The REDPINE Study: Efficacy and Safety of Remdesivir in People With Moderately and Severely Reduced Kidney Function Hospitalised for COVID-19 Pneumonia

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Introduction

— Kidney disease is a major risk factor for mortality from COVID-19[1]
  - COVID-19–associated acute kidney injury (AKI) has been shown to correlate with higher mortality and long-term loss of renal function[2]
  - Increased COVID-19 mortality risk has been observed in select populations receiving renal replacement therapy (RRT) and chronic dialysis[3]
  - There are no conventional antiviral treatment options for hospitalised individuals with severely reduced kidney function due to chronic kidney disease (CKD; estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2), end-stage kidney disease (ESKD), or AKI

— Remdesivir (RDV; Veklury®) is a broad-spectrum antiviral drug approved for individuals with COVID-19 who have an eGFR ≥30 mL/min/1.73 m^2 and are either hospitalised or not hospitalised but at risk for progression to severe disease[4]

— When RDV was initially approved for the treatment of COVID-19, the pharmacokinetics (PK) of RDV and the safety of its metabolites and its sulfobutylether-β-cyclodextrin sodium (SBECD) excipient had yet to be established in those with low eGFR

— Pending PK and safety data in moderate-to-severe renal insufficiency, it was initially recommended that RDV only be used in those with eGFR <30 mL/min/1.73 m^2 if the potential benefits outweighed the potential risks[5]

Objective

— To evaluate the efficacy, safety, and PK of RDV in participants hospitalised for COVID-19 pneumonia with moderately and severely reduced kidney function (eGFR <30 mL/min/1.73 m^2) or AKI

Methods

— REDPINE was a Phase 3, randomised, double-blind, placebo-controlled, parallel-group, multicentre study conducted internationally at 55 centres across 5 countries (Brazil, Portugal, Spain, the United Kingdom, and the United States; EudraCT Registration Number: 2020-005416-22; ClinicalTrials.gov Identifier: NCT04745351)

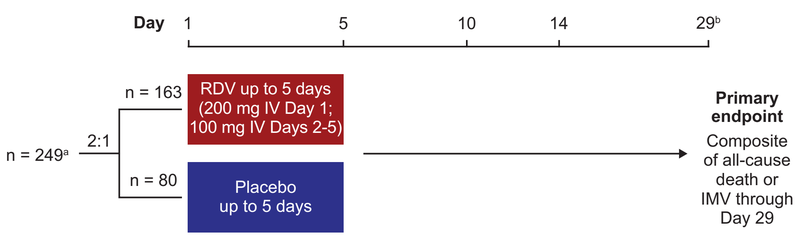
— Eligible participants had confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, were hospitalised with severe COVID-19, were aged ≥12 years, weighed ≥40 kg, had oxygen saturation ≤94% on room air or required oxygen supplementation, and had eGFR <30 mL/min/1.73 m^2 due to either CKD or AKI
  - Kidney transplant recipients with reduced allograft function were eligible
  - Individuals who required invasive or noninvasive mechanical ventilation, extracorporeal membrane oxygenation, or RRT for AKI were excluded

— Participants were randomly assigned (2:1) to receive intravenous RDV (**200 mg on Day 1 followed by 100 mg once daily on Days 2-5**) or placebo to match, in addition to standard-of-care therapy (**Figure 1**)

— Randomisation was stratified by chronic dialysis requirement, high-flow oxygen requirement, and region (United States vs ex–United States)

— Enrolment was halted after 249 participants were randomised because of ongoing challenges with recruitment
  - Low enrolment was due in part to loss of clinical equipoise at many study centres, such that patients were often receiving treatment with RDV outside the scope of the trial

Figure 1. Study Design



RDV, remdesivir; IV, intravenous; IMV, invasive mechanical ventilation.
[a]249 participants were randomised, but 6 were not treated.
[b]If a participant was discharged prior to Day 29, a phone follow-up was completed on Days 29 and 60.

