CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22309Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	April 29, 2011
From	George S. Benson, MD
Subject	Division Deputy Director Summary Review
NDA/BLA # **Supplement #**	22-309
Applicant Name	Abbott Products
Date of Submission	October 29, 2010
PDUFA Goal Date	April 29, 2011
Proprietary Name / **Established (USAN) Name**	AndroGel testosterone gel
Dosage Forms / Strength	Multi-dose pump which delivers 1.25 grams of 1.62% testosterone gel with each depression
Proposed Indication(s)	Testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone
Action	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Roger Wiederhorn, MD
Statistical Review	Mahboob Sobhan, Ph. D.
Pharmacology Toxicology Review	Jeffrey Bray, Ph.D. Lynnda Reid, Ph.D.
CMC Review	Hitesh Shroff, Ph.D. Donna Christner, Ph.D. Moo Jhong Rhee, Ph.D.
Microbiology Review	Robert Mello, Ph.D. Bryan Riley, Ph.D.
Clinical Pharmacology Review	Sandhya Apparaju, PhD Hyunjin Kim, PharmD, MS Myong Jin Kim, PharmD Edward D. Bashaw, PharmD
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OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader
SEALD = Study Endpoints and Label Development

1. Introduction
2. Background
3. Chemistry, Manufacturing, and Controls
4. Nonclinical Pharmacology/Toxicology
5. Clinical Pharmacology/Biopharmaceutics
6. Clinical Microbiology
7. Efficacy – Clinical/Statistical
8. Safety
9. Advisory Committee Meeting
10. Pediatrics
11. Other Relevant Regulatory Issues
12. Labeling
13. Decision/Action/Risk Benefit

1. Introduction

AndroGel (testosterone gel) 1% (NDA 21-015) was approved for the indication of testosterone "replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone" in February, 2000. NDA 22-309 for AndroGel (testosterone gel) 1.62% was initially submitted on February 11, 2009. A Complete Response action (after a three month review extension) was taken on March 12, 2010. The sponsor (Abbott Products) resubmitted the NDA on October 29, 2010. This new testosterone gel formulation has a lower volume of application (b) (4) (b) (4) compared to Androgel 1%.

Two testosterone gels, AndroGel 1% and Testim, and one testosterone solution (Axiron) are currently approved for cutaneous application for testosterone replacement therapy in men. A variety of other dosage forms and routes of administration of testosterone including intramuscular injection, testosterone implants, buccal tablets, and transdermal patches are also approved for this indication.

The transfer of testosterone gel products from patients to others (particularly children) has been recognized as a significant safety concern. An Advisory Committee meeting regarding this issue was held on June 23, 2009. Both AndroGel 1% and Testim (as well as Axiron) currently have black box warnings and Medication Guides relating to the increased awareness of secondary exposure of children to testosterone gels.

Because the initial "transfer study" demonstrated that AndroGel 1.62% (at the 5 gram dose applied to the abdomen) could be transferred to others through clothing, the sponsor submitted an additional transfer study utilizing additional application sites during the original review cycle. In addition, data were submitted which the sponsor believed demonstrated that the testosterone pharmacokinetics (PK) were comparable between the original two site application regimen and a new three and four site application regimen. A

Complete Response (CR) action was taken on March 12, 2010. The primary reason for the CR was that "The information that you provided to support comparability of testosterone concentrations associated with the new application method and those associated with the Phase 3 method is considered inadequate…"

The CR submission contains a pharmacokinetic study comparing differing sites of application, a female partner transfer study following application of drug to the arms/shoulders only, and an updated study report of the 12 month data from an additional six month open-label extension study following the six month double-blind period of the primary phase 3 study.

2. Background

All studies for AndroGel 1.62% were conducted under IND 50,377 which was the original AndroGel 1% IND. The Division agreed at the EOP2 Meeting on October 18, 2006, that a single Phase 3 study evaluating the efficacy and safety of testosterone gel 1.62% (in addition to the Phase 1 safety studies) would be sufficient for NDA submission.

A Pre-NDA meeting was held on January 21, 2008, and NDA 22-309 was submitted on February 11, 2009. During review of the phase 1 "transfer studies," it was noted that a T-shirt adequately blocked transfer of the 2.5 g dose, but not the 5 g dose, applied to two sites on the abdomen. The sponsor subsequently submitted data (during the initial NDA review) from an additional "transfer study" utilizing 4 sites (5.0 g dose applied to 2 abdominal and 2 shoulder sites) and additional data which the sponsor believed demonstrate PK comparability between applying 5 g of the gel to either 2 abdominal sites or 4 sites (2 abdominal and 2 shoulder). A three month PDUFA goal date extension was granted to allow review of these additional data. The new PDUFA goal date was, therefore, March 12, 2010.

A Complete Response action was taken on March 12, 2010. The primary reason for the CR was that "The information that you provided to support comparability of testosterone concentrations associated with the new application method and those associated with the Phase 3 method is considered inadequate…" On April 29, 2010, a Type A meeting was held to discuss the content of the Complete Response letter and what additional studies were needed to formulate a Complete Response.

On October 29, 2010, to address the CR issues, the sponsor submitted:

1) Study S176.1.010 (Study 010) entitled "*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.*"

2) Study S176.1.011 (Study 011) entitled "*An Open-Label Study of Serum Testosterone Levels in Non-dosed Females after Secondary Exposure to Testosterone Gel 1.62% Applied to the Upper Arms and Shoulders and Use of a T-shirt Barrier.*"

In addition, the sponsor submitted an updated report for the Phase III pivotal safety and efficacy study S176.3.104 which contains the data from the 6 month open-label period of the study in addition to the 6 month double-blind period of the study.

3. CMC/Device

The CMC reviewer concluded that "based on 1) sufficient CMC information provided to assure the identity, strength, and purity and quality of the drug product; 2) "Acceptable" cGMP compliance of all facilities; and 3) adequate CMC labels/labeling information, CMC Review #2 made a recommendation of approval of this NDA.

