Absence of QT Prolongation Associated with Relacorilant, a Selective Glucocorticoid Receptor Modulator in Development for the Treatment of Cushing Syndrome

PRESENTER:
Andreas G. Moraitis, MD
Contact: amoraitis@corcept.com

Diane M. Donegan[1], Rosario Pivonello[2], Antonio Stigliano[3], Pina Lardo[3], Tara Kearney[4], Emese Mezosi[5], Ezio Ghigo[6], Roberta Giordano[6], Cary N. Mariash[7], Richard Feelders[8], Kirsteen Donaldson[9], Borje Darpo[10], Joseph M. Custodio[11], Austin L. Hand[11], Andreas Moraitis[11]

[1]Indiana University School of Medicine, Indianapolis, IN; [2]Università "Federico II" di Napoli, Naples, Italy; [3]Sant'Andrea University Hospital, Sapienza University of Rome, Rome, Italy; [4]Salford Royal Foundation Trust, Manchester, UK; [5]Clinical Center, University of Pecs, Pecs, Hungary; [6]University of Turin, Torino, Italy; [7]Indiana University and Indiana University Health, Indianapolis, IN; [8]Erasmus Medical Center, Rotterdam, The Netherlands; [9]Jade Consultants (Cambridge) Limited, Cambridge, UK; [10]Clario, Rochester, NY; [11]Corcept Therapeutics Incorporated, Menlo Park, CA.

Summary & Conclusions

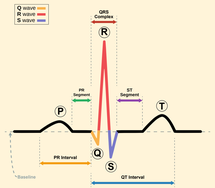
- QT prolongation is a serious condition that is prevalent in patients with Cushing syndrome (CS) and can lead to fatal arrhythmias.
  - Currently approved CS medications may have an untoward effect on the QT interval.
- Based on a thorough QT study and supported by additional data in healthy volunteers and patients with CS, relacorilant is not associated with QT prolongation.
  - No effects on ECG parameters were observed with relacorilant doses up to 800 mg for 5 days (2x the maximum dose currently evaluated in patients with CS).
  - No instances of drug-induced hypokalemia, a known risk factor for QT prolongation and common feature in patients with CS, have been reported with relacorilant.
- The effects of relacorilant on the QT interval continue to be evaluated in ongoing phase 3 studies in patients with hypercortisolism (GRACE: NCT03697109; GRADIENT: NCT04308590).

The authors want to thank all those who participated in these studies: The study patients and their families, the investigators, and the sponsor team.

Scan QR code to download poster

Background

- Prolongation of the QT interval is an important risk factor for the development of cardio-vascular comorbidities, including cardiac arrhythmia, syncope, incident stroke, and sudden cardiac arrest.[1–3]
- QT prolongation can be detected on ECG and can be caused or potentiated by a range of factors, including drugs.
- Thorough evaluation of the potential for QT prolongation is often required for new drug candidates.



QT interval: The interval from the onset of ventricular depolarization to the end of ventricular repolarization.

- Drug-induced QT prolongation is a serious concern in patients with Cushing syndrome (CS).
  - QT prolongation and increased QT dispersion have been reported in patients with CS compared with healthy individuals.[4,5]
  - Elevated cortisol and electrolyte abnormalities, such as hypokalemia, may affect the QT interval.[6,7]
  - About 26% of men with CS present with QT prolongation, and the risk of cardiac arrhythmic events correlates with the extent of QT prolongation.[8]
    - Excess cortisol secretion can lower testosterone levels in men, which may explain QT prolongation in male patients with CS.[8]
  - Most medications currently approved or widely used for the treatment of CS are associated with QT prolongation.[9–13]
  - Many drugs used to treat comorbidities of CS may also lead to QT prolongation.

Aim

- We evaluate the impact of relacorilant, an investigational selective glucocorticoid receptor modulator (SGRM), on the QT interval in healthy volunteers and patients with CS.

Methods

First-in-human study

- A phase 1, randomized, placebo-controlled, first-in-human study (NCT03508635)
- 103 healthy volunteers received single or multiple ascending doses (SAD/MAD) of relacorilant (up to 500 mg QD) for up to 14 days; 24 received placebo.

