# The results of a phase I study assessing the effects of CIN-102 (a novel formulation of the dopamine receptor antagonist domperidone designed to treat gastroparesis) on cardiac repolarization in healthy subjects

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## 1. Background

CIN-102 (deudomperidone) is an orally active dopamine D2/D3 antagonist in development for treating patients with gastroparesis. Currently, the only US-approved treatment for gastroparesis is metoclopramide.

Domperidone has been associated with increased risk of QT prolongation, particularly at high plasma concentrations.

CIN-102 is a deuterated version of domperidone with select excipients designed to blunt peak concentration (Cmax) and extend half-life as compared to a given oral dose of domperidone.

The deudomperidone formulation is intended to provide similar or better therapeutic effects than domperidone with less QT liability.

## 2. Aim

This study's objective was to assess the effect of CIN-102 on ECG parameters, including concentration-QTc (C-QTc) analysis.

## 3. Methods

This was a randomized, partially double-blind, placebo- and active-controlled, single dose, crossover study in healthy subjects 18-55 years of age.

Subjects were randomized to receive a single dose of each of the following in separate periods (≥10 days between doses):

- CIN-102, 30 mg deudomperidone (represents steady-state [SS] therapeutic exposure)
- CIN-102, 100 mg deudomperidone (represents SS supratherapeutic exposure)
- 400 mg open-label moxifloxacin (positive control)
- CIN-102 placebo

The study drug was dispensed in a double-blind (CIN-102) or open-label (moxifloxacin) manner.

Continuous 12-lead ECGs were recorded starting at least 1 hour prior to dosing and ending approximately 48 hours postdose. The central ECG laboratory (ERT/Clario, Philadelphia, PA) extracted up to 10 12-lead ECGs at each prespecified time point. The QT interval was heart rate corrected using the Fridericia's formula (QTcF).

Primary analysis was based on concentration-QTc modeling of the relationship between plasma drug concentrations and change-from-baseline QTcF (ΔQTcF) with the intent to exclude an effect of placebo-corrected ΔQTcF (ΔΔQTcF) >10 milliseconds (ms) at clinically relevant plasma levels.

## 4. Results

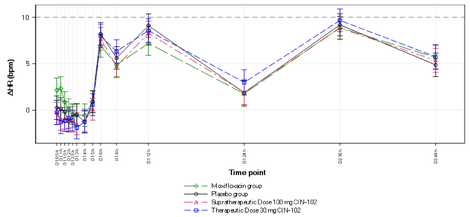
At baseline, data were available from 55 subjects receiving placebo, 52 subjects receiving 30 mg CIN-102, 52 subjects receiving 100 mg CIN-102, and 51 subjects receiving moxifloxacin.

The mean (SD) age of subjects was 38.5 (9.20) years, and the mean (SD) BMI of the subjects was 26.3 (2.48) kg/m2. Sixty-one percent of the subjects were male and 39% were female.

Baseline ECG parameters were within expectations for a healthy subject population.

CIN-102 at the studied doses did not have a clinically relevant effect on heart rate (**Figure 1**) or cardiac conduction (i.e., the PR and QRS intervals).

**Figure 1:** Change-from-baseline HR (ΔHR) across time points (QT/QTc population)




*LS mean and 90% CI based on a linear mixed-effects model for active and placebo treatment groups: ΔHR= Time + Treatment + Time × Treatment + Baseline HR + Period + Sequence.*

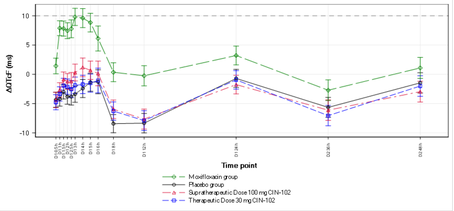
LS mean ΔΔQTcF was very small on both CIN-102 doses and varied within a narrow range during the first 4 hours post-dose:

- Between -0.3 and 1.8 ms at 0.5 and 2 hour(s) post-dose, respectively, in the 30 mg treatment group (**Figure 2**).
- Between 0.1 and 3.7 ms at 0.5 and 3 hour(s) post-dose, respectively, in the 100 mg treatment group (**Figure 2**).

Notably, the upper bound of the 90% CI of ΔΔQTcF was below 10 ms with both CIN-102 doses across all time points, demonstrating that an effect on ΔΔQTcF exceeding 10 ms could be excluded on both CIN-102 doses (**Figure 2**).

Moxifloxacin caused clear QTc prolongation.

