#046

Exposure-Response Analysis to Inform QT Prolongation Potential for Cedirogant

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OBJECTIVE

To characterize the QT prolongation potential of cedirogant through exposure-response analysis using QT data collected from a Phase 1 study.

CONCLUSIONS

Cedirogant plasma concentration is positively correlated with ΔQTcF.

The model-derived extent of QT prolongation by cedirogant under the high clinical exposure scenario is not considered of regulatory concern.

The exposure-response analysis suggests that expanded ECG safety evaluation may not be necessary in later phases of drug development of cedirogant.

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Reference
1. Mohamed et al., Clin Pharmacol Ther. 2018; 103(5):836-842

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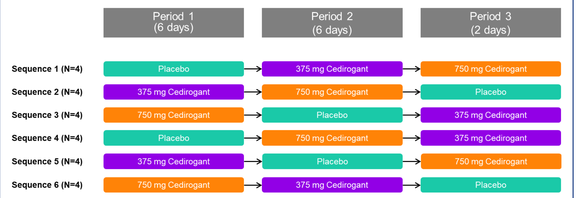
INTRODUCTION

- Investigational drugs with systemic availability should be assessed for the potential to delay cardiac ventricular repolarization, typically in a thorough QT study. Exposure-response analysis of QT data collected from early-phase studies provides an alternative approach.
- Cedirogant is an orally available inverse agonist of retinoic acid-related orphan receptor gamma, thymus (RORγt) which was being developed for treatment of chronic plaque psoriasis.

METHODS

- In a double-blinded, balanced crossover study, healthy participants (N=24) were randomized to one of six sequences to receive a single dose of 375 mg cedirogant, 750 mg cedirogant, or placebo under fasting conditions over three different periods (**Figure 1**).
- Blood samples and triplicate electrocardiograms (ECGs) were collected to obtain cedirogant plasma concentrations and QT data, respectively. QT intervals were corrected using Fridericia's formula (QTcF) and further analyzed in a linear mixed effects model.
- ECG sensitivity was assessed by evaluating the effect of food on QTcF in Period 2. A linear mixed effects analysis was performed using ECG data collected in participants receiving placebo on Day 1 and their corresponding ECG data collected on Day 6 before and after breakfast.

Figure 1. Study design



RESULTS

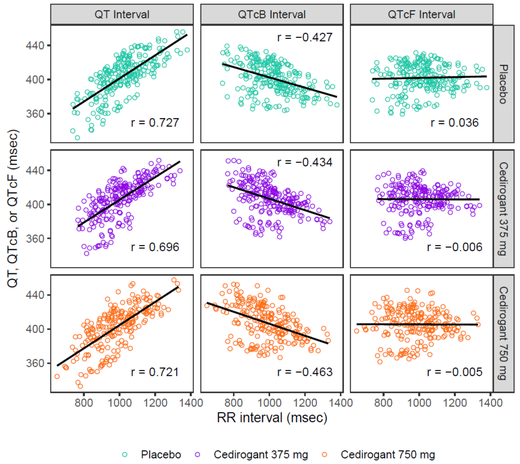
- Demographics of the study participants are presented in **Table 1**.
- Corrected QT utilizing Fridericia's formula is an adequate heart rate correction method and was used for the analysis (**Figure 2**).

Table 1. Study Participant Demographics

	Mean ± SD (N = 24)
Age (years)	42.5 ± 10.4
Weight (kg)	80.9 ± 10.5
Height (cm)	175 ± 8.5
BMI (kg/m²)	26.5 ± 3.5
Sex	19 Males (79%), 5 Females (21%)
Race	12 White (50%), 9 Black (38%), 1 Asian (4%), 2 Multiple (8%)

BMI = body mass index; SD = standard deviation.