— The primary endpoint (composite of all-cause mortality or invasive mechanical ventilation [IMV] through Day 29) was analysed with a stratified log-rank test using the randomisation strata; the hazard ratio (HR) and 95% confidence interval (CI) were estimated using a Cox model with stratification factors as covariates

— Adverse events (AEs) and serious AEs (SAEs) were collected for all participants from Day 1 to 29 and summarised using descriptive statistics
  - Treatment-emergent AEs (TEAEs), serious TEAEs, and TEAEs leading to discontinuation were defined as AE/SAEs occurring on or after the first dose date up to the last dose date plus 30 days
  - Following hospital discharge, events were collected by phone on Days 29 and 60

— PK parameters for RDV, its renally eliminated metabolite (GS-441524), and SBECD were determined using liquid chromatography-tandem mass spectrometry

Results

Participants

— Of the 258 participants screened, 243 were randomised and treated (RDV, n = 163; placebo, n = 80)

— Demographic and select baseline disease characteristics are displayed in **Table 1**
  - Although eligible per the protocol, no participants aged 12 to 17 years were enrolled
  - Despite randomisation, placebo-enrolled patients were more often ≥65 years of age
  - At baseline, 89 (37%) participants had ESKD requiring chronic dialysis (RDV, 59 [36%]; placebo, 30 [38%])
  - Most participants (198 [81%]) had no high-flow oxygen requirements, with no difference between groups (*P* = 0.95)
  - Proportionally, more solid-organ transplant recipients were randomly assigned to the RDV group (RDV, 35 [21%]; placebo, 7 [9%])

Efficacy

— Kaplan–Meier estimates for all randomised and treated participants with all-cause death or IMV by Day 29 were 30% for the RDV group and 34% for the placebo group (HR, 0.82; 95% CI, 0.50-1.32; *P* = 0.61; **Figure 2A**)

— All-cause death by Day 29 occurred in 41 (25%) and 23 (29%) participants in the RDV and placebo groups, respectively (HR, 0.83; 95% CI, 0.50-1.39; *P* = 0.39)

— There were no statistically significant differences observed for the primary efficacy endpoint between the RDV and placebo groups by kidney disease status (**Figure 2B-2D**)

Table 1. Baseline Characteristics of Trial Participants (Safety Analysis Set[a])

	RDV (n = 163)	Placebo (n = 80)	Total (n = 243)	RDV vs placebo *P* value[b]
Age				
Mean (SD; years)	68 (14)	71 (13)	69 (14)	0.05
Distribution, n (%)				0.02
18-64 years	70 (43)	22 (28)	92 (38)	
≥65 years	93 (57)	58 (73)	151 (62)	
Sex at birth, n (%)				0.73
Male	92 (56)	47 (59)	139 (57)	
Female	71 (44)	33 (41)	104 (43)	
Race, n (%)[c]				0.90
American Indian or Alaska Native	1 (1)	0	1 (0.4)	
Asian	4 (2)	2 (3)	6 (3)	
Black	43 (27)	18 (23)	61 (26)	
White	104 (65)	55 (71)	159 (67)	
Other[d]	11 (6)	5 (4)	16 (5)	
Baseline BMI (kg/m^2), n	158	77	235	0.63
Mean (SD)	29.5 (7)	28.9 (6)	29.3 (7)	
Kidney disease status, n (%)				0.95
AKI	60 (37)	30 (38)	90 (37)	
CKD	44 (27)	20 (25)	64 (26)	
ESKD	59 (36)	30 (38)	89 (37)	
Serum creatinine (mg/dL) by kidney disease status				
AKI, n	60	30		
Mean (SD)	3.36 (2)	3.45 (3)	–	0.39
CKD, n	44	20		
Mean (SD)	3.28 (1)	2.78 (1)	–	0.17
High-flow oxygen requirement, n (%)				0.95
Yes	30 (18)	15 (19)	45 (19)	
No	133 (82)	65 (81)	198 (81)	
History of solid organ transplant, n (%)				0.01
Yes	35 (21)	7 (9)	42 (17)	
No	128 (79)	73 (91)	201 (83)	
Transplant recipient, n (%)				
Kidney	13 (8)	5 (6)	18 (7)	
Lung	4 (2)	1 (1)	5 (2)	
Heart	3 (2)	0	3 (1)	
Pancreas	2 (1)	0	2 (1)	
Kidney and pancreas	1 (1)	0	1 (0.4)	

RDV, remdesivir; SD, standard deviation; BMI, body mass index; AKI, acute kidney injury; CKD, chronic kidney disease; ESKD, end-stage kidney disease.
[a]The safety analysis set included all participants who were randomised into the study and received ≥1 dose of study drug.
[b]For categorical data, *P* value was from the Cochran–Mantel–Haenszel test (general association statistic was used for nominal data, and row means score differ statistic was used for ordinal data). For continuous data, *P* value was from the Wilcoxon rank-sum test.
[c]Some participants were not permitted to disclose their race because local regulators did not allow collection of such information. Values for those not permitted to disclose were excluded from percentage and *P* value calculations.
[d]Includes participants who were Native Hawaiian or Pacific Islander, other, or not permitted to disclose race.

