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Thorough QT/QTc Clinical Study to Evaluate the Effect of Remdesivir on Cardiac Repolarization in Healthy Participants

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Conclusions

- Pharmacokinetic exposures of remdesivir and its metabolites after a single 600-mg dose were approximately dose proportional compared to a previous study in which 200-mg remdesivir was administered to healthy participants
- A single 600-mg dose of remdesivir was generally safe and well tolerated, with no reported deaths, serious adverse events, or adverse events associated with QT prolongation
- When administered to healthy participants, the supratherapeutic 600-mg dose of remdesivir did not affect the QT interval corrected for heart rate compared to placebo

Plain Language Summary

- Remdesivir is an antiviral drug that is approved for the treatment of COVID-19
- Certain drugs can prolong the QT interval, which may result in the development of cardiac arrhythmias
- This Phase 1 study in healthy adults explored QT interval prolongation after a supratherapeutic dose of remdesivir as part of standard practice in drug development[1]
- A supratherapeutic dose is a dose that is higher than that which is given to patients and lets us find out what will happen if drug levels are higher than we normally expect
- In this study, a supratherapeutic 600-mg dose of remdesivir did not cause QT interval prolongation
- Therefore, treatment with remdesivir has no potential for causing cardiac arrhythmias

Introduction

- Remdesivir (RDV) is an intravenous (IV) nucleotide prodrug approved for COVID-19 treatment[2]
- Prolongation of the QT interval (ie, delay in cardiac repolarization) associated with drug administration may result in the development of cardiac arrhythmias[3]
- A previous Phase 1 study (GS-US-399-1954) found that neither RDV nor its metabolites (GS-704277 and GS-441524) caused QT interval prolongation at therapeutic concentrations in healthy adults
- Patients receiving the clinical regimen of RDV (200-mg loading dose and 100-mg maintenance doses once daily for up to 10 days) may experience increased pharmacokinetic (PK) exposures due to factors related to COVID-19 disease, organ impairment, or drug-drug interactions
- A supratherapeutic dose of RDV administered to healthy participants was selected to assess the potential of RDV to prolong the QT interval over the possible range of clinical exposures
  - This dose was informed by the range of PK exposures of RDV and its metabolites observed in patients with COVID-19 following administration of the clinical regimen, drug-drug interaction potential, and preliminary results of the Phase 1 renal and hepatic impairment studies of RDV in participants without COVID-19

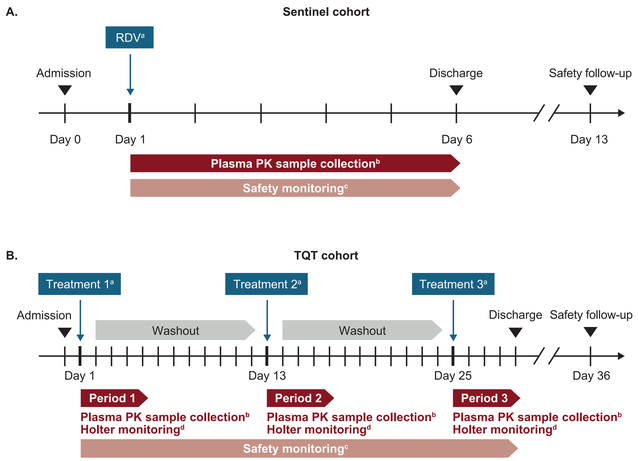
Objective

- To evaluate the safety, tolerability, PK, and change in QTc (ie, the QT interval corrected for heart rate) when a single supratherapeutic 600-mg dose of IV RDV was administered to healthy participants

Methods

- This was a Phase 1, partially blinded, randomized, placebo- and positive-controlled trial that included 2 cohorts of healthy participants aged 18 to 55 years
- The study design and schedule of study procedures are summarized in **Figure 1**

