2696

Safety and Efficacy of Remdesivir in a Pediatric COVID-19 Population

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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
- Remdesivir (RDV) is approved for the treatment of COVID-19 in patients aged ≥12 y and weighing ≥40 kg requiring hospitalization (USA) or with pneumonia requiring hospitalization (conditional approval in European Union)
- Results from the 1st part of the Adaptive COVID-19 Treatment Trial (ACTT-1) showed that RDV was superior to placebo in shortening the time to recovery in adult participants hospitalized with COVID-19 who had evidence of lower respiratory tract infection[1]
- An evaluation of 77 pediatric participants who received RDV through compassionate use showed that most participants recovered and the rate of serious adverse events (AEs) was low[2]

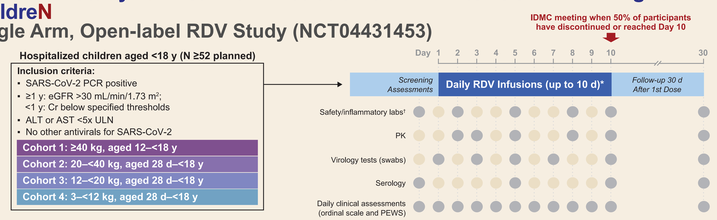
Objectives

- To evaluate the safety, tolerability, pharmacokinetics (PK), and efficacy of RDV in pediatric participants hospitalized with COVID-19

Methods

CARAVAN Study: Clinical Administration of RDV After COVID-19 DiAgnosis in ChildreN

Single Arm, Open-label RDV Study (NCT04431453)



*Cohort 1: RDV 200-mg loading–100 mg; cohorts 2–4: RDV 5-mg/kg loading–2.5 mg/kg; †treatment duration at investigators' clinical discretion; ‡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 27 children enrolled in the USA (n=20) and Spain (n=7)
  - Data cut: Dec 17, 2020

Endpoints

- Safety
- PK (not yet reported)
- Clinical status assessments:
  - Ordinal scale

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.

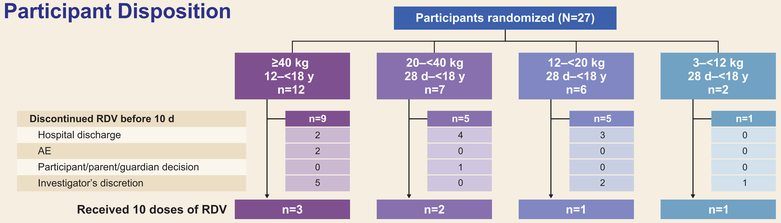
  - PEWS[3]

Behavior		Cardiovascular		Respiratory	
0	Playing appropriate	0	Within normal levels; pink; capillary refill 1–2 s	0	Within normal levels; no retractions
1	Sleeping	1	Tachycardia <20 above normal; pale; capillary refill 3 s	1	Respiratory rate >10 above normal; ≥30% FiO_2 or ≥3 L/min
2	Irritable	2	Tachycardia 20–29 above normal; gray; capillary refill 4 s	2	Respiratory rate >20 above normal and retractions; ≥40% FiO_2 or ≥6 L/min
3	Lethargic; confused; reduced response to pain	3	Tachycardia ≥30 above or bradycardia ≥10 below normal; gray; capillary refill 5 s	3	Respiratory rate ≥5 below normal with retractions and grunting; 50% FiO_2 or ≥8 L/min

FiO_2, fraction of inspired oxygen.

Results

Participant Disposition



- The overall median exposure to RDV was 5 doses (interquartile range [IQR] 5, 10)
- Most treatment durations <10 d were due to hospital discharge or investigator discretion based on improved clinical status

