SYNOPSIS

Name of Sponsor:

Abbott Products, Inc.

Individual Study Table

(For National Authority Use only)

Name of Finished Product:

Testosterone Gel 1.62%

Name of Active Ingredient:

Testosterone

Study Title:

A Multiple Dose Pharmacokinetic and Comparative Bioavailability Study of Testosterone Absorption after Administration of 5 g Testosterone Gel 1.62% to the Upper Arms/Shoulders using an Application Site Rotation or a Combination of Application Sites in Hypogonadal Males

Investigator(s):

Pedro Ylisastigui, M.D. (PI from June 9, 2010 through study completion)

Melanie Fein, M.D. (PI through June 9, 2010)

Study Center(s):

One investigational site in the United States (US): [redacted]

Publication (Reference):

Not applicable

Studied Period:

17 May 2010 (first subject first visit) to
29 Jul 2010 (last subject last visit)

Phase of Development:

Phase I

Objectives:

- To determine the multiple dose pharmacokinetics of testosterone after administration of 5.00 g Testosterone Gel 1.62% in hypogonadal males.
- To determine the relative bioavailability of observed testosterone after administration of 5.00 g Testosterone Gel 1.62% using an application site rotation between the upper arms/shoulders and abdomen or combination of the upper arms/shoulders and abdomen application sites.

Methodology:

This study was an open-label, randomized, two period, two treatment, crossover study in hypogonadal male volunteers.

Number of Subjects (Planned and Analyzed):

A total of 62 hypogonadal subjects were enrolled, received at least one dose of study medication, and completed this study. No subjects were prematurely discontinued or withdrew. All subjects (N=62) were included in both the PK and safety analyses.

Main Criteria for Inclusion:

- Documentation of written informed consent. The subject had adequate written and oral fluency to understand the informed consent and converse with the investigator in the language in which the informed consent was written.
- Male subjects 18 - 80 years of age, inclusive.
- Serum total testosterone < 300 ng/dL. Documented lab result was obtained during screening visit, within 6 weeks of Day -2 for subjects not currently on androgen replacement therapy, or following washout of androgen replacement therapy.
- Subjects naïve to androgen replacement *or* washout of 16 weeks following intramuscular androgen injections; 4 weeks following topical or buccal androgens; and 3 weeks following oral androgens.
- Subjects with a Body Mass Index (BMI) of 20 - 35 kg/m^2, inclusive.
- In the opinion of the investigator the subject was determined otherwise healthy by vital signs, medical history, physical exam, electrocardiogram (ECG), and laboratory examination (hematology, clinical chemistry, and urinalysis).

Test Product, Dose and Mode of Administration, Batch Number:

The test product was 5.00 g of Testosterone Gel 1.62% containing 81 mg of testosterone (a single batch of lot number 90015 [expiration: 04/12]).

Volunteers who consented to participate in this study and met the inclusion/exclusion criteria underwent two treatment periods in randomized order. There was a one week washout between treatments. The two treatments were as follows:

Treatment A:

Once daily application of Testosterone Gel 1.62% to the abdomen for 3 days (2.5 g to each the right and left sides of the abdomen) followed by application to the upper arms/shoulders (2.5 g to each the right and left upper arm/shoulder) for 4 days. The total daily gel dose was 5.00 g.

Treatment B:

Once daily application of Testosterone Gel 1.62% to a combination of the upper arms/shoulders and abdomen for 7 days. The total daily gel dose was 5.00 g consisting of 1.25 g applied to the left upper arm/shoulder, 1.25 g applied to the right upper arm/shoulder, 1.25 g applied to the left abdomen and 1.25 g applied to the right abdomen.

Duration of Treatment:

24 days

Criteria for Evaluation

Pharmacokinetics:

Whole blood samples (6 mL) were collected in [redacted] for determination of total testosterone, dihydrotestosterone, and estradiol at the following times:

- Day -1 and Day 14 (baseline) at: 0, 1, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hours with respect to the projected time of Testosterone Gel 1.62% dose administration
- Days 7 and 21 at: 0, 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours post Testosterone Gel 1.62% dose administration

- Days 5, 6, 19, 20 at: predose

A total of 288 mL of whole blood were obtained from each subject for pharmacokinetic assessments during the course of this trial (approximately 24 days). Serum levels of testosterone, dihydrotestosterone, and estradiol were determined. C_{max}, C_{av}, t_{max}, and AUC_{0-24} were calculated for observed and baseline-adjusted testosterone. Samples were analyzed using validated bioanalytical methods.

Safety:

Screening assessments included medical history, vital signs, 12-lead ECG, physical examination (including weight and height), clinical laboratory determinations (including testosterone and prostate specific antigen [PSA] measurement), digital rectal examination (DRE) and International Prostate Symptom Score (IPSS). Final assessments included physical examination (including weight), vital signs, 12-lead ECG, clinical laboratory determinations (including PSA measurement), DRE and IPSS, and application site evaluation. Throughout the study vital signs, application site evaluation, adverse events and concomitant medications will be monitored.