In order to comply with the new labeling approach for the testosterone pump products, the CMC information on the label and labeling were revised and re-submitted via e-mails. These changes of the labels and labeling are deemed satisfactory, making the previous "Approval" recommendation from the CMC perspective still effective."

CMC reviewed the final container/carton labels and deemed them to be satisfactory.

Comment: There are no outstanding CMC issues.

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology reviewer concluded that "nonclinical data support approval of AndroGel 1.62% for topical testosterone replacement in hypogonadal men."

Pharmacology/toxicology reviewed the final labeling and "finds it acceptable."

Comment: I agree with the pharmacology/toxicology reviewer that there are no outstanding pharmacology/toxicology issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

Multiple pharmacokinetic studies with varying sites and numbers of sites of application and female transfer studies were conducted. Study 1.003 had demonstrated that clothing (T-shirt) did not adequately block transfer of the 5.0 gram dose applied to two abdominal sites to a female partner. Study 1.008 demonstrated that washing the application site (via showering) did prevent transfer. The clinical review team did not believe that the transfer risk could be adequately labeled and, therefore, adequately mitigated by requiring (b) (4) . These concerns were communicated to the sponsor in a teleconference held with the Division on October 1, 2009. In this meeting, the sponsor expressed their interest in conducting a new transfer study to evaluate whether spreading out the gel on multiple sites (i.e. both upper arms/shoulders and both sides of abdomen, instead of either

site alone) would minimize transfer potential. The Division acknowledged the sponsor's proposal but also noted that even if the new application instructions proved successful in preventing transfer further information may be needed to link the existing safety and efficacy data derived from trial S176.3.104 to the new mode of administration (3 or 4 site administration versus 1 or 2 sites administration).

An additional transfer study (1.009) showed that the transfer risk was mitigated by applying the 5.0 gram dose to four sites (both sides of the abdomen and both shoulders/arms) (b) (4) The question of comparability of testosterone serum levels between 2 site versus 3 or 4 site application was raised. The sponsor submitted PK data from protocol violators in phase 3 study S176.3.104 who applied the testosterone gel to multiple sites. The sponsor believed that these data support the comparability of testosterone serum levels whether a given dose of the drug is applied to 2, 3, or 4 sites.

In my review of March 12, 2010 I stated that *"I agree with the clinical pharmacology and clinical reviewers that the issue of testosterone transfer potential and the sponsor's revised dosing regimen to mitigate transfer at the 3.75 and 5.0 gram doses currently preclude approval of NDA 22-309. Specifically, testosterone PK data are inadequate to conclude that the testosterone exposures obtained with the use of the 4 site application method (for 5 gm) or the use of the 3 site application method (for 3.75 gm) are comparable to the data obtained in the primary phase 3 study where drug was applied to 2 sites (arm/shoulders on the days when PK measurements were performed). Knowing the comparability of testosterone with the various dosing regimens is particularly important because testosterone PK data served as the primary efficacy endpoint and as the most important safety surrogate marker in the single primary trial S176.3.104."*

On October 29, 2010, to address the CR issues, the sponsor submitted:

1) Study S176.1.010 (Study 010) entitled "*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.*"

2) Study S176.1.011 (Study 011) entitled "*An Open-Label Study of Serum Testosterone Levels in Non-dosed Females after Secondary Exposure to Testosterone Gel 1.62% Applied to the Upper Arms and Shoulders and Use of a T-shirt Barrier.*"

In addition, the sponsor submitted an updated report for the Phase 3 pivotal safety and efficacy study S176.3.104 which contains the data from the 6 month open-label period of the study in addition to the 6 month double-blind period of the study.

The Clinical Pharmacology review states that "The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds the clinical pharmacology information submitted

in NDA 022309 acceptable provided that an agreement is reached between the sponsor and the Division regarding the language in the package insert."

In addition, the Clinical Pharmacology review recommended that a Post Marketing Requirement should be performed. A clinical trial entitled "An Evaluation of the Effect of Hand Washing on the Amount of Residual T on the Hands after Application of Androgel 1.62%" to assess the amount of residual testosterone before and after washing the primary user's hands will be conducted with the following timeline which was agreed upon between the Division and the sponsor:

- Final Protocol Submission: July, 2011
- Trial Completion: October, 2011
- Final Report Submission: July, 2012

A summary of the important Clinical Pharmacology findings follows:

For "application of Androgel 1.62% to both upper arms/shoulders and abdomen"

- Transferability: Study S176.1.009 (submitted during the original review cycle) demonstrated that the transferability by application of Androgel 1.62% 5.0 g to both upper arms/shoulders and abdomen while covering the application sites with T-shirts was not significant (increase of C_{max} and AUC by 6 and 7%, respectively).
- Exposure comparison: Study S176.1.010 is the comparative bioavailability study (Androgel 1.62% 5 g) which was requested by the Division in the Complete Response letter. This new application method (treatment B; both upper arms/shoulders and abdomen for 7 days) was associated with 16 to 27% lower total T exposure compared to the application method (treatment A; abdomen for 3 days and upper arms/shoulders for 4 days) representing the application method (either upper arms/shoulders or abdomen but not to both at the same time) used in the pivotal phase 3 study.
- Therefore,the clinical pharmacology review concluded that the (b) (4) application method of applying Androgel 1.62% to both upper arms/shoulders and abdomen is not acceptable due to the lower testosterone exposure which could lead to lower efficacy.

