Pharmacokinetics, Pharmacodynamics, and Safety of a Supra-Therapeutic Dose of Cetrorelix Pamoate in Healthy Males

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OBJECTIVES

To investigate the pharmacokinetics, pharmacodynamics, and safety of cetrorelix pamoate, a luteinising-hormone releasing-hormone antagonist, administered at a supra-therapeutic dose in a thorough QT study.

METHODOLOGY

This was a randomized, double-blind, double-dummy, placebo-controlled, 3-arm, parallel study in 105 healthy males. 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 test product, cetrorelix (CET) pamoate, was a dry powder (lyophilisate) formulation that delivered 26 mg CET (peptide base) per glass vial. Placebo for the test drug was provided in glass vials of 10 mL, (matched with CET 26 mg vials). Each dose comprised a set of 2 IM injections, 1 injection into each buttock. The positive control was moxifloxacin 400 mg tablet (Avelox®), masked by the use of a matching placebo tablet. The oral dose was administered with 240 mL of water, immediately prior to the IM injections on Day 15.

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

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

Pharmacokinetic and Pharmacodynamic Assessments

Pharmacokinetic samples for the determination of CET peptide base in plasma were collected prior to the first dose, prior to the second dose, at 1, 2, 4, 6, 8, 12, 24, 30, 36, 42, and 48 hours after the Day 15 CET dose, as well as on Days 21, 29, 43, and 57.

Pharmacodynamic samples for the determination of testosterone, dihydroxytestosterone (DHT) and estradiol in serum were collected prior to the first dose, prior to the second dose, at 12, 24, 30, 36, 42, and 48 hours after the Day 15 CET dose, as well as on Days 21, 29, 43, and 57.

Plasma CET (peptide base) concentrations and serum testosterone, DHT, and estradiol were analyzed using a validated HPLC-MS/MS method. Safety assessments were vital signs, physical examination, 12-lead ECGs, clinical laboratory evaluations, adverse events (AE), and local tolerance to IM injections.

RESULTS

Pharmacokinetic Analysis

After the last 2 IM injections of 26 mg CET (peptide base) each on Day 15, peak plasma concentrations were reached at approximately 48 hours postdose. Following peak concentration of CET, mean plasma levels declined in a biexponential manner and remained above the lower limit of quantitation (0.300 ng/mL) up to 42 days after the Day 15 dosing, which corresponded to the end of the observation period in this study.

Cetrorelix in Plasma

Figure 1: Mean Plasma Cetrorelix Concentrations Versus Time Following Two Injections of Cetrorelix Two Weeks Apart

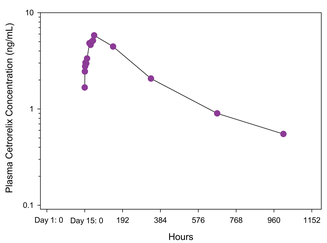


Table 1: Summary of Cetrorelix PK Parameters Following Treatment A

Pharmacokinetic Parameters	Treatment A (N = 34)
Geometric Mean (CV%)	
C_{max} (ng/mL)	5.77 (26.2)
$AUC_{0\text{-}t}$ (ng·hr/mL)	2018 (23.5)
Median (Min – Max)	
T_{max} (hr)	47.9 (23.8 – 147)
Arithmetic Mean ± SD	
$t_{1/2}$ (hr)	370 ± 121

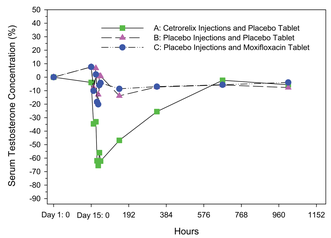
Treatment A = 2 cetrorelix injections 2 weeks apart and a placebo tablet with the second set of injections

Following 2 injections of 26 mg CET 2 weeks apart (dose equivalent to 52 mg of peptide base), the mean extent of exposure ($AUC_{0\text{-}t}$) to CET peptide base was 2018 ng·hr/mL. The mean maximum plasma concentration (C_{max}) was 5.77 ng/mL and was reached at approximately 48 hours postdose. The mean half-life of CET peptide base when given as a pamoate salt was 370 hours. The intersubject variability of CET PK parameters was around 25%.

