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RESEARCH**

APPLICATION NUMBER:

202763Orig1s000

MEDICAL REVIEW(S)

Medical Officer's NDA Filing Memorandum

NDA 202763

NDA Submission Date: January 13, 2011
NDA Received Date: January 14, 2011
45-Day Filing Meeting Date: February 24, 2011
60-Day Filing Date: March 15, 2011
74-Day Filing Letter Date: March 29, 2011
PDUFA Goal Date: November 14, 2011
Sponsor: Teva Pharmaceuticals., 400 Chestnut Ridge Rd.,
Woodcliff Lake, NJ 07677 (201-930-3610; Fax 201-
489-1403; Email: rob.vincent@tevausa.com)
Generic Name: Testosterone Gel 1%
Proposed Trade Name: None submitted
Chemical Name: Testosterone
Molecular Formula: C₁₉H₂₈O₂ (Molecular weight: 288.42)
Dosage Forms: 2.5 gm, 5 gm, Sachets, and (b) (4)
Route of Administration: Transdermal
Indication: Adult Male Hypogonadism
Manufacturer: Cipla Limited, (b) (4)
India
Medical Officer: Guodong Fang, M.D., DRUP
Medical Team Leader: Mark Hirsch, M.D., DRUP

Summary

This NDA is filable. Several comments to Sponsor for the 74-Day letter are listed in final section of this memo.

The following is a brief clinical outline of this 505(b)(2) NDA submission including the contents of the Clinical section and current preliminary comments from the Clinical review team

On January 14, 2011, Teva Pharmaceuticals USA submitted a New Drug Application as **NDA 202763** for the drug product Testosterone Gel 1% in accord with Section 505 (b)(2) of the Federal Food, Drug and Cosmetic Act. The product was manufactured, packaged and tested at Cipla Ltd., India, a contract manufacturer for the Sponsor.

1. Background:

The Sponsor had submitted an original ANDA (b) (4) for the same product (testosterone Gel, 1%) to the Office of Generic Drug (OGD) on December 29, 2008 and received a Refuse to Receive Letter dated April 7, 2009 from the Agency, based on the fact that the formulation of the product contained different ingredients than those contained in the

reference listed drug (RLD).

(b) (4)

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The Sponsor believes that its proposed drug product, Testosterone Gel 1%, is suitable for submission as a NDA under section 505 (b) 2, based on the following:

1. A testosterone transdermal gel product in which the formulation contains different inactive ingredients, from those in the RLD can not be submitted as an ANDA.
(b) (4)
2. The active ingredients for the proposed drug product are otherwise the same as those of the RLD.
3. The route of administration, dosage form and strength of the proposed drug product are the same as those of the RLD.
4. Information demonstrating that the proposed drug product is bioequivalent to the RLD is provided in the NDA.
5. A skin irritation and sensitization study demonstrating that the proposed product will not cause any more irritation or sensitization than the RLD is provided in this NDA.
6. A transfer study quantifying and comparing the relative bioavailability between the proposed drug product and the RLD in female subjects following direct transfer from healthy male subjects is provided in the NDA.
7. A hand-washing study quantifying and comparing the residual testosterone following hand washing between the proposed drug product and the RLD is provided in the NDA.
8. The labeling for the proposed drug product is the same as that of the reference listed drug, with the exception of those changes annotated in the side-by-side labeling comparison.

2. Clinical Studies: The clinical section of this NDA contains the following study reports:

Table: Clinical Studies in NDA 202763

Type of Study (#)	Objectives of the Study	Study Design	Test Product(s)	Numbers of Subjects	Patients / Healthy	Single / Multi Dose
<u>Bio-equivalence (BE) Study 70343</u>	Determine the BE between Teva drug product and RLD under fasting conditions	Multi-centre, BE, open-label, randomized 2-way crossover study	Testosterone 1% Topical Gel	93 (90 Completed)	Hypo-gonadal adult male subject	Single-dose
<u>Irritation & Sensitization Study 10936025</u>	Compare cumulative skin irritation & sensitization potential between 2 test products and 2 marketed RLDs	Multi-sites, multi-application, 2-phase, DB, randomized, irritation & sensitization study	Testosterone 1% Topical Gel	265 (233 included in PPPI and 222 included in PPS)	Healthy adult male subjects	Multiple-dose
<u>Hand-Washing Study CRI-00018704</u>	Quantify and compare the amount of residual drug remaining on the hands between a test product and a marketed RLD.	Open-label, 2-period, crossover, pivotal study on healthy adult male subjects	10 g of Testosterone 1% Topical Gel in each study period, topical	48 (46 Completed)	Healthy adult male subjects	Single dose
<u>Bio-availability (BA) Transfer Study M1FX10001</u>	Quantify and compare the relative BA between a test product and a marketed RLD in female subjects following direct transfer from healthy male subjects	Open-label, randomized, 4-period, 4-treatment crossover study. Test drug: A and B RLD: C and D	Testosterone 1% Topical Gel Without T-Shirt	A vs. C, 48 M and F couples (47 couples completed)	Healthy adult male & female subjects	Single-dose
			Testosterone 1% Topical Gel With T-Shirt	B vs. D, 48 M and F couples (43 couples completed)		