For "application of Androgel 1.62% to upper arms/shoulders"

- Transferability: Study S176.1.011 (submitted in the current resubmission) demonstrated that the transferability by application of Androgel 1.62% 5.0 g to upper arms/shoulders while covering the application sites with a T-shirt was not significant (increase of C_{max} and AUC by 11 and 6%, respectively).
- Exposure comparison: Study S176.1.007 (submitted during original review cycle) demonstrated that the new application method (treatment B: upper arms/shoulder for 7 days) was bioequivalent to the application method (treatment A; abdomen for 3 days and upper arms/shoulders for 4 days) representing the application method (either upper arms/shoulders or abdomen but not to both at the same time) used in the pivotal phase 3 study (Table 1).
- Skin irritation comparison: The clinical review team determined that the skin irritation potential from the new application method (treatment B: upper

arms/shoulders for 7 days) was comparable to the application method (treatment A; abdomen for 3 days and upper arms/shoulders for 4 days) representing the application method (either upper arms/shoulders or abdomen but not to both at the same time) used in the pivotal phase 3 study.

- Therefore, the new proposed application method of applying Androgel 1.62% to the upper arms/shoulders is acceptable.

Table 1. Mean PK Parameters of Total T on Day 7 – Exposure Comparison while Androgel 1.62% was Applied to Upper Arms/Shoulders; S176.1.007 (original review cycle)

	Treatment	N	Geometric mean	Geometric mean ratio (B/C)	90% CI
C_{max} (ng/dL)	C	33	942	1.06	0.94 – 1.20
	B	33	1000		
AUC_{0-24} (ng·hr/dL)	C	33	15400	1.04	0.95 – 1.14
	B	33	16000		
C_{avg} (ng/dL)	C	33	642	1.04	0.95 – 1.14
	B	33	666		

B: Once daily application of Androgel 1.62% to upper arms/shoulders for 7 days; C: Once daily application of Androgel 1.62% to the abdomen for 3 days followed by application to the upper arms/shoulders for 4 days.

The Clinical Pharmacology review team concluded that the sponsor has provided adequate evidence to justify that the safety and efficacy of the drug would remain unchanged under the proposed new application method (application of Androgel 1.62% to upper arms/shoulders only).

This new application method:

- mitigated transfer of testosterone to non-dosed females.
- demonstrated the comparable exposure of total T by the application method used in the phase 3 study.
- demonstrated the comparable skin irritation potential by the application method used in the phase 3 study.

<u>1 year Efficacy Data</u>

- The efficacy of Androgel 1.62% was established for six months in the original review cycle of the NDA based on the pivotal phase 3 clinical study, S176.3.104. The sponsor's resubmission included additional efficacy data from the open-label period (from Days 183 to 364) of S176.3.104.
- On Days 266 and 364, the proportion of responders for the continuing active Androgel 1.62% group was 78.4 and 77.9%, suggesting the long term efficacy of Androgel 1.62% for up to 1 year (Table 2).

Table 2. Number and Percentage of Subjects Achieving Target Range for T C_{avg} by Day and Treatment in the Full Analysis Sample; Open-Label; S176.3.104

Study Day	Continuing Active Androgel 1.62%		Formerly Placebo		Total	
	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI
266	109/139 (78.4)	(70.6, 84.9)	18/26 (69.2)	(48.2, 85.7)	127/165 (77.0)	(69.8, 83.2)
364	106/136 (77.9)	(70.0, 84.6)	20/23 (87.0)	(66.4, 97.2)	126/159 (79.2)	(72.1, 85.3)

The clinical pharmacology review recommends that the one-year efficacy data be included in product labeling. The primary medical officer, cross-discipline team leader, statistical reviewer, and I agree.

Clinical pharmacology reviewed the final agreed upon labeling and "there are no pending issues from the Office of Clinical Pharmacology." In addition, "The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology, finds the NDA 022309 acceptable."

6. Clinical Microbiology

The Microbiology review concluded that "this application is recommended for approval from microbiology product quality standpoint." The reviewer recommended that the following comment, which is not a deficiency, be communicated to the sponsor: "It is acceptable to omit microbial limits testing for routine drug product release and stability testing. Nonetheless, the acceptance criteria for the microbiological quality of the of the drug product should be listed in Table 2 and Table 3, respectively of the NDA submission Section 3.2.P.5.1, along with a statement that the drug product will comply with the acceptance criteria if tested at anytime during its shelf life." The comment was conveyed to Sponsor on November 30, 2009 and the NDA was amended accordingly.

No new microbiology data were submitted in the October 29, 2010, CR.

7. Clinical/Statistical-Efficacy

A single phase 3 efficacy trial (S176.3.104), supported by multiple phase 1 studies, was submitted with the initial application on February 11, 2009. This was a multi-center (53 United States sites), randomized, double-blind, placebo-controlled study of testosterone gel 1.62% for the indication testosterone replacement therapy in hypogonadal men.

Eligible subjects were randomized to receive active treatment or placebo. The pivotal portion of the study utilized four active testosterone gel 1.62% doses (1.25 g, 2.50 g, 3.75

g and 5.00 g) and placebo administered over a period of 182 days. Two hundred seventy-four subjects (testosterone gel 1.62%: 234 subjects, placebo: 40 subjects) were randomized and analyzed for safety; 206 subjects (testosterone gel 1.62%: 179; placebo: 27 subjects) were analyzed for efficacy. All eligible subjects were started at a dose of 2.50 g testosterone gel 1.62% or matching placebo on Day 1 of the study. Subjects returned to the clinic at Day 14 (Week 2), Day 28 (Week 4), and Day 42 (Week 6) for pre-dose (trough) serum total testosterone assessments. Within two days of each of these visits, the subject's dose was titrated up or down in 1.25 g increments, if necessary, based on the results of the single C_{trough} serum concentration and pre-specified criteria (see Table 3 below). No dose was to be titrated below 1.25 g, or above 5.0 g. Sham titrations occurred in placebo-treated subjects. Subjects were maintained at their respective Day 42 (Week 6) dose until Day 182 (Week 26).

