CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22309Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	22-309
Drug Name:	Androgel (testosterone gel) 1.62%
Indication(s):	Treatment of hypogandism in adult male.
Applicant:	Abbott.
Date (s):	Submitted: 10/28/2010
Review Priority:	Standard
Biometrics Division:	Division of Biometrics III (HFD-725)
Statistical Reviewer:	Mahboob Sobhan, Ph.D. (HFD-725)
Medical Division:	Division of Reproductive and Urological Drug Products (HFD-580)
Clinical Team:	Mark Hirsch, M.D. (HFD-580)
	Roger Weiderhorn, M.D. (HFD-580)
Project Manager:	Jeannie Roule (HFD-580)

Keywords: NDA review, Clinical studies.

Table of Contents

1.0 EXECUTIVE SUMMARY

1.1 Conclusion and Recommendations

Efficacy data from the six month open-label period of the original double-blind study provided in this Complete Response appear to support the continuing efficacy of Testosterone gel 1.62% in providing testosterone replacement for up to 364 days. Based on the full analysis population C_{avg} was in the normal range in more than 77.9% of the patients without exceeding C_{max} values >1500 ng/dL in more than 85% of the patients. Based on the per-protocol population, the point estimate was 76.1% and the lower bound of the 95% of the confidence interval for this estimate was below 65%, thus not meeting the efficacy criteria. The weaker result seen in the later population was due to exclusion of 50% of the subjects from the analysis for protocol violations at day 364.

From a statistical perspective, however, the open-label efficacy data trended in the same direction as the double-blind efficacy data and do support treatment effect of testosterone gel 1.62% up to one-year.

1.2 Brief Overview of Clinical Studies

The applicant, Abbott, reports safety data to address the deficiencies identified in the Complete Response letter issued by the Agency on March 12, 2010. Main safety issues were lack of data to fully mitigate the transfer of testosterone after male application to a female partner and bioavailability of testosterone absorption applied to the upper arms/shoulders and use of a t-shirt barrier. To address the above issues, the sponsor submitted data from two safety studies. In addition, they also provided efficacy data from the open-label period of their original efficacy and safety study S176.3.104, in order to revise the language in the indication by claiming that (b) (4)

The focus of this review is on the efficacy data from the open-label period of the study. Safety issues are reported in the Clinical reviewer's report.

The primary efficacy evaluated in the open-label period was similar to the double-blind period of the study - the percentage of subjects (in >=75%) with serum testosterone time-averaged concentration over the dosing interval of 24 hours (C_{avg}) within the normal range of 300-1000 ng/dL with the lower bound of a 2-sided 95% confidence interval not below 65% on the day 112 PK results.

The secondary endpoints were that the maximum serum concentration (C_{max}) values fall in the following ranges:

- C_{max} values ≤1500 ng/dL in >=85% of the subjects
- C_{max} between 1800 -2500 ng/dL in ≤5% of the subjects
- C_{max} >2500 ng/dL in none of the subject.

1.3 Statistical Issues and Principal Findings

There were no statistical issues in this submission. However, we do not agree with the sponsor's (b) (4)

(b) (4)

Although the number of subject excluded due to protocol violations in the open-label period was similar to the double-blind period of the study, but due to the reduction in the number of subjects for the open-label period and the potential bias due to broken blind, the robustness of the results of such an analysis are not guaranteed. Note also that 50% of the subjects were excluded for the per-protocol analysis population because of major protocol violations. Based on the available data, the efficacy findings can be summarized as follows:

1) Treatment with androgel 1.62% provided testosterone replacement therapy in 77.9% of the hypogonadal men, with the lower bound of the 95% confidence interval for the above point estimate not below 65%. The lower bound of the 95% CI using the per-protocol population was below 65%, thus not meeting the efficacy criteria.

2) Approximately 93% of the subjects testosterone (C_{max}) values were <=1500 ng/dL.

3) A total of 4 subjects (2.9%) had values (C_{max}) in the range of 1500-2500 ng/dL and none of the subject had values >2500 ng/dL.

