GILEAD | Medical Information

Veklury® (remdesivir) Use in Pediatric Patients

This document is in response to your request for information regarding the use of Veklury® (remdesivir [RDV]) in pediatric patients for the treatment of COVID-19. This response was developed according to principles of evidence-based medicine and contains data from phase 2/3 clinical studies.

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.

Use of RDV in pediatric patients from birth to <18 years of age and weighing ≥1.5 kg is supported by Study 5823, where 58 hospitalized pediatric participants were treated with weight-based RDV for up to 10 days.

The safety and pharmacokinetic results in pediatric participants were similar to those in adults (see Adverse Reactions [Section 6.1], Clinical Pharmacology [Section 12.3], Clinical Studies [Section 14.6]).

Please refer to Section 8.4 Pediatric Use in the US Prescribing Information for complete product information.

Clinical Data on the Use of RDV in Pediatric Patients

In the CARAVAN study, which evaluated RDV use in hospitalized pediatric participants aged <18 years, the clinical status of participants improved in 75% at Day 10 and in 85% at the last study assessment; 60% and 83% of participants were discharged by Days 10 and 30, respectively. No new safety signals were observed, and RDV was well tolerated.[2]

In the outpatient PINETREE study, which included 8 non-hospitalized pediatric participants aged <18 years (RDV, n=3; placebo, n=5), none experienced a COVID-19–related hospitalization or death by Day 28.[3] Of the participants aged <18 years, 1 participant in the placebo group had an AE of mild fatigue.[4]

Clinical Data on the Use of RDV in Pediatric Patients

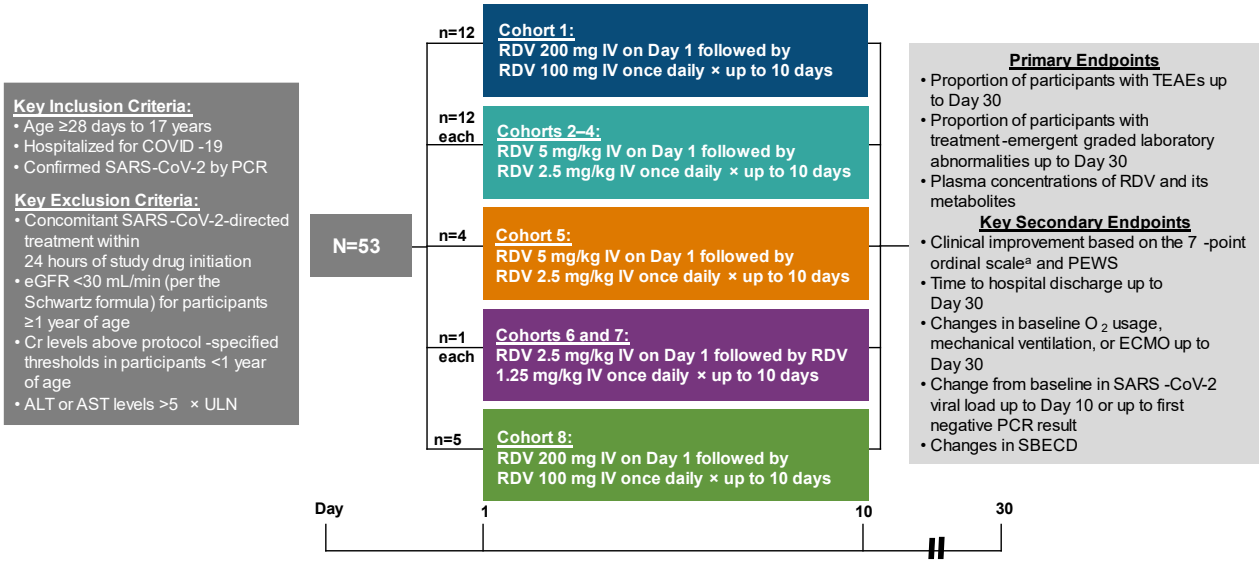
CARAVAN Study: RDV Use in Pediatric Participants Hospitalized With COVID-19