Table 3: Pre-specified Testosterone Gel 1.62% Dose Titration Criteria

Total Testosterone Trough Concentration	Titration Criteria
<350 ng/dL	Increase dose by 1.25 g
>750 ng/dL	Decrease dose by 1.25 g
350-750 ng/dL	Remain on previously dispensed dose

*each pump actuation delivers 1.25 g of testosterone gel 1.62 %

Study medication was applied once every morning at 8 AM (+/- two hours) to the skin's surface by the subject on an outpatient basis. Over any seven-day period, study gel could be rotated between the upper arms/shoulders or abdomen (e.g., four days upper arms/shoulders; three days abdomen) as long as the correct application technique occurred during PK visits.

Demographics: The phase 3 study population in trial S176.3.104 appears to be similar to that of other approved testosterone replacement products. Mean baseline concentrations of total testosterone were similar in the testosterone gel 1.62% (282 ng/dL) and the placebo group (294 ng/dL). Subject 046-06 had Klinefelter's Syndrome. There were no patients with the diagnosis of Kallmann's Syndrome entered into the study.

Patient Disposition: Study S176.3.104 was conducted at 53 sites throughout the United States. The trial enrolled and randomized 274 patients (234 to T-Gel 1.62% and 40 to placebo). Of these 274 patients, 196 completed the 182 day pivotal double-blind period (168 T-Gel [71.8% of randomized] and 28 [70.0% of randomized] placebo). The most common last titrated dose was 5.00 g testosterone gel 1.62%. Similar percentages of placebo and T-Gel patients discontinued from the study groups. The most common AE leading to discontinuation was increased PSA which was prespecified as a discontinuation criteria and will be discussed in the Safety section of this review. Patient disposition is shown in Table 4.

Table 4: Consented Subject Disposition S176.3.104-182 Day Pivotal Period

Subjects	Placebo N=40	T-Gel 1.25g N=17	T-Gel 2.5g N=60	T-Gel 3.75g N=66	T-Gel 5.0g N=91	Total T-Gel N=234
	n (%)					
Completed	28(70.0)	12 (70.6)	35(58.3)	50(75.8)	71(78)	168(71.8)
Premature Terminate	12(30.0)	5(29.4)	25(41.7)	16(24.2)	20(22.0)	66(28.2)
Reasons						
Adv event	0	1(5.9)	6(10.0)	8(12.1)	10(11.0)	25(9.1)
Lack of Efficacy	0	1(5.9)	0	1(1.5)	0	2(0.7)
Lost to Follow-up	2(5.0)	0	3(5.0)	0	2(2.2)	7(2.6)
Withdrew Consent	8(20.0)	1(5.9)	10(16.7)	4(6.1)	4(4.4)	27(9.9)
Admin	1(2.5)	0	1(1.7)	1(1.5)	3(3.3)	6(2.2)
Protocol Violation	1(2.2)	1(11.8)	5(8.3)	2(3.0)	1(1.1)	11(4.0)

Note: Treatment groups are based on subject's last titrated dose.
Source: Clinical Study Report S176.3.104 adapted from Table 1.0.0: page 184

Comment: The majority of subjects were titrated to the 3.75 and 5.0 g doses.

The primary efficacy endpoint was the percentage of subjects with serum testosterone C_{avg} within the normal range of 300-1000 ng/dL at Day 112. Success in the study was defined as ≥75% of subjects on active treatment within the normal serum testosterone concentration range of 300-1000 ng/dL. The lower bound of the 95% CI was to be not less than 65% based on the Day 112 PK results for the pivotal phase of the trial.

An important secondary safety endpoint was to evaluate total testosterone C_{max} values during the first 182 Days of the study. The individual total testosterone C_{max} values were to be in the following ranges:

- C_{max} ≤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 subjects

Results:

On Day 112, 81.6% of subjects on testosterone treatment (95% CI of 75.1% -87.0%) had C_{avg} values within the target range, which met the criteria for efficacy. (See Table 5.)

Table 5. Percentage of Patients Achieving Target Testosterone Concentration

		T-Gel	T-Gel	Placebo	
Study Day	Total T(Cav) ng/DL	n/N (%)	95% CI	n/N (%)	p-value
14	<300	66/210(31.4)		26/37(70.3)	
	300-1000	138/210(65.7)	(58.9, 72.1)	11/37(29.7)	<0.0001
	>1000	6/210(2.9)		0/37(0.0%)	
56	<300	30/183(16.4)		20/32(62.5)	
	300-1000	151/183(82.5)	(76.2, 87.7)	11/32(34.4)	<0.0001
	>1000	2/183(1.1)		1/32(3.1)	
112	<300	19/179(10.6)		17/27(63.0)	
	300-1000	146/179(81.6)	(75.1, 87.0)	10/27(37.0)	<0.0001
	>1000	14/179(7.8)		0/27(0.0)	
182	<300	24/169(14.2)		20/28(71.4)	
	300-1000	139/169(82.2)	(75.6, 87.7)	8/28(28.6)	<0.0001
	>1000	6/169(3.6)		0/28(0.0)	

Source: Adapted from Clinical Study Report S176.3.104, Table 11.1.3 page 400

Statistical review: Following review of primary study S176.3.104, the statistical reviewer concluded that "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) therapy in 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."

During the double-blind phase of the protocol (first 182 days), a critical secondary endpoint was to evaluate total testosterone $C_{max.}$ The individual total testosterone C_{max} values were to be in the following ranges:

- $C_{max} \leq 1500$ ng/dL in $\geq 85\%$ of the subjects
- C_{max} between 1800-2500 ng/dL in $\leq 5\%$ of the subjects
- $C_{max} > 2500$ ng/dL in none of the subjects

For the first criterion, in the full analysis sample, ≥88.8% of subjects on testosterone treatment had C_{max} values ≤1500 ng/dL. For the second criterion, in the full analysis sample, 3.0% (22/741) of all C_{max} observations were in the range of 1800-2500 ng/dL, when considering the four PK days combined. For the third criterion, there were to be no subjects with a C_{max} for serum testosterone >2500 ng/dL. However, within the 182 day double-blind period there 10 subjects with $C_{max} > 2500$ ng/dL. Each of these 10 outlier cases was reviewed in detail by the Sponsor, the primary medical officer, and the cross-discipline team leader (see pages 20-24 of the CDTL review).