2.0 INTRODUCTION

2.1 Background

This submission is in response to deficiency identified in the Complete Response Letter issued by the Agency to Unimed Pharmaceuticals, LLC and Solvay Pharmaceuticals, Inc. on March 12, 2010. Two main deficiencies lack of data to fully mitigate the transfer of testosterone after male application to a female partner and bioavailability of testosterone absorption applied to the upper arms/shoulders and use of a t-shirt barrier. To address the above issues, the current applicant, Abbott, has submitted results from two studies.

(b) (4)

2.2 Data Sources

The submission is in an electronic format and the data quality of the submission was within acceptable limits.

2.3 Indication

Androgel (testosterone gel) 1.62% is indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone

3.0 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Efficacy data on the double-blind phase of the study was reported in our earlier review dated….This review will focus only on the 6-month open-label maintenance phase of the study.

3.1.1 Open-label Phase of the Study Design

The design of the double-blind phase of the Study S176.3.104 was also reported in our earlier review. In the 6-month open-label phase, a total of 191 subjects were treated: 163 subjects who had received testosterone gel 1.62% during the double-blind period and 28 subjects who had received placebo during the double-blind period. Twenty four hour PK sampling assessments were conducted on days 14, 56, 112, and 182.

Efficacy Endpoint: The efficacy endpoints in the open-label period were similar to double-blind period of the study. The primary and the secondary efficacy endpoints were the assessment of total

testosterone concentration C_{avg} and C_{max} on day 364. To demonstrate efficacy the testosterone parameters must fall in the ranges defined below:

(1) At least 75% of the patients have C_{avg} falling in the range of 300 – 1000ng/dL, with the lower bound of 2-sided 95% confidence interval for this point estimate not below 65%,

(2) Individual C_{max} values are within the following ranges: ≤1500 ng/dL in ≥85% of the subjects, between 1800 - 2500 ng/dL in ≤5% of the subjects, and >2500 ng/dL in none of the subjects.

Analysis Population: The sponsor considered **the following t**hree analysis populations for evaluating efficacy:

1) Full analyses (FA) population, defined as all subjects allocated to treatment and had at least one dose of study medication administered;
2) Efficacy analyses (EA) population, defined as all subjects in FA and had any efficacy data for day 112;
3) Per-protocol (PP) population, defined as all subjects in FA who did not have any major protocol violations.

Our evaluation will focus on the FA and PP populations.

3.1.2 Results

Disposition of Patients: A total of 191 subjects were treated for the open-label period and 163 of these subjects had also received testosterone gel 1.62% during the double-blind period. Of the 191 subjects, 30 (15.7%) discontinued from the study, and the main reasons for discontinuation were adverse events (8.9%, rate similar to AE in the double-blind period) and withdrawal from the study (3.1%). The demographics and baseline characteristics of these subjects were similar to the characteristics of the subjects in the double-blind period of the study.

Efficacy: Based on the FA analysis population, the percentage of the patients meeting the efficacy threshold (C_{avg} within the normal range of 300-1000ng/dL) is 77.9% (106/136) for subjects treated with T-gel 1.62% with the lower bound of the 95% confidence interval of 70% as shown in Table 1. Table 2 shows that using testosterone C_{max} assessment, 93% of the T-gel subjects had values <=1500 ng/dL, which is greater than the acceptable limit of >=85%. Only 4 of 136 (2.9%) subjects had values in the range of 1800-2500 ng/dL and 0% of the subjects had values more than 2500 ng/dL, thus meeting the efficacy threshold pre-specified to demonstrate efficacy. The results were consistently similar in the PP population.

Therefore, treatment with T-Gel 1.62% provided continued testosterone replacement up to one year in hypogonadal men.

Table 1: Number and Percent of Subjects in the Target Range for Testosterone C_{avg}, Open-label Period, Study S176.3.104.

Population	Study day	Continuing Active Testosterone Gel 1.62%	
		%(n/N)	95% CI
FA	362	77.9 (106/136)	70.0, 84.6
PP	362	76.1 (54/ 71)	64.5, 85.4

FA= Full Analysis population
PP= Per protocol population

Table 2: Number and Percent of Subjects in the Target Range for Testosterone C_{max}, Open-label Period, Study S176.3.104.