Study design and demographics

A phase 2/3, single-arm, open-label study in the US and Europe evaluated the safety, tolerability, pharmacokinetics, and efficacy of RDV in pediatric participants aged ≥28 days to 17 years, weighing ≥3 kg, and hospitalized with COVID-19 (Figure 1). The primary endpoints were the proportion of participants with any TEAEs, the proportion of participants with treatment-emergent laboratory abnormalities, and the plasma concentrations of RDV and its metabolites.[2]

An assessment of 53 participants enrolled in Cohorts 1 through 4 and Cohort 8 from July 2020 to May 2021 was conducted. Overall, the median treatment duration was 5 days. The most common reasons for a treatment duration <10 days were hospital discharge (42%) and investigator discretion (25%). Among the 53 participants, the mean (IQR) age was 7 (2–12) years; the median (IQR) weight was 25 (13–55) kg; 57% were assigned female at birth; racial makeup consisted of 33 White participants (70%), 14 Black participants (30%), and 23 Hispanic/Latinx participants (44%). Medical conditions included obesity in 19 participants (37%), cardiac disorders in 11 (21%), and asthma in 11 (21%).[2]

Figure 1. CARAVAN: Overall Study Design[2,5]



Abbreviations: PCR=polymerase chain reaction; PEWS=Pediatric Early Warning Score; SBECD=sulfobutylether β-cyclodextrin; ULN=upper limit of normal.

[a]Clinical status was assessed using a 7-point ordinal scale: 1) death; 2) hospitalized and required IMV or ECMO; 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 other than RDV administration; 7) not hospitalized.

Primary endpoints: results for Cohorts 1 through 4 and Cohort 8[2]

Overall, 38 participants (72%) experienced ≥1 AE during the study; Grade ≥3 AEs were reported in 15 participants (28%). No treatment-related SAEs were reported. Overall, 2 (4%) treatment discontinuations due to AEs were reported, and 3 (6%) deaths occurred that were considered unrelated to study drug (Table 1).

Table 1. CARAVAN: Primary Safety Results for Cohorts 1–4 and Cohort 8[2]

AEs, n (%)	Total (N=53)	Cohort 1: ≥40 kg and 12 to 17 y (n=12)	Cohort 2: 20 to <40 kg and 28 d to 17 y (n=12)	Cohort 3: 12 to <20 kg and 28 d to 17 y (n=12)	Cohort 4: 3 to <12 kg and 28 d to 17 y (n=12)	Cohort 8: ≥40 kg and <12 y (n=5)
Any AE	38 (72)	11 (92)	7 (58)	9 (75)	7 (58)	4 (80)
AEs that occurred in ≥9% of participants overall						
Constipation	9 (17)	3 (25)	1 (8)	1 (8)	1 (8)	3 (60)
AKI	6 (11)	4 (33)	0	0	1 (8)	1 (20)
Hyperglycemia	5 (9)	1 (8)	1 (8)	1 (8)	2 (17)	0
Pyrexia	5 (9)	1 (8)	2 (17)	1 (8)	1 (8)	0
Any Grade ≥3 AEs	15 (28)	6 (50)	2 (17)	1 (8)	4 (33)	2 (40)
Treatment-related Grade ≥3 AEs	3 (6)	3 (25)	0	0	0	0
SAEs[a]	11 (21)	5 (42)	2 (17)	0	3 (25)	1 (20)
Treatment-related SAEs	0	0	0	0	0	0
Treatment discontinuation due to an AE[b]	2 (4)	2 (17)	0	0	0	0
Death[c]	3 (6)	1 (8)	1 (8)	0	0	1 (20)
Laboratory abnormalities						
Grade 3–4	22 (42)	9 (75)	2 (17)	4 (33)	4 (36)	3 (60)

Abbreviation: AKI=acute kidney injury.

[a]Included cardiorespiratory arrest, multiple organ dysfunction syndrome, pyrexia, respiratory distress, septic shock, and thrombosis (each, n=2).

