Safety of Remdesivir vs Placebo in Nonhospitalized Patients With COVID-19

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
800-445-3235

Brandon Webb,[1] Godson Oguchi,[2] Yessica Sachdeva,[3] John Cafardi,[4] Alan S. Go,[5] Kavita Juneja,[6] Santosh Davies,[6] Shuguang Chen,[6] Chen-Yu Wang,[6] Anu Osinusi,[6] Frank Duff,[6] Pablo Ryan,[7] Carlos Vaca,[8] Jorge Mera[9]

[1]Intermountain Medical Center, Murray, UT; [2]Midland Florida Clinical Research Center, Deland, FL; [3]Arizona Liver Health, Mesa, AZ; [4]The Christ Hospital, Cincinnati, OH; [5]Kaiser Permanente Northern California Division of Research, Oakland, CA; [6]Gilead Sciences, Inc., Foster City, CA; [7]Hospital Universitario Infanta Leonor, Madrid, Spain; [8]Nuren Medical & Research Center, Miami, FL; [9]Cherokee Nation Health Services, Tahlequah, OK

Introduction

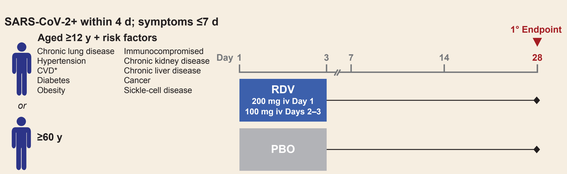
- Remdesivir (RDV), a potent nucleotide inhibitor of the severe acute respiratory syndrome–coronavirus-2 (SARS-CoV-2) RNA-dependent RNA polymerase, effectively reduces COVID-19-related hospitalization (87% reduction; hazard ratio 0.13; 95% confidence interval 0.03, 0.59)[1] and is approved by the FDA to treat nonhospitalized individuals at high risk for progression to severe disease[2]
- Risk of adverse outcomes from COVID-19 increases with age and comorbidities; early antiviral treatment may prevent disease progression for individuals at highest risk[3]
- Here we present additional safety data of RDV, focusing on renal, hepatic, and cardiac safety, and safety by select baseline demographic characteristics including treatment setting, from the PINETREE Study (GS-US-540-9012; NCT04501952)

Objective

- To report the safety of a 3-d RDV regimen in nonhospitalized individuals at risk for disease progression (aged >60 y or with underlying comorbid condition), analyzed by types of adverse events (AEs), age, sex at birth, and healthcare settings

Methods

PINETREE Study Design



*Cerebrovascular or cardiovascular disease (CVD). PBO, placebo.

- Phase 3, double-blind, PBO-controlled study including 64 sites in Denmark, Spain, UK, and USA
- 1:1 randomization stratified by age, location (USA vs outside USA), and outpatient vs skilled nursing facility
- Broad inclusion of participants at high risk for severe COVID-19
- Enrolled Sep 18, 2020–Apr 8, 2021
  - Halted for administrative reasons (single-infusion monoclonal antibody and vaccine availability; slowing enrollment)
  - 1264 participant goal enrollment; at halt: 584 randomized and 562 received ≥1 dose of study drug
- Primary safety endpoint: proportion of participants with treatment-emergent AEs
  - AEs were evaluated through Day 28 and lab abnormalities through Day 14

Results

Baseline Characteristics

	RDV n=279	PBO n=283	Total N=562
Mean age, y (SD)	50 (15)	51 (15)	50 (15)
Age, n (%)			
≥65 y	40 (14)	54 (19)	94 (17)
<18 y	3 (1)	5 (2)	8 (1)
Female sex at birth, n (%)	131 (47)	138 (49)	269 (48)
Mean BMI, kg/m^2 (SD)	31.2 (6.7)	30.8 (5.8)	31.0 (6.2)
Comorbidities, n (%)			
Diabetes mellitus	173 (62)	173 (61)	346 (62)
Obesity	154 (56)	156 (55)	310 (55)
Hypertension	138 (50)	130 (46)	268 (48)
Chronic lung disease	67 (24)	68 (24)	135 (24)
CVD	20 (7)	24 (9)	44 (8)
Cancer	12 (4)	18 (6)	30 (5)
Immunocompromised	14 (5)	9 (3)	23 (4)
Mild or moderate chronic kidney disease	7 (3)	11 (4)	18 (3)
Chronic liver disease	1 (<1)	1 (<1)	2 (<1)
Median duration of symptoms prior to 1st dose, d (IQR)	5 (3, 6)	5 (4, 6)	5 (3, 6)
Median duration from PCR confirmation to 1st dose, d (IQR)	2 (1, 3)	3 (1, 4)	2 (1, 4)
Mean SARS-CoV-2 RNA viral load, $\log_{10}$ copies/mL (SD)	5.95 (1.96)	5.92 (1.99)	5.94 (1.97)
Resident of skilled nursing facility, n (%)	8 (3)	7 (2)	15 (3)

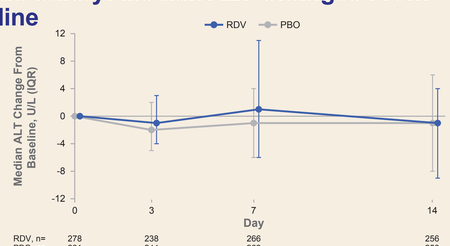
BMI, body mass index; IQR, interquartile range; PCR, polymerase chain reaction; SD, standard deviation.