Taken together, of the ten patients with testosterone concentrations above 2500 ng/dL, 5 were adjudicated as being related to sample contamination or artifact and one (1) had documented "overcompliance"; that is, applying a larger dose than assigned.

In the remaining 4 patients with testosterone concentrations above 2500 ng/d:

- There was a question of overdosage ("overcompliance") in Subjects 015-005 and 049-008. These subjects (015-005 and 049-008) had testosterone concentrations above 2500 ng/dL at baseline or 0.5 hours post dose. Following dosing, their testosterone concentrations declined over the next 4 hours. This finding appears to support possible overdosage prior to the blood draw in both cases, as suspected by history.

- Patient 058-006 had a testosterone concentration of 2510 ng/dL at 2 hours post-dose on Day 112. The pre-dose, 1 hour and 4 hour post dose concentrations were 1300, "cancelled", and 764 ng/dL, which show that the 2 hour sample is higher than the 4 hour sample.

- Subject 007-006 had a testosterone of 2500 ng/dL at 8 hours post dose. The testosterone concentrations at 4 hours and 12 hours were 881 and 1760 ng/dL respectively.

Overall, these events were sporadic, isolated, and non-recurrent. There were no concentrations of testosterone >2500 ng/dL in the open-label period.

Efficacy summary:

AndroGel 1.62%, in once daily doses of 1.25 g, 2.5 g, 3.75 g, and 5 g (determined by titration), was found to be efficacious in the treatment of male hypogonadism as measured by the primary endpoint. Two of three important secondary endpoints were achieved. The third important secondary endpoint, testosterone C_{max} >2500 ng/dL in none of the subjects, was not achieved. The ten subjects not achieving this endpoint were examined in depth, and 5 of these could be eliminated due to sample contamination or artifact, and 1 due to "overcompliance." In the other 4 cases, overdosage was possible in two. There was no clear evidence of an androgen effect related to any of the high testosterone concentrations. Overall, the primary medical officer and the cross discipline team leader concluded that these sporadic events did not pose a safety risk and that the product is considered efficacious. I agree.

The impact of the new dosing regimen proposed by the sponsor during the first review cycle to mitigate the potential for drug transfer to others on testosterone PK could not be determined.. The use of 4 sites (rather than 2 sites) for the two highest doses may alter testosterone absorption pharmacokinetics. A CR action was initially taken on March 12, 2010, and the sponsor submitted the following additional studies in their CR submission of October 29, 2020:

1) Study S176.1.010 (Study 010) entitled "*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.*"

2) Study S176.1.011 (Study 011) entitled "*An Open-Label Study of Serum Testosterone Levels in Non-dosed Females after Secondary Exposure to Testosterone Gel 1.62% Applied to the Upper Arms and Shoulders and Use of a T-shirt Barrier.*"

In addition, the sponsor submitted a reissued report for the Phase 3 pivotal safety and efficacy study S176.3.104 which now contains the data from the 6- month open-label period of the study in addition to the 6 month double-blind period of the study.

The results of these new data supported the use of application of AndroGel 1.62% (testosterone gel) to only the shoulders/upper arms. The rationale for this decision is included in the Clinical Pharmacology section (pages 5 to 8 of this review).

In summary:

This new application method (shoulders/arms only):

- mitigated transfer of testosterone to non-dosed females.
- demonstrated comparable exposure of total testosterone to the application method used in the phase 3 study and therefore linked the shoulder/arms application site method to the Phase 3 safety and efficacy data.
- demonstrated comparable skin irritation potential to the application method used in the phase 3 study.

1 year Efficacy Data

The efficacy of Androgel 1.62% was established for six months in the original review cycle of the NDA based on the pivotal phase 3 clinical study S176.3.104. The sponsor's resubmission included additional efficacy data from the open-label period (from Days 183 to 364) of S176.3.104.

On Days 266 and 364, the proportion of responders for the continuing active Androgel 1.62% group was 78.4 and 77.9%, suggesting the long term efficacy of Androgel 1.62% for up to 1 year (Table 6).

Table 6. Number and Percentage of Subjects Achieving Target Range for T C_{avg} by Day and Treatment in the Full Analysis Sample; Open-Label; S176.3.104

Study Day	Continuing Active Androgel 1.62%		Formerly Placebo		Total	
	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI
266	109/139 (78.4)	(70.6, 84.9)	18/26 (69.2)	(48.2, 85.7)	127/165 (77.0)	(69.8, 83.2)
364	106/136 (77.9)	(70.0, 84.6)	20/23 (87.0)	(66.4, 97.2)	126/159 (79.2)	(72.1, 85.3)

The clinical pharmacology review recommends that the one-year efficacy data be included in product labeling (see pages 8-9 of the Clinical pharmacology section of this memorandum). The primary medical officer, cross-discipline team leader, statistical reviewer, and I agree. The statistical reviewer notes that the lower bound of the 95% CI for the per-protocol population was 64.5%. Because of patient exclusions, the per-protocol population at day 364 included only 71 patients. The per-protocol point estimate was 76.1%. The pre-specified primary endpoint at day 364 was the "Full Analysis Sample" and not the per-protocol population (Table 6).

Efficacy summary:

The primary endpoint(s) for the phase 3 study were met. Adequate "bridging data" were submitted for the use of the shoulder/arm application site. The submitted data support the approval of AndroGel 1.62% (testosterone gel) from an efficacy standpoint. The maintenance of effect for up to one year will be included in labeling.

