GILEAD | Medical Information

Veklury® (remdesivir) Use With IMV/ECMO

This document is in response to your request for information regarding Veklury® (remdesivir [RDV]) for the treatment of COVID-19 in patients requiring invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO) therapy.

This response was developed according to principles of evidence-based medicine and contains data from phase 3 clinical studies that reported primary outcome data for patients who required IMV/ECMO and from real-world studies that included >2500 patients who required IMV/ECMO.

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.

The recommended total treatment duration for hospitalized patients requiring IMV and/or ECMO is 10 days.

Clinical Study Data on RDV Use With IMV/ECMO

In the ACTT-1 study, 131 participants in the RDV group and 154 in the placebo group required IMV/ECMO.[2,3] The recovery RR of these participants was 0.98 (95% CI: 0.7–1.36), and the median (95% CI) time to recovery was 29 (24–NE) days and 28 (24–NE) days, respectively.[2]

Real-World Studies on RDV Use With IMV/ECMO

In a US PINC AI Healthcare database analysis that included PS-matched cohorts across VOC periods from December 1, 2020, to April 30, 2022, treatment with RDV within 2 days of hospital admission in patients who required IMV/ECMO (n=4164 matched patients per cohort) was associated with a significantly lower risk of mortality at Day 14 and at Day 28; similar results were observed across all VOC periods.[4]

In a Premier Healthcare database analysis that included PS-matched cohorts from August 1 to November 30, 2020, RDV initiation within 2 days of hospital admission was associated with decreased mortality by Day 14 and Day 28 among those who required IMV/ECMO (n=1296).[5]

Product Labeling[1]

Dosage and Administration

Dosage and administration overview

RDV may only be administered in settings in which healthcare providers have immediate access to medications to treat a severe infusion or hypersensitivity reaction, such as anaphylaxis, and the ability to activate the emergency medical system, as necessary.

Administer RDV for the treatment of COVID-19 in adults and pediatric patients (birth to <18 years of age weighing ≥1.5 kg) by IV infusion only. Do not administer by any other route.

Recommended dosage in adults and pediatric patients (birth to <18 years of age weighing ≥1.5 kg)

The recommended dosage for adults and pediatric patients weighing ≥40 kg is a single loading dose of RDV 200 mg on Day 1 via IV infusion followed by once-daily maintenance doses of RDV 100 mg from Day 2 via IV infusion. Please see the prescribing information for the recommended dosage for pediatric patients weighing 1.5 kg to <40 kg.

The recommended total treatment duration for hospitalized patients requiring IMV and/or ECMO is 10 days.

Clinical Study Data on RDV Use With IMV/ECMO

NIAID Sponsored Study: ACTT-1

Study design and demographics

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 and with evidence of lower respiratory tract infection. Eligible participants were required to be hospitalized with confirmed SARS-CoV-2 and have illness of any length and ≥1 of the following: infiltrates on imaging, SpO_2 ≤94% on room air, required supplemental O_2, or required mechanical ventilation. The primary outcome measure was the time to recovery up to Day 29, which was 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 activity limitations; 2) not hospitalized and had activity limitations 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 HFO devices; 7) hospitalized and required IMV or ECMO; 8) death. Efficacy outcomes were reported according to the overall population and the baseline clinical status score, which grouped participants who required IMV or ECMO. Participants were randomly assigned to receive either RDV for up to 10 days or the duration of hospitalization or placebo for the duration of hospitalization.[2]

The ITT population included a total of 1062 participants who were randomly assigned to receive either RDV (n=541) or placebo (n=521).[2] Overall, 131 participants (24.2%) who

received RDV and 154 (29.6%) participants who received placebo required IMV/ECMO at baseline (ordinal score of 7). Approximately 55% of participants had ≥2 coexisting conditions.[2,3]

Table 1. ACTT-1: Select Baseline Demographics and Disease Characteristics[2,3]

