Clinical Trial Results Summary
Study AUX-TG-222

Name of Sponsor/Company: Auxilium Pharmaceuticals, Inc.	
Name of Finished Product: Testim® (testosterone gel)	
Name of Active Ingredient: Testosterone	
Study Title: A Randomized, Double-Blind, Two-Way Crossover Study to Determine the Bioequivalence of a Single Dose of Testim® 1% With Pentadecalactone 1% Relative to a Single Dose of Testim® 1% With Pentadecalactone 8% in Hypogonadal Males	
Study Centers: Dr. Henk Mulder, Rotterdam Research Institute, Schieweg 52a, Rotterdam, Netherlands	
Publication (Reference): None	
Study Period: Initiation Date: 20-Apr-2007 Completion Date: 07-Jun-2007	**Clinical Phase:** 2
Objectives: The objective of this study was to evaluate the pharmacokinetics and safety of Testim® 1% with 1% pentadecalactone (oxacyclohexadecan-2-one; cyclopentadecanolide [CPD]) relative to Testim® 1% with 8% CPD in hypogonadal men.	
Methodology: This was a randomized, double-blind, 2-way crossover study in hypogonadal men who were otherwise healthy. Subjects were screened for eligibility within 28 days before the first dose of study drug. On Day 1 and Day 8, subjects received single doses of Testim® 1% with 1% CPD and Testim® 1% with 8% CPD according to randomization. Blood samples for the determination of serum testosterone levels were collected before the 08:00 AM dose and at predetermined time points after each dose.	
Diagnosis and Main Criteria for Inclusion: Eligible subjects were consenting men between 18 and 80 years of age who had an 8 AM serum testosterone level ≤ 350 ng/dL.	
Number of Subjects (Planned, Enrolled, Analyzed): At least 36 subjects, expected maximum of 80 subjects. 36 subjects were planned; 34 subjects were analyzed for pharmacokinetics and 35 were analyzed for safety.	
Duration of Treatment: Two single doses separated by a 7-day washout period	
Study Drug, Dose and Mode of Administration, Lot Number: Each 5 g tube of the Testim® 1% with 1% CPD: Testosterone 50 mg and the following inactive ingredients: carbopol, acrylates, propylene glycol, glycerin, polyethylene glycol, ethanol, tromethamine, CPD, and purified water. Lot number XML-C.	
Reference Therapy, Dose and Mode of Administration, Batch Number: Each 5 g tube of the Testim® 1% with 8% CPD: Testosterone 50 mg and the following inactive ingredients: carbopol, acrylates, propylene glycol, glycerin, polyethylene glycol, ethanol, tromethamine, CPD, and purified water. Lot number XEC-C.	
Phamacokinetic Assessments: Blood samples for the determination of serum testosterone levels were collected at the following time points relative to each dose: before the 08:00 AM dose and 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, and 24 hours after each single dose on Day 1 and Day 8.	
Safety Assessments: Safety assessments included vital sign measurements, skin irritation assessments, clinical laboratory testing, and reporting of adverse events.	

Statistical Methods:

Pharmacokinetics: Pharmacokinetic parameter values were estimated using validated pharmacokinetic software. A non-compartmental approach was used to generate parameters estimates for testosterone, dihydrotestosterone (DHT), and free testosterone. The following pharmacokinetic parameter estimates were calculated:

- Maximum observed concentration (C_{max})
- Time to maximum observed concentration (T_{max})
- Area under the concentration-time curve (AUC) for 24 hours

Following logarithmic transformation AUC_{0-24} and C_{max} values for testosterone, DHT, and free testosterone were analyzed using an analysis of variance (ANOVA), including terms for sequence, subject within sequence, period, and formulation.

Point estimates and 90% confidence intervals for the difference of the test formulation (Testim® 1% with 1% CPD) relative to the reference formulation (Testim® 1% with 8% CPD) were constructed using the error variance obtained from the ANOVA. The point and interval estimates were back transformed to give estimates of the ratio of the test formulation relative to the reference formulation. If the 90% confidence interval for the measures of relative bioavailability (ie, AUC ratio and C_{max} for testosterone) were within the range of 0.80 and 1.25 then the two formulations were judged bioequivalent.

Safety: Adverse events including skin irritation were mapped to the preferred term using the Medical Dictionary of Regulatory Activities (MedDRA) and summarized by proportion of subjects within each formulation group who reported each event. Change from pre-dose values for each clinical laboratory test, skin irritation score, and vital signs were summarized by formulation group using descriptive statistics at each time point collected.

Interim Analysis: Following the completion of the first 36 subjects, an interim analysis was conducted by an independent statistician in order to evaluate the sample size assumptions. The AUC_{0-24} and the Cmax for testosterone were computed. The sample size assumptions regarding formulation equivalence in testosterone concentration and the within subject variability were evaluated.

SUMMARY

PHARMACOKINETIC RESULTS: Statistical analysis of log transformed geometric mean AUC_{0-24} estimates indicated that total systemic exposure to total testosterone, free testosterone, and DHT did not differ significantly between the two formulations, indicating that bioequivalence could be concluded between the two Testim® formulations. However, bioequivalence based on C_{max} estimates could not be concluded for total testosterone and free testosterone.

Following application of a dose of Testim® 1% with CPD 1% and Testim® 1% with CPD 8% to hypogonadal male subjects, the time taken to achieve maximum serum concentrations of total testosterone, free testosterone and DHT was variable and ranged from 0.0 to 24.1 hours after dosing (ie, across the entire sampling range) and was reflective of the multiple concentration maxima observed in the individual concentration versus time profiles.

SAFETY RESULTS: Single doses of each Testim® 1% formulation were well tolerated among hypogonodal men who were otherwise healthy. No deaths or other serious adverse events were reported. One subject was discontinued after the first treatment sequence due to an unrelated adverse event.

The vast majority of the subjects had no visible skin reaction to either Testim® 1% formulation over the 24-hour observation period. Mean changes in hematology, serum chemistry, and vital sign parameters from baseline to the final evaluation were small and not considered clinically meaningful.