Figure 1. Study Design



[a]Study treatments: IV infusion of 600-mg RDV over 30 minutes, IV infusion of placebo over 30 minutes (TQT cohort only), and 400-mg MOXI tablet (TQT cohort only).
[b]Intensive PK sampling: sentinel cohort, Day 1 for up to 120 hours post dose; TQT cohort, Days 1, 13, and 25 for up to 96 hours post dose.
[c]12-lead safety ECGs for the sentinel cohort were collected on Days 0, 1, 2, 4, and 6 (discharge); on Day 1, ECGs were assessed at predose (≤5 minutes before dose) and 2 hours post dose. 12-lead safety ECGs for the TQT cohort were collected on Days 0, 1, 13, 25, and 29 (discharge); on Days 1, 13, and 25, ECGs were assessed at predose (≤5 minutes before dose) and 2 hours post dose.
[d]Holter monitoring was performed on Days 1, 13, and 25 for each predetermined time point (n3 replicates within 5 minutes for each time point). Predose baseline time points: 1.5, 1, and 0.5 hours prior to the start of treatment. Postdose time points: 15 minutes (middle of infusion), 30 minutes (end of infusion), 45 minutes, 1 hour, 1 hour 20 minutes, 1 hour 40 minutes, and 2 hours, 2.5 hours, 3 hours, 4 hours, 6 hours, 8 hours, 12 hours, and 24 hours following the start of treatment.
ECG, electrocardiogram; IV, intravenous; MOXI, moxifloxacin; PK, pharmacokinetic; RDV, remdesivir; TQT, thorough QT.

Sentinel Cohort

- Eligible participants (n = 6) received a single 600-mg RDV infusion on Day 1
- This dose was selected to cover potential increases in PK exposures after administration of the clinical RDV dosing regimen due to factors related to COVID-19 disease, organ impairment, or drug-drug interactions
- The primary endpoints were incidences of adverse events (AEs) and laboratory abnormalities and plasma PK parameters of RDV and its metabolites (GS-704277 and GS-441524)
- Upon review of all safety and available PK data, the 600-mg RDV dose was found to be well tolerated and was selected as the supratherapeutic dose for the thorough QT (TQT) cohort

TQT Cohort

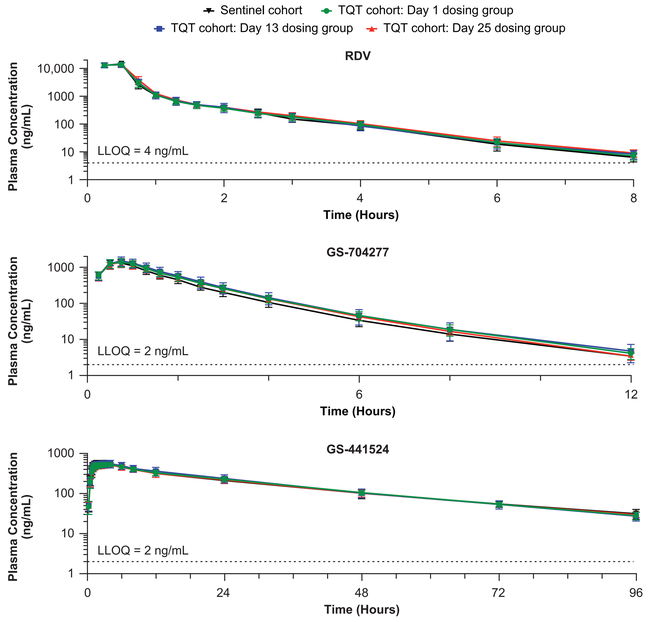
- Eligible participants (N = 55) were randomized 1:1:1 to 1 of 3 treatment arms in a 3-period, single-dose, crossover study design
- Treatment arms: 600-mg RDV, placebo-to-match RDV (placebo), and 400-mg moxifloxacin (MOXI; positive control)
- Primary endpoint: difference between baseline-adjusted QTcF (ie, the QT interval corrected for heart rate using the Fridericia formula) in the RDV treatment period and the baseline-adjusted QTcF in the placebo period at each postdose time point
- Plasma PK parameters, AEs, and laboratory abnormalities were also assessed
- Least squares means and CIs were based on a mixed-effects model, which included treatment sequence, period, treatment, nominal time point, treatment by time point interaction, and predose baseline QTcF as fixed effects and participant within sequence as a random effect
  - The dependent variable in the model was the change from predose baseline in QTcF
  - Assay sensitivity was based on time points at 1, 2, and 3 hours post dose