Statistical Methods:

Pharmacokinetics:

The statistical objectives of this study were to evaluate the comparative bioavailability of observed testosterone after administration of 5.00 g Testosterone Gel 1.62% when applied using a rotation between the upper arms/shoulders and abdomen or using a combination of both the upper arms/shoulders and the abdomen after multiple dosing. Relative bioavailability comparisons were based on ratios of C_{max} and AUC_{0-24}. The reference treatment for comparison was Treatment A.

Comparisons of Treatment B to reference Treatment A were made for both observed and baseline-adjusted testosterone within the framework of a linear mixed effects model with treatment, period, and sequence as fixed effects and subject within sequence as random effect. Parameters were log-transformed prior to analysis, and for the baseline adjusted parameters, the log-transformed baseline value were included in the model as a covariate. A non-parametric analysis was performed if the assumption of the parametric approach was not supported by the data. Inter and intrasubject CVs and 90% confidence intervals for the ratios of test:reference were provided.

Safety:

Treatment emergent adverse events (TEAEs) were summarized by unique treatment. Severity and drug-event relationship of TEAEs were summarized separately. Laboratory variables, including changes from baseline were summarized. A frequency table was presented for markedly abnormal values. Shift tables were presented according to the reference ranges (low, normal or high). Vitals signs, including changes from baseline were summarized. A frequency table was presented for markedly abnormal values.

Sample size:

Based on data from a previous [redacted] study that assessed application site pharmacokinetics of the upper arms/shoulders compared to the abdomen ([redacted]), assuming a mean C_{av} of 700 ng/dL and standard deviation of 347, 60 subjects would provide 90% power to detect a 30% difference between application sites at the two-sided 0.05 significance level. A total of 62 hypogonadal subjects were enrolled to allow for at least 60 subjects to complete the full trial.

Summary – Conclusions

Pharmacokinetic Results:

Observed and baseline-adjusted testosterone:

Mean baseline (Day -1/Day 14) concentrations of observed testosterone ranged from 263-371 ng/dL for Treatment A and 262-338 ng/dL for Treatment B, representing values just below or at the lower end of the eugonadal range of 300-1000 ng/dL.

Following treatment with 5.00 g Testosterone Gel 1.62%, mean observed testosterone concentrations were comparable for Treatments A and B. Mean observed testosterone concentrations were within the eugonadal range over the entire 24-hour profile.

The baseline-adjusted concentration-time profiles for testosterone followed the same pattern as the observed data.

After application of 5.00 g Testosterone Gel 1.62%, 7 subjects that received Treatment A had testosterone concentrations >2500 ng/dL. No subject on Treatment B had testosterone concentrations >2500 ng/dL.

Observed dihydrotestosterone and estradiol:

[redacted]

Pharmacokinetic and statistical results:

Pharmacokinetic parameters for observed and baseline-adjusted testosterone by treatment are summarized below.

Mean (SD) Testosterone Pharmacokinetic Parameters

	Observed				Baseline-Adjusted			
	n	Treatment A	n	Treatment B	n	Treatment A	n [(a)]	Treatment B
C_{max} (ng/dL)	62	1283 (817)	62	866 (369)	60	1000 (833)	58	578 (380)
AUC_{0-24} (ng*hr/dL)	62	14433 (5880)	62	11817 (3981)	60	7891 (5578)	58	5270 (3647)
C_{av} (ng/dL)	62	601 (245)	62	492 (166)	60	329 (232)	58	220 (152)
[redacted]								

Note: SD = standard deviation.

[a] Negative concentrations were treated as missing and subjects with more than half of all concentrations negative for a given treatment are not included in the summary.

[b] Median (min, max) presented for t_{max}.

Mean observed C_{max} values were within the eugonadal range (300-1000 ng/dL) for Treatment B and were above the upper limit of the eugonadal range (>1000 ng/dL) for Treatment A. Mean observed C_{av} values were within the normal range for both treatments. Median t_{max} was 1 hour for both treatments.

[redacted]

The statistical comparison of PK parameters was performed for Treatments A and B for observed (analysis of variance [ANOVA]) and baseline-adjusted testosterone (ANOVA and analysis of covariance [ANCOVA]). Results are presented in the table below.

Statistical Comparison of PK Parameters for Testosterone

Parameter	Analyte	Treatment	n	Comparison [a]		
				Geo LS Mean [b]	Ratio (%)	90% CI
AUC_{0-24} (ng*hr/dL)	Observed Testosterone (ANOVA)	A	62	13459	0.836	0.781, 0.895
		B	62	11256		
C_{av} (ng/dL)		A	62	561	0.836	0.781, 0.895
		B	62	469		
C_{max} (ng/dL)		A	62	1095	0.733	0.663, 0.812
		B	62	803		
AUC_{0-24} (ng*hr/dL)	Baseline-adjusted Testosterone (ANOVA)	A	60	6092	0.672	0.565, 0.800
		B	58	4094		
C_{av} (ng/dL)		A	60	254	0.672	0.565, 0.800
		B	58	171		
C_{max} (ng/dL)		A	60	752	0.627	0.533, 0.737
		B	58	471		
AUC_{0-24} (ng*hr/dL)	Baseline-adjusted Testosterone (ANCOVA) [c]	A	62	13461	0.836	0.782, 0.894
		B	62	11255		
C_{av} (ng/dL)		A	62	561	0.836	0.782, 0.894
		B	62	469		
C_{max} (ng/dL)		A	62	1095	0.734	0.663, 0.812
		B	62	803		

[redacted]
B vs A comparison.
Geometric least squares mean.
The ANCOVA analysis included baseline testosterone values in the model as a covariate, thus accounting for negative baseline adjusted values.

