A Phase 1, Ascending-Dose Study to Assess the Potential Effects of Trofinetide on QTc Interval, Safety and Tolerability, and Pharmacokinetics in Healthy Adults

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INTRODUCTION

- Trofinetide is an investigational drug developed for the treatment of Rett syndrome (RTT), a debilitating genetic neurodevelopmental disorder for which there is no approved treatment
- In the phase 3 LAVENDER study (NCT04181723) in which trofinetide was administered orally or via gastrostomy tube twice daily using weight-based dosing (up to 12 g for participants weighing >50 kg) to achieve the target exposure (area under the concentration-time curve from 0 to 12 at steady state [$AUC_{0–12,ss}$] = 800–1200 µg•h/mL), statistically significant improvements were demonstrated with trofinetide over placebo in caregiver- and clinician-rated efficacy measures, and trofinetide was well tolerated in females with RTT 5–20 years of age[1]
- In nonclinical and clinical studies in healthy participants, trofinetide doses associated with exposures similar to or higher than those anticipated in phase 3 studies were not associated with clinically significant changes in QT/QTc interval or other electrocardiogram (ECG) parameters (data on file)
- There is evidence of an increased risk of QTc prolongation in individuals with RTT,[2–4] which may manifest over time[5]; thus, it is important to assess the potential impact of trofinetide on QTc prolongation at doses that target the therapeutic exposure range (12 g) and at supratherapeutic doses associated with exposures beyond the target range (18 g and 24 g)

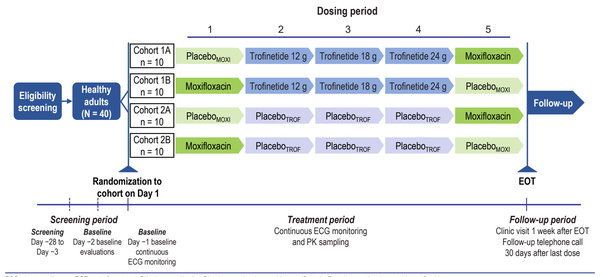
OBJECTIVES

- To provide a formal evaluation of the safety and tolerability, including effects on the QTc interval using Fridericia's correction method (QTcF) and other ECG parameters and the pharmacokinetics (PK) of single therapeutic (12 g) and supratherapeutic doses (18 g and 24 g) of trofinetide in healthy adults
  - The QTcF shows the best-rate correction, prediction of all-cause mortality, and estimates of potentially dangerous QT prolongation compared with Bazett's QT correction formula[6]

METHODS

- This was a phase 1, randomized, double-blind, placebo-controlled, ascending-dose, nested crossover study that was conducted at a single study center and consisted of a screening period, treatment period, and safety follow-up period with an overall maximum duration of 14 weeks
- Eligible participants were 18–45 years of age, weighed >50 kg and <100 kg at screening, did not have a history of acute or chronic cardiac and/or cardiovascular disease or surgery, and did not have cardiac conduction abnormalities at screening
- A total of 40 healthy adult participants were enrolled and randomized in a 1:1:1:1 ratio to cohorts 1A, 1B, 2A, and 2B for the treatment period, during which each participant received 1 treatment in each of the 5 dosing periods (Figure 1)
  - During Dosing Periods 2–4, each participant received single therapeutic (12 g [60 mL]) and supratherapeutic (18 g [90 mL] and 24 g [120 mL]) orally administered doses of trofinetide (provided as a 200-mg/mL solution) or matching placebo, and in Dosing Periods 1 and 5, each participant received oral doses of moxifloxacin 400 mg (positive control for assay sensitivity) or matching placebo
  - A minimum of 4 days of washout was required between all administrations of study drug; continuous ECG monitoring was conducted from predose to 24 hours postdose (Dosing Periods 2–4), or predose to 6 hours postdose (Dosing Periods 1 and 5); PK blood sampling was conducted predose and for 48 hours postdose (Dosing Periods 2–4 only)

Figure 1. Schematic of study design



ECG, electrocardiogram; EOT, end of treatment; PK, pharmacokinetics; Placebo$_{MOXI}$, placebo-matching moxifloxacin; Placebo$_{TROF}$, placebo-matching trofinetide