Key Demographics and Characteristics		RDV (n=541)	Placebo (n=521)
Age, mean (SD), years		58.6 (14.6)	59.2 (15.4)
Male, n (%)		352 (65.1)	332 (63.7)
Race, White/Black or African American/ Asian/American Indian or Alaska Native, %		51.6/20.1/ 14.6/0.7	55.1/22.5/ 10.7/0.6
Hispanic/Latinx, n (%)		134 (24.8)	116 (22.3)
Key coexisting conditions, n/N (%)	HTN	269/532 (50.6)	264/519 (50.9)
	Obesity	242/531 (45.6)	234/518 (45.2)
	Type 2 diabetes mellitus	164/532 (30.8)	158/519 (30.4)
≤10/>10 days of symptoms prior to enrollment, %		66/34	61/38
Duration of time from symptom onset to randomization, median (IQR), days		9 (6–12)	9 (7–13)
Mild or moderate/severe disease,[a] n/N		55/486	50/471

[a]Mild/moderate disease was defined as SpO_2 >94% and respiratory rate <24 breaths/minute with no requirement for supplemental O_2. Severe disease was defined as SpO_2 ≤94% on room air or respiratory rate ≥24 breaths/minute and requirement for mechanical ventilation or supplemental O_2.

Primary endpoint

Overall, recovery occurred in 399/541 participants and 352/521 participants in the RDV and placebo groups, respectively. Participants who received RDV had a significantly faster median time to recovery than did participants who received placebo (10 days; 95% CI: 9–11 days; 15 days; 95% CI: 13–18 days), which yielded a 29% increased recovery rate (RR, 1.29; 95% CI: 1.12–1.49; *P*<0.001). After adjusting for baseline ordinal score, the overall treatment effect estimate was similar to the result for the primary outcome (recovery RR, 1.26; 95% CI: 1.09–1.46). Recovery occurred in 63/131 participants and 77/154 participants in the RDV and placebo groups, respectively, who required IMV or ECMO at baseline. Median times to recovery for these participants were similar in the RDV and placebo groups (29 days; 95% CI: 24 days–NE; 28 days; 95% CI: 24 days–NE; recovery RR, 0.98; 95% CI: 0.7–1.36). *P*-value and CIs were not adjusted for multiple comparisons and should not be used to infer RDV treatment effects.[2,3]

Safety[2]

Safety outcomes were not reported specifically for patients who received IMV/ECMO therapy. Significantly lower rates of serious AEs were reported for participants in the RDV group than for those in the placebo group (24.6% vs 31.6%, respectively; *P*=0.01), and a lower incidence of Grade 3 or 4 AEs was reported for the RDV group than for the placebo group (51% vs 57%; *P*=0.058). No treatment-related deaths were reported. Rates of non-serious AEs were similar between the treatment groups.

Real-World Studies on RDV Use With IMV/ECMO

US PINC AI Healthcare Database: PS-Matched Cohort Study[4]

Study design and demographics

A retrospective, multicenter, comparative effectiveness cohort study of the US PINC AI Healthcare database (formerly Premier Healthcare Database) compared survival outcomes between adult patients hospitalized for COVID-19 who required supplemental O_2 with and without RDV treatment across VOC periods from December 1, 2020, through April 30, 2022. The RDV cohort comprised patients who received RDV within the first 2 days of hospitalization. A PS model was used to match cohorts, and analyses were stratified by supplemental O_2 requirement (low-flow O_2, HFO/NIV, or IMV/ECMO) and VOC period: pre-Delta (December 2020 to April 2021), Delta predominant (May to November 2021), and Omicron predominant (December 2021 to April 2022).

The primary endpoint was 14- and 28-day all-cause inpatient mortality, defined as a discharge status of “expired” or “hospice”. Of patients who required IMV/ECMO within 2 days of hospital admission, 4164 were included in the RDV cohort and were matched to 1880 patients in the non-RDV cohort (n=4164 weighted, after matching with replacement). After matching, all covariates had a standardized difference absolute value of ≤0.1.

In the PS-matched RDV and non-RDV cohorts, among patients who required IMV/ECMO, select demographics were as follows: 43.2% in each group were aged ≥65 years; 45.1% in each group were female; 68.2% and 65.5%, respectively, were White; 17.2% and 19.3% were Black; 15.1% and 14.1% were Hispanic; 89.5% and 90.6% had CVD; 53.3% and 55.3% were obese; 50.2% and 50.9% had diabetes mellitus; 30.1% and 31.7% had COPD; 28.2% and 30.3% had an immunocompromised condition; and 21.5% and 23.9% had renal disease.