Population	Study day	% (n/N) Achieving Testosterone C_{max} Range		
		≤1500 ng/dL	1800- 2500 ng/dL	>2500 ng/dL
FA	362	93.4 (127/136)	2.9 (4/136)	0.0 (0/136)
PP	362	93.0 (66/ 71)	1.4 (1/71)	0.0 (0/71)

4.0 SUMMARY AND CONCLUSIONS

The results from the open-label period of the study do support the efficacy of T-Gel 1.62% in providing testosterone replacement as shown by C_{avg} in the normal range in more than 77.9% of the patients without exceeding C_{max} values >1500 ng/dL in more than 93% of the hypogonadal men. These results based on per-protocol population trended in the same direction, although not meeting the efficacy criteria of the lower bound above 65%, because of the exclusion of 50% of the subjects due to protocol violations.

(b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAHBOOB SOBHAN
04/26/2011

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	22-309
Drug Name:	Androgel (testosterone gel) 1.62%
Indication(s):	Treatment of hypogandism in adult male.
Applicant:	Solvay Pharmaceuticals.
Date (s):	Submitted: 3/10/2009
Review Priority:	Standard
Biometrics Division:	Division of Biometrics III (HFD-725)
Statistical Reviewer:	Mahboob Sobhan, Ph.D. (HFD-725)
Medical Division:	Division of Reproductive and Urological Drug Products (HFD-580)
Clinical Team:	Mark Hirsch, M.D. (HFD-580)
	Roger Weiderhorn, M.D. (HFD-580)
Project Manager:	Jeannie Roule (HFD-580)

Keywords: NDA review, Clinical studies.

Table of Contents

1.0 EXECUTIVE SUMMARY

1.1 Conclusion and Recommendations

The results support the efficacy of T-Gel 1.62% in providing adequate testosterone replacement (as shown by C_{avg} in the normal range in more than 81% of the patients without exceeding C_{max} values >1500 ng/dL in more than 85% of the patients) therapy in hypogonadal men.

(b) (4)

1.2 Brief Overview of Clinical Studies

The applicant, Solvay Pharmaceuticals, Inc., reports efficacy and safety data from a single placebo-controlled, double-blind study (S176.3.104) to demonstrate that treatment with Androgel (T-Gel 1.62%) will provide testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.

The study was conducted in 274 subjects (40 placebo and 234 T-Gel 1.62%), 18-80 years of age with serum testosterone concentration of <300 ng/dL.

The objective of the study was to demonstrate the efficacy and safety of testosterone gel 1.62% following administration of active treatment (four doses based on titration) or placebo to hypogonadal men for a period of 182 days.

The primary efficacy was the percentage of subjects (in >=75%) with serum testosterone time-averaged concentration over the dosing interval of 24 hours (C_{avg}) within the normal range of 300-1000 ng/dL with the lower bound of a 2-sided 95% confidence interval not below 65% on the day 112 PK results.

The secondary endpoints were that the maximum serum concentration (C_{max}) values fall in the following ranges:

- C_{max} values ≤1500 ng/dL in >=85% of the subjects
- C_{max} between 1800 -2500 ng/dL in ≤5% of the subjects
- C_{max} >2500 ng/dL in none of the subject.

1.3 Statistical Issues and Principal Findings

There were no statistical issues in this submission. However, the sponsor reported 10 subjects who had a total of 11 observations of total testosterone concentrations of >2500 during the double-blind phase of the study. They claimed that in 9 of the 10 subjects, such sporadic observations were made on one occasion on 1 PK day and resolved during the treatment period, and therefore, had no impact on the overall testosterone level at endpoint. The clinical reviewer further investigated these

outliers and came to a resolution that it should not affect the primary efficacy. We verified the sponsor's results using the analyses datasets provided in the submission

Despite inadequate number of placebo controls in the study, the sample size used for demonstrating efficacy (using percent of responder's as point estimate) compared to FDA threshold for successful testosterone replacement therapy appeared to be adequate. The efficacy results were descriptive in nature and presented as percentage of the patients whose C_{avg} is within the normal range of 300 – 1000ng/dL and the 95% confidence interval about the point estimate. Details of safety issues can be found in the Medical Officer's report. The principal efficacy findings are summarized as follows:

1) Treatment with androgel 1.62% provided adequate testosterone replacement therapy in 81% of the hypogonadal men, with the lower bound of the 95% confidence interval for the above point estimate not below 65%.

