RDV]) PINETREE study that evaluated the safety and efficacy of a 3-day course of RDV in nonhospitalized participants with COVID-19.

Some data may be outside of the US FDA-approved prescribing information. In providing this data, Gilead Sciences, Inc. is not making any representation as to its clinical relevance or to the use of any Gilead product(s). For information about the approved conditions of use of any Gilead drug product, please consult the FDA-approved prescribing information.

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]

RDV is indicated for the treatment of COVID-19 in adults and pediatric patients (birth to <18 years of age weighing ≥1.5 kg) who are:

- Hospitalized, or
- Not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.

PINETREE Study: Outpatient Use of RDV

- In PINETREE, a study that evaluated the safety and efficacy of a 3-day course of RDV in nonhospitalized participants with COVID-19, treatment with RDV, in comparison with placebo, was associated with an 87% reduction in the risk of COVID-19–related hospitalization or all-cause death by Day 28 (HR: 0.13; 95% CI: 0.03–0.59; *P*=0.008).[2]
- Treatment with RDV resulted in an 81% reduction in the risk of COVID-19–related MAVs or all-cause death by Day 28 compared with placebo (HR: 0.19; 95% CI: 0.07–0.56; *P*=0.002).[2]
- No deaths occurred in either study group by Day 28.[2]
- The safety profile was similar between the RDV and placebo groups. No participants experienced an SAE or discontinued RDV due to hypersensitivity.[2]

PINETREE Study: Outpatient Use of RDV

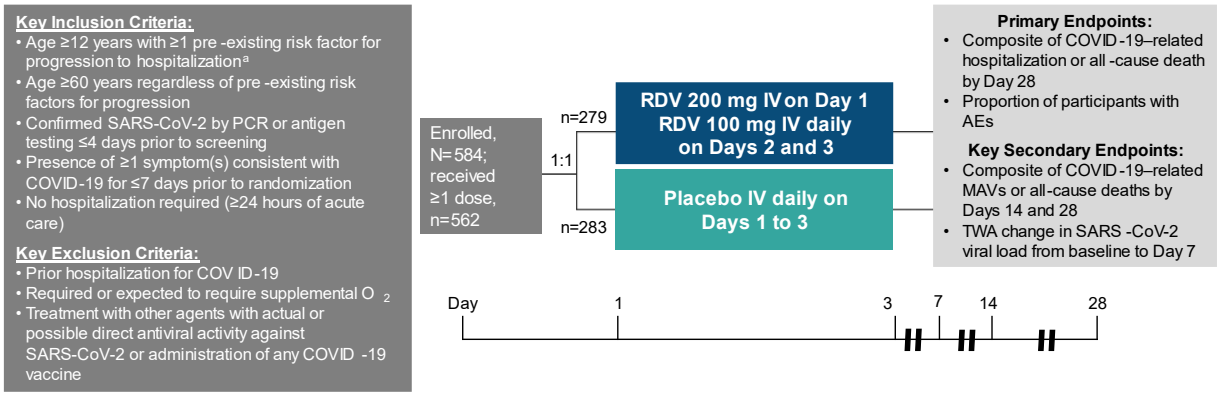
Study Design and Demographics

A phase 3, randomized, double-blind, placebo-controlled, multicenter study evaluated the safety and efficacy of a 3-day course of IV RDV administered to nonhospitalized participants who had baseline characteristics that increased their risk for COVID-19 disease progression. Participants could receive study treatment at outpatient infusion facilities, skilled nursing facilities, or at home.[2]

The primary efficacy endpoint was the composite of COVID-19–related hospitalizations (defined as ≥24 hours of acute care; determined by site investigators who were blinded regarding treatment assignments) or all-cause death by Day 28. The primary safety endpoint was the proportion of participants who experienced AEs.[2]

The study stopped enrollment in April 2021 for administrative reasons associated with the evolving pandemic and increased access of additional treatment options at the time. No interim analysis or Data Monitoring Committee review of study data was performed before the study was halted.[2]

Figure 1. PINETREE: Study Design[2]



Abbreviations: O_2=oxygen; PCR=polymerase chain reaction; TWA=time-weighted average.
[a]Pre-existing risk factors for progression to hospitalization included chronic lung disease, hypertension (systemic or pulmonary), cardiovascular or cerebrovascular disease, diabetes mellitus, obesity (BMI ≥30 kg/m^2), immunocompromised state, chronic kidney disease (mild or moderate), chronic liver disease, current cancer, and sickle cell disease.

