Remdesivir Treatment for COVID-19 in Hospitalized Children: CARAVAN Interim Results

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

Amina Ahmed,[1] Pablo Rojo,[2] Allison Agwu,[3] David Kimberlin,[4] Jamie Deville,[5] Ana Mendez-Echevarria,[6] Paul K. Sue,[7] Luisa Galli,[8] Zongbo Shang,[9] Kavita Juneja,[9] Henry Hulter,[9] Charlotte Hedskog,[9] Kathryn Kersey,[9] William Muller,[10] Flor M. Munoz[11]

[1]Atrium Health Levine Children's Hospital, Charlotte, NC; [2]Hospital Universitario 12 de Octubre, Madrid, Spain; [3]Johns Hopkins Children's Center, Baltimore, MD; [4]University of Alabama at Birmingham; [5]Ronald Reagan UCLA Medical Center, Los Angeles, CA; [6]Hospital Universitario La Paz, Madrid, Spain; [7]The University of Texas Southwestern Medical Center, Dallas; [8]Azienda Ospedaliero-Universitaria Meyer, Firenze, Italy; [9]Gilead Sciences, Inc., Foster City, CA; [10]Ann & Robert H. Lurie Children's Hospital of Chicago, IL; [11]Texas Children's Hospital, Baylor College of Medicine, Houston, TX

Introduction

- COVID-19 is generally a mild disease in children, including infants; however, a small proportion develop severe disease requiring intensive care unit admission and prolonged ventilation[1]
- Remdesivir (RDV) has been shown to shorten time to recovery in hospitalized adults with COVID-19 and is approved for the treatment of COVID-19 in hospitalized individuals aged ≥12 y[2]
- The CARAVAN Study (Clinical Administration of RDV After COVID-19 Diagnosis in Children; NCT04431453) is being conducted to evaluate the safety, pharmacokinetics (PK), and clinical and virologic effects of RDV in infants and children
  - Results of an interim analysis in participants aged 28 d–<18 y and weighing ≥3 kg are presented here

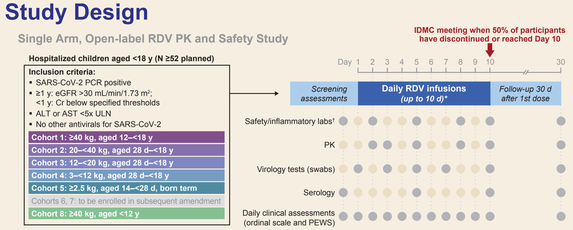
Objectives

- Primary: to evaluate the safety, tolerability, and PK of RDV in pediatric participants with COVID-19
- Secondary: to evaluate the antiviral activity and efficacy of RDV in pediatric participants with COVID-19

Methods

Study Design

Single Arm, Open-label RDV PK and Safety Study



*Cohorts 1 and 8: RDV 200-mg loading→100 mg qd; cohorts 2–4: RDV 5-mg/kg loading→2.5 mg/kg; treatment duration at investigators' clinical discretion and could be discontinued early based on clinical improvement; †Includes complete blood count, comprehensive metabolic panel, prothrombin/partial thromboplastin time, D-dimers, ferritin, quantitative C-reactive protein, erythrocyte sedimentation rate, procalcitonin, and interleukin 6. ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; eGFR, estimated glomerular filtration rate; IDMC, independent data monitoring committee; PCR, polymerase chain reaction; PEWS, Pediatric Early Warning Score; SARS-CoV-2, severe acute respiratory syndrome coronavirus; ULN, upper limit of normal.

- We report data on 53 children enrolled in the USA (n=41), Spain (n=9), Italy (n=2), and UK (n=1)
- Safety was assessed by adverse events (AEs) and laboratory tests; efficacy was assessed by clinical improvement on a 7-point ordinal scale, time to discharge, change in oxygenation use, and days to confirmed negative SARS-CoV-2 PCR (defined as 2 consecutive negative results)
  - Samples for SARS-CoV-2 testing could be nasopharyngeal, oropharyngeal, rectal or fecal, or endotracheal aspirates

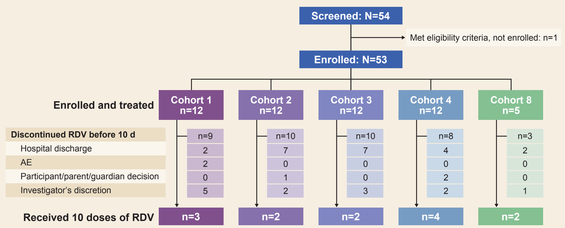
Ordinal Scale

Hospitalized	1	Death
	2	IMV or ECMO
	3	Noninvasive ventilation or high-flow O_2
	4	Low-flow O_2
	5	Room air, ongoing medical care (COVID-19 related or otherwise)
	6	Room air, no ongoing medical care (other than per-protocol RDV administration)
	7	Discharged

ECMO, extracorporeal membrane oxygenation; IMV, invasive mechanical ventilation.

