A THOROUGH QT ASSESSMENT OF CETRORELIX PAMOATE FOLLOWING INTRAMUSCULAR ADMINISTRATION IN HEALTHY SUBJECTS

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OBJECTIVES

The purpose of this thorough QT (TQT) study was to demonstrate that cetrorelix (CET) pamoate, a luteinizing hormone releasing-hormone antagonist, does not prolong cardiac repolarization at time of maximum plasma concentrations or at trough testosterone levels.

The primary objectives were to show that:

- CET did not increase QTc at either T_{max} of CET ($Cetro_{max}$) or at the time of trough testosterone level ($Test_{min}$).
- The assay for testing for prolongation of cardiac repolarization was sufficiently sensitive, as reflected by detection of the regulatory minimum increase in QTc associated with the administration of moxifloxacin.
- If any changes in repolarization were detected at either $Cetro_{max}$ or $Test_{min}$ after the second dose, these effects were transient.

METHODOLOGY

This was a randomized, double-blind, double-dummy, placebo-controlled TQT study to assess the effects of CET pamoate on cardiovascular safety (QT/QTc interval assessment). All subjects enrolled in this study were judged by the Principal Investigator to be normal, healthy, male volunteers between the ages of 50 and 70 years (inclusive), who met all inclusion and none of the exclusion criteria.

The dose and mode of administration were as follows for the 3 treatment arms:

A. (CET): Subjects received a dose of 52 mg CET (as 2 x 26 mg IM injections), on Day 1 and Day 15 (equivalent to a total of 104 mg CET), and a placebo tablet on the morning of Day 15.

B. (Placebo): Subjects received 2 placebo IM injections, on Day 1 and Day 15, and a placebo tablet on the morning of Day 15.

C. (Moxifloxacin): Subjects received 2 placebo IM injections, on Day 1 and Day 15, and a single oral dose of Avelox® on the morning of Day 15.

All subjects were fasted from bedtime on Day 14 until at least 4 hours after dose administration on Day 15.

Cardiodynamic Analysis

Time-matched ECGs from 12-lead Holter monitors were extracted in triplicates on the day prior to the first dose (baseline) and on Day 15 (predose and at 1, 2, 4, 6, 8, 12, 24, 30, 36, 42, and 48 hours postdose). ECGs were also recorded on Days 21, 29, 43, and 57 but only data from Day 21 were extracted for analysis.

QT was corrected for HR by both Bazett's (QTcB) and Fridericia's (QTcF) methods, but QTcF was used as the primary measure of change in QT interval. The average of the triplicate measurements for HR, RR, PR, QRS, QT, QTcB, and QTcF was rounded to the nearest integer. The time-matched change from baseline in QT/QTc interval (dQT/dQTc) at each postdose time point was used in an analysis of variance (ANOVA) which was performed by time point (at 30, 36, 42, and 48 hours postdose). The upper confidence limit (UCL) of the 1-sided 95% CI of the treatment difference between the least-squares (LS) means of CET and placebo dQTcF (ddQTcF) at the 4 time points constituted the primary analysis.

An analysis of assay sensitivity using the same ANOVA model was used to estimate the differences in dQTcF between moxifloxacin and placebo at 1, 2, and 4 hours postdose. In addition, QT/QTc intervals (absolute and change from time-matched baseline) and morphological changes of ECG waveforms were summarized categorically. Clinically significant ECG abnormalities were summarized by treatment and abnormality.

$Cetro_{max}$ and $Test_{min}$ were determined from the PKPD profile of CET. The slope from the regression plot of individual dQTcF intervals versus individual concentrations of CET and testosterone was used to predict dQTcF values at $Cetro_{max}$ and $Test_{min}$, respectively, in order to characterize the PKPD/cardiodynamic relationship.

RESULTS

Dataset Analyzed and Demographic Characteristics

A total of 105 male subjects were enrolled in the study. Five (5) subjects discontinued the study before dosing on Day 15; therefore, 100 subjects were included in the cardiodynamic analysis. A total of 99 subjects completed the study through Day 57.

QT Correction

As QT varies inversely with HR, it is necessary to correct it. Ideally, after applying a correction factor, the relationship between QTc versus RR interval should be horizontal (slope of zero). QTcF was used as the primary measure of change in QT interval. The slopes of dQTcF versus RR for the 3 treatment groups are shown in Figure 1 through Figure 3.