Eight participants aged <18 years were included in the study (RDV, n=3; placebo, n=5); all were White, and the median (IQR) ages in the RDV and placebo groups were 13 (13–17) and 16 (15–16) years, respectively. At least 1 dose of study drug was administered at home for 16.5% of participants, and 2.7% received ≥1 dose at a skilled nursing facility. Each group received a median of 3 doses of study drug.[2,3]

Table 1. PINETREE: Baseline Demographics and Disease Characteristics[2,3]

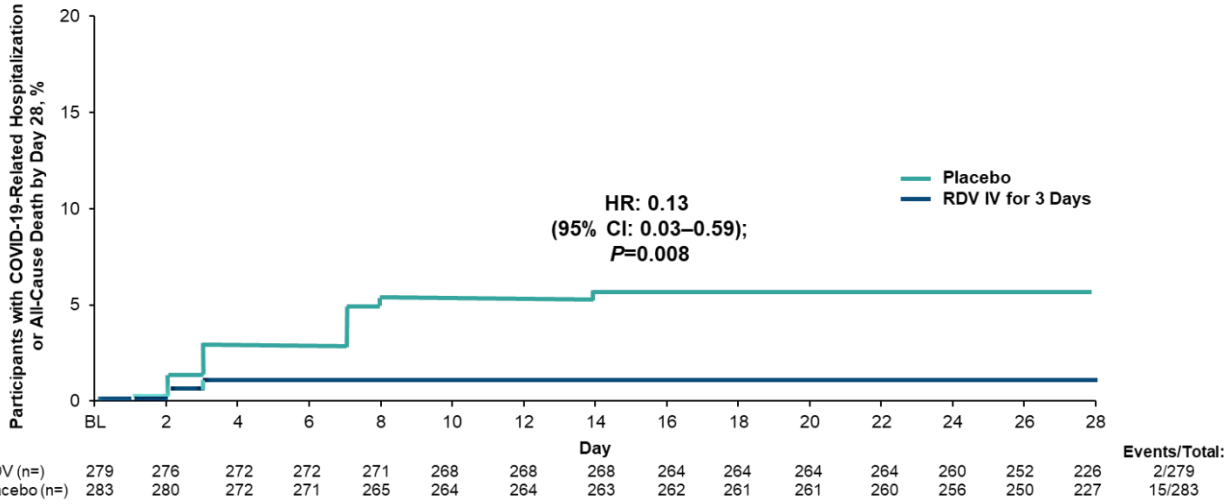
Key Demographics and Characteristics		RDV (n=279)	Placebo (n=283)	Total (N=562)
Age, mean (SD), years		50 (15)	51 (15)	50 (15)
Aged ≥65 years, n (%)		40 (14)	54 (19)	94 (17)
Aged <18 years, n (%)		3 (1)	5 (2)	8 (1)
Female sex at birth, n (%)		131 (47)	138 (48.8)	269 (47.9)
Most commonly reported comorbidities (>5% in either group), n (%)	Diabetes mellitus	173 (62)	173 (61.1)	346 (61.6)
	Obesity	154 (55.2)	156 (55.1)	310 (55.2)
	Hypertension	138 (49.5)	130 (45.9)	268 (47.7)
	Chronic lung disease	67 (24)	68 (24)	135 (24)
	Cardiovascular or cerebrovascular disease	20 (7.2)	24 (8.5)	44 (7.8)
	Immunocompromised	14 (5)	9 (3.2)	23 (4.1)
	Current cancer	12 (4.3)	18 (6.4)	30 (5.3)
Duration of symptoms before first dose of RDV, median (IQR), days		5 (3–6)	5 (4–6)	5 (3–6)

Efficacy

Primary endpoint[2]

Treatment with RDV, in comparison with placebo, was associated with an 87% reduction in the risk of COVID-19–related hospitalization or all-cause death by Day 28 (HR: 0.13; 95% CI: 0.03–0.59; *P*=0.008; Figure 2).

Figure 2. PINETREE: COVID-19–Related Hospitalizations or All-Cause Death by Day 28 (Primary Endpoint; Kaplan-Meier Estimate)[2]



Note: The HR, 95% CI, and *P*-value were calculated using a Cox regression model that used baseline stratification characteristics as covariates.

In prespecified subgroup analyses (presence of diabetes, obesity, and hypertension; male sex; and non-Hispanic or Latinx ethnicity), rates of COVID-19–related hospitalization or all-cause death at Day 28 were lower in the RDV group than in the placebo group.

Key secondary endpoints[2]

Treatment with RDV, in comparison with placebo, resulted in an 81% reduction in the risk of COVID-19–related MAVs or all-cause death by Day 28 (HR: 0.19; 95% CI: 0.07–0.56; Table 2). No participants aged <18 years had a COVID-19–related hospitalization or all-cause death by Day 28. No deaths occurred in either study group by Day 28 (Table 2).