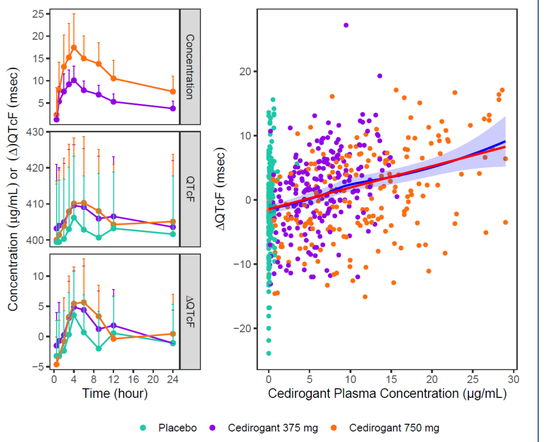
Figure 2. Correlation between QT, QTcB, QTcF and heart rate by dose



QTcB, corrected QT interval using Bazett's formula; QTcF, corrected QT interval using Fridericia's formula. Circles represent individual data points. Solid lines represent linear regression.

- Cedirogant reached maximum plasma concentration (C_{max}) with a median time of 4 hours. The observed cedirogant C_{max} were 10.2 and 17.5 μg/mL following administration of 375 mg and 750 mg doses, respectively.
- Visual inspection of cedirogant plasma concentration and QTcF over time showed no apparent hysteresis (**Figure 3**).
- QTcF was shortened by 5.4 and 7.1 msec at 3 and 4 hours, respectively, after food relative to fasting conditions (**Table 2**), which are statistically significant and within the range of food effect previously reported.[1]

Figure 3. Profiles of cedirogant plasma concentration, QTcF, and ΔQTcF over time



Left Panel: Data points and error bars represent mean and standard deviation of individual observations, respectively.
Right Panel: Data points represent paired ΔQTcF and concentration data. Red line represents the linear regression line, and the blue line and shaded area represent the loess smooth line and 95% confidence intervals.

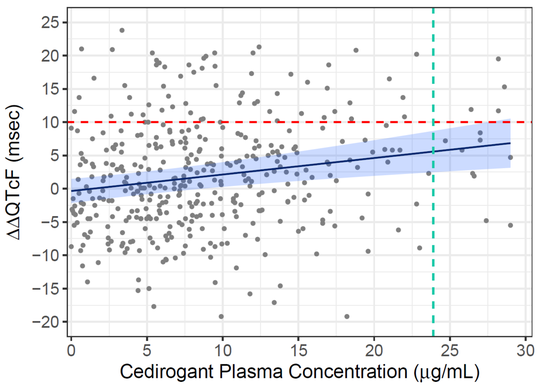
Table 2. Effects of food on QTcF intervals

	LS Means of Change from Baseline		Difference of Change from Fasting	
Time (hr)	**Fasting (msec)**	**Fed (msec)**	**Estimate (msec)**	**90% Confidence Interval (msec)**
2	-0.22	0.02	0.24	(-2.09, 2.56)
3	2.99	-2.45	-5.44	(-7.77, -3.11)
4	6.19	-0.95	-7.14	(-9.47, -4.81)

LS, least square.

- The model-derived upper bound of the one-sided 95% confidence interval of placebo-corrected ΔQTcF (ΔΔQTcF) at the highest clinically relevant mean was 8.7 msec (**Figure 4**), which was lower than the threshold level of regulatory concern.

Figure 4. Observed and model-predicted relationship between placebo-corrected ΔQTcF and cedirogant plasma concentration



Grey data points represent individual observed ΔΔQTcF. Black solid line represents model-derived mean ΔΔQTcF over the studied cedirogant plasma concentration range, and blue shaded area represents the associated two-sided 90% confidence interval. The horizontal red dashed line represents a change of ΔΔQTcF by 10 msec, a cutoff value considered as clinically significant by regulatory agencies. The vertical green dashed line represents the projected highest clinically relevant mean cedirogant Cmax in psoriasis patients (23.9 μg/mL). ΔΔQTcF, time-matched placebo-corrected change from baseline in Fridericia-corrected QT.