Results

Participant Disposition and Study Drug Exposure



- The median number of study drug doses received was 5 for all cohorts

Demographics and Baseline Characteristics

Participants		Cohort 1 n=12	Cohort 2 n=12	Cohort 3 n=12	Cohort 4 n=12	Cohort 8 n=5	Total N=53
Mean age, y (range)		15 (12–17)	10 (4–16)	4 (2–7)	0.4 (0.1–0.9)	10 (8–11)	8 (0.1–17)
Median weight, kg (IQR)		84 (57, 107)	27 (25, 31)	15 (13, 18)	5 (4, 9)	73 (55, 80)	25 (13, 55)
Median BMI, kg/m² (IQR)		33.8 (21.6, 46.5)	17.8 (14.9, 20.2)	16.2 (15.6, 18.1)	16.3 (14.7, 20.0)	28 (27.2, 35.6)	18.8 (16, 24.8)
Female sex at birth, n (%)		8 (67)	7 (58)	5 (42)	7 (58)	3 (60)	30 (57)
Race, n (%)							
White		7 (58)	9 (82)	6 (60)	8 (80)	3 (75)	33 (70)
Black		5 (42)	2 (18)	4 (40)	2 (20)	1 (25)	14 (30)
Not specified*		0	1	2	2	1	6
Hispanic or Latino, n (%)		3 (27)	7 (58)	7 (58)	3 (25)	3 (60)	23 (44)
Clinical status per 7-point ordinal scale, n (%)	2	1 (8)	3 (25)	3 (25)	5 (42)	0	12 (23)
	3	6 (50)	4 (33)	3 (25)	3 (25)	2 (40)	18 (34)
	4	2 (17)	3 (25)	0	3 (25)	2 (40)	10 (19)
	5	3 (25)	2 (17)	6 (50)	0	1 (20)	12 (23)
	6	0	0	0	1 (8)	0	1 (2)
Median duration of symptoms, d (IQR)		7 (3, 11)	5 (3, 7)	3 (3, 7)	5 (2, 8)	5 (5, 7)	5 (2, 8)
Median duration of hospitalization, d (IQR)		1 (0, 3)	1 (1, 2)	2 (1, 3)	2 (1, 7)	1 (0, 1)	1 (1, 3)
Medical conditions, n (%)							
Obesity, n (%)†		7 (58)	2 (17)	3 (27)	3 (27)	4 (80)	19 (37)
Asthma		3 (25)	5 (42)	2 (17)	0	1 (20)	11 (21)
Cardiac disorders		2 (17)	3 (25)	2 (17)	4 (33)	0	11 (21)

*Excluded from percentage calculation; †Classified as having obesity if body mass index (BMI) was >95th percentile for age and sex on basis of World Health Organization standard growth charts (participants aged <24 mo) and Centers for Disease Control and Prevention growth charts (participants aged ≥24 mo); participants with missing BMI were excluded from percentage calculation. IQR, interquartile range.

Clinical Outcomes

Oxygenation Status

Participants Discharged Alive on or Prior to Day 10	Cohort 1 n=12	Cohort 2 n=12	Cohort 3 n=12	Cohort 4 n=12	Cohort 8 n=5	Total N=53
IMV, n	0	0	3	0	0	3
Median days (IQR)			3 (2, 10)			3 (2, 10)
High-flow O_2, n	1	6	3	3	1	14
Median days (IQR)	5 (5, 5)	6 (2, 6)	3 (1, 4)	2 (2, 5)	4 (4, 4)	4 (2, 5)
Low-flow O_2, n	2	6	2	3	2	15
Median days (IQR)	3 (1, 5)	2 (1, 2)	3 (2, 4)	1 (1, 6)	3 (2, 4)	2 (1, 4)

- Overall, 25% (3/12) of participants who were invasively ventilated at baseline (BL) were on IMV at the last available assessment

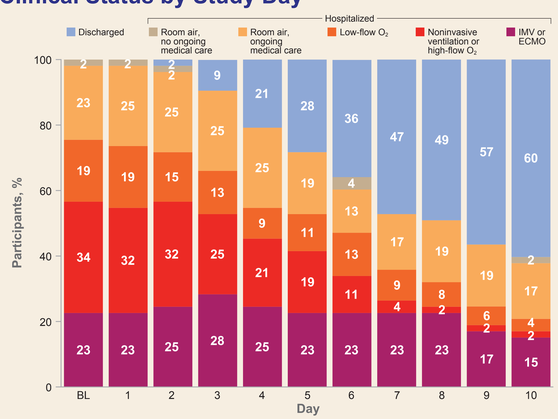
Hospitalization Status

Participants, n (%)	Cohort 1 n=12	Cohort 2 n=12	Cohort 3 n=12	Cohort 4 n=12	Cohort 8 n=5	Total N=53
Discharged by Day 10	3 (25)	9 (75)	11 (92)	6 (50)	3 (60)	32 (60)
Discharged by Day 30	9 (75)	10 (83)	12 (100)	9 (75)	4 (80)	44 (83)
Median duration of hospitalization from Day 1, d (IQR)	12 (8, 15)	7 (5, 9)	6 (4, 9)	7 (4, 17)	7 (4, 14)	7 (5, 12)