8. Safety

The safety data submitted in the original submission are derived from non-integrated studies S176.1.003, S176.1.004, S176.1.008, S176.1.009 (transfer, washing and skin irritation studies), and integrated studies S176.1.001, S176.1.002, S176.1.005, S176.1.006, S176.1.007, and the 182 day double-blind period of the Phase 3 Study S176.3.104.

In total, the original submission contained safety data from 801 subjects exposed to AndroGel 1.62%. In the single Phase 3 Study, S176.3.104, a total of 234 patients were exposed to T-Gel 1.62 % for a mean of 151.9 days. A total of 191 subjects participated in the 182-Day Open Label Period with a total of 161 subjects completing that study.

In addition, the Complete Response submission contained two new Phase 1 studies [Study S176.1.010 (a comparative bioavailability of 4 sites versus 2 sites of application) and S176.1.011 (a transfer study of arms/shoulders application site for the 5 gm dose). In addition, a finalized study report of the efficacy and safety data from the 6-month open-label extension of Phase 3 study S176.3.104 was submitted in the Complete Response submission.

The majority of data on adverse events are derived from the single Phase 3 study (S176.3.104).

Deaths:

No deaths occurred in the Phase I integrated studies or in the Phase 3 double-blind protocol or in the 182 day Open-Label Period.

Serious adverse events (SAEs):

In regard to serious adverse events, in the integrated Phase I studies, one subject in the 6.25 g dose group had a cardiac disorder (atrial fibrillation and supraventricular arrhythmias) and a second subject experienced right lower leg superficial and deep perivasvascular dermatitis with eosinophilia. Both events, in the investigator's opinion, were unrelated to the study drug. In both cases the patients recovered.

A total of 6 SAEs were reported in the double-blind period of the Phase 3 Study S176.3.104. Five subjects were in the testosterone gel 1.62% group and one was in the placebo group. The five patients in the testosterone gel group experienced myocardial infarction, tachycardia, back pain, pituitary tumor, radicular pain, and malignant hypertension. One subject (Subject 3104-044-003; 3.75 g testosterone gel 1.62%) reported two events: back pain and radicular pain. The clinical investigator considered the malignant hypertension "possibly related" (hematocrit was also increased in this patient) and the myocardial infarction as" unlikely related." A retinal detachment was the only SAE reported by a subject in the placebo group.

A total of 4 SAEs were reported in the 182 day Open-Label Period. Subject 012-08 experienced prostate cancer on Day 314 and was discontinued. This subject had had a testosterone in excess of 2500 ng/dL in the double-blind study period. A prostate nodule was noted during a study- related digital exam (DRE) and a subsequent biopsy diagnosed prostate cancer. This SAE was captured with a start date of Day 314. Subject 013-04 reported non-cardiac chest pain on Day 260 with resolution on Day 261 and completed the study. Subject 033-01 reported atrial fibrillation on Day 197 with recovery on Day 199. He completed the study. Subject 058-02 experienced an acute gastrointestinal hemorrhage on Day 296 with resolution of Day 299. He completed the study.

Study discontinuation:

Overall, in the placebo-controlled, Phase 3 study, 25 of 234 patients treated with testosterone gel 1.62% withdrew due to an adverse event. None of 40 placebo patients withdrew due an adverse event. There were no AEs leading to study discontinuation due to skin irritation.

The only adverse event leading to discontinuation that occurred in more than one subject in the testosterone gel 1.62% group (18/234, 7.7 % versus no subject in the placebo group) was the event of "increased PSA." Most of the subjects who discontinued due to

increased PSA discontinued because they met only the criterion of change from baseline >0.75ng/mL. Four other subjects had a PSA value >4 ng/mL. These subjects, however, had PSA ≤ 4.0 ng/mL upon repeat testing. The criteria for discontinuation due to an "increased PSA" were more stringent in this protocol than in the studies leading to approval of other testosterone products. Specifically, patients were discontinued from the trial if their PSA increased >0.75 ng/ml over baseline. It should be noted that 234 patients were randomized to the treatment group and only 40 to the placebo group.

In the Open-Label Safety Extension (Days 183-364), 9 patients discontinued secondary to an adverse event. One subject discontinued secondary to the adverse event of prostate cancer (discussed above). Six subjects discontinued due to PSA changes meeting the pre-specified discontinuation criteria. Two subjects discontinued for hematocrit meeting the pre-specified discontinuation criteria.

Overall adverse events:

In the controlled Phase 3 study, the most common (≥2% in the testosterone gel 1.62% groups and greater than in the placebo control group) adverse events by preferred term were: increased PSA (23/234, 9.8% versus no subject), upper respiratory infection (11/234, 4.7% versus no subject), back pain (7/234, 3.0% versus no subject), headache (7/234, 3% versus no subject), insomnia (7/234, 3.0% versus 1/40, 2.5%), hypertension (6/243, 2.6% versus no subject), and diarrhea, nasopharyngitis, myalgia, and dermatitis contact (5/234, 2.1% versus no subject) for each preferred term. The six events of hypertension did not include the event of malignant hypertension.

There were pre-specified criteria for abnormal PSA values in the protocol (> 4.0 ng/mL and /or change from baseline >0.75 ng/mL) for discontinuation of subjects. The incidence of increased PSA across the testosterone gel 1.62% groups was: 1.25 g: 1/17 (5.9%), 2.5 g: 2/60 (3.3%), 3.75 g: 10/66 (15.2%), 5.0 g: 10/91 (11.0%). Across all the testosterone gel 1.62% groups, 7/209 (3.3%) subjects had a PSA value >4.0 ng/mL.

Adverse reactions reported in at least 2% of patients in a treatment group and more frequently in drug treated than in placebo patients are shown in Table 7.