Pharmacodynamic Analysis

Testosterone in Serum

Figure 2: Mean Percent Change from Baseline of Serum Testosterone Following Treatments A, B, and C



The mean change from baseline in serum testosterone decreased rapidly after the last 2 IM injections of 26 mg CET (dose equivalent to 52 mg of peptide base). The mean testosterone concentrations returned to baseline levels at the end of the sampling schedule (42 days after the Day 15 CET dose). The time course of serum testosterone concentrations following placebo and moxifloxacin reflected the normal variability in hormone levels of healthy subjects.

Table 2: Summary of Testosterone PD Parameters Following Treatments A, B, and C

Pharmacodynamic Parameters	Treatment A (N)	Treatment B (N)	Treatment C (N)
Geometric Mean (CV%)			
Baseline (pg/mL)	4680 (36.1) (34)	4190 (32.1) (34)	4700 (26.9) (32)
Nadir (pg/mL)	1060 (116) (34)	2980 (34.0) (34)	3300 (22.7) (32)
Arithmetic Mean ± SD			
Percent Change from Baseline at Nadir (%)	-68.3 ± 22.6 (34)	-27.3 ± 15.9 (34)	-28.7 ± 12.8 (32)
Median (Min – Max)			
Time to Nadir (hr)*	39.0 (30.0 – 1008) (34)	96.0 (12.0 -1008) (34)	36.0 (12.0 – 672) (32)
Duration of Suppression Below 50% Baseline (hr)	53.8 (0.00 – 651) (34)	0.00 (0.00 – 7.08) (34)	0.00 (0.00 – 238) (32)
Time to 80% Baseline Recovery (hr)	324 (41.2 – 1011) (33)	98.5 (19.9 – 1011) (25)	41.5 (31.0 – 1011) (26)

* Nadir time relative to the Day 15
Treatment A = 2 cetrorelix injections 2 weeks apart and a placebo tablet with the second set of injections
Treatment B = 2 placebo injections 2 weeks apart and a placebo tablet with the second set of injections
Treatment C = 2 placebo injections 2 weeks apart and a moxifloxacin tablet with the second set of injections

Compared with placebo, a significant decrease in testosterone concentrations was observed after the last 2 injections of 26 mg CET on Day 15. The average testosterone concentration at nadir accounted for a 68.3% decrease from baseline following CET versus an approximately 28% decrease following both placebo and moxifloxacin.

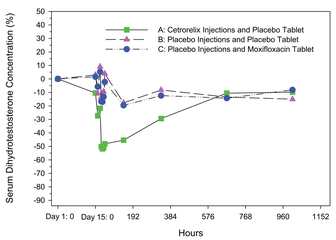
Maximum testosterone suppression was observed 39.0 hours post CET dosing on Day 15. Mean testosterone concentration at the nadir was 1060 pg/mL following CET treatment, as compared to 2980 and 3300 pg/mL following treatment with placebo and moxifloxacin, respectively.

The duration of action calculated as the time period over which testosterone concentrations were below 50% of baseline was approximately 54 hours (2.25 days) post CET dosing on Day 15. In the control groups, only 1 and 2 subjects showed a decrease in testosterone levels below 50% of baseline following treatment with moxifloxacin and placebo, respectively, compared to 29 subjects with CET treatment.

The mean recovery time for testosterone concentrations to return to 80% of their baseline levels was 13.5 days after the Day 15 CET dose. Only subjects who had a decrease of at least 20% from baseline were included in this analysis. One subject administered CET had testosterone concentrations above 80% of baseline throughout the sampling schedule. In the control groups, testosterone concentrations remained above 80% of baseline for a total of 9 subjects following placebo and 6 subjects following moxifloxacin.

Dihydrotestosterone in Serum

Figure 3: Mean Percent Change from Baseline of Serum Dihydrotestoterone Following Treatments A, B, and C



The mean change from baseline in serum DHT decreased rapidly after the last 2 IM injections of 26 mg CET (dose equivalent to 52 mg of peptide base). The mean DHT concentrations returned to close to baseline levels at the end of the sampling schedule (42 days postdose). In the control groups, the time course of serum DHT concentrations following placebo and moxifloxacin reflected the normal variability in hormone levels of healthy subjects.