Figure 1: Change From Time-Matched Baseline in QTcF Versus RR (Treatment A: CET)

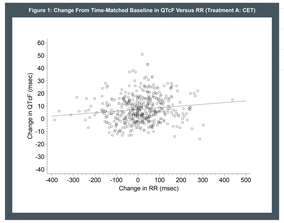


Figure 2: Change From Time-Matched Baseline in QTcF Versus RR (Treatment B: Placebo)

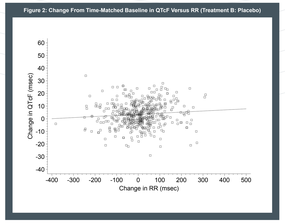
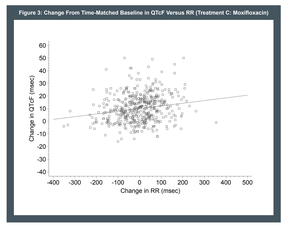


Figure 3: Change From Time-Matched Baseline in QTcF Versus RR (Treatment C: Moxifloxacin)



The slopes were close to 0 (range: 0.009 to 0.021) indicating that the QTcF adequately corrected for changes in HR.

ANOVA for Change From Time-Matched Baseline in QT/QTc Intervals

Cetrorelix QTcF prolongation effects were compared to placebo over the time range of the expected $Cetro_{max}$ and $Test_{min}$ (time points Hours 30, 36, 42, and 48 after the Day 15 CET dose). Table 1 details the UCL for the CET comparison at each time point.

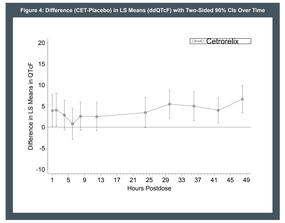
Table 1: Statistical Comparisons of Change From Time-Matched Baseline in QTcF Between Cetrorelix and Placebo

Time Point (hour)	CET dQTcF LS Mean (msec)	Placebo dQTcF LS Mean (msec)	Difference of LS Means (ddQTcF) (msec)	p-Value	UCL* (msec)
30	0.85	-4.62	5.47	0.0069	8.75
36	5.82	0.82	4.99	0.0165	8.39
42	2.50	-1.48	3.98	0.0272	6.93
48	2.66	-4.00	6.66	0.0008	9.83

*UCL = Upper confidence limit of the 1-sided 95% CI for the difference of the LS means.

Cetrorelix did not prolong QTcF interval above the regulatory threshold, either directly or indirectly through its effect on testosterone, as the UCL of the difference between the LS means of CET and placebo dQTcF (ddQTcF) at all 4 time points was <10 msec.
In addition to the cardiodynamic analysis performed at the expected $Cetro_{max}$ and $Test_{min}$ time points, the analysis was also done for all postdose time points following the second dose of 52 mg CET (Figure 4).

Figure 4: Difference (CET-Placebo) in LS Means (ddQTcF) with Two-Sided 90% CIs Over Time



The results showed that at no time point post dosing did the UCL of ddQTcF exceed 10 msec.

Analysis of Day 21 Data

Although CET did not prolong the QTcF interval above the regulatory threshold, an analysis was carried out on the Day 21 cardiodynamic data to confirm that any changes in cardiac repolarization were transient. The ECGs taken on Day 21 (7 days after the second set of CET injections) were from a 30-minute recording, which was time-matched with Hour 2 at baseline. Two baselines were used in the analysis: time-matched baseline using the Hour 2 intervals and an average baseline which consisted of the average of all intervals recorded on Day -1. Both analyses are presented in Table 2.

Table 2: Statistical Comparisons of Change From Time-Matched Baseline in QTcF Between Cetrorelix and Placebo at Day 21

Time Point (hour)	CET dQTcF LS Mean (msec)	Placebo dQTcF LS Mean (msec)	Difference of LS Means (ddQTcF) (msec)	p-Value	UCL* (msec)
Hour 2	10.84	6.15	4.69	0.0648	8.86
Average+	9.81	5.15	4.66	0.0388	8.36

\+ *Average is the average of all time points on Day -1.*
* *UCL = Upper confidence limit of the 1-sided 95% CI for the difference of the LS means.*

The 21-day analysis supports the conclusion of the primary analysis, i.e., CET does not prolong the QTcF interval above the regulatory threshold, based on the criteria outlined in the ICH E14 guidance.

Analysis of Assay Sensitivity

The moxifloxacin treatment arm C was included in the study design in order to serve as a positive control and, thus, to show that the study had the ability to detect a QTcF prolongation of regulatory concern (> 5 msec).