Table 2. Summary of TEAEs and Top 3 Most Common TEAEs by Preferred Term[a]

n (%)	RDV (n = 163)	Placebo (n = 80)
Any TEAE	131 (80)	62 (78)
Grade ≥3 TEAE	102 (63)	49 (61)
TEAE related to study drug	13 (8)	3 (4)
Grade ≥3 TEAE related to study drug	2 (1)	0
Serious TEAE	82 (50)	40 (50)
Serious TEAE related to study drug	0	0
TEAE leading to premature discontinuation of study drug	8 (5)	1 (1)
Treatment-emergent death[b]	47 (29)	23 (29)
TEAE by preferred term		
Hypotension	18 (11)	4 (5)
Respiratory failure	10 (6)	10 (13)
Constipation	12 (7)	7 (9)

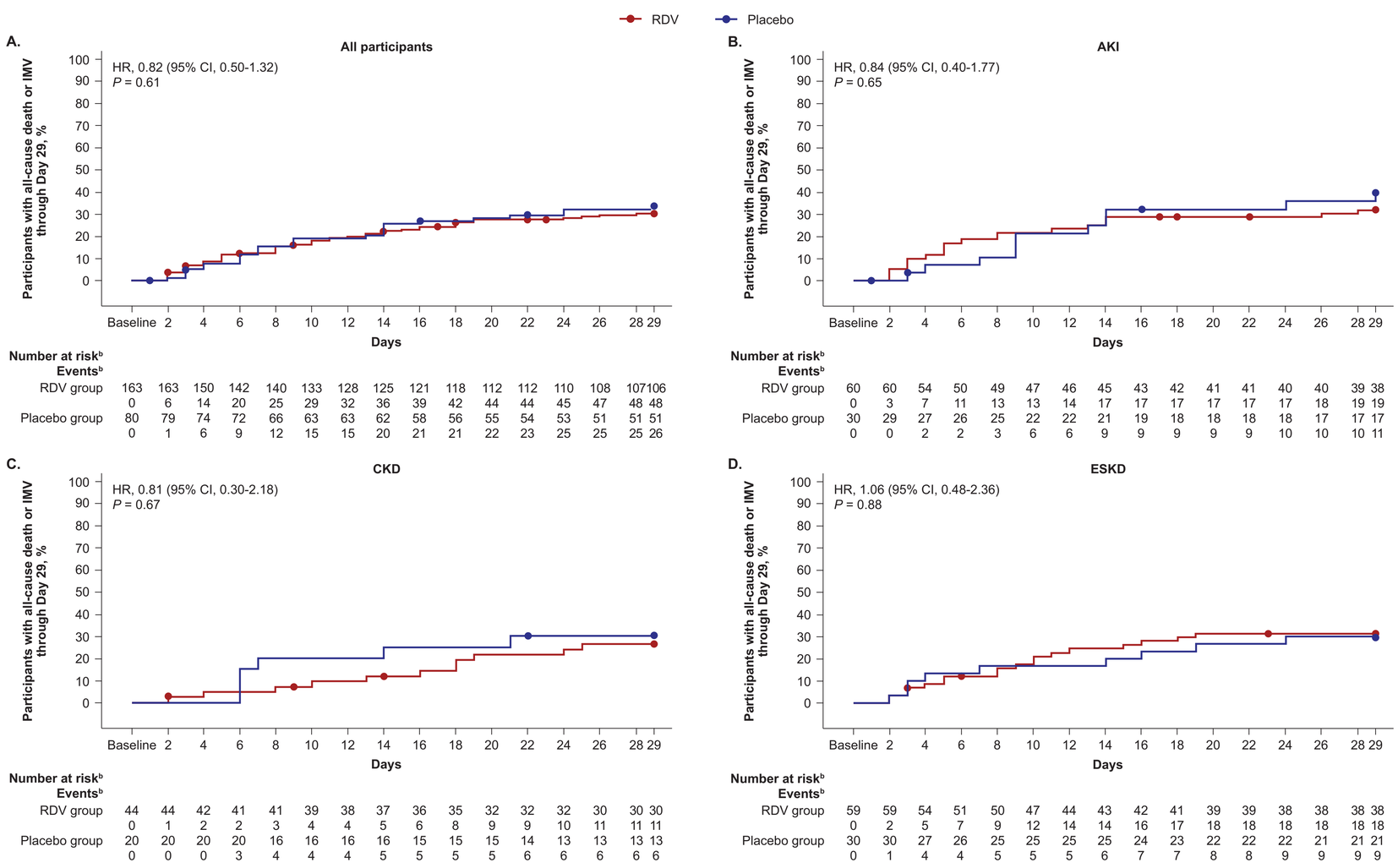
TEAE, treatment-emergent adverse event; RDV, remdesivir.
[a]TEAEs were coded using the *Medical Dictionary for Regulatory Activities*, Version 25.0. Severity grades were defined using the Division of AIDS Toxicity Grading Scale, Version 2.1 (July 2017).
[b]Refers to deaths that occurred between the first and last dose date plus 30 days (inclusive).