Table 7: Common Adverse Events (>2% for T-gel 1.62% and greater than placebo) for the Double-Blind Phase III Study (Safety Population)

SOC Preferred Term	Placebo N=40 n(%)	T-Gel 1.62% N=234 n (%)
Subjects with ≥ 1 TEAE	15(37.5)	130(55.6)
PSA increased	0(0.0)	20(9.8)
Upper Respiratory Infection	0(0.0)	11(4.7)
Back Pain	0(0.0)	7(3.0)
Headache	2(5.0)	7(3.0)
Insomnia	1(2.5)	7(3.0)
Hypertension	0(0.0)	6(2.6)
Dermatitis Contact	0(0.0)	5(2.1)
Diarrhea	0(0.0)	5(2.1)
Nasopharyngitis	0(0.0)	5(2.1)
Myalgia	0(0.0)	5(2.1)

Source: Clinical Study Report S176.3.104, Table 22, page 144.

Skin-related adverse events were infrequently reported in the Phase 3 study, accounting for <2% of all reported AEs. No patient discontinued the Phase 3 study due to a skin-related adverse event.

In the open-label period, the incidence and categories of AEs reported were comparable to those noted in the double-blind period.

Laboratory and vital signs:

Laboratory and vital signs data from the Phase 3 study demonstrated no unexpected findings:

- In the testosterone-treated group, 4.8% of patients had a shift in hemoglobin from normal at baseline to high at endpoint versus none for placebo. There was a similar shift for hematocrit, and a total of 5 subjects had hematocrit >54%. One of these subjects discontinued per protocol on Day 86. Four subjects had elevations of hematocrit >54% in the open-label extension and were also discontinued.

- A total of 34 subjects in the Phase 3 controlled study had a serum PSA post-baseline that was >4.0 ng/dL and/or an increase in serum PSA from Baseline >0.75 ng/mL. A total of 17 subjects discontinued from the study during the double-blind phase due to an AE of "increased PSA." Four of the subjects who discontinued had maximum PSA levels between 1 and 1.4 ng/mL, while two subjects had maximum PSA levels between 2 and 2.8 ng/mL. Of the remaining subjects with higher PSA levels, four subjects discontinued with PSA >4 ng/mL, but these subjects had PSA ≤4.0 ng/mL upon repeat testing.

The primary medical officer and CDTL reviewed several safety issues which are known to be associated with testosterone replacement therapy:

1) Testosterone is known to stimulate erythropoiesis. In Study S176.3.104, a modest increase in mean hematotcrit was observed overall for the testosterone gel 1.62% groups compared with placebo. Several incidents of markedly high hematocrit were reported in subjects who had been receiving study medication for 12 or more weeks. The majority of the discontinuations due to increased hematocrit occurred in the open-label period of the study. Androgen class labeling instructs prescribers to monitor hemoglobin and hematocrit.

2) Testosterone is known to increase serum PSA. In Study S176.3.104, the mean change from baseline in serum PSA at endpoint was 0.14 ng/mL for the testosterone gel 1.62% group versus -0.12 ng/mL for the placebo group. The labeling will include information concerning PSA elevation.

3) It is not known whether replacement of testosterone in men with hypogonadism increases the risk of prostate cancer. This potential risk and the need for monitoring of serum PSA and digital rectal examination are included in androgen class labeling and will be included in the Androgel 1.62% labeling. Prostate cancer occurred in one patient in this drug development program.

4) Hypertension is a known potential adverse event associated with testosterone therapy. Testosterone can increase fluid retention and red blood cell mass, potentially increasing blood pressure. A total of 13 subjects experienced the adverse event of hypertension while enrolled in Study S176.3.104. One of the six subjects in the double-blind period experienced malignant hypertension. This patient had marginally controlled hypertension at baseline.

A post-marketing safety update for Androgel 1% was included in the CR submission. No new or unexpected findings were found following review of these data.

Safety overview:

The safety profile and adverse events associated with AndroGel 1.62% are essentially the same as for AndroGel 1% except for the issue of testosterone transfer. Studies dealing with the potential transfer of AndroGel 1.62% are further discussed in the Clinical Pharmacology section of this review and in the Clinical Pharmacology and Primary Medical Officer reviews. The approved site of application for AndroGel (testosterone gel) 1.62% is the arms/shoulders. This application site:

- mitigated transfer of testosterone to non-dosed females.
- demonstrated a comparable exposure of total testosterone to the application method used in the phase 3 study.

- demonstrated the comparable skin irritation potential by the application method used in the phase 3 study.

In terms of the safety results from the clinical studies conducted for this NDA submission, there are no other issues which preclude approval. The data show the expected effects of a testosterone gel including increased hemoglobin and hematocrit, increased PSA, a single report of prostate cancer, lower urinary tract symptoms, acne, and skin inflammation. The medical officer and CDTL carefully reviewed 10 individual cases of supraphysiological testosterone concentrations and found them to be artifactural in 6 cases, related to likely overdose in 2 cases, and for unknown reason, though isolated and sporadic, in 2 cases. These results alone do not preclude approval.

9. Advisory Committee Meeting

No advisory committee was convened to discuss the approval of Androgel (testosterone gel) 1.62%. There are currently two testosterone gel preparations (Androgel 1% and Testim) and one testosterone solution (Axiron) which are approved. An Advisory Committee was held on June 23, 2009, to discuss the transfer potential of testosterone gels from patients to others, particularly children. The Advisory Committee agreed with the Division's plans to require labeling revisions (including a black box warning) and a Medication Guide for Androgel 1% and Testim. The same labeling and a Medication Guide dealing with the potential transfer of testosterone to others will be applied to Androgel (testosterone gel) 1.62%.

10. Pediatrics

The Pediatric Review Committee (PeRC) was consulted for the sponsor's request for a pediatric waiver. A hearing was set for September 23, 2009. The Division was informed (on August 26, 2009) that a determination had been made by PeRC that this NDA application does not trigger PREA requirements.