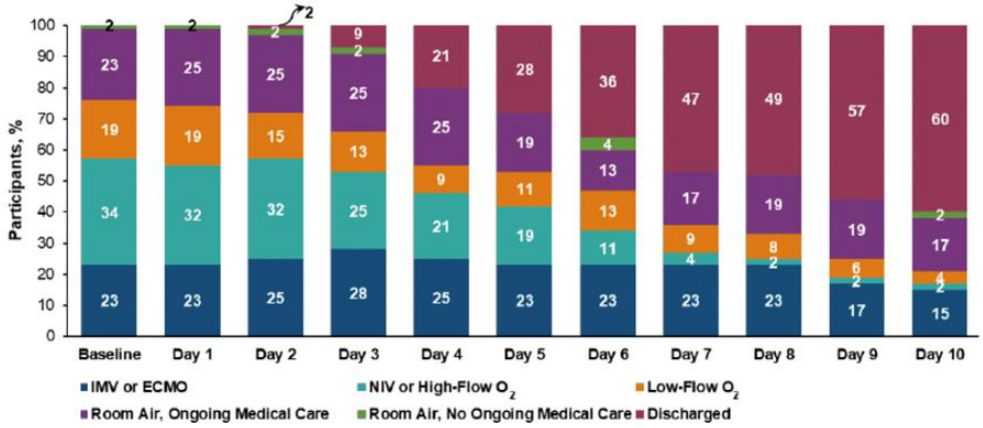
[b]Grade 3 ALT increase (n=1); Grade 4 hyperbilirubinemia, Grade 3 ALT increase, Grade 3 AST increase, and Grade 4 increased serum sodium level (all in 1 participant). Both participants had elevated transaminase levels at baseline.

[c]Immediate causes of death included multisystem organ failure and cardiorespiratory arrest. No deaths were considered treatment related. One additional participant died 32 days after the last RDV dose.

Secondary endpoints: efficacy in Cohorts 1 through 4 and Cohort 8[2]

Overall, 60% of participants (32/53) were discharged by Day 10, and 83% of participants (44/53) were discharged by Day 30. Among participants who were discharged alive by Day 30, the median (IQR) duration of hospitalization from Day 1 of RDV was 7 (5–12) days. Additionally, 75% and 85% of participants showed clinical improvement (defined as a ≥2-point increase in ordinal score from baseline) at Day 10 and at the last clinical assessment, respectively. The overall recovery rate (improvement from a baseline ordinal score of 2–5 to score of 6 or 7 or from a baseline score of 6 to a score of 7) was 83%.

Figure 2. CARAVAN: Clinical Status Results According to Ordinal Scale by Study Day[2]



Interim results for Cohorts 5 through 7[6]

Cohort 5 included participants who were 14 to <28 days old, had a GA >37 weeks, and weighed ≥2.5 kg (n=3). Cohort 6 included participants who were <14 days old, had a GA >37 weeks, and weighed ≥2.5 kg at birth (n=1); Cohort 7 included participants who were <56 days old, had a GA ≤37 weeks, and weighed ≥1.5 kg at birth (n=1). At baseline, participants were 12 to 30 days old; 3/5 were female, 4/5 were White, and 1/5 were Black; and their weight ranged from 2.2 to 3.5 kg. Three participants were on IMV, and 2 were on high-flow O_2. Symptom duration prior to first RDV dose was 2 to 9 days.

Among the neonate and infant participants in Cohorts 5 through 7, laboratory abnormalities (Grades 3–4) were reported in 3/5 participants and included APTT increased (2/5), direct bilirubin increased (1/5), creatinine increased (1/5), prothrombin time increased (1/5), prothrombin/INR increased (1/5), and potassium increased (1/5).

Three participants who received RDV recovered, including 1 participant who recovered by Day 10. Time to recovery ranged from 9 to 19 days. Overall, 3 participants were discharged by Day 30; one of these participants was discharged by Day 10. No participants from Cohorts 5 through 7 died during the study.