2) Approximately 89% of the subjects testosterone (C_{max}) values were <=1500 ng/dL.

3) A total of 10 subjects (5.6%) had values (C_{max}) in the range of 1500-2500 ng/dL and 2 (1.1%) had values >2500 ng/dL, slightly more than the pre-defined threshold.

2.0 INTRODUCTION

2.1 Background

The applicant, Solvay Pharmaceuticals, is seeking approval of Androgel (testosterone gel) 1.62%, a topical testosterone product to be used for once a day dosing for the treatment of conditions associated with a deficiency or absence of endogenous testosterone.

This new formulation has higher viscosity, and may provide the opportunity to reduce the volume of application and better subject compliance.

To support the safety and efficacy of Androgel 1.62%, this submission contains data from one pivotal study (S176.3.104) with supportive evidence from five Phase 1 PK and safety studies.

2.2 Data Sources

The submission is in an electronic format and the data quality of the submission was within acceptable limits.

2.3 Indication

Androgel (testosterone gel) 1.62% is indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone

3.0 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

This review will focus mostly on the clinical efficacy data evaluated in study (S176.3.104). Safety issues such as transfer issue and sporadic T level exceeding 2500 ng/dL will be discussed in the clinical reviewer's report. However, our evaluation will also evaluate the impact of sporadic T level on the overall study results.

3.1.1 Study Design

Study S176.3.104 was a multicenter, 2-arm, randomized, placebo-controlled study of testosterone gel 1.62% for the treatment of hypogonadism in adult males. Eligible patients, 18-80 years of age, with average testosterone concentration of <300 ng/dL were randomized to receive either androgel 1.62% doses (1.25g, 2.50g, 3.75g and 5.00g) or placebo for a period of 182 days. All patients were administered with a dose of 1.25g androgel 1.62% or placebo on day 1 and returned to the clinic on days 14, 28, and 56 for pre-dose serum concentration assessments. Within 2-days of these visits, patients dose was titrated up or down in 1.25g increments based on the pre-specified normal range criteria. Twenty four hour PK sampling

assessments were conducted on days 14, 56, 112, and 182.

Efficacy Endpoint: The primary and the secondary efficacy endpoints were the assessment of T concentration C_{avg} and C_{max} based on day 112 PK results compared to FDA threshold for demonstration of efficacy for testosterone replacement therapies defined below:

(1) At least 75% of the patients have C_{avg} fell within the normal range of 300 – 1000ng/dL, with the lower bound of a 2-sided 95% confidence interval not below 65% and;

(2) Individual C_{max} values were to be ≤1500 ng/dL in ≥85% of patients have, be between 1800 - 2500 ng/dL in ≤5% of patients, and be >2500 ng/dL in none of the patients.

Additional secondary endpoints included the assessment of SHBG, LH, FSH and selected serum inflammatory and cardiovascular risk markers, as well as serum markers of bone metabolism.

Analysis Population: Three analysis populations were considered for evaluating efficacy:

1) Full analyses (FA) population, defined as all subjects allocated to treatment and had at least one dose of study medication administered;
2) Efficacy analyses (EA) population, defined as all subjects in FA and had any efficacy data for day 112;
3) Per-protocol (PP) population, defined as all subjects in FA who did not have any major protocol violations.

3.1.2 Results

Disposition of Patients: A total of 274 (40 in placebo arm and 234 in T-Gel 1.62% group) subjects were randomized. Both treatment arms were similar with respect to age and ethnicity, although majority of the subjects (>83%) were Caucasian. Approximately 90% of the subjects took at least one concomitant medication.

