Hepatic Safety of Remdesivir Across Phase 3 Placebo-controlled COVID-19 Studies

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Key Findings

- Overall, hepatic adverse events (AEs) and hepatic laboratory abnormalities, including increased levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin, were reported in a similar proportion of participants with coronavirus disease 2019 (COVID-19) treated with remdesivir (RDV) and placebo
- A review of data from 26 participants with a history of chronic liver disease did not identify any safety concerns in this population

Conclusion

This review of three Phase 3 placebo-controlled studies demonstrated the hepatic safety of RDV and characterized the background incidence of liver function test abnormalities in patients with COVID-19

References: **1.** Veklury® (remdesivir) injection, for intravenous use [package insert]. Gilead Sciences, Inc.; 2023. **2.** Beigel JH, et al. *N Engl J Med*. 2020;383(19):1813-1826. **3.** Gottlieb RL, et al. *N Engl J Med*. 2022;386(4):305-315. **4.** Zhang C, et al. *Lancet Gastroenterol Hepatol*. 2020;5(5):428-430. **5.** Humeniuk R, et al. *Clin Transl Sci*. 2020;13(5):896-906. **6.** Regan S, et al. Presented at: American Society for Clinical Pharmacology & Therapeutics (ASCPT) Annual Meeting; March 22-24, 2023; Atlanta, GA, USA. Poster PI-007. **7.** Santos JR, et al. Presented at: 33rd European Congress of Clinical Microbiology and Infectious Diseases (ECCMID); April 15-18, 2023; Copenhagen, Denmark. Poster P2635.

Acknowledgments: This study was funded by Gilead Sciences, Inc. Medical writing and editorial support were provided by Kim Fuller, PhD, of Lumanity Communications Inc., and were funded by Gilead Sciences, Inc.

Disclosure: **LF**, **CB**, **JD**, **MA**, **N-QN**, **RHH**, **SD**, **SC**, **YZ**, and **OF** are stockholders and employees of Gilead Sciences, Inc.

Introduction

- RDV is a ribonucleic acid (RNA) polymerase inhibitor approved to treat COVID-19 in adult and pediatric patients[1]
- In Phase 3 studies, RDV has demonstrated efficacy in shortening the time to recovery in hospitalized COVID-19 patients[2] and in reducing the risk of COVID-19–related hospitalization or death in high-risk outpatients[3]
- COVID-19 can impact hepatic function, and elevated levels of ALT and AST enzymes have been reported in 14% to 53% of patients, with higher rates of dysfunction occurring in patients with severe disease[4]
- RDV is extensively metabolized in the liver,[1] and transient Grade 1 to 2 elevations in transaminase enzyme levels were observed in Phase 1 clinical trials of RDV in healthy participants[1,5]; therefore, subsequent studies have aimed to assess the hepatic safety of RDV
- Evaluations of the pharmacokinetics of RDV and its metabolites in healthy participants and those with hepatic impairment have revealed no clinically relevant area under the concentration curve (AUC) increases or safety concerns[6]
- Postmarketing exposure based on sales data for a 5-day regimen of RDV is estimated to be >4 million patients, with no safety signals of hepatotoxicity observed in the COVID-19 population to date (unpublished data)

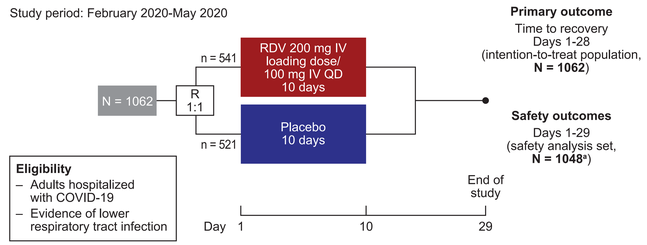
Objective

- To assess hepatic AEs and hepatic laboratory abnormalities across three Phase 3 studies of RDV in participants with COVID-19