PPPI= *per-protocol population irritation*

PPPS = *per-protocol population sensitization*

Clinical Study 1: Single *in vivo* Bioequivalence study (Study No. 10936025)

Randomized, open-label, 2-way crossover, bioequivalence study of Testosterone 1% Topical Gel Formulation and Androgel (Reference) following a 100 mg dose in hypogonadal male volunteers

TESTOSTERONE CONCENTRATIONS – SHOWN AS BASELINE CORRECTED VALUES (N = 77)

Table 1.1 Pharmacokinetic Parameters

Parameters	Test (5 g packet of T 1% topical gel) (A)			Reference (Androgel) (B)		
	Mean	SD	CV (%)	Mean	SD	CV (%)
AUC _{0-t} (pg·h/mL)	69205.67	36636.42	52.94	64668.40	29802.94	46.09
C _{max} (pg/mL)	3918.77	2449.46	62.51	3445.78	1897.45	55.07
T _{max} (h)	19.2	10.8	56.19	19.6	11.1	56.64
T _{max} * (h)	20.0	4.0	—	20.0	6.0	—

Table 1.2 Testosterone 5 g packet of 1% topical gel (A) vs Androgel (B)

	AUC _{0-t}	C _{max}
Ratio ¹	104.04%	112.38%
90 % Geometric C.I. ²	94.95 % to 114.00 %	103.49 % to 122.04 %
Intra-Subject CV	34.86%	31.25%

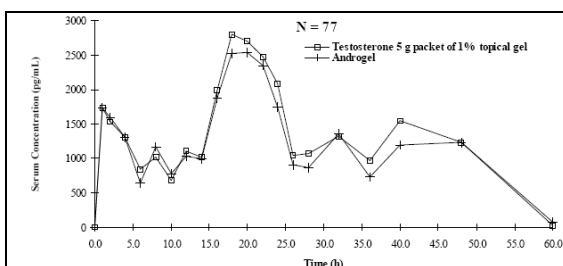


Figure 1.1 Testosterone Baseline Corrected Mean Concentration – Time Profile

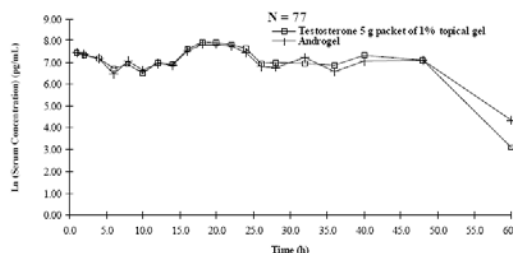


Figure 1.2 Testosterone Baseline Corrected Ln (Mean Concentration) – Time Profile

Sponsor's Conclusion: The test testosterone 5 g packet of 1% topical gel (Treatment A) is bioequivalent to the reference Androgel (Treatment B) following a 100 mg dose in hypogonadal male volunteers.

Reviewer's comments:

1. The study design and execution, and the results of this BE study appear acceptable.
2. The BE study was conducted using the arms/shoulders only as the application site for all 100mg of testosterone. Users of AndroGel 1% apply 100mg of testosterone to both arms/shoulders and both sides of the abdomen. The Sponsor should comment on whether this has any impact on the final determination of bioequivalence to the reference listed drug.

Clinical Study 2 Irritation and Sensitization Study (Study No. 10936025)

- 1) Irritation Assessment: During the irritation/induction period, the 0.1 ml gels (0.025 ml/cm² of gel which is equivalent to 0.25 mg/cm² of testosterone) were applied to an area of 2 cm x 2 cm and replaced once daily to the same application

site for a total of 21 days. On Day 22, the Day 21 applications were removed and no new product applied. Signs and symptoms of irritation were evaluated by trained, blinded evaluators daily during the irritation/induction period. Standardized rating scales were utilized. To ensure the integrity of the study blinding, a member of the clinic staff who was not involved in any of the skin irritation grading assessments applied the formulations to each subject according to the randomization schedule. The study subject and staff members performing the irritation assessments were blinded to the treatment allocation.