Table 3. Proportion of Participants With Baseline AKI or CKD Who Had Worsening AKI, Need for RRT, or Death by Day 29 (Full Analysis Set)

n (%)[a]	RDV	Placebo	*P* value
New or progressive AKI in participants with AKI at baseline, n	60	30	
AKI Stage 2 or 3, RRT, or death by Day 29	20 (33)	12 (40)	0.32
AKI Stage 2	0	0	
AKI Stage 3	0	0	
RRT	5 (8)	2 (7)	
Death	17 (28)	11 (37)	
CKD at baseline, n	44	20	
AKI Stage 2 or 3, RRT, or death by Day 29	15 (34)	6 (30)	0.81
AKI Stage 2	0	0	
AKI Stage 3	8 (18)	3 (15)	
AKI Stage 3 - death	1 (2)	2 (10)	
AKI Stage 3 - no death	7 (16)	1 (5)	
RRT	3 (7)	2 (10)	
Death	8 (18)	5 (25)	

AKI, acute kidney injury; CKD, chronic kidney disease; RRT, renal replacement therapy; RDV, remdesivir.
[a]Outcomes of AKI Stage 2 or 3, RRT, and death are not mutually exclusive.

Figure 2. Kaplan–Meier Estimate of Time to All-cause Death or IMV Through Day 29 for (A) All Participants or Those With (B) AKI, (C) CKD, or (D) ESKD at Baseline[a] (Full Analysis Set)



IMV, invasive mechanical ventilation; AKI, acute kidney injury; CKD, chronic kidney disease; ESKD, end-stage kidney disease; RDV, remdesivir; HR, hazard ratio; CI, confidence interval.
[a]Participants who did not initiate IMV or die by Day 29 were censored on their last study day or Day 29, whichever was earlier.
[b]Represents the number of participants remaining at the beginning of the interval.

Safety

— Overall, 193 (79%) participants had ≥1 TEAE, including 131 (80%) in the RDV group and 62 (78%) in the placebo group (**Table 2**)
  - The most frequently reported TEAE (n [%]) in the RDV group was hypotension (18 [11%]), whereas respiratory failure (10 [13%]) was most common in the placebo group

— Serious TEAEs were reported in 82 (50%) and 40 (50%) participants in the RDV and placebo groups, respectively; none were considered related to the study drug

— Overall, 9 (4%) participants had TEAEs leading to discontinuation (RDV, 8 [5%]; placebo, 1 [1%])

— Similar proportions of participants treated with RDV or placebo went on to have AKI Stage 2 or 3, RRT, or death, irrespective of baseline AKI status (RDV, 20/60 [33%]; placebo, 12/30 [40%]; *P* = 0.32) or CKD (RDV, 15/44 [34%]; placebo, 6/20 [30%]; *P* = 0.81; **Table 3**)

PK

— Baseline eGFR was highly correlated with increasing exposure of the renally eliminated metabolite, GS-441524; in those with kidney failure (5th percentile eGFR of 2.54 mL/min/1.73 m^2), median GS-441524 area under the concentration-time curve over the dosing interval (AUC_{tau}) increased up to 5-fold compared with participants with normal renal function[6]