Viral Load

- Median times to 1st confirmed negative SARS-CoV-2 PCR were 5 and 7 d from nasal/oropharyngeal samples in Cohorts 2 and 3, respectively, and not estimable in the other cohorts
- Among participants with BL and post-BL sequencing data available, substitutions in the viral RNA-dependent RNA polymerase were observed in 1 of 23 participants; the substitutions observed have not been associated with resistance to RDV

Percentages of Participants at Each Ordinal Clinical Status by Study Day



- In all, 85% of participants showed clinical improvement (≥2-point increase from baseline) at their last assessment and the recovery rate (score of 6 or 7) was 83% at last assessment

Overall Safety

Participants, n (%)	Cohort 1 n=12	Cohort 2 n=12	Cohort 3 n=12	Cohort 4 n=12	Cohort 8 n=5	Total N=53
Any AE	11 (92)	7 (58)	9 (75)	7 (58)	4 (80)	38 (72)
Grade ≥3 AE	6 (50)	2 (17)	1 (8)	4 (33)	2 (40)	15 (28)
Treatment-related Grade ≥3 AE	3 (25)	0	0	0	0	3 (6)
SAE	5 (42)	2 (17)	0	3 (25)	1 (20)	11 (21)
Treatment-related SAE	0	0	0	0	0	0
Treatment discontinuation due to AE*	2 (17)	0	0	0	0	2 (4)
Treatment-emergent death	1 (8)	1 (8)	0	0	1 (20)	3 (6)
Laboratory abnormalities						
Grade 3	6 (50)	0	3 (25)	4 (36)	2 (40)	15 (29)
Grade 4	3 (25)	2 (17)	1 (8)	0	1 (20)	7 (13)

*Elevated ALT (n=1); hyperbilirubinemia, elevated ALT and AST, and increased serum sodium (all in 1 participant). SAE, serious AE.

- 11 participants had SAEs, none of which were considered treatment related; these SAEs were consistent with COVID-19 and/or the participants' underlying medical conditions
- 3 participants died; all had complex medical histories including multisystem organ failure and cardiorespiratory arrest, among others, which were not considered treatment related
- The most common Grade 3–4 laboratory abnormalities were decreased hemoglobin (n=9) and decreased eGFR (n=7)

Adverse Events in >5% of Total Participants

Participants, n (%)	Cohort 1 n=12	Cohort 2 n=12	Cohort 3 n=12	Cohort 4 n=12	Cohort 8 n=5	Total N=53
Constipation	3 (25)	1 (8)	1 (8)	1 (8)	3 (60)	9 (17)
Acute kidney injury	4 (33)	0	0	1 (8)	1 (20)	6 (11)
Hyperglycemia	1 (8)	1 (8)	1 (8)	2 (17)	0	5 (9)
Pyrexia	1 (8)	2 (17)	1 (8)	1 (8)	0	5 (9)
Increased ALT	2 (17)	0	0	1 (8)	1 (20)	4 (8)
Hypertension	2 (17)	1 (8)	0	0	1 (20)	4 (8)
Hypomagnesemia	0	1 (8)	0	1 (8)	2 (40)	4 (8)
Vomiting	1 (8)	1 (8)	1 (8)	0	1 (20)	4 (8)
Anemia	1 (8)	1 (8)	0	1 (8)	0	3 (6)
Nausea	1 (8)	0	0	1 (8)	1 (20)	3 (6)
Agitation	0	1 (8)	2 (17)	0	0	3 (6)
Bradycardia	0	2 (17)	0	1 (8)	0	3 (6)

Conclusions

- RDV was safe and well tolerated among children aged 28 d–<18 y treated for COVID-19
- Overall, no new safety trends for RDV were apparent
- A high proportion (85%) of participants had clinical improvement based on the clinical ordinal scale
- The study is ongoing, with enrollment of full-term and preterm neonates pending dose determination
- RDV provides a treatment option for pediatric patients with COVID-19

References: 1. Götzinger F, et al. Lancet Child Adolesc Health 2020;4:653-61; 2. Beigel JH, et al. N Engl J Med 2020;383:1813-26. **Acknowledgments:** We express our solidarity with those who are or have been ill with COVID-19, their families, and the healthcare workers on the frontlines of this pandemic. We extend our thanks and appreciation to the CARAVAN study participants, their families, the frontline healthcare workers caring for them, the study staff, and the study investigators. This study was funded by Gilead Sciences, Inc. Editing and production assistance were provided by BioScience Communications, New York, NY, funded by Gilead.