Table 3: Summary of DHT PD Parameters Following Treatments A, B, and C

Pharmacodynamic Parameters	Treatment A (N)	Treatment B (N)	Treatment C (N)
Geometric Mean (CV%)			
Baseline (pg/mL)	532 (38.8) (34)	481 (33.1) (34)	469 (32.3) (31)
Nadir (pg/mL)	182 (68.2) (34)	323 (35.5) (34)	315 (37.0) (32)
Arithmetic Mean ± SD			
Percent Change from Baseline at Nadir (%)	-59.4 ± 26.8 (34)	-31.8 ± 12.0 (34)	-31.6 ± 15.7 (31)
Median (Min – Max)			
Time to Nadir (hr)*	42.0 (30.0 – 336) (34)	336 (12.0 -1008) (34)	144 (30.0 – 1008) (32)
Duration of Suppression Below 50% Baseline (hr)	49.5 (0.00 – 673) (34)	0.00 (0.00 – 2.87) (34)	0.00 (0.00 – 108) (32)
Time to 80% Baseline Recovery (hr)	479 (40.1 – 1011) (33)	878 (14.1 – 1011) (29)	252 (30.7 – 1011) (26)

* Nadir time relative to the Day 15
Treatment A = 2 cetrorelix injections 2 weeks apart and a placebo tablet with the second set of injections
Treatment B = 2 placebo injections 2 weeks apart and a placebo tablet with the second set of injections
Treatment C = 2 placebo injections 2 weeks apart and a moxifloxacin tablet with the second set of injections

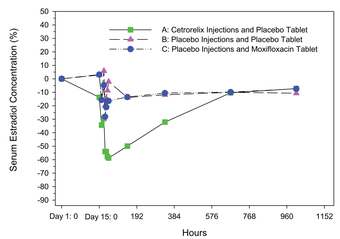
Compared with placebo, a significant decrease of DHT concentrations was observed after the last 2 injections of 26 mg CET on Day 15. The average DHT concentration at nadir accounted for a 59.4% decrease from baseline following CET versus an approximately 32% decrease following both placebo and moxifloxacin. Maximum DHT suppression was observed at 42.0 hours postdose on Day 15. Mean DHT concentration was 182 pg/mL after CET as compared to 323 and 315 pg/mL following treatment with placebo and moxifloxacin, respectively.

The duration of action, where DHT concentrations were below 50% of baseline, was approximately 49.5 hours (2.1 days) following the second set of 26 mg CET injections. In the control groups, only 1 and 3 subjects showed a decrease in DHT levels below 50% of baseline following treatment with placebo and moxifloxacin, respectively, compared to 24 subjects with CET.

The mean recovery time for DHT concentrations to return to 80% of their baseline levels was 20 days after the Day 15 CET dose. Only subjects who had a decrease of at least 20% from baseline were included in this analysis. One subject had DHT concentrations above 80% of baseline throughout the sampling schedule. In the control groups, DHT concentrations remained above 80% of baseline for a total of 5 subjects following placebo and moxifloxacin administration. Post-nadir time to return to 80% of its baseline value was greater than the last blood collected time for 13 subjects receiving placebo compared to 9 and 6 subjects receiving CET and moxifloxacin. Consequently, the time to 80% baseline recovery seemed greater in the placebo group.

Estradiol in Serum

Figure 4: Mean Percent Change from Baseline of Serum Estradiol Following Treatments A, B, and C



The mean change from baseline in serum estradiol decreased rapidly after the last 2 IM injections of 26 mg CET (dose equivalent to 52 mg of peptide base). The mean estradiol concentrations returned close to baseline levels at the end of the sampling schedule (42 days after the second set of injections). In the control groups, the time course of serum estradiol concentrations following placebo and moxifloxacin reflected the normal variability in hormone levels of healthy subjects.

