Phase 1, Single-Center, Randomized, Placebo-Controlled, Partially Blinded, Single Ascending Dose Study on the Effects of Troriluzole on corrected QT in Healthy Subjects

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Introduction

Troriluzole is a novel, rationally designed, third-generation tripeptide prodrug of the glutamate modulating agent riluzole that is being developed for the treatment of neurodegenerative and neuropsychiatric diseases.[1] Troriluzole was designed to increase oral bioavailability, deliver consistent drug exposures, bypass first-pass metabolism, allow for once daily (QD) dosing, and avoid the negative food effect associated with riluzole.[2,3,4]

Cardiac safety assessments are critical in drug development because some compounds can delay cardiac repolarization, resulting in QT interval prolongation which may cause potentially fatal pro-arrythmias. A Phase 1 randomized, placebo-controlled, and partially blinded study (BHV4157-108, **Figure 1**) was conducted to assess troriluzole PK and QT prolongation potential in healthy adult subjects. A primary objective was to evaluate the effect of a single dose of troriluzole on the Fridericia heart-rate corrected QT interval (QTcF) using concentration-QT (C-QT) analysis with riluzole as the analyte. A secondary objective was to determine PK of riluzole following single ascending doses of troriluzole.

Methods

Seventy-two subjects (70 of whom were included in the cQTcF analysis due to absence of particular ECG results for 2 subjects) received single doses of either a therapeutic dose (280 mg) or supratherapeutic doses (560 or 840 mg) of troriluzole, matched placebo, or 400 mg moxifloxacin. Moxifloxacin was used as a positive control in accordance with ICH E14 Guidance (2005) that recommends a positive control to validate the study. Troriluzole and placebo were administered in a double-blind manner, and moxifloxacin was administered open-label. For the 560 and 840 mg dose groups, sentinel subjects were dosed prior to the main cohort.

cQTcF Analysis:

- The relationship between plasma concentrations of riluzole and change-from-baseline (Δ) QTcF was quantified using a linear mixed-effects modeling approach using data for subjects receiving troriluzole or placebo from Cohorts 1 to 3
- The predicted effect and its 2-sided 90% confidence interval (CI) for placebo-corrected ΔQTcF (ΔΔQTcF) (i.e., slope estimate × concentration + treatment effect-specific intercept) was determined at the geometric mean of the individual C_{max} values of riluzole for subjects in each active dose group
- Assay sensitivity was determined using moxifloxacin

PK Methods:

- Blood samples up to 72 hours after each dose of troriluzole were collected for riluzole PK analysis
- Riluzole PK parameters were calculated by non-compartmental analysis

Results

Cardiodynamic Results (**Table 1**, **Figure 2**, **Figure 3**):

- Based on the C-QT analysis, a corrected QT interval (QTc) effect (ΔΔQTcF) exceeding 10 msec was excluded within the full range of observed riluzole plasma concentrations, up to ~1364 ng/mL
- Least square (LS) mean ΔΔQTcF was negative for troriluzole across most post-dose time points, ranging from -8.1 msec (at 2.5 hours post-dose in the 840 mg dose group) to 2.5 msec (at 1 hour post-dose in the 280 mg dose group), indicating no QT prolongation across the doses
- After dosing with moxifloxacin, a clear increase of LS mean ΔΔQTcF was observed with a peak value of 14.1 msec (90% CI: 11.03 to 17.15) at 3 hours post-dose, demonstrating appropriateness as a positive control

PK for Riluzole and Moxifloxacin Results (**Table 1**):

- Riluzole geometric mean C_{max} ranged from 358 to 1130 ng/mL across the single doses
- Plasma concentrations of riluzole peaked at approximately 2.5-3.0 hours (T_{max}) following troriluzole single doses
- Overall, riluzole was approximately dose proportional across 280 to 840 mg single doses
- The geometric mean C_{max} moxifloxacin was 1720 ng/mL, which occurred approximately 2.5 hours (T_{max}) following dosing

Conclusion

There was no clinically meaningful effect on the QTc interval following single troriluzole doses up to 840 mg (3-fold higher than the proposed therapeutic dose for treatment of OCD). Overall, this constitutes a negative thorough QT study as described in the ICH E14 clinical guidance.