Resistance analyses in pediatric participants and preterm neonates[7]

Overall, baseline sequencing data were obtained from 37 of the 58 pediatric participants in Cohorts 1 through 4 and Cohort 8 and in preterm neonates in Cohorts 5 through 7. None of the 6 amino acid polymorphisms that met the criteria for phenotyping impacted RDV susceptibility, with a 0.53- to 1.55-fold change in EC_{50} compared with the WT reference. Of the 28 participants with baseline and postbaseline sequencing data, 6 had 11 postbaseline substitutions: 5 substitutions in Nsp12 as mixtures with WT Nsp12 (n=3) and 6 substitutions in Nsp9, Nsp10, and Nsp13 (n=3). The only substitutions with low-level reduced susceptibility to RDV were Nsp12 V792I alone (3.2-fold change in EC_{50}) and in combination with V166L (6.12-fold change in EC_{50}). The participant with Nsp12 V166V/L and V792V/I substitutions achieved clinical recovery and was discharged from the hospital on Day 13.

PINETREE Outpatient Study: RDV in Non-Hospitalized Participants With COVID-19

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 RDV administered in an outpatient setting in non-hospitalized participants with baseline characteristics that increased their risk for COVID-19 disease progression (N=584). Participants received RDV 200 mg IV on Day 1 and RDV 100 mg IV daily on Days 2 and 3. Participants in the placebo group received IV placebo daily on Days 1 to 3. Participants could receive study treatment at outpatient infusion facilities, skilled nursing facilities, or at their home.[3,8] 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.[3]

Overall, 8 participants aged <18 years were included in the study (RDV, n=3; placebo, n=5). All pediatric participants were White; the median (IQR) ages in the RDV and placebo groups were 13 (13–17) years and 16 (15–16) years, respectively, and the median (IQR) BMIs in the RDV and placebo groups were 25.7 (21.1–31.7) kg/m^2 and 28.7 (23.2–29.1) kg/m^2, respectively.[3,4]

Efficacy and safety

Overall, treatment with RDV was associated with an 87% reduction in the risk of COVID-19–related hospitalization or all-cause death by Day 28 compared with placebo (hazard ratio, 0.13; 95% CI: 0.03–0.59; *P*=0.008). No pediatric participants aged <18 years experienced a COVID-19–related hospitalization or death by Day 28.[3]

By Day 28, the safety profile of RDV was similar to that of placebo.[3,4] Of the 8 pediatric participants aged <18 years, 1 participant in the placebo group had an AE of mild fatigue. None of the 8 pediatric participants in either group reported study drug-related AEs, SAEs, AEs that led to drug discontinuation, hospitalization, death, or Grade ≥3 laboratory abnormalities.[4]

References

1. VEKLURY®, Gilead Sciences Inc. Veklury® (remdesivir) for injection, for intravenous use. U.S. Prescribing Information. Foster City, CA.
2. Ahmed A, Munoz FM, Muller WJ, et al. Remdesivir for COVID-19 in Hospitalized Children: A Phase 2/3 Study. *Pediatrics.* 2024;153(3):e2023063775.
3. 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.
4. 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.
5. ClinicalTrials.gov. Study of Remdesivir in Participants Below 18 Years Old With COVID-19 (CARAVAN) Available at: https://classic.clinicaltrials.gov/ct2/show/NCT04431453 Accessed: 14 May 2024. Last Updated: 06 February. 2024.
6. VEKLURY®, Gilead Sciences Inc. Veklury® (remdesivir) for injection, for intravenous use. U.S. Prescribing Information. Foster City, CA. Revised August. 2023.

7. Moshiri J, Li J, Rodriguez L, et al. Resistance Analyses From the Remdesivir Phase 2/3 CARAVAN Study in Pediatric and Neonatal Participants Hospitalized With COVID-19 [Poster P-2025]. Paper presented at: IDWeek; October 16-19, 2024; Los Angeles, CA.
8. Gottlieb RL, Vaca CE, Paredes R, et al. Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients [Protocol]. *N Eng J Med.* 2021.

Abbreviations

AE=adverse event(s)
APTT=activated partial thromboplastin time
CARAVAN=Clinical Administration of Remdesivir After COVID-19 Diagnosis in Children
EC_{50}=half-maximal effective concentration
ECMO=extracorporeal membrane oxygenation
GA=gestational age
IMV=invasive mechanical ventilation
NIV=non-invasive ventilation
Nsp=nonstructural protein
O_2=oxygen
RDV=remdesivir
SAE=serious adverse event
TEAE=treatment-emergent adverse event
WT=wild type

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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