Results

PK Evaluation

- Following administration of 600-mg RDV, mean plasma concentrations and PK parameters of RDV, GS-704277, and GS-441524 were similar between cohorts, indicating sufficient drug washout from the previous period within the TQT cohort (**Figure 2**; **Table 1**)
- Mean plasma concentrations and PK parameters of RDV and its metabolites after a single 600-mg dose were approximately dose proportional compared to a previous Phase 1 study in which 200-mg RDV was administered to healthy participants

Figure 2. Mean (SD) Plasma Concentrations of RDV and Its Metabolites Over Time



LLOQ, lower limit of quantitation; RDV, remdesivir; TQT, thorough QT.

Table 1. Plasma PK Parameters for RDV and Its Metabolites Following a Single 600-mg Dose of RDV

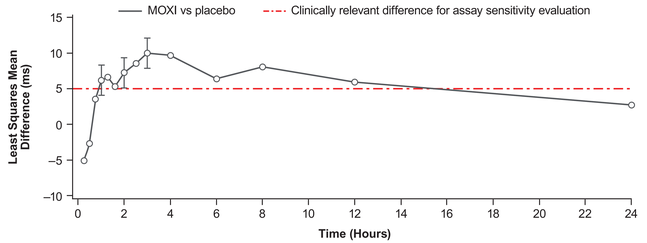
PK Parameter	Sentinel Cohort (n = 6)			TQT Cohort (n = 54[a])		
	RDV	GS-704277	GS-441524	RDV	GS-704277	GS-441524
C_{max}, ng/mL, mean (%CV)	14,500 (12.4)	1400 (20.5)	606 (12.2)	14,000 (16.3)	1400 (25.6)	557 (17.2)
T_{max}, hours, median (IQR)	0.50 (0.25-0.50)	0.75 (0.50-0.75)	1.84 (1.67-3.00)	0.50 (0.50-0.50)	0.75 (0.75-0.75)	3.00 (1.67-4.00)
T_{last}, hours, median (IQR)	8.00 (8.00-8.00)	12.00 (8.00-12.00)	120.00 (120.00-120.00)	8.00 (8.00-8.00)	12.00 (12.00-12.00)	96.00 (96.00-96.00)
AUC_{last}, h•ng/mL, mean (%CV)	8290 (9.4)	2320 (19.5)	15,400 (12.2)	8500 (15.2)	2630 (23.9)	15,000 (14.8)
AUC_{inf}, h•ng/mL, mean (%CV)	8300 (9.4)	2330 (19.5)	15,900 (12.2)	8510 (15.2)	2640 (23.8)	16,100 (14.3)
$t_{1/2}$, hours, median (IQR)	0.99 (0.96-1.05)	1.71 (1.25-1.73)	24.6 (23.7-26.0)	1.03 (0.953-1.09)	1.69 (1.52-1.81)	24.6 (22.5-28.6)

[a]The TQT cohort enrolled 55 participants; 54 participants received RDV.
AUC_{inf}, area under the concentration-time curve extrapolated to infinite time; AUC_{last}, area under the concentration-time curve from dosing to last measurable concentration; C_{max}, maximum observed concentration; %CV, percentage coefficient of variance; PK, pharmacokinetic; RDV, remdesivir; $t_{1/2}$, half-life; T_{last}, time at which last quantifiable concentration was observed; T_{max}, time at which maximum concentration was observed; TQT, thorough QT.