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Figure 1: BHV4157-108 Study Design

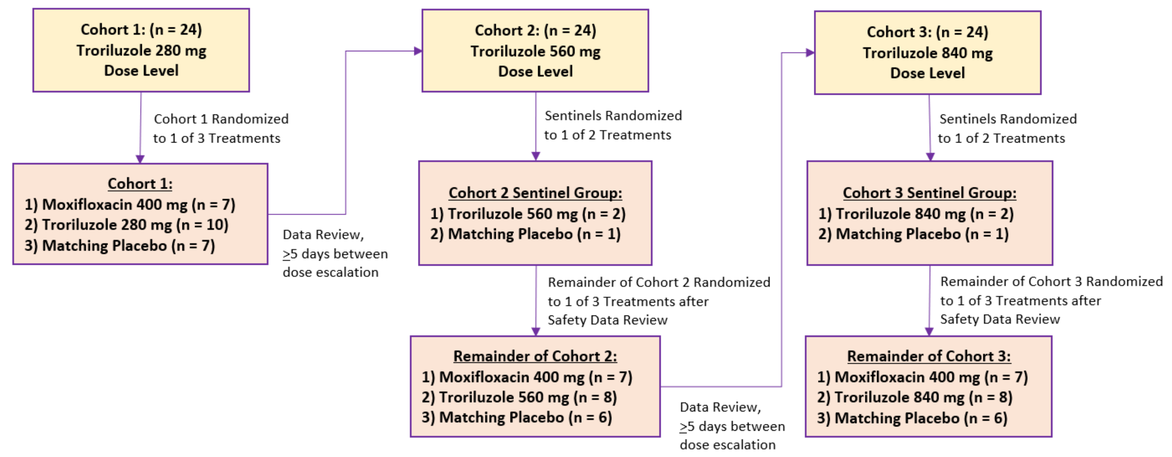
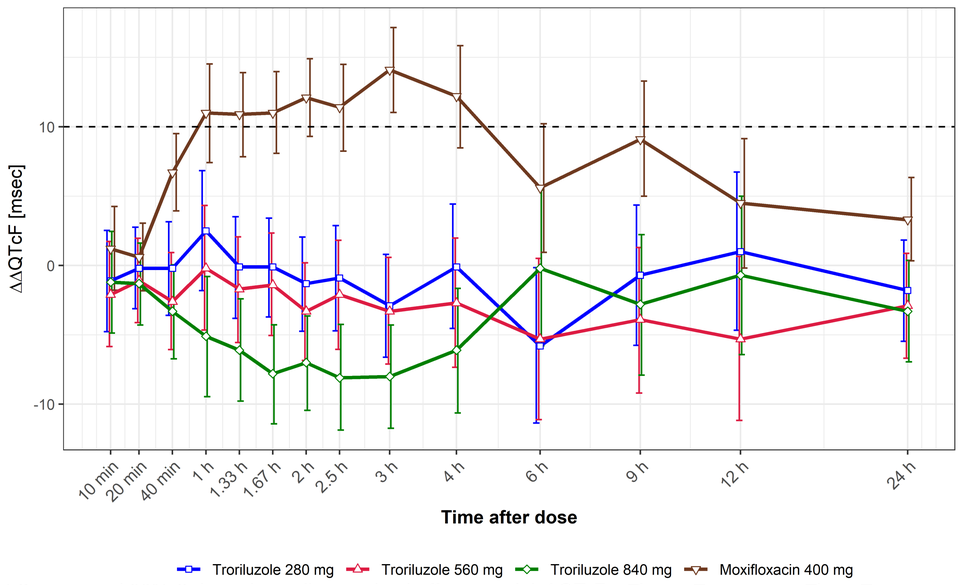


Figure 2: LS Mean (90% CI) Placebo-corrected Change from Baseline in QTcF (ΔΔQTcF) after Troriluzole, Moxifloxacin, and Placebo Administration Across Time Points