- The primary analysis utilized concentration-QTc (C-QTc) modeling to assess the QTc prolongation risk and included change from time-matched baseline in QTcF (ΔQTcF) as the dependent variable, with time, treatment, and period as fixed effects, and the corresponding time-matched blood concentrations and predose QTcF as covariates, with subject and subject-by-period interaction as the random effects
- The primary endpoints were the evaluation of safety and tolerability (treatment-emergent adverse events [TEAEs], clinically significant findings on ECG parameters, vital signs, laboratory tests, and physical examination) and the relationship between ΔQTcF and trofinetide blood concentrations (C-ΔQTcF) and placebo-adjusted ΔQTcF (ΔΔQTcF) and trofinetide blood concentrations (C-ΔΔQTcF) using linear mixed-effects modeling
  - The mixed-effects model was used to estimate the population mean ΔΔQTcF and its corresponding 2-sided 90% confidence interval (CI) at the mean maximum observed drug concentration (C_{max}) for each trofinetide dose
  - If the upper bounds of the 2-sided 90% CI of the predicted mean ΔΔQTcF was <10 ms (the threshold of concern for cardiac repolarization) at the largest observed mean C_{max}, then it was concluded that trofinetide did not have a clinically significant effect on QT prolongation
- Secondary and other endpoints included change from time-matched baseline in ECG parameters (heart rate, PR interval, QRS interval, QTcF interval, and ECG morphological patterns) and trofinetide PK in blood
  - Clinically meaningful changes in ECG parameters were defined using the following criteria: heart rate <50 bpm and ≥25% decrease or >100 bpm and ≥25% increase from baseline; PR interval >200 ms and ≥25% increase from baseline; QRS interval >120 ms and ≥25% increase from baseline; QTcF interval ≤450, >450 to ≤480, >480 to ≤500, and >500 ms; ≤30, >30 to ≤60, and >60 ms change from baseline

RESULTS

Demographics and Baseline Characteristics

- Of the 40 randomized participants, 15 participants (37.5%) were White and 25 participants (62.5%) were Black or African American (62.5%); 35 participants (87.5%) completed the study
- Mean age at screening was 33.9 years, and the majority of participants were male (60%)

Pharmacokinetics

- The PK profiles of trofinetide were qualitatively similar across dose groups (Table 1 and Figure 2)
  - Trofinetide was rapidly absorbed into the circulation (median time to maximum observed drug concentration [T_{max}] approximately 2.5–3 hours), with an initial rapid decline followed by a relatively slow elimination phase; the apparent terminal elimination half-life ($t_{½}$) representing the rapid decline is considered the effective $t_{½}$, as the contribution of the terminal phase is negligible
  - At supratherapeutic doses, the increase in exposure to trofinetide was slightly less than dose-proportional

Table 1. Mean (SD) PK parameters in blood for trofinetide following a single dose of trofinetide (PK analysis set)

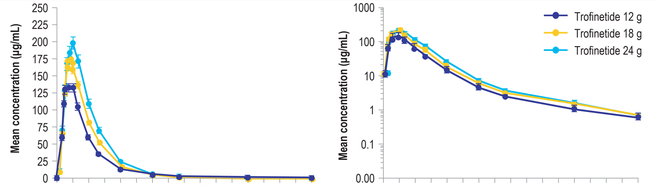
PK parameter	Trofinetide 12 g (n = 20)	Trofinetide 18 g (n = 18)	Trofinetide 24 g (n = 14)
C_{max}, µg/mL	146 (21.8)	183 (22.7)	206 (32.9)
AUC_{last}, µg•h/mL	837 (124)	1097 (105)	1330 (181)
$AUC_{0–∞}$, µg•h/mL	848 (125)	1110 (107)	1342 (181)
AUC_{extrap}, %	1.28 (0.34)	1.20 (0.33)	0.89 (0.26)
T_{max},[a] h	2.51 (2.00, 4.01)	2.51 (1.99, 3.30)	3.00 (2.00, 4.00)
$t_{½}$, h	12.3 (1.50)	12.1 (1.11)	11.0 (1.23)
λ_z, 1/h	0.057 (0.008)	0.058 (0.005)	0.064 (0.007)
CL/F, L/h	14.4 (1.99)	16.4 (1.69)	18.2 (2.51)
V_z/F, L	255 (45.9)	286 (41.3)	290 (51.4)

The PK analysis set consisted of all participants who received ≥1 dose of study drug and had sufficient blood concentration data to calculate ≥1 PK parameter; units are mean (SD) unless otherwise noted

[a]Median (min, max)

λ_z, terminal phase elimination rate constant; $AUC_{0–∞}$, area under the concentration-time curve from 0 to infinity; AUC_{extrap}, extrapolated area under the concentration-time curve; AUC_{last}, area under the concentration-time curve from time 0 to the time of the last detectable concentration; C_{max}, maximum observed drug concentration; CL/F, apparent systemic clearance following oral administration; PK, pharmacokinetics; SD, standard deviation; $t_{½}$, apparent terminal elimination half-life; T_{max}, time to maximum observed drug concentration; V_z/F, apparent volume of distribution following oral administration

