P038

Lorundrostat Concentration-QTc Results From the First-in-Human Study in Healthy Participants Demonstrate Lack of Relevant Effect and Replaces the Thorough QT Study

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INTRODUCTION

- Lorundrostat is a highly selective inhibitor of aldosterone synthase (cytochrome P450 11B2) that produces suppression of aldosterone production and is currently under investigation for the treatment of patients with uncontrolled hypertension, including treatment-resistant hypertension[1]
- Regulatory guidance recommends that the effects of new drug candidates on ventricular depolarization and subsequent repolarization (QT interval) be rigorously investigated[2,3]
  - Drug-induced prolongation of the QT interval is associated with the development of cardiovascular comorbidities, including syncope, cardiac arrhythmias, torsades de pointes, and sudden cardiac arrest[4]
  - Recent revisions of E14[5] and nonclinical S7B regulatory guidance documents allow for a waiver of a thorough QT study in the case that a >10 ms effect on the heart-rate corrected QT (QTc) interval at clinically relevant drug concentrations can be excluded[6,7]
- Premarketing safety studies of lorundrostat included in vitro human ether-a-go-go-related channel (hERG) inhibition assay, an in vivo cardiovascular safety in cynomolgus monkeys, and a cardiodynamic evaluation, including QTc interval prolongation, in healthy human participants

METHODS

In Vitro hERG Inhibition Assay

- Recombinant hERG channels were expressed in HEK-293 cells lacking an endogenous rapid delayed rectifier current (IKr)
  - hERG inhibition by lorundrostat was assessed using whole-cell patch clamp methods

Cardiovascular Safety in Cynomolgus Monkeys

- Conscious cynomolgus monkeys were administered a single dose of lorundrostat 10-100 mg/kg or vehicle (n=4 per treatment)
  - Blood pressure, heart rate (HR), and electrocardiogram (ECG) parameters (PR interval, QRS duration, QT interval, and QTc [corrected using Bazett's formula]) were collected before dosing (predose) and at 1, 3, 7, and 24 hours after dosing (postdose)

First-in-Human Cardiodynamic Evaluation

- The effect of lorundrostat on the QTc interval was assessed as part of a first-in-human study with 64 participants who received a single dose of lorundrostat 5-800 mg or placebo (single ascending dose [SAD]) and 36 participants who received multiple doses of lorundrostat 40-360 mg/day or placebo for 7 days (multiple ascending dose [MAD])
- Serial ECGs were extracted from continuous recordings (Holter) at prespecified time points and were matched with blood collections for pharmacokinetic analysis through 24 hours postdose on Day 1 in the SAD study and on Days 1 and 7 in the MAD study
- The primary analysis was an assessment of the relationship of the plasma concentration of lorundrostat and change from baseline in QTc, corrected for HR using Fridericia's method (ΔQTcF)
- The secondary analysis was a by-timepoint analysis of ΔQTcF for lorundrostat versus placebo
  - Change from baseline in HR, PR, and QRS were also included in the secondary analysis
- Categorical analyses were performed to identify categorical outliers (number of participants or number of timepoints) by lorundrostat dose
- All cardiodynamic analyses were performed separately for the SAD and MAD studies

RESULTS

hERG Assay

- Lorundrostat was a weak inhibitor of hERG (mean [SEM] inhibition of 6.9% [2.5%] at 10 µM) with a half-maximal inhibitory concentration (IC50) of 95.4 µmol/L

Cardiovascular Safety in Cynomolgus Monkeys

- There were no statistically significant differences in blood pressure, QRS duration, QT interval, or QTc for lorundrostat up to 100 mg/kg versus placebo at any of the assessed time points
  - Statistically significant differences were seen in HR 7 hours after dosing at 30 mg/kg and in PR interval 24 hours after dosing at 100 mg/kg
    - However, these differences were judged as not related to lorundrostat on the basis of comparability to predose values and the absence of dose dependency