Pharmacodynamic Evaluation

- In the TQT cohort, the estimated lower CI bounds for the least squares mean difference in baseline-adjusted QTcF between MOXI and placebo were >5 milliseconds at 2 of the 3 prespecified postdose time points (around the time of maximum observed concentration [T_{max}] for MOXI), thereby establishing assay sensitivity (**Figure 3**)

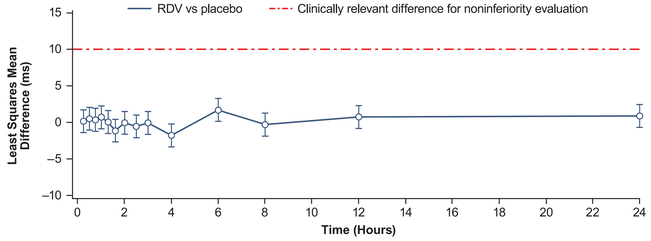
Figure 3. Least Squares Mean Difference in Baseline-adjusted QTcF Between MOXI and Placebo for Assay Sensitivity Evaluation (TQT Cohort)



Error bars represent 96.67% CIs.
MOXI, moxifloxacin; QTcF, QT interval corrected for heart rate using the Fridericia formula; TQT, thorough QT.

- In the TQT cohort, the estimated upper bounds of the 90% CI for the least squares mean difference between the supratherapeutic dose of RDV and placebo were <10 milliseconds at all postdose time points, indicating that RDV had no clinically relevant QTcF prolongation effect (**Figure 4**)

Figure 4. Least Squares Mean Difference in Baseline-adjusted QTcF Between RDV and Placebo for Noninferiority Evaluation (TQT Cohort)



Error bars represent 90% CIs.
QTcF, QT interval corrected for heart rate using the Fridericia formula; RDV, remdesivir; TQT, thorough QT.

Safety Evaluation

- Most AEs were Grade 1 or 2 in severity; no serious AEs were reported (**Table 2**)
  - The most common AEs following 600-mg RDV administration were nausea and/or vomiting (33/60 [55%] participants)
- One participant (2%) receiving 600-mg RDV in the TQT cohort had a Grade 3 AE (transaminase increased)
  - There were no other Grade ≥3 AEs, tachycardias, or heart rate AEs

Table 2. Treatment-emergent AEs and Grade ≥3 Treatment-emergent Laboratory Abnormalities

n (%)	Sentinel Cohort	TQT Cohort		
	RDV (n = 6)	RDV (n = 54)	Placebo (n = 53)	MOXI (n = 54)
AE	5 (83)	31 (57)	10 (19)	7 (13)
Grade ≥3	0	1 (2)	0	0
AE related to study drug	5 (83)	30 (56)	6 (11)	5 (9)
Grade ≥3	0	1 (2)	0	0
Laboratory abnormality, Grade ≥3	0	1 (2)	1 (2)	0

AEs were coded using the *Medical Dictionary for Regulatory Activities* Version 26.1. Severity grades were defined using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Corrected Version 2.1 (July 2017).
AE, adverse event; MOXI, moxifloxacin; RDV, remdesivir; TQT, thorough QT.

References: **1.** US Food and Drug Administration. Guidance document: E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. Accessed August 15, 2024. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e14-clinical-evaluation-qtqtc-interval-prolongation-and-proarrhythmic-potential-non-antiarrhythmic-0. **2.** VEKLURY® (remdesivir) for injection, for intravenous use [package insert]. Gilead Sciences, Inc.; 2024. **3.** Tisdale JE, et al. *Circulation*. 2020;142:e214-33.

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Disclosure: **OA**, **MA**, **RHH**, **SD**, **AK**, **RD**, and **AK** are employees of and may own stock or stock options in Gilead Sciences, Inc.