Demographics and Baseline Characteristics

			≥40 kg 12–<18 y n=12	20–<40 kg 28 d–<18 y n=7	12–<20 kg 28 d–<18 y n=6	3–<12 kg 28 d–<18 y n=2	Total n=27
Demographics	Mean age, y (range)		5 (12–17)	8 (4–16)	3 (2–5)	0.5 (0.2–0.9)	10 (0.2–17)
	Median weight, kg (IQR)		84 (56, 100)	27 (26, 34)	16 (14, 18)	7 (3, 10)	34 (18, 82)
	Female sex at birth, n (%)		8 (67)	4 (57)	3 (50)	0	15 (56)
	Race, n (%)	White	7 (58)	5 (83)	4 (67)	2 (100)	18 (67)
		Black	5 (42)	1 (17)	2 (33)	0	8 (30)
	Hispanic/Latinx ethnicity, n (%)		3 (27)	4 (57)	4 (67)	0	11 (41)
Baseline Characteristics	Clinical status, n (%)	IMV or ECMO	1 (8)	3 (43)	1 (17)	1 (50)	6 (22)
		Noninvasive ventilation or high-flow O_2	6 (50)	1 (14)	0	0	7 (26)
		Low-flow O_2	2 (17)	2 (29)	0	1 (50)	5 (19)
		Room air	3 (25)	1 (14)	5 (83)	0	9 (33)
	Median duration of symptoms, d (IQR)*		7 (3, 11)	4 (2, 7)	3 (2, 3)	N/A (0, 1)	3 (2, 8)
	Median duration of hospitalization, d (IQR)*		1 (0, 3)	1 (1, 3)	3 (3, 4)	N/A (2, 54)	2 (1, 3)
	Median lab values (IQR)	ALT, U/L	27 (22, 48)	16 (11, 47)	21 (17, 25)	23 (12, 33)	22 (15, 47)
		AST, U/L	61 (32, 82)	27 (22, 61)	29 (24, 39)	101 (53, 148)	45 (25, 67)
		SCr, mg/dL	0.70 (0.53, 0.85)	0.34 (0.27, 0.69)	0.23 (0.17, 0.26)	0.41 (0.30, 0.52)	0.51 (0.30, 0.70)
		eGFR, mL/min/1.73 m²	92.3 (78.5, 117.7)	122.7 (82.1, 177.4)	161.6 (134.5, 259.9)	N/A	111.4 (82.1, 144.1)
Medical History, n (%)	Asthma		3 (25)	1 (14)	1 (17)	0	5 (19)
	Malignancy		1 (8)	0	1 (17)	1 (50)	3 (11)
	Epilepsy		0	2 (29)	1 (17)	0	3 (11)
	Congenital cardiac disorders		0	0	0	2 (100)	2 (7)
	Sickle cell disease		1 (8)	0	0	0	1 (4)
	Chromosomal abnormalities (trisomy 21)		2 (17)	0	0	0	2 (7)
	Obesity		3 (25)	0	0	0	3 (11)
	Immune system disorders		2 (17)	2 (29)	0	0	4 (15)
	Multisystem inflammatory syndrome in children		0	2 (29)	0	0	2 (7)

*Before initiating RDV. N/A, not applicable; SCr, serum Cr.

Overall Safety

n (%)		≥40 kg 12–<18 y n=12	20–<40 kg 28 d–<18 y n=7	12–<20 kg 28 d–<18 y n=6	3–<12 kg 28 d–<18 y n=2	Total n=27
Any AE		11 (92)	2 (29)	6 (100)	2 (100)	21 (78)
AEs occurring in ≥3 participants overall	Acute kidney injury	4 (33)	0	0	1 (50)	5 (19)
	Constipation	3 (25)	1 (14)	0	0	4 (15)
	ALT increased	2 (17)	0	0	1 (50)	3 (11)
	Hyperglycemia	1 (8)	1 (14)	1 (17)	0	3 (11)
	Hypertension	2 (17)	1 (14)	0	0	3 (11)
	Pyrexia	1 (8)	1 (14)	0	1 (50)	3 (11)
Any Grade ≥3 AE		6 (50)	2 (29)	1 (17)	2 (100)	11 (41)
Treatment-related Grade ≥3 AE		3 (25)	0	0	0	3 (11)
Serious AE		5 (42)	2 (29)	0	2 (100)	9 (33)
Treatment-related serious AE		0	0	0	0	0
AE leading to discontinued treatment*		2 (17)	0	0	0	2 (7)
Death†		1 (8)	1 (14)	0	0	2 (7)

*Elevated ALT (n=1); hyperbilirubinemia, elevated ALT and AST, and increased serum sodium (all in 1 participant); †Immediate cause of death: respiratory failure secondary to removal of life support (n=1); multisystem failure (n=1); 1 additional death occurred >30 d after last dose.