Figure 2. Mean (±SE) blood trofinetide concentration-time profiles after single-dose administrations of 12 g, 18 g, or 24 g trofinetide oral solution in linear (left) and semi-log (right) scales (PK analysis set)



The PK analysis set consisted of all participants who received ≥1 dose of study drug and had sufficient blood concentration data to calculate ≥1 PK parameter

PK, pharmacokinetics; SE, standard error

Primary ECG Analyses: Concentration-Effect Modeling

- There was no clinically relevant effect on ECG parameters at single trofinetide doses ≤24 g as determined by concentration-effect modeling
- C-QTc analysis showed the upper 90% 2-sided confidence bounds for C-ΔQTcF and C-ΔΔQTcF were <10 ms for each of the 3 trofinetide doses
  - The model-predicted ΔΔQTcF at the mean C_{max} and at the individual C_{max} values of the 3 trofinetide doses were all ≤2.36 ms, with upper 90% CIs of ≤6.010 ms (Table 2)
  - The C-ΔQTcF and C-ΔΔQTcF regressions for the 24-g dose of trofinetide are shown in Figure 3

Table 2. Summary of C-ΔQTcF analyses (PK/PD analysis set)

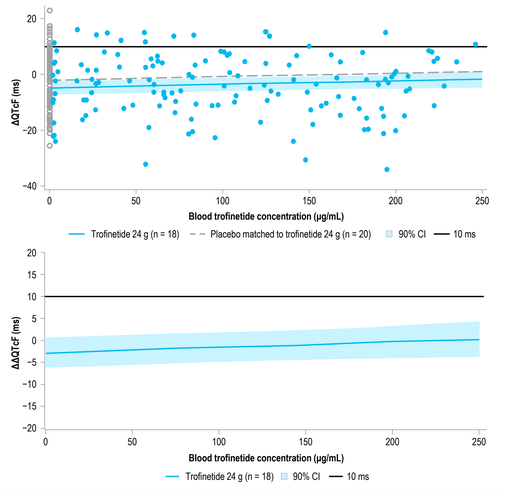
Model parameter predictions	N	Estimate[a] (SE)	90% CI
ΔQTcF-blood trofinetide concentration (slope)	40	0.0121	0.0003 to 0.0239
ΔΔQTcF trofinetide 12 g			
Mean C_{max} (146 µg/mL)	20	1.96 (2.109)	−1.555 to 5.473
Maximum BC (179 µg/mL)	20	2.36 (2.195)	−1.295 to 6.010
ΔΔQTcF trofinetide 18 g			
Mean C_{max} (183 µg/mL)	20	1.87 (2.150)	−1.706 to 5.455
Maximum BC (212 µg/mL)	20	2.22 (2.237)	−1.496 to 5.945
ΔΔQTcF trofinetide 24 g			
Mean C_{max} (206 µg/mL)	18	−0.31 (2.213)	−3.989 to 3.376
Maximum BC (268 µg/mL)	18	0.44 (2.424)	−3.582 to 4.466

The PK/PD analysis set consisted of participants in the ECG analysis set with time-matched blood concentrations to ≥1 baseline and ≥1 1- to 23-hour postdose triplicate continuous ECG data extraction; the ECG analysis set consisted of all participants who were randomized, received ≥1 dose of study drug (trofinetide, moxifloxacin, or placebo), and had ≥1 baseline and ≥1 1- to 23-hour postdose triplicate continuous ECG data extraction

[a]Estimates were obtained using a linear mixed-effects model as ΔECG = Timepoint + Treatment + Concentration + Predose ECG, with Subject as a random effect and Subject×Period as a repeated effect using unstructured covariance structure

ΔQTcF, change from the time-matched baseline in QTcF; ΔΔQTcF, placebo-adjusted change from time-matched baseline in QTcF; BC, blood concentration; CI, confidence interval; C_{max}, maximum observed drug concentration; ECG, electrocardiogram; PD, pharmacodynamic; PK, pharmacokinetics; QTcF, QT interval using Fridericia's correction method; SE, standard error

Figure 3. ΔQTcF (top) and ΔΔQTcF (bottom) blood concentration regressions with trofinetide 24 g (PK/PD analysis set)



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ΔQTcF, change from the time-matched baseline in QTcF; ΔΔQTcF, placebo-adjusted change from time-matched baseline in QTcF; CI, confidence interval; ECG, electrocardiogram; PD, pharmacodynamic; PK, pharmacokinetics