Methods

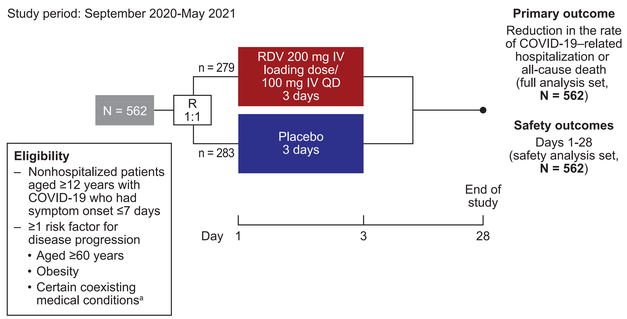
- Hepatic AEs and hepatic laboratory abnormalities were collected from 3 randomized, double-blind, Phase 3 placebo-controlled clinical studies in participants aged ≥12 years with COVID-19
  - The Adaptive COVID-19 Treatment Trial 1 (ACTT-1; CO-US-540-5776, ClinicalTrials.gov Identifier: NCT04280705) was an adaptive, multicenter study to assess the efficacy and safety of RDV in hospitalized adults[2] (**Figure 1**)
  - PINETREE (GS-US-540-9012; ClinicalTrials.gov Identifier: NCT04501952) was a multicenter study to evaluate the efficacy and safety of RDV in an outpatient setting in participants with confirmed COVID-19 who were at risk for disease progression[3] (**Figure 2**)
  - REDPINE (GS-US-540-5912; ClinicalTrials.gov Identifier: NCT04745351) was a parallel-group, multicenter study to evaluate the efficacy and safety of RDV in participants with severely reduced kidney function who were hospitalized for COVID-19[7] (**Figure 3**)
- In all 3 studies, RDV was administered intravenously at 200 mg on Day 1 and 100 mg daily thereafter
- Participants were excluded (or RDV was discontinued or held) if ALT and/or AST were >5 × upper limit of normal (ULN; all 3 studies) or ALT was >3 × ULN and total bilirubin was >2 × ULN (additional PINETREE discontinuation only)
- AEs were also assessed in participants with a history of chronic liver disease
  - For ACTT-1, participants with a history of chronic liver disease were defined by the investigator as per the case report form
  - For PINETREE and REDPINE, participants with chronic liver disease were identified via their baseline medical history for any chronic liver disease (eg, hepatic cirrhosis or nonalcoholic steatohepatitis)

Figure 1. ACTT-1 Study Design[2]



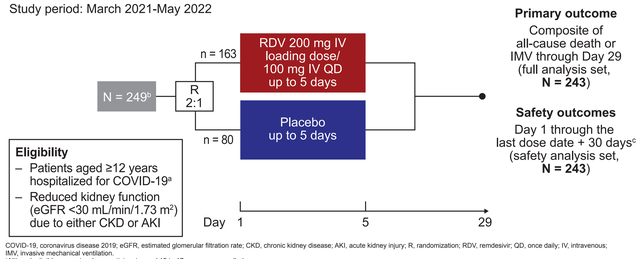
ACTT-1, Adaptive COVID-19 Treatment Trial 1; COVID-19, coronavirus disease 2019; R, randomization; RDV, remdesivir; QD, once daily; IV, intravenous.
[a]The safety population for ACTT-1 included all participants who received any study treatment infusion, even if the infusion was halted or slowed, analyzed as treated, and was labeled as the "as-treated population."

Figure 2. PINETREE Study Design[3]



COVID-19, coronavirus disease 2019; R, randomization; RDV, remdesivir; QD, once daily; IV, intravenous.
[a]Other risk factors included hypertension, cardiovascular or cerebrovascular disease, diabetes mellitus, immune compromise, chronic mild or moderate kidney disease, chronic liver disease, chronic lung disease, current cancer, or sickle cell disease.

Figure 3. REDPINE Study Design[7]



COVID-19, coronavirus disease 2019; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; AKI, acute kidney injury; R, randomization; RDV, remdesivir; QD, once daily; IV, intravenous; IMV, invasive mechanical ventilation.
[a]Although eligible per protocol, no participants aged 12 to 17 years were enrolled.
[b]Of the 249 randomized participants, 6 were not treated.
[c]If a participant was discharged prior to Day 29, a phone follow-up was completed on Days 29 and 60.

Results

Hepatic AEs

- Hepatic AEs were reported in a similar proportion of participants for each treatment group in ACTT-1 (RDV, 71 [13.3%]; placebo, 80 [15.5%]) and PINETREE (RDV, 1 [0.4%]; placebo, 4 [1.4%]; **Table 1**)
- In REDPINE, 12 (7.4%) and 2 (2.5%) participants in the RDV and placebo groups, respectively, reported hepatic AEs, most of which were increased levels of ALT- or AST-related terms (**Table 1**)

Hepatic Laboratory Abnormalities

- In ACTT-1, increased levels of ALT, AST, and bilirubin of any grade were each reported in lower proportions of participants in the RDV group compared with the placebo group (RDV vs placebo: ALT, 32.4% vs 42.9%; AST, 33.2% vs 43.9%; bilirubin, 10.3% vs 13.3%; **Table 2**)
- Increased levels of ALT, AST, and bilirubin of any grade were each reported in a similar proportion of participants in the RDV group compared with the placebo group in PINETREE (RDV vs placebo: ALT, 12.5% vs 13.5%; AST, 7.3% vs 6.5%; bilirubin, 1.1% vs 1.8%) and REDPINE (RDV vs placebo: ALT, 17.2% vs 20.5%; AST, 22.4% vs 19.2%; bilirubin, 5.1% vs 5.1%; **Table 2**)
- The majority of graded hepatic laboratory abnormalities reported for increased levels of ALT and AST were Grade 1 or 2 across the studies (**Table 2**)

Participants With Chronic Liver Disease

- Among participants who received RDV in the 3 studies, 26 participants with a history of chronic liver disease were identified (14 participants in ACTT-1, 1 participant in PINETREE, and 11 participants in REDPINE)
- Review of the AEs reported for these 26 participants identified no safety concerns in this population