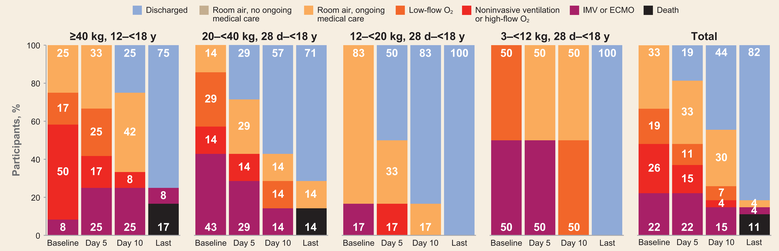
- Grade 3 or 4 lab abnormalities were reported in 14 participants (52%) overall
  - Grade 3 or 4 lab abnormalities in >1 participant were decreased hemoglobin (5/27 [19%]), decreased eGFR (4/24 [17%]), increased partial thromboplastin time (3/25 [12%]), increased prothrombin time (2/26 [8%]), glycosuria (2/24 [8%]), and hyperglycemia and increased Cr (2/27 [7%] each)
- No notable trends were observed in ALT and AST

Treatment-Emergent Serious AEs

Baseline Clinical Status	Age/Sex	Serious AE	Death	Discontinued Study Drug Due to AE
IMV	16 y/F	Multiple organ dysfunction syndrome	Y	Y (due to hyperbilirubinemia, increased ALT, AST, and blood sodium)
	16 y/F	Hypotension, cardiorespiratory arrest, and respiratory failure	Y	N
	9 y/F	Cardiogenic shock and cellulitis	N	N
	11 mo/M	Septic shock	N	N
High-flow O_2	17 y/F	Thrombosis and vomiting	N	N
	14 y/F	Respiratory distress, pyrexia, and acute kidney injury	N	N
	13 y/F	Septic shock and pulmonary hemorrhage	Y (>30 d post RDV)	N
Low-flow O_2	17 y/F	Empyema and negative pressure pulmonary edema	N	N
	55 d/M	Pyrexia	N	N

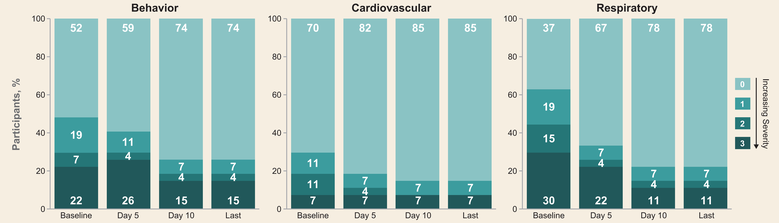
F, female; M, male, N, no; Y, yes.

Clinical Status by Study Day: Ordinal Scale



Last, last available assessment.

Clinical Status by Study Day: PEWS



Conclusions

- This preliminary assessment includes 27 pediatric participants aged 28 d–<18 y hospitalized with COVID-19 who were treated with RDV for up to 10 d
  - Median no. of RDV doses received was 5 (IQR 5, 10)
  - AEs and lab abnormalities observed were consistent with the complex medical status of the participants
  - 2 participants (8%) had AEs leading to discontinuation
- This study is ongoing, with 48 children enrolled as of Feb 10, 2021
  - Data on PK, viral load, and serology will be analyzed when follow-up is completed
  - Enrollment of full-term neonates and preterm infants from birth to age 56 d will be informed by PK data

References: 1. Beigel JH, et al. N Engl J Med 2020;383:1813-26; 2. Choto K, et al. IAS COVID-19 Conference 2020, abstr 11763; 3. Akre M, et al. Pediatrics 2010;125:763-9. **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 GS-US-540-5823 study participants, their partners and families, the frontline healthcare workers caring for them, the study staff, study investigators, Rita Humeniuk, and Cheryl Pikora. This study was funded by Gilead Sciences, Inc.