— SBECD PK exposures (AUC_{tau}) increased up to 26-fold in participants with kidney failure compared with participants with normal renal function

— RDV plasma exposure was not affected by renal function[6]

Conclusions

— **There was no significant difference in all-cause death or IMV by Day 29 between the RDV and placebo groups; however, the study was underpowered for efficacy due to insufficient enrolment**

— **RDV dosed at 200 mg on Day 1 followed by 100 mg once daily up to Day 5 was generally safe and well tolerated**

— **No new safety signals were identified with increasing plasma exposures of the predominant metabolite (GS-441524) or the excipient SBECD**

— **No dose adjustment is recommended in patients who have an eGFR <30 mL/min/1.73 m^2, regardless of the need for dialysis**

References: 1. ERA-EDTA Council, ERACODA Working Group. *Nephrol Dial Transplant*. 2021;36(1):87-94. **2.** Tan BWL, et al. *EClinicalMedicine*. 2023;55:101724. **3.** Jager KJ, et al. *Kidney Int*. 2020;98(6):1540-1548. **4.** Veklury (remdesivir) injection, for intravenous use [package insert]. Gilead Sciences, Inc.; 2022. **5.** Gilead Sciences, Inc. Fact sheet for health care providers emergency use authorization (EUA) of Veklury (remdesivir). Accessed 15 February 2023. https://www.samc.com/assets/documents/covid19/nursing/remdesivir_eua-hcp-fact-sheet-8-2020.pdf. **6.** Humeniuk R, et al. Poster presented at: Conference on Retroviruses and Opportunistic Infections (CROI); 19-22 February 2023; Seattle, WA. Poster P514.

Acknowledgements: This study is funded by Gilead Sciences, Inc. Medical writing and editorial support were provided by Laura Watts, PhD, of Lumanity Communications Inc., and were funded by Gilead Sciences, Inc.

Disclosures: **JRS** received research funding, consulting fees, and lecture sponsorships from and served on advisory boards for Abbott, Boehringer Ingelheim, Gilead Sciences, Inc., GSK, Janssen-Cilag, Bristol Myers Squibb, ViiV Healthcare, Merck Sharp & Dohme, and Pfizer. **JDG** consulted for Gilead Sciences, Inc., Eli Lilly, GSK, and Karius; received research support or grants from Gilead Sciences, Inc., Eli Lilly, Regeneron, and Merck Sharp & Dohme (Biomedical Advanced Research and Development Authority); and received nonfinancial support from Adaptive Biotechnologies, Monogram Biosciences, and Labcorp (outside of this study). **JPT** is a consultant for Outset Medical and owns stock and/or stock options in Novo Nordisk A/S. **YK**, **JL**, **YZ**, **H Huang**, **RHH**, **AO**, and **RH** are stockholders and employees of Gilead Sciences, Inc. **H Hulter** received consulting fees from Gilead Sciences, Inc. **RLG** served as a consultant for AbbVie, Gilead Sciences, Inc., Johnson & Johnson, Roivant Pharmaceuticals, Roche Pharmaceuticals, GSK, and Eli Lilly; is a national coordinating PI for Johnson & Johnson; served on an academic steering committee for Roivant Pharmaceuticals; received a gift in kind to Baylor Scott & White Research Institute to facilitate NCT03383419 from Gilead Sciences, Inc.; owns de minimis stock in AbCellera Biologics; and served as a speaker for Pfizer, outside the scope of COVID-19. **DNF** served on an advisory board for Gilead Sciences, Inc., outside the scope of COVID-19; and served as a site PI for clinical trials with Gilead Sciences, Inc., Regeneron, and MetroBiotech, LLC. **RB** served on a scientific advisory board for AstraZeneca, Bayer, Boehringer Ingelheim, Merck Sharp & Dohme, and Mundipharma; and served as a speaker for AstraZeneca, Bayer, Merck Sharp & Dohme, Mundipharma, and Gilead Sciences, Inc., outside the scope of COVID-19. **MS** received research funding from Gilead Sciences, Inc., EMD Serono, AbbVie, Angion, and Otsuka; and served as a scientific advisory board member for Travere, Novartis, and Mallinckrodt. **KRT**, **FFS**, **CRL**, and **MJM** have nothing to disclose.

Poster presented at the 33rd European Congress of Clinical Microbiology and Infectious Diseases (ECCMID); 15-18 April 2023; Copenhagen, Denmark.