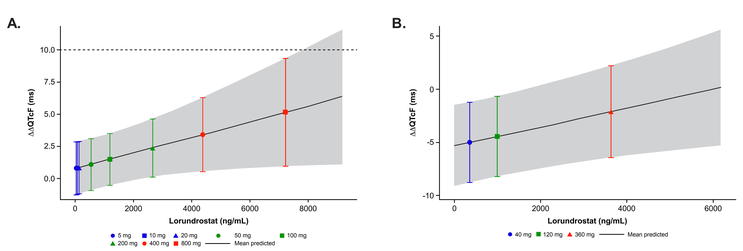
Cardiodynamic Evaluation Participant Population

- The SAD and MAD QT/QTcF analysis groups included 60 (46 lorundrostat, 14 placebo) and 32 (23 lorundrostat, 9 placebo) healthy participants, respectively
- For both groups, mean baseline ECG parameters were consistent with those from healthy populations, with mean QTcF between 388.7 and 401.0 ms (SAD) and 394.8 and 402.1 ms (MAD)

Concentration -QTc Analyses

- In the SAD study, the estimated population slope (90% CI) of the concentration-QTc relationship was 0.00061 ms per ng/mL (0.00004-0.00118 ms per ng/mL; P=0.0797) with a not statistically significant treatment effect-specific intercept (90% CI) of 0.77 ms (-1.29, 2.82; P=0.5351; **Figure 1A**)
  - On the basis of this analysis, an effect on placebo-corrected ΔQTcF (ΔΔQTcF) >10 ms can be excluded within the observed range of plasma lorundrostat concentrations up to ~7800 ng/mL
- In the MAD study, the estimated population slope (90% CI) of the concentration-QTc relationship was very shallow (0.00088 ms per ng/mL; 0.00017-0.00159 ms per ng/mL; P=0.0421) with a large and statistically significant negative treatment effect-specific intercept (90% CI) of -5.29 ms (-9.08, -1.51 ms; P=0.0243; **Figure 1B**)
  - On the basis of the MAD results, an effect on ΔΔQTcF exceeding 10 ms can be excluded within the observed range of plasma lorundrostat concentrations up to ~6175 ng/mL

Figure 1. Concentration-QTc Analysis: Model-Predicted ΔΔQTcF at Geometric Mean Peak Concentrations of Lorundrostat in the (A) SAD and (B) MAD Studies

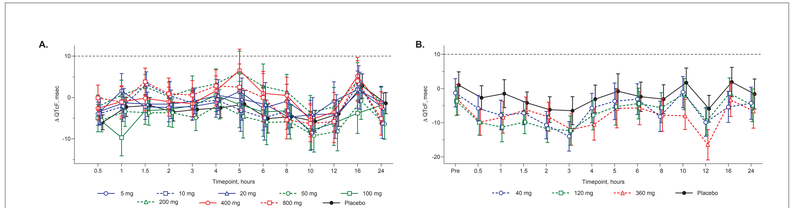


The relationship of lorundrostat plasma concentration and the ΔΔQTcF was assessed in the PK/QTc analysis set (defined as all participants with ≥1 set of PK and ΔQTcF data from the same time point) using linear mixed-effects modeling with ΔQTcF as the dependent variable, lorundrostat concentration as the explanatory variable, and treatment and time as fixed effects. The solid black lines and gray shaded areas denote the model-predicted mean ΔΔQTcF and associated 90% CI for the equations ΔΔQTcF (ms) = 0.77 (ms) + 0.0061 (ms per ng/mL) × lorundrostat plasma concentration (ng/mL) for Panel A and ΔΔQTcF (ms) = -5.29 (ms) + 0.00088 (ms per ng/mL) × lorundrostat plasma concentration (ng/mL) for Panel B. In Panel A, the grey dashed line shows the 10 ms regulatory ΔQTcF effect threshold.[2,3]

ΔQTcF, change from baseline QTcF; ΔΔQTcF, placebo-corrected change from baseline QTcF; MAD, multiple ascending dose; PK, pharmacokinetic; QTcF, QT interval corrected for heart rate using Fridericia's method; SAD, single ascending dose.