Mortality outcomes

In the RDV cohort relative to the non-RDV cohort, a lower proportion of patients died by Day 14 (27.8% vs 35.3%, respectively) and Day 28 (41.4% vs 50.6%). After adjustment for baseline factors, treatment with RDV within 2 days of hospital admission was associated with a significantly lower risk of mortality at Day 14 (aHR, 0.73; 95% CI: 0.65–0.82; $P<0.0001$) and at Day 28 (aHR, 0.74; 95% CI: 0.67–0.82; $P<0.0001$). Mortality rates and risk by VOC period were consistent with those in the overall IMV/ECMO cohort. Safety outcomes were not reported in this analysis.

Premier Analysis: Retrospective PS-Matched Cohort Study[5]

Study design and demographics

A retrospective, multicenter, comparative effectiveness cohort study of data from the US Premier Healthcare database compared survival outcomes between adult patients hospitalized for COVID-19 with and without RDV treatment between August 1 and November 30, 2020. The RDV cohort comprised patients who received RDV within the first 2 days of hospitalization. A PS model was used to match cohorts. The primary endpoint was

14- and 28-day all-cause inpatient mortality, defined as a discharge status of “expired” or “hospice”.

A total of 28,855 patients were included in the RDV cohort and were matched to 16,687 patients in the non-RDV cohort (n=28,855 weighted, due to variable ratio matching of 1:10). After matching, and with the exception of age group and renal disease status, all covariates had a standardized difference absolute value of <0.15.

In each PS-matched cohort, 1296 patients (4.5%) required IMV/ECMO at baseline. In the PS-matched RDV and non-RDV cohorts, select demographics were as follows: 53% and 58%, respectively, were aged ≥65 years; approximately 44% were female; 72.8% and 73.5% were White; 12.8% and 12.7% were Black; 16.6% and 15.5% were Hispanic; 79.1% and 83.3% had CVD, including HTN; 42.9% and 44.4% had diabetes; 40.8% and 39.5% were obese; 27.2% and 29.3% had COPD; 17.2% and 23.6% had renal disease; 4.1% and 4.4% had an immunosuppressive condition; and 3.8% and 4.1% had cancer.

Mortality outcomes

The 14-day mortality rates in the RDV and non-RDV cohorts were 32.3% and 43.8%, respectively, and the 28-day mortality rates were 48.4% and 55.8%. In the overall PS-matched population, initiation of RDV within 2 days of hospital admission was associated with significantly decreased mortality by Day 14 (aHR, 0.76; 95% CI: 0.69–0.83; *P*<0.0001) and Day 28 (aHR, 0.88; 95% CI: 0.81–0.96; *P*=0.0024); similar results at Day 14 (aHR, 0.7; 95% CI: 0.58–0.84; *P*=0.0001) and Day 28 (aHR, 0.81; 95% CI: 0.69–0.94; *P*=0.0071) were observed among those who required IMV/ECMO. Safety outcomes were not reported in this analysis.

References

1. VEKLURY®, Gilead Sciences Inc. VEKLURY® (remdesivir) for injection, for intravenous use. U.S. Prescribing Information. Foster City, CA.
2. 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.
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.
4. Mozaffari E, Chandak A, Gottlieb RL, et al. Remdesivir Is Associated With Reduced Mortality in COVID-19 Patients Requiring Supplemental Oxygen Including Invasive Mechanical Ventilation Across SARS-CoV-2 Variants. *Open forum infectious diseases.* 2023;10(10):ofad482.
5. Mozaffari E, Chandak A, Zhang Z, et al. Remdesivir Treatment in Hospitalized Patients With Coronavirus Disease 2019 (COVID-19): A Comparative Analysis of In-hospital All-cause Mortality in a Large Multicenter Observational Cohort. *Clin Infect Dis.* 2022;75(1):e450-e458.

Abbreviations

ACTT-1=Adaptive COVID-19 Treatment Trial-1
AE=adverse event
aHR=adjusted hazard ratio
COPD=chronic obstructive pulmonary disease
CVD=cardiovascular disease
ECMO=extracorporeal membrane oxygenation
HFO=high-flow oxygen
HTN=hypertension
IMV=invasive mechanical ventilation
NE=not estimable
NIV=noninvasive ventilation
O_2=oxygen
PINC AI=Premier Inc. Artificial Intelligence
PS=propensity score
RDV=remdesivir
RR=rate ratio
SOC=standard of care
SpO_2=peripheral capillary oxygen saturation
VOC=variant of concern

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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