Safety

- A single oral dose of 12 g, 18 g, or 24 g of trofinetide was well tolerated in healthy adult participants
  - There were no deaths reported during the study; 1 serious TEAE of COVID-19 that required hospitalization (cohort 1B, Dosing Period 4) was reported and was not considered to be related to study drug, and there were no participants with TEAEs leading to study discontinuation
  - TEAEs were reported in 28 of 40 participants (70.0%), and the majority (70.0%) were mild in severity
  - The most common TEAEs (≥4 participants in any preferred term) were diarrhea and nausea (n = 12; 30.0% each); headache (n = 10; 25.0%); constipation and medical device site irritation (n = 6; 15.0% each); abdominal pain and COVID-19 (n = 5; 12.5% each); and upper abdominal pain, vomiting, and vessel puncture site reaction (n = 4; 10.0% each) (Table 3)
    - Diarrhea, nausea, vomiting, and headache were more frequent in participants treated with trofinetide, and the frequency of gastrointestinal-related TEAEs increased in a dose-dependent manner
    - There were no TEAEs suggestive of proarrhythmic potential and no clinically significant cardiovascular TEAEs
  - There were no clear trends or clinically meaningful changes in the ECG parameters of heart rate, PR interval, QRS interval, QTcF interval, and cardiac morphology from baseline to 3 and 48 hours postdose between trofinetide and matching placebo, and there were no clinically meaningful changes in individual laboratory tests, vital signs, or physical examination

Table 3. TEAEs reported by ≥4 participants for any preferred term (safety analysis set)

MedDRA preferred term, n (%)	MOXI (n = 39)	PBO MOXI (n = 37)	Trofinetide 12 g (n = 20)	Trofinetide 18 g (n = 20)	Trofinetide 24 g (n = 18)	Placebo-matching trofinetide 12 g (n = 20)	Placebo-matching trofinetide 18 g (n = 20)	Placebo-matching trofinetide 24 g (n = 20)	All (n = 20)	Overall (N = 40)
Any TEAE	6 (15.4)	12 (32.4)	6 (30.0)	11 (55.0)	11 (61.1)	6 (30.0)	10 (50.0)	9 (45.0)	14 (70.0)	28 (70.0)
Abdominal pain	0	0	0	1 (5.0)	0	0	1 (5.0)	3 (15.0)	4 (20.0)	5 (12.5)
Abdominal pain upper	0	0	0	0	3 (16.7)	0	0	1 (5.0)	1 (5.0)	4 (10.0)
Constipation	0	0	0	0	2 (11.1)	2 (10.0)	1 (5.0)	2 (10.0)	4 (20.0)	6 (15.0)
Diarrhea	1 (2.6)	1 (2.7)	1 (5.0)	5 (25.0)	7 (38.9)	0	0	1 (5.0)	1 (5.0)	12 (30.0)
Nausea	0	0	1 (5.0)	6 (30.0)	10 (55.6)	1 (5.0)	0	0	1 (5.0)	12 (30.0)
Vomiting	0	0	0	2 (10.0)	4 (22.2)	0	0	0	0	4 (10.0)
Medical device site irritation	0	3 (8.1)	1 (5.0)	3 (15.0)	0	0	1 (5.0)	0	1 (5.0)	6 (15.0)
Vessel puncture site reaction	0	0	1 (5.0)	0	0	0	0	3 (15.0)	3 (15.0)	4 (10.0)
COVID-19	1 (2.6)	1 (2.7)	0	0	2 (11.1)	0	0	1 (5.0)	1 (5.0)	5 (12.5)
Headache	2 (5.1)	2 (5.4)	2 (10.0)	5 (25.0)	2 (11.1)	0	3 (15.0)	0	3 (15.0)	10 (25.0)

Percentages are based on the number of participants in each treatment in the safety analysis set (all participants who received ≥1 dose of study drug). Participants are counted once per treatment (12 g, 18 g, and 24 g) per category (trofinetide or matching placebo) and once overall. *Denominators* for the percentages are the number of participants in each treatment group

Adverse events were coded using MedDRA Version 23.0. A TEAE is an adverse event that occurred on or after the first administration of study drug

MedDRA, *Medical Dictionary for Regulatory Activities*; MOXI, moxifloxacin; PBO MOXI, placebo-matching moxifloxacin; TEAE, treatment-emergent adverse event

CONCLUSIONS

- The upper 90% confidence bounds for ΔQTcF and ΔΔQTcF were <10 ms (below the threshold of concern for cardiac repolarization); thus, no evidence of cardiac repolarization following therapeutic or supratherapeutic trofinetide doses was observed
- There were no clinically meaningful effects on ECG parameters
- Trofinetide was safe and well tolerated, with no unexpected safety findings or negative trends

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DISCLOSURES

MD, JMY, DD, and **SS** are employees of and stakeholders in Acadia Pharmaceuticals Inc.

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