Table 1. Treatment-emergent Hepatic AEs in >1 Participant by Preferred Term and Treatment Group in ACTT-1, PINETREE, and REDPINE

Number of participants experiencing event, n (%)	ACTT-1[a]		PINETREE		REDPINE	
	RDV (N = 532)	Placebo (N = 516)	RDV (N = 279)	Placebo (N = 283)	RDV (N = 163)	Placebo (N = 80)
Any treatment-emergent hepatic AE	71 (13.3)	80 (15.5)	1 (0.4)	4 (1.4)	12 (7.4)	2 (2.5)
Preferred term						
ALT increased	12 (2.3)	24 (4.7)	1 (0.4)	3 (1.1)	4 (2.5)	1 (1.3)
AST increased	18 (3.4)	33 (6.4)	1 (0.4)	1 (0.4)	4 (2.5)	1 (1.3)
Prothrombin time prolonged	26 (4.9)	8 (1.6)	0	0	0	0
Blood bilirubin increased	9 (1.7)	16 (3.1)	0	0	0	0
Transaminases abnormal	7 (1.3)	11 (2.1)	0	0	0	1 (1.3)
Liver function test abnormal	3 (0.6)	3 (0.6)	0	0	1 (0.6)	0
Hyperbilirubinemia	2 (0.4)	3 (0.6)	0	0	2 (1.2)	0
International normalized ratio increased	3 (0.6)	1 (0.2)	0	1 (0.4)	0	0
Liver injury	2 (0.4)	0	0	0	0	0
Blood alkaline phosphatase increased	1 (0.2)	0	0	0	1 (0.6)	0

AE, adverse event; ACTT-1, Adaptive COVID-19 Treatment Trial 1; n, number of participants who reported event; RDV, remdesivir; N, number of participants in the safety analysis set; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a]In ACTT-1, per protocol, all Grade 3 and 4 AEs and any Grade ≥2 suspected drug-related hypersensitivity reactions were reported as AEs. Data for other Grade 1 and 2 AEs were not collected.

Table 2. Treatment-emergent Hepatic Laboratory Abnormalities[a] by Treatment Group in ACTT-1, PINETREE, and REDPINE Participants

Number of participants experiencing event, n (%)	ACTT-1		PINETREE		REDPINE	
	RDV (N = 532)	Placebo (N = 516)	RDV (N = 279)	Placebo (N = 283)	RDV (N = 163)	Placebo (N = 80)
Participants with measured ALT	516	503	273	275	157	78
Any grade ALT increased	167 (32.4)	216 (42.9)	34 (12.5)	37 (13.5)	27 (17.2)	16 (20.5)
Grade 1	103 (20.0)	108 (21.5)	29 (10.6)	27 (9.8)	7 (4.5)	8 (10.3)
Grade 2	48 (9.3)	77 (15.3)	4 (1.5)	8 (2.9)	12 (7.6)	3 (3.8)
Grade 3	11 (2.1)	22 (4.4)	1 (0.4)	2 (0.7)	5 (3.2)	5 (6.4)
Grade 4	5 (1.0)	9 (1.8)	0	0	3 (1.9)	0
Participants with measured AST	503	492	274	275	156	78
Any grade AST increased	167 (33.2)	216 (43.9)	20 (7.3)	18 (6.5)	35 (22.4)	15 (19.2)
Grade 1	83 (16.5)	102 (20.7)	16 (5.8)	12 (4.4)	21 (13.5)	7 (9.0)
Grade 2	55 (10.9)	74 (15.0)	3 (1.1)	5 (1.8)	5 (3.2)	5 (6.4)
Grade 3	24 (4.8)	30 (6.1)	1 (0.4)	1 (0.4)	4 (2.6)	3 (3.8)
Grade 4	5 (1.0)	10 (2.0)	0	0	5 (3.2)	0
Participants with measured bilirubin	513	498	274	275	157	78
Any grade hyperbilirubinemia	53 (10.3)	66 (13.3)	3 (1.1)	5 (1.8)	8 (5.1)	4 (5.1)
Grade 1	26 (5.1)	22 (4.4)	3 (1.1)	5 (1.8)	3 (1.9)	1 (1.3)
Grade 2	15 (2.9)	21 (4.2)	0	0	1 (0.6)	1 (1.3)
Grade 3	4 (0.8)	16 (3.2)	0	0	2 (1.3)	1 (1.3)
Grade 4	8 (1.6)	7 (1.4)	0	0	2 (1.3)	1 (1.3)

ACTT-1, Adaptive COVID-19 Treatment Trial 1; n, number of participants reporting event; RDV, remdesivir; N, number of participants in the safety analysis set; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a]Severity grades were defined by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1, July 2017.

Limitations

- There were limited data from participants infected with more recently circulating SARS-CoV-2 variants, such as Omicron and its subvariants
- It is possible that protocol discontinuation criteria for hepatic laboratory abnormalities reduced the observed rate of hepatic AEs and laboratory abnormalities

Poster presented at IDWeek; October 11-15, 2023; Boston, MA, USA.