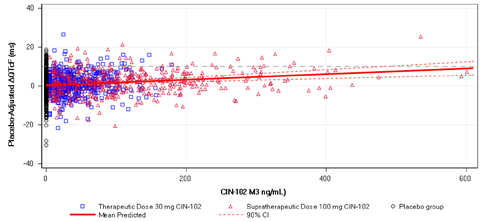
**Figure 2:** Change-from-baseline QTcF (ΔQTcF) across time points (QT/QTc population)




*LS mean and 90% CI based on a linear mixed-effects model for active and placebo treatment groups: ΔQTcF = Time + Treatment + Time × Treatment + Baseline QTcF + Period + Sequence.*

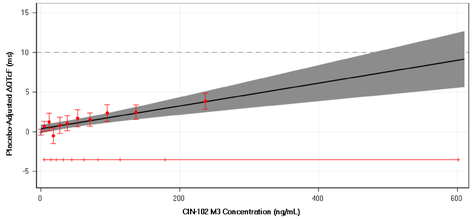
The estimated population slope of the concentration-QTc relationship was very shallow: 0.14 ms per ng/mL (90% CI: 0.08 to 0.20) with a small treatment effect-specific intercept of 0.37 ms (90% CI: -0.16 to 0.89) (**Figure 3 and Figure 4**).

**Figure 3:** Observed CIN-102-M3 plasma concentrations and estimated placebo-adjusted ΔQTcF (PK/QTc population14.2.9.)




*The solid red line with dashed red lines denotes the model-predicted mean ΔΔQTcF with 90% CI, which is calculated from the equation ΔΔQTcF = 0.3678 (ms) + 0.1439 (ms per ng/mL) × CIN-102 M3 concentration (ng/mL).*

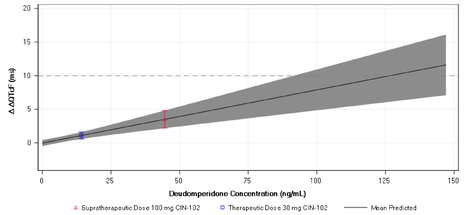
**Figure 4:** Model-predicted ΔΔQTcF (mean and 90% CI) and estimated placebo-adjusted ΔQTcF (mean and 90% CI) across deciles of CIN-102 M3 plasma concentrations (PK/QTc population)




*The solid black line with gray shaded area denotes the model-predicted mean ΔΔQTcF with 90% CI, which is calculated from the equation ΔΔQTcF = 0.3678 (ms) + 0.1439 (ms per ng/mL) × CIN-102 M3 concentration (ng/mL).*

Based on the concentration-QTc analysis, an effect on ΔΔQTcF exceeding 10 ms can be excluded up to deudomperidone plasma concentrations of ~92 ng/mL which is approximately 5 times the therapeutic steady state concentration (**Figure 5**).

**Figure 5:** Model-predicted ΔΔQTcF interval following administration of 30 mg and 100 mg CIN-102 (PK/QTc population)




*The solid black line with gray shaded area denotes the model-predicted mean (90% CI) ΔΔQTcF, which is calculated from the equation ΔΔQTcF = -0.02844 (ms) + 0.7918 (ms per ng/mL) × deudomperidone concentration (ng/mL). The vertical blue and red lines denote the estimated mean (90% CI) ΔΔQTcF with plotted points at the geometric mean Cmax of deudomperidone.*

The effect on ΔΔQTcF can be predicted to 1.10 ms (90% CI: 0.58 to 1.61) and 3.50 ms (90% CI: 2.18 to 4.82) for 30 and 100 mg treatment groups, respectively.

Based on this concentration-QTc analysis, an effect on ΔΔQTcF exceeding 10 ms can be excluded up to CIN102-M3 plasma concentrations of ~480 ng/mL.

The same linear model was used for moxifloxacin. The slope of the relationship was positive and statistically significant. The lower bound of the 2-sided CI of the predicted QT effect at geometric mean peak moxifloxacin concentrations was >5 ms, demonstrating assay sensitivity.

There were no clinically relevant effects of CIN-102 on heart rate or cardiac conduction. No deaths or serious adverse events occurred during the study.

## 5. Conclusion

This thorough QT study demonstrated that CIN-102 at therapeutic and supratherapeutic doses does not have a clinically meaningful effect on ECG parameters, including the QT interval. This modified formulation of domperidone provides a potential treatment for gastroparesis while decreasing the risk of QT prolongation associated with the traditional formulation of domperidone.

### Disclosures:

*This study was funded by CinDome Pharma, Inc. a subsidiary of CinRx Pharma LLC. Mary Bond, Brian Murphy, Brendan Doran, and Jonathan Isaacsohn are employees of CinRx Pharma and have an equity stake in the company. Borje Darpo and Leela Vrishabhendra have no financial interest in CinRx.*