Table 4: Summary of Estradiol PD Parameters Following Treatments A, B, and C

Pharmacodynamic Parameters	Treatment A (N)	Treatment B (N)	Treatment C (N)
Geometric Mean (CV%)			
Baseline (pg/mL)	23.2 (37.0) (34)	24.3 (29.5) (34)	24.3 (32.6) (32)
Nadir (pg/mL)	7.51 (76.4) (34)	17.1 (27.8) (34)	16.1 (29.1) (32)
Arithmetic Mean ± SD			
Percent Change from Baseline at Nadir (%)	-61.8 ± 20.8 (34)	-28.9 ± 8.42 (34)	-32.9 ± 12.2 (32)
Median (Min – Max)			
Time to Nadir (hr)*	48.0 (24.0 – 336) (34)	39.0 (12.0 -1008) (34)	30.0 (12.0 – 672) (32)
Duration of Suppression Below 50% Baseline (hr)	82.6 (0.00 – 614) (34)	0.00 (0.00 – 168) (34)	0.00 (0.00 – 11.4) (32)
Time to 80% Baseline Recovery (hr)	474 (47.5 – 1011) (33)	94.6 (12.3 – 1011) (31)	55.0 (17.5 – 1011) (28)

* Nadir time relative to the Day 15
Treatment A = 2 cetrorelix injections 2 weeks apart and a placebo tablet with the second set of injections
Treatment B = 2 placebo injections 2 weeks apart and a placebo tablet with the second set of injections
Treatment C = 2 placebo injections 2 weeks apart and a moxifloxacin tablet with the second set of injections

Compared with placebo, a significant decrease of estradiol concentrations was observed after the last 2 injections of 26 mg CET on Day 15. The average estradiol concentration at nadir accounted for a 61.8% decrease from baseline following CET versus an approximately 29 to 33% decrease following both placebo and moxifloxacin.

Maximum estradiol suppression was observed at 48.0 hours postdose on Day 15. The mean estradiol concentration at the nadir was 7.51 pg/mL after CET treatment as compared to 17.1 and 16.1 pg/mL following treatment with placebo and moxifloxacin, respectively. The duration of action, calculated as the time period over which estradiol concentrations were below 50% of baseline, was approximately 82.6 hours (3.4 days) following the second set of 26 mg post CET injections on Day 15. In the control groups, only 1 and 2 subjects showed a decrease in estradiol levels below 50% of baseline following treatment with placebo and moxifloxacin, respectively, compared to 28 subjects with CET.

The mean recovery time for estradiol concentrations to return to 80% of their baseline levels was approximately 20 days after the Day 15 CET dose. Only subjects who had a decrease of at least 20% from baseline were included in this analysis. One subject had estradiol concentrations above 80% of baseline throughout the sampling schedule. In the control groups, estradiol concentrations remained above 80% of baseline for a total of 3 subjects following placebo and 4 subjects following moxifloxacin.

SAFETY

There were no SAEs reported on this study and 2 subjects were withdrawn from the study due to unlikely/unrelated AEs, 1 each in the CET and moxifloxacin groups. Injection site pain was considered the most common AE at least likely related to study treatment, although subject incidence was low overall (5%) and comparable following CET and placebo. The most common AE reported overall was mild headache with comparable incidence across treatments. There were no clinically meaningful changes in the mean laboratory parameters and mean vital sign measurements were stable during the study with minimal changes from baseline.

CONCLUSIONS

Pharmacokinetic / Pharmacodynamic

The mean extent of exposure to CET peptide base after the second set of injections on Day 15 was 2018 ng·hr/mL. The mean C_{max} was 5.77 ng/mL and was reached at approximately 48 hours after the Day 15 dose. The mean half-life of CET peptide base, when administered as a pamoate salt, was 370 hours. A significant suppression of testosterone, DHT, and estradiol was observed postdose on Day 15, with an average percent decrease from baseline at nadir ranging between 59 and 68%. Maximum suppression was observed after 39.0 to 48.0 hours postdose.

Safety

CET administered as 2 injections of 26 mg CET 2 weeks apart appeared to be clinically safe and well tolerated in healthy male subjects. The TQT study was negative for supra-therapeutic doses of CET. CET did not prolong the QTcF interval either directly or through its effect on testosterone and DHT.

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