11. Other Relevant Regulatory Issues

A. Division of Scientific Investigations (DSI)

Clinical site inspections by the DSI were not requested. At the request of the Division of Clinical Pharmacology III, DSI audited the analytical portion of the primary clinical trial S176.3.104. The analytical portion of the study was conducted at (b) (4), (b) (4). The DSI (November 9, 2009) "recommends that the analytical portion of study S176.3.104 is acceptable for review."

B. Compliance

Compliance (December 7, 2009) determined that the inspections of the drug substance and drug product manufacturing and testing operations are acceptable.

C. Office of Surveillance and Epidemiology

i. Division of Medication Error Prevention and Analysis (DMEPA):

DMEPA found the tradename and the container and carton labeling to be acceptable. DMEPA also reviewed the Sponsor's proposal for an education and communication plan. The target audience is largely healthcare professionals and the goal is to educate physicians and pharmacists on how to correctly prescribe and dispense the two strengths of AndroGel. DMEPA found the plan to be "comprehensive to introduce the AndroGel 1.62% product overall." DMEPA stressed that the plan should emphasize the new strength presentation (milligrams of testosterone) and the application site differences between AndroGel 1% and AndroGel 1.62%.

ii. Division of Risk Management (DRISK):

DRISK found the Medication Guide and the Risk Evaluation and Mitigation Strategy (REMS) to be acceptable.

D. Controlled Substance Staff (CSS)

The Controlled Substance Staff recommended revised labeling under Section 9 in the label ("Drug Abuse and Dependence" section). The recommended changes (specifically dealing with abuse, (b) (4) and dependence) were made to the labeling.

E. Financial Disclosure

Form FDA 3454, signed June 26, 2008, was provided in the submission. Financial disclosures were submitted for the principal investigators in Protocols S176.1.001, S176.1.002, S176.1.003, S176.1.004, S176.1.005, S176.1.006, S176.1.007, S176.1.008, and the pivotal Phase 3 study S176.3.104.

A total of 88 investigators (all from all protocols and study sites) had no disclosures in the categories of compensation potentially affected by the outcome of the covered study [21 CFR 54, 2(a)], proprietary interest in the covered product or significant equity interest in the Sponsor of the covered product [21 CFR 54.2(b)], or significant payments of other sorts from the Sponsor of the covered study [12 CFR 54.2(f)]. There was no missing financial disclosure information for investigators in the above listed studies.

12. Labeling

The AndroGel (testosterone gel) 1.62% labeling is consistent with the two previously approved testosterone gel products and the testosterone solution with respect to transfer potential (particularly to children). This includes a black box warning and a Medication Guide.

The Division of Risk Management (DRISK) found the Medication Guide to be acceptable.

A consultation from the Controlled Substance Staff (CSS) recommended changes to the Drug Abuse and Dependency portion (Section 9) of the label. These recommendations were incorporated into the AndroGel (testosterone gel) 1.62% labeling.

The Division of Drug Marketing and Communication (DDMAC) reviewed the label and the Medication Guide and their recommendations were considered during labeling negotiations with the sponsor.

The final labeling was acceptable to the Study Endpoints and Label Development (SEALD) Team.

13. Decision/Action/Risk Benefit Assessment

- **Regulatory Action**

I agree with the Cross Discipline Team Leader, the primary medical officer, and the clinical pharmacology, pharmacology/toxicology, CMC, and statistical reviewers that NDA 22309 [Androgel (testosterone gel) 1.62%] should be approved.

- **Risk Benefit Assessment**

The primary endpoint for the phase 3 study (Trial S176.3.104) was met and these data are supported by numerous phase 1 studies. Adequate "bridging data" were submitted for the use of the shoulder/arm application site. The submitted data support the approval of AndroGel (testosterone gel) 1.62% from an efficacy standpoint. In addition, one year efficacy data were submitted and the CDTL, primary medical officer, and the clinical pharmacology and statistical reviewers believe that these data can be included in labeling and I agree.

The data submitted in this NDA demonstrate that the product provides acceptable testosterone exposure when used at titrated doses of 1.25 gm to 5 gm. The requisite percentage of patients met the C_{avg} criteria, and, in addition, two of the three required C_{max} criteria were met. In the 10 individual cases where C_{max} was > 2500 ng/dL, 5 cases can be ascribed to artifact, 1 case was likely to have been an artifact, and 2 cases were probably related to excessive dosing. In the two cases where no reason for the supraphysiologic concentration was obvious, the incident was isolated and sporadic, without clear clinical consequence. I agree with the primary medical officer and the CDTL that these results alone should not preclude approval.

In regard to general safety issues, the NDA provides evidence of well-known testosterone-related pharmacological adverse effects, and these effects unto themselves would not preclude approval. These reactions include: increased hemoglobin and hematocrit, increased PSA, a single report of prostate cancer, lower urinary tract symptoms, and skin inflammation (predominantly seen in phase 1 studies). All of these events are known to occur following testosterone administration and can be adequately labeled.

Labeling, including the package insert, the Medication Guide and container/carton labeling has been completed. The REMS, which pertains to the potential risk of secondary exposure to children and women (and includes a Medication Guide), has been deemed acceptable.

- **Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies**

A REMS to include a Medication Guide and assessment plan will be required. This is consistent with all currently marketed testosterone gels to mitigate the potential for drug transfer, primarily to children and women.

- **Recommendation for other Postmarketing Requirements and Commitments**

Although washing the application site has been demonstrated to remove a significant portion of the applied AndroGel (testosterone gel) 1.62%, a hand washing study is also currently required for all testosterone gel products. The sponsor has agreed to conduct this study as a post-marketing requirement and has submitted a protocol for the study (Study S176.1.012) entitled, "An Evaluation of the Effect of Hand Washing on the Amount of Residual Testosterone on the Hands after Application of Testosterone Gel 1.62%." The following timeline was agreed to with the sponsor:

- Final Protocol Submission: July, 2011
- Trial Completion: October, 2011
- Final Report Submission: July, 2012

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

/s/

GEORGE S BENSON
04/29/2011