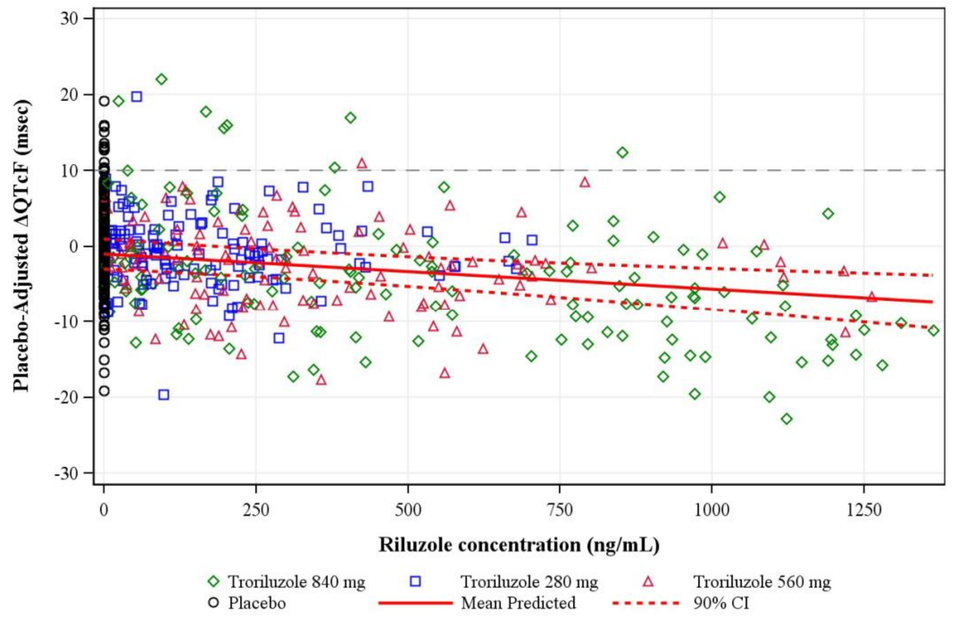
LS mean and 90% CI based on a linear mixed-effects model: ΔQTcF = Time + Treatment + Time×Treatment + Baseline QTcF. Dashed line represents the ΔΔQTcF = 10 msec.

Table 1: Predicted ΔΔQTcF Interval at Geometric Mean Peak Riluzole Concentrations (PK/QTc Population)

Treatment	Geometric Mean (ng/mL) C_{max} of Riluzole	ΔΔQTcF Estimate (msec) (90% Confidence Interval)
Troriluzole 280 mg (n=10)	358	-2.72 (-4.59, -0.84)
Troriluzole 560 mg (n=9)	796	-4.68 (-7.02, -2.33)
Troriluzole 840 mg (n=10)	1130	-6.17 (-9.14, -3.19)

Based on a linear mixed effects model with ΔQTcF as the dependent variable, time-matched riluzole plasma concentration as an explanatory variate, centered baseline QTcF as an additional covariate, treatment (active = 1 or placebo = 0) and time as fixed effects, and a random intercept and slope per subject.

Figure 3: Scatter Plot of Observed Riluzole Plasma Concentrations and Estimated Placebo-adjusted ΔQTcF (PK/QTc Population)



Note: The solid red line with dashed red lines denotes the model-predicted mean ΔΔQTcF with 90% CI, which is calculated from the equation ΔΔQTcF = −1.11 (ms) - 0.0045 (ms per ng/mL) × riluzole concentration (ng/mL). The plotted points denote the pairs of observed drug plasma concentrations and estimated placebo-adjusted ΔQTcF (ΔΔQTcF) by subjects for each active dose group and placebo dose group. The individually estimated placebo-adjusted $\Delta QTcF_{i,k}$ ($\Delta\Delta QTcF_{i,k}$) equals the individual $\Delta QTcF_{i,k}$ for subject $_i$ administered with active drug or placebo at time point k minus the estimation of the time effect at time point $_k$.

References

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