Dedicated TQT study

- A phase 1, randomized, partial double-blind, crossover thorough QT study (NCT04795479) to assess the effect of multiple doses of relacorilant on cardiac repolarization in healthy volunteers
- Participants were randomized to dosing sequences to receive relacorilant at therapeutic (400 mg QD, n=25) or supra-therapeutic (800 mg QD, n=28) doses, or placebo (n=29; negative control) for 5 days.
- Moxifloxacin (400 mg single dose, n=28) was used as a positive control.

CS phase 2 study

- A phase 2, single-arm, open-label study (NCT02804750) in patients with CS
- 17 patients received low-dose relacorilant (100–200 mg QD) for 12 weeks; 18 patients received high-dose relacorilant (250–400 mg QD) for 16 weeks.[14]

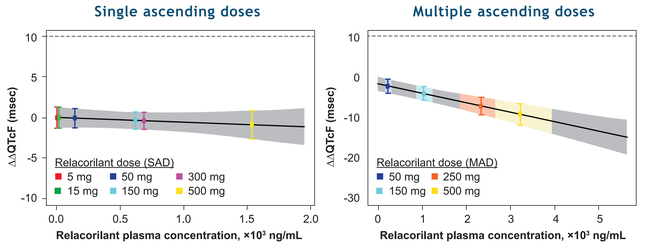
QT evaluation

- In all studies, ECG data were collected and the heart rate-corrected QT interval (QTc) using Fridericia's formula (QTcF) was calculated.
- Participants with a family history of or risk factors for torsades de pointes or with a prolonged QT interval at screening were not eligible to participate.
- Exposure-response analysis of the effect of relacorilant on QTc was conducted using a linear model with an intercept.

1 Relacorilant Did Not Adversely Affect ECG Parameters in First-in-Human Study

- In the first-in-human study, relacorilant up to 500 mg QD for 14 days showed no notable mean changes from baseline for any ECG parameters measured.
  - No notable differences were observed between relacorilant dose levels or between relacorilant and placebo.
  - No instances of post-dose QTcF interval >450 msec or QTcF interval increases of >30 msec were reported.
- Change-from-baseline QTcF (ΔQTcF) was similarly small and mostly negative throughout the study and across dose groups; no dose-dependence was observed.
- An effect of relacorilant on placebo-corrected ΔQTcF (ΔΔQTcF) >10 msec was excluded.
- Exposure-response analysis showed a slightly negative relationship between relacorilant plasma levels and ΔΔQTcF, excluding a positive concentration-dependent effect.

Model-predicted placebo-corrected change from baseline QTcF (ΔΔQTcF)



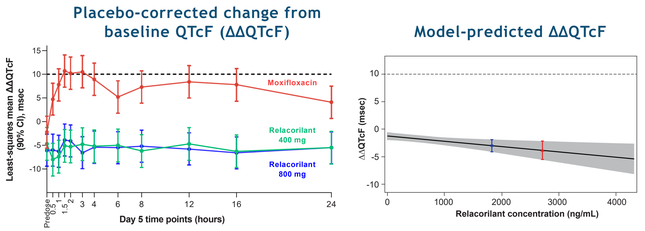
Colored markers & error bars: Predicted mean (90% CI) ΔΔQTcF at the observed geometric mean relacorilant maximum concentration (C_{max}). Dashed lines: 10-msec ΔΔQTcF effect threshold. Solid lines & gray shaded areas: Predicted mean ΔΔQTcF with 90% CI. CI, confidence interval.
SAD equation: ΔΔQTcF = -0.005 (msec) − 0.588 (msec/ng/mL) × relacorilant concentration (ng/mL);
MAD equation: ΔΔQTcF = -1.804 (msec) − 2.341 (msec/ng/mL) × relacorilant concentration (ng/mL).

2 Relacorilant Did Not Adversely Affect ECG Parameters in Dedicated TQT Study

- In the TQT study, therapeutic and supra-therapeutic doses of relacorilant had no adverse effects on ECG parameters.
- Moxifloxacin positive control showed the expected rapid increase in QTc, confirming assay sensitivity.
- ΔQTcF values for therapeutic and supra-therapeutic relacorilant were generally similar to those for placebo.
- Based on concentration-QTc analysis, an effect on ΔΔQTcF above 10 msec was excluded within the full observed range of relacorilant plasma concentrations (up to ~4500 ng/mL).
- Similar to the first-in-human study, the estimated slope of the relacorilant concentration-QTc curve was shallow and negative, with a statistically significant treatment effect-specific intercept.
- These results constitute a negative TQT study.