The mean ratios for C_{av} and C_{max} demonstrate that Treatment B was approximately 16% and 27% lower than Treatment A, respectively. These results suggest that the bioavailability of Treatment A and Treatment B is comparable.

Safety Results:

The proportion of subjects with non-serious TEAEs was the same for both study Treatments (27% [17 of 62 subjects). No subjects experienced TEAEs of severe intensity. No subjects were discontinued from the study due to a study-related TEAE.

No individual TEAE occurred in ≥5% of subjects for either Treatment A or Treatment B. Gastrointestinal disorder TEAEs were the most frequent non-serious TEAEs reported in 11 subjects (18%) across both Treatments. Non-serious gastrointestinal disorder TEAEs included diarrhea (4 subjects, 6.5%), constipation (2 subjects, 3%), nausea (2 subjects, 3%), and in 1 subject each abdominal discomfort, toothache, and dry mouth (2%) across both Treatments. Other non-serious TEAEs reported most frequently were skin and subcutaneous tissue disorders (9 subjects, 14.5%), general disorders and administrative site conditions (6 subjects, 9.6%) and headaches (4 subjects, 6.5%) for both Treatments combined.

The majority of non-serious TEAEs reported during the course of this study were mild in severity. Three subjects experienced mild TEAEs that were possibly related to study drug, including a mildly enlarged prostate (Treatment A, Day 7) in 1 subject and mild headaches (Treatment A, Day 7; Treatment B, Day 7) in 1 subject for each treatment. Three subjects (4.8%) experienced events of moderate severity, include 1 subject with tooth pain/toothache (Treatment A, Day 1), 1 subject with moderate erythema on the right upper back, shoulder, and neck (Treatment A, Day 6), and 1 subject with erythema on the chests, abdomen, and back (Treatment B, Day 3). All events were identified as being unlikely related to study drug. No subjects reported AEs of severe intensity.

Treatment-emergent AEs related to application site assessments were recorded for 3 (4.8%) subjects receiving Treatment B. All 3 subjects developed one or more papules at the administration site. No TEAEs related to application site assessments were reported for Treatment A. All the application site TEAEs were deemed mild in intensity and assessed as unlikely related to study drug by the investigator.

There were no deaths, serious adverse events (SAEs), other significant AEs, or discontinuations during the course of this study.

Group mean values for hematology, chemistry, and urinalysis variables generally remained consistent and within normal reference ranges throughout the study. When comparing the two treatment sequences, there were no clinically meaningful differences in mean observed values or in mean changes from Baseline. Similarly, there were no clinically relevant shifts in safety laboratory variables from Baseline to post treatment. No laboratory abnormalities were assessed as clinically significant by the investigator.

No clinically important trends were noted in vital sign and ECG data.

There were no clinically significant DREs throughout the study. One subject had a normal DRE at Screening, but an abnormal, non-clinically significant DRE at study exit. At a subsequent follow-up assessment approximately 1 month later, the subject's DRE was normal.

Both increases and decreases in IPSS from Baseline to post treatment were observed, with most increases being of a magnitude of 1-2 points. One subject had a notable increase in IPSS at the end of study, with an increase from 1 to 11. No AEs related to IPSS results were reported.

Conclusion:

Pharmacokinetic Conclusions:

- Both application methods, combination of abdomen and upper/arms shoulders or a rotation from the abdomen to upper arms shoulders, at a fixed 5.00 g Testosterone Gel 1.62% dose, resulted in mean testosterone C_{av} and C_{max} values within or just above the eugonadal range of 300 – 1000 ng/dL.
- Based on statistical comparisons, application of 1.62% Testosterone Gel to a combination of the upper arms/shoulders and abdomen results in 16% lower C_{av} and 27% lower C_{max} compared to application of gel with rotation from the abdomen to the upper arms/shoulders.
- [redacted]

Safety Conclusions:

- Testosterone Gel 1.62% appeared to be safe and well tolerated in this population of hypogonadal males when administered as a once daily fixed dose of 5.00 g applied to the abdomen for 3 days followed by the upper arms/shoulders for 4 days *or* a combination of the abdomen and upper arms/shoulders for 7 days.
- No deaths, SAEs, or discontinuations due to AEs occurred during this study.
- Individual TEAE occurred in fewer than 5% of subjects for both Treatments. The most common SOCs for the TEAEs were gastrointestinal, skin and subcutaneous tissue disorders, general disorders and administrative site conditions, and nervous system disorders.
- No trends or clinically significant changes were noted in clinical laboratory data, vital sign data, ECG data, DRE results, or IPSS data.