As shown in Table 1, approximately 28% of the subjects in T-Gel 1.62% group and 30% in placebo group discontinued the study prematurely. The primary reason for discontinuation was due to adverse event (10.7%) in the T-gel group and due to withdrawal of consent. in the placebo group. For the primary efficacy analysis at day 112, PK sampling was available for 76% of the T-gel subjects and 67% of the placebo subjects, respectively.

Table 1: Disposition of Patients, Study S176.3.104.

	Placebo	**T-Gel 1.62%**	Total
Randomized	40	234	274
Number Who completed the study	28 (70.0%)	168 (72.0%)	196 (71.5%)
Premature Discontinuation	12 (30.7%)	66 (28.0%)	78 (28.5%)
Reasons for Discontinuation:			
Adverse Events	0 (0%)	25 (10.7%)	25 (9.0%)

Lack of Efficacy	0 (0%)	2 (0.9)	2 (0.7%)
Lost to Follow-up	2 (5.0%)	5 (2.1%)	7 (2.6%)
Withdrew consent	8 (20.0%)	19 (8.1%)	27 (9.8%)
Administrative	1 (2.5 %)	5 (2.1%)	6 (2.2%)
Protocol violation	1 (2.5%)	10 (4.3%)	11 (4.0%)
Full analyses population Efficacy analyses population[1]	27 (67.5%)	179 (76.5%)	206 (75.2%)
[1] No efficacy data at day 112 for 13 and 55 subjects in placebo and T-Gel arm, respectively.			

Efficacy: The sponsor reported 10 subjects who had a total of 11 observations of total testosterone concentrations of >2500 during the double-blind phase of the study. They claimed that in 9 of 10 subjects, such sporadic observations were made on one occasion on 1 PK day and resolved during the treatment period, and therefore, had no impact on the overall testosterone level at endpoint. The clinical reviewer further investigated these outliers and came to a resolution that it should not affect the primary efficacy. Based on the analyses dataset provided, we confirmed the sponsor's results.

As shown in Table 2, the point estimates, i.e., the percentage of the patients meeting FDA threshold (C_{avg} within the normal range of 300-1000ng/dL) is 81% for subjects treated with T-gel 1.62% with the lower bound of the 95% confidence interval of 75%. Using testosterone C_{max} assessment, 88% of the T-gel subjects had values <=1500 ng/dL, which is greater than the acceptable limit of >=85%. However, slightly higher percent of subjects (5.6%) in the T-gel group had values in the range of 1800-2500 ng/dL and 1.1% of the subjects had values more than 2500 ng/dL, which exceeded the FDA threshold of 0 subjects in the later group.

Therefore, treatment with T-Gel 1.62% provided adequate testosterone replacement in hypogonadal men.

Table 2: Number and Percent of Patients Meeting FDA C_{avg} Threshold for Success with 95% Confidence interval, Study S176.3.104.

Outcome	Placebo (N=27)		T-Gel 1.62% (N=179)	
	N (%)	95% CI	N (%)	95% CI
C_{avg} (300, 1000) ng/dL	10 (37.0)	(19.4, 57.6)	146 (81.6)	(75.1, 87.0)
C_{avg} Outside (300, 1000) ng/dL	17 (63.0)	--	33 (18.4)	---

Table 3: Number and Percent of Patients Exceeding FDA C_{max} Threshold, Study S176.3.104.

Outcome	Placebo (N=27)	T-Gel 1.62% (N=179)
C_{max}	N (%) Exceeding	N (%) Exceeding
<=1500 ng/dL	26 (96.3)	159 (88.8)
>=1800 - <2500 ng/dL	0 (0)	10 (5.6)
>=2500 ng/dL	0 (0)	2 (1.1)

4.0 SUMMARY AND CONCLUSIONS

The results support the efficacy of T-Gel 1.62% in providing adequate testosterone replacement (as shown by C_{avg} in the normal range in more than 81% of the patients without exceeding C_{max} values >1500 ng/dL in more than 85% of the hypogonadal men.

From a statistical perspective, the efficacy data provided in this application do support the efficacy of T-Gel 1.62% as testosterone replacement therapy.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22309	ORIG-1	UNIMED PHARMACEUTICALS INC	ANDROGEL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAHBOOB SOBHAN
11/04/2009