- In the by-timepoint analyses of the SAD study, the least squares (LS) mean ΔQTcF for lorundrostat generally followed the placebo pattern across all postdose time points (**Figure 2A**)
  - LS mean ΔΔQTcF ranged from -7.4 ms at 1 hour postdose (100-mg dose group) to 8.3 ms at 5 hours postdose (400-mg dose group), with no indication of dose dependency
    - The largest mean ΔΔQTcF was 6.0 ms at 0.5 hours postdose and was observed in the 800-mg dose group
    - In the 200- and 400-mg dose groups, the largest ΔΔQTcF values were 7.7 ms at 5 and 6 hours postdose and 8.3 ms at 5 hours postdose, respectively
- In the by-timepoint analysis of the MAD study, LS mean ΔQTcF for lorundrostat generally followed the placebo pattern across postdose time points with lower mean ΔQTcF values seen across all time points in all dose groups (**Figure 2B**)
  - ΔΔQTcF values ranged from -10.6 ms at 12 hours postdose (360-mg dose group) to -0.7 ms at 6 hours postdose (40-mg dose group)
- There were no participants in the SAD and MAD studies with QTcF >450 ms or ΔQTcF >30 ms

Figure 2. By-Timepoint Analysis: ΔQTcF With Lorundrostat or Placebo in the (A) SAD and (B) MAD Studies



LS mean and 90% CI ΔQTcF values for lorundrostat and placebo based on MMRM with the ΔQTcF parameters as the dependent variable, with time, treatment, and time-by-treatment interaction as fixed effects, and with baseline QTcF as a covariate. An unstructured covariance matrix was specified for the repeated measures at post-baseline time points for SAD and MAD participants within treatment. The gray dashed lines show the 10 ms regulatory ΔQTcF effect threshold.[2,3]

ΔQTcF, change from baseline QTcF; LS, least squares; MAD, multiple ascending dose; MMRM, mixed model for repeated measures; Pre, predose; QTcF, QT interval corrected for heart rate using Fridericia's method; SAD, single ascending dose.

- In both the SAD and MAD studies and at all studied doses, lorundrostat did not have clinically relevant effects on the other assessed cardiodynamic and ECG parameters
  - LS mean changes from baseline in HR and PR for lorundrostat generally followed the pattern observed for placebo
  - LS mean changes from baseline in QRS were small and ranged from -1.5 to 3.3 ms and from -0.5 to 2.3 ms in the SAD and MAD studies, respectively
- In the categorical analyses, there was 1 bradycardic outlier at 1 time point in the SAD study
  - There were no outliers for HR in the MAD study, or for PR or QRS (both studies)

CONCLUSIONS

- **These results demonstrate the absence of QT interval prolongation by plasma exposure of up to approximately 7800 ng/mL lorundrostat**
  - **This concentration is 4.8-fold higher than the predicted maximum observed plasma concentration (C_{max}) at the maximum clinically efficacious dosage of 100 mg once daily and is also higher than the high clinical exposure scenario when lorundrostat is given with strong CYP3A4 inhibitors (~1.2-fold increase in C_{max})**
- **On the basis of these data, the regulatory requirement for a thorough QT study was waived**

REFERENCES

1. Laffin LJ, et al. *JAMA*. 2023;330(12):1140-50.
2. U.S. Food and Drug Administration. 2005. https://www.fda.gov/media/71372/download.
3. European Medicines Agency. 2005. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-14-clinical-evaluation-qt/qts-interval-prolongation-proarrhythmic-potential-non-antiarrhythmic-drugs-step-5_en.pdf.
4. Roden DM. *N Engl J Med*. 2004;350(10):1013-22.
5. US Food and Drug Administration. 2017. https://www.fda.gov/media/71379/download.
6. US Food and Drug Administration. 2022. https://www.fda.gov/media/161198/download.
7. Darpo B, Leishman DJ. *J Clin Pharmacol*. 2023;63(11):1256-74.

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DISCLOSURES

MAT and DAR: Employment: Mineralys Therapeutics; **BD:** Employment: Clario; stock ownership: Clario; **HX:** Employment: Clario; **SS:** Consultant: Mineralys Therapeutics.

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