Table 2. PINETREE: Key Secondary Efficacy Endpoints[2,4]

Secondary Endpoints		RDV (n=279)	Placebo (n=283)	HR (95% CI)
COVID-19–related hospitalization or all-cause death by Day 14, n (%)		2 (0.7)	15 (5.3)	0.13 (0.03–0.59)
COVID-19–related MAV or all-cause death,[a] n/N (%)	By Day 14	2/246 (0.8)	20/252 (7.9)	0.1 (0.02–0.43)
	By Day 28	4/246 (1.6)	21/252 (8.3)	0.19 (0.07–0.56)
All-cause death by Day 28, n		0	0[b]	Not calculated
All-cause hospitalization by Day 28,[c] n (%)		5 (1.8)	18 (6.4)	0.28 (0.1–0.75)

[a]N reflects the number of participants who underwent randomization, received ≥1 dose of study drug, and met eligibility criteria outlined in protocol amendment 2.
[b]One participant in the placebo group died on Day 59 (cause was not disclosed).
[c]Post hoc analysis.

Note: Baseline stratification factors (residence in a skilled nursing facility [yes or no], age [<60 or ≥60 years of age], and country [US or outside of US]) were used as covariates.

Safety[2,3]

Overall, by Day 28, the safety profile of RDV was similar to that of placebo. More SAEs were observed in the placebo group than in the RDV group (Table 3); this was associated with a higher rate of hospitalization within the placebo group. No participants experienced an SAE or discontinued RDV due to hypersensitivity. Minimal changes in ALT levels from baseline were observed in each group. No clinically significant changes in hepatic parameters (ie, albumin, alkaline phosphatase, total bilirubin levels, or INR) were noted, and the rate of hepatic AEs was similar between groups. Minimal changes in CrCl from baseline were observed in each group, and no renal AEs were reported in either group.

Table 3. PINETREE: Safety Summary[2,3]

Safety Outcomes[a]		RDV (n=279)	Placebo (n=283)
Any AE, n (%)		118 (42.3)	131 (46.3)
AEs (≥5% of participants in either group), n (%)	Nausea	30 (10.8)	21 (7.4)
	Headache	16 (5.7)	17 (6)
	Cough	10 (3.6)	18 (6.4)
	Dyspnea	7 (2.5)	15 (5.3)
Grade ≥3 AEs, n (%)		10 (4)	20 (7)
Study drug-related AEs, n (%)		34 (12.2)	25 (8.8)
SAEs, n (%)		5 (1.8)	19 (6.7)
AEs that led to premature discontinuation of study drug, n (%)		2 (0.7)	5 (1.8)
Grade ≥3 laboratory abnormalities, n (%)		29 (10.4)	23 (8.1)
Change from baseline in ALT levels at Day 14, mean (SD), U/L		-3 (21.6)	-1 (27.4)
ALT/AST level increased, n (%)		1 (<1)/1 (<1)	3 (1)/1 (<1)
Change from baseline in CrCl at Day 14, mean (SD), mL/min		0.26 (21.2)	1.9 (18.6)

[a]The Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric AEs, Version 2.1, was used to grade AEs and laboratory abnormalities.

Table 4. PINETREE: Cardiac Safety[3]

Cardiac Safety Outcomes, n (%)	RDV (n=279)	Placebo (n=283)
Palpitations	2 (1)	3 (1)
Atrial fibrillation	2 (1)	0
Tachycardia	1 (<1)	2 (1)
Angina pectoris	1 (<1)	1 (<1)
Cardiac failure congestive	1 (<1)	0
Acute left ventricular failure	1 (<1)	0
Bradycardia	0	2 (1)
Acute myocardial infarction	0	1 (<1)
Mitral valve prolapse	0	1 (<1)

References

1. Veklury. Gilead Sciences Inc. Veklury® (remdesivir) for injection, for intravenous use. VEKLURY® (remdesivir) injection, for intravenous use. U.S. Prescribing Information. Foster City, CA.

2. Gottlieb RL, Vaca CE, Paredes R, et al. Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients. *N Eng J Med.* 2022;386(4):305-315.
3. Webb B, Oguchi G, Sachdeva Y, et al. Safety of Remdesivir vs Placebo in Nonhospitalized Patients With COVID-19 [Poster 456]. Paper presented at: Virtual Conference on Retroviruses and Opportunistic Infections (CROI) 2022; 12-16 February, 2022.
4. Gottlieb RL, Vaca CE, Paredes R, et al. Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients [Supplementary Appendix]. *N Eng J Med.* 2021.

Abbreviations

AE=adverse event
HR=hazard ratio
MAV=medically attended visit
RDV=remdesivir
SAE=serious adverse event

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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