The analysis, termed analysis of assay sensitivity, used the same ANOVA as the primary analysis but compared the moxifloxacin and placebo LS means of the dQTcF at Hours 1, 2, and 4 (when moxifloxacin is expected to have the largest effect on QTcF prolongation), as well as for the average of the 3 time points following moxifloxacin administration on Day 15. Table 3 details the 1-sided, 95% lower confidence limit (LCL) for the moxifloxacin comparison at each time point.

Table 3: Statistical Comparisons of Change From Time-Matched Baseline in QTcF Between Moxifloxacin and Placebo

Time Point (hour)	Moxifloxacin dQTcF LS Mean (msec)	Placebo dQTcF LS Mean (msec)	Difference of LS Means (ddQTcF) (msec)	p-Value	UCL* (msec)
1	25.06	9.38	15.68	<0.0001	11.88
2	22.63	8.06	14.57	<0.0001	10.68
4	18.28	6.18	12.10	<0.0001	8.56
Average	21.99	7.87	14.12	<0.0001	10.94

\+ *Time point is hour after moxifloxacin administration corresponding to the time after the second injection of CET. Average is the average of the 3 time points.*
* *LCL = Lower confidence limit of the 1-sided 95% CI for the difference of the LS means.*

The assay for testing for prolongation of cardiac repolarization was sufficiently sensitive, as the LCL was greater than 5 msec at all 3 time points.

Categorical Summary of QT/QTc Intervals

A total of 3 subjects (9%) had QTcF values > 450 to ≤ 480 msec following CET, and in comparison, 2 subjects (6%) following placebo had QTcF values > 450 msec. QTcF values > 450 msec most commonly occurred at Hour 4 on Day 15 following both CET and placebo. None of the subjects following CET treatment had QTcF values > 480 msec. One (1) subject (3%) following moxifloxacin had a QTcF value > 480 to ≤ 500 msec. No values for QTcF exceeded 500 msec.

Categorical Summary of Maximum Postdose QT/QTc Change from Time-Matched Baseline

A total of 6 subjects (18%) following CET had dQTcF values > 30 to ≤ 60 msec; these increases were observed at Hours 1 through 6 and on Day 21. No QTcF increases following placebo exceeded 30 msec, and 10 subjects (31%) had QTcF increases > 30 msec following moxifloxacin. No dQTcF values exceeded 60 msec.

Drug Concentration and Relationship to Response

Table 4: Change from Baseline in QT, QTcB, and QTcF (msec) versus CET Plasma Concentration (ng/mL) Following Treatment A - Estimates from Linear Regression

dQT Parameter	Slope	R^2	p-value	Predicted dQT/dQTc at $Cetro_{max}$
dQT	-4.6350	0.1750	0.0001	-1.33
dQTcB	-0.5086	0.0054	0.1527	4.59
dQTcF	-1.8466	0.0914	0.0001	2.69

The results of the PK/cardiodynamic relationship showed that the slope of the linear regression of dQTcF on CET concentrations at predose on Day 15 and at 1, 2, 4, 6, 8, 12, 24, 30, 36, 42, and 48 hours following the Day 15 CET dose was -1.8466, with a predicted dQTcF at $Cetro_{max}$ of 2.69 msec. These data do not support any effect of CET on cardiac repolarization (QT/QTc interval).

Table 5: Change from Baseline in QT, QTcB and QTcF (msec) versus Testosterone Serum Concentration (pg/mL) Following Treatment A - Estimates from Linear Regression

dQT Parameter	Slope	R^2	p-value	Predicted dQT/dQTc at $Test_{min}$
dQT	0.2150	0.1330	0.0001	30.5
dQTcB	0.0037	0.0001	0.8708	5.77
dQTcF	0.0749	0.0619	0.0002	14.1

The results of the PD/cardiodynamic relationship showed that the slope of the linear regression of dQTcF on testosterone concentrations was 0.0749 with a predicted dQTcF at $Test_{min}$ of 14.1 msec. The data seem to indicate a potential effect of testosterone on cardiac repolarization at trough concentrations. However, the proportion of the variability explained by the linear regression (coefficient of determination, R^2) was only 6%.

CONCLUSIONS

This TQT study was negative for supratherapeutic doses of CET pamoate administered as 2 IM doses 2 weeks apart (each dose equivalent to 52 mg peptide base):

- CET pamoate did not prolong the QTcF interval either directly or through its effect on testosterone (the upper limit of the 95% CI of the mean effect on QTc was <10 msec at all time points).
- CET pamoate had no effect on cardiac repolarization based on PK/PD analyses.