Overall Safety Summary

Participants, n (%)	RDV n=279	PBO n=283
AEs	118 (42)	131 (46)
Grade ≥3 AEs	10 (4)	20 (7)
Study drug-related AEs	34 (12)	25 (9)
Serious AEs	5 (2)	19 (7)
AEs leading to premature study drug discontinuation	2 (1)	5 (2)
Deaths by Day 28	0	0
Grade ≥3 lab abnormalities	29 (11)	23 (8)
AEs experienced by ≥5% total population		
Nausea	30 (11)	21 (7)
Headache	16 (6)	17 (6)
Cough	10 (4)	18 (6)

- No participant experienced a serious AE or drug discontinuation due to hypersensitivity

Hepatic Safety: Median ALT Changes From Baseline

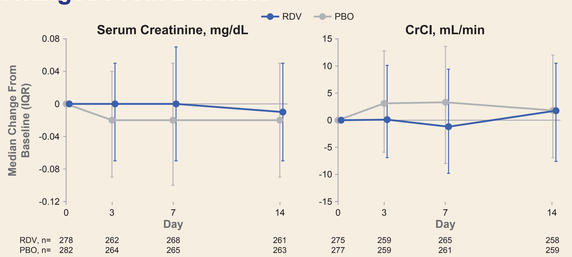


Hepatic AEs, n (%)	RDV n=279	PBO n=283
ALT increased	1 (<1)	3 (1)
AST increased	1 (<1)	1 (<1)

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

- There were no clinically relevant mean changes from baseline in other hepatic parameters including albumin, alkaline phosphatase, total bilirubin, and international normalized ratio
- Incidence of hepatic AEs was similar between RDV and PBO groups

Renal Safety: Median Serum Creatinine and CrCl Changes From Baseline



CrCl, creatinine clearance.

- No AEs related to nephrotoxicity were reported in RDV or PBO groups

Cardiac Adverse Events

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

- Incidence of cardiac-related AEs was similar between RDV and PBO groups
- All bradycardia AEs occurred in the PBO group

Safety Analyses by Age < vs ≥65 Years

	Age <65 y		Age ≥65 y	
Participants, n (%)	RDV n=239	PBO n=229	RDV n=40	PBO n=54
AEs	96 (40)	105 (46)	22 (55)	26 (48)
Serious AEs	3 (1)	12 (5)	2 (5)	7 (13)
Grade ≥3 lab abnormalities	20 (8)	18 (8)	9 (23)	5 (9)

Baseline Characteristics and Safety Analyses in Adolescents

		Age <18 y	
		RDV n=3	PBO n=5
Baseline Characteristics	Median age, y (IQR)	13 (13, 17)	16 (15, 16)
	Female sex at birth, n (%)	1 (33)	2 (40)
	White, n (%)	3 (100)	5 (100)
	Median BMI, kg/m^2 (IQR)	25.7 (21.1, 31.7)	28.7 (23.2, 29.1)
Safety Analysis, n (%)	AEs	0	1 (20)*
	Study drug-related AEs	0	0
	Serious AEs	0	0
	AEs leading to premature study drug discontinuation	0	0
	Hospitalization or death	0	0
	Grade ≥3 lab abnormalities	0	0

*Mild fatigue.

Safety Analyses by Sex at Birth

	Male		Female	
Participants, n (%)	RDV n=148	PBO n=145	RDV n=131	PBO n=138
AEs	56 (38)	68 (47)	62 (47)	63 (46)
Serious AEs	3 (2)	11 (8)	2 (2)	8 (6)
Grade ≥3 lab abnormalities	15 (10)	15 (10)	14 (11)	8 (6)

Safety Analyses by Race

	Asian		Black		White		Other	
Participants, n (%)	RDV n=6	PBO n=7	RDV n=20	PBO n=22	RDV n=228	PBO n=224	RDV n=25	PBO n=30
AEs	5 (83)	3 (43)	12 (60)	7 (32)	83 (36)	101 (45)	18 (72)	20 (67)
Serious AEs	0	0	1 (5)	2 (9)	2 (1)	14 (6)	2 (8)	3 (10)
Grade ≥3 lab abnormalities	1 (17)	1 (14)	2 (10)	2 (9)	23 (10)	20 (9)	3 (12)	0

Adverse Event Rates by Location of Administration

	Skilled Nursing Facility		Home Health Care		Outpatient Facility	
Participants, n (%)	RDV n=8	PBO n=7	RDV n=43	PBO n=46	RDV n=228	PBO n=230
AEs	3 (38)	4 (57)	21 (49)	22 (48)	94 (41)	105 (46)

- There was parity between RDV and PBO arms in terms of AE by location

Conclusions

- RDV treatment was safe and well tolerated in nonhospitalized individuals with risk factors for COVID-19 disease progression; no new safety signals were observed with RDV treatment
- The most commonly reported AEs in the RDV-treated arm were nausea and headache
- No organ-specific toxicities were noted with RDV treatment
- RDV treatment was safe irrespective of age, sex at birth, race, or location of administration

References: **1.** Gottlieb RL, et al, N Engl J Med 2022;386:305-15; **2.** Veklury [package insert]. Foster City, CA: Gilead Sciences, Inc., 1/22; **3.** Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. Zhonghua Liu Xing Bing Xue Za Zhi 2020;41:145-51.
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