Placebo-corrected change from baseline QTcF (ΔΔQTcF)

Model-predicted ΔΔQTcF

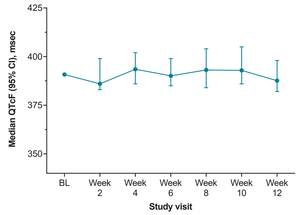


Right Figure. Colored markers & error bars: Estimated mean (90% CI) ΔΔQTcF at the observed geometric mean maximum relacorilant concentration with therapeutic (blue) and supra-therapeutic (red) dosing. Dashed line: 10-ms ΔΔQTcF effect threshold. Solid line & shaded area: Predicted mean ΔΔQTcF with 90% CI, calculated from ΔΔQTcF = -1.2501 (msec) − 0.97 (× 10^{-3} msec/ng/mL) × relacorilant concentration (ng/mL).

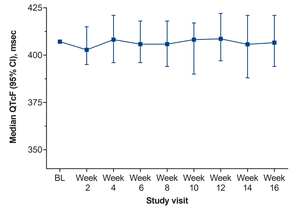
3 Favorable QT Findings Confirmed in Phase 2 Study in Patients With CS

- In the CS open-label phase 2 study, relacorilant had no adverse effects on ECG parameters.
- Throughout the study, no significant changes in median QTcF were observed in either dose group.
- No instances of hypokalemia were reported in the study.

QTcF in Patients with CS (Low-dose Group)



QTcF in Patients with CS (High-dose Group)



References

(1) Straus SM, et al. *J Am Coll Cardiol*. 2006;47:362–7.
(2) Beinart R et al. *J Am Coll Cardiol*. 2014;64:2111–9.
(3) Soliman EZ et al. *J Am Coll Cardiol*. 2012;59:1460–7.
(4) Bayram NA et al. *Endocrine Abstracts*. 2010;22:P59.
(5) Alexandraki KI et al. *Clin Endocrinol (Oxf)*. 2011;74:558–64.
(6) Muiesan ML et al. *J Am Coll Cardiol*. 2003;41:2275–9.
(7) Takagi S et al. *Endocr J*. 2009;56:1009–18.
(8) Pecori Giraldi F et al. *Exp Clin Endocrinol Diabetes*. 2011;119(4): 221–224.
(9) Pivonello R et al. *Front Endocrinol (Lausanne)*. 2020;11:648.
(10) Fleseriu M et al. *Pituitary*. 2016;19:138–48.
(11) Fleseriu M et al. *Lancet Diabetes Endocrinol*. 2019;7:855–65.
(12) Breitschaft A et al. *J Clin Pharmacol*. 2014;54(1):75–86.
(13) Dougherty JA et al. *Ann Pharmacother*. 2021;55(8):1050–1060.
(14) Pivonello R et al. *Front Endocrinol (Lausanne)*. 2021;12:662865.

Acknowledgments

The presented studies were sponsored by Corcept Therapeutics. Editorial support was provided by Tina Schlafly, PhD, CMPP, of Corcept Therapeutics.

Disclosures

AS, EG, PL, RG, TK: None. **BD**: Stock and/or stock options- Clario; Clario was contracted by Corcept to perform this research. **CNM, EM**: Grants/contracts- Corcept Therapeutics. **DMD**: Research investigator- Corcept Therapeutics. **KD**: Consulting fees- Corcept Therapeutics. **RAF**: Research grant- Corcept Therapeutics; honoraria for lectures- Corcept Therapeutics. **RP**: Grants/contracts- Corcept Therapeutics; consulting fees- Corcept Therapeutics. **AGM:** Employee- Corcept Therapeutics. **ALH:** Employee- Corcept Therapeutics; stock and/or stock options- Corcept Therapeutics. **JMC:** Employee- Corcept Therapeutics; stock and/or stock options- Corcept Therapeutics; patents- Corcept Therapeutics.