- 2) Sensitization Assessment: Following Day 22 removal and assessments, subjects underwent a 14 day washout period when no gels were applied. The subjects returned to the clinical facility on Day 36 where the gels were applied to complementary sites on the opposite arm used in the irritation/induction period. These applications were removed on Day 38 after at least 48 hours of application and the sites of application monitored over the next 72 hours (30 minutes, 24, 48, and 72 hours after removal) for signs and symptoms of possible sensitization reactions using the same rating scales as for the induction/irritation period.

A scale of 0-7 was used to evaluate skin irritation (0 = no evidence of irritation, 7 = strong reaction spreading beyond test (i.e. application) site), based upon a previous FDA Draft Guidance. However, the Sponsor points out that this scale works well when mild irritation is present; however, if irritation is not present at all (e.g., scores of 0) it produces a skewed outcome. To resolve this issue, the mean cumulative total irritation results were “re-scaled” using an adjusted (modified) scale, where 1-8 is the same as 0-7. The original definitions of skin appearance have remained the same (i.e., 1 = no evidence of irritation, 8 = strong reaction spreading beyond test site in one case).

Table 2.1: Mean Cumulative Total Irritation (sum of irritation + “other effects” scores on Days 1 through 22) with the adjusted irritation scale of 1–8.

	Product*	N	Mean (SD)	Min.	Median	Max.
Mean Total Irritation Score Day 1 through Day 22	A	233	23.79 (4.12)	22.00	22.00	51.00
	B	233	26.26 (7.11)	22.00	23.00	57.00
	C	233	23.72 (4.39)	22.00	22.00	50.00
	D	233	27.30 (7.73)	22.00	24.00	59.00

* **Test Formulation A**: 0.1 ml of testosterone 1% topical gel (Manufactured by Cipla Ltd. for TEVA Pharmaceuticals USA). Represents one batch.

* **Test Formulation B**: 0.1 ml of testosterone 1% topical gel (Manufactured by Cipla Ltd. for TEVA Pharmaceuticals USA). Represents a different batch.

* **Reference Formulation C**: 0.1 ml of Androgel[®] (testosterone gel) 1% (Manufactured by Laboratories Besins International for Unimed Pharmaceuticals, LLC [Unimed]).

* **Reference Formulation D**: 0.1 ml of Testim[®] 1% (testosterone gel) (Manufactured by DPT Laboratories, Ltd for Auxilium Pharmaceuticals Inc. [Auxilium]).

Table 2.2: Difference of Means and Locke's 90% Confidence Intervals of PPPI with the adjusted irritation scale of 1-8.

	Mean Cumulative Total Irritation				
	Mean Test	Mean Ref x 1.25	Difference	Lower CI	Upper CI*
Product A v C	23.79	29.65	-5.85	-6.59	-5.11
Product B v D	26.26	34.13	-7.87	-9.16	-6.57

*If Upper CI is ≤ 0 then test product is considered non-inferior to the reference product.

PPPI = per protocol population irritation phase

Using both of these modified scales, the upper bound of the 95% one-sided CI (upper limit of the 90% two-sided confidence interval) of the difference between the mean cumulative irritation score for test product A minus 1.25 times the mean cumulative irritation score for reference product C was determined to be ≤ 0 , the difference between the mean cumulative irritation score for test product B minus 1.25 times the mean cumulative irritation score for reference product D was determined also to be ≤ 0 , therefore it appears that the Sponsor's testosterone, 1% topical gel product was no more irritating (non-inferior) to 1% Androgel[®], and to 1% Testim[®].

Sponsor's Conclusions:

- None of the applications for any subject for any product were halted prematurely for excessive irritation during the study.
- None of the four products tested showed any cumulative irritations effects that were of clinical significance.
- No subjects demonstrated any sensitization reaction to the four products.
- There was no significant difference between the number and severity of localized application site reactions reported between the four treatments during the study.

Reviewer's comments:

1. *Most of the individual scores during the irritation and sensitization phases were either zero or 1.*
2. *The design, execution, and results of this irritation and sensitization study appear acceptable.*

Clinical Study 3: Hand Washing Study (Study No. CRI-00018704)

This was an open-label, two-period crossover, pivotal study in healthy adult male subjects; comparing the amount of residual drug remaining on the hands, between the Sponsor's test product Testosterone Gel 1% and AndroGel[®] (testosterone gel) 1% following a hand washing procedure. The subjects applied each dose to their arm and shoulder. At five minutes after dose application, the subjects washed their hands as described in the protocol. The subject's hands were wiped with three ethanol dampened gauze per hand (sample for assessment).

Table 3.1 Residual Testosterone (in µg) from Hand Washing Study

	Test Product (A)	Androgel (B)
N	39	39
Mean	284.9303	287.0479
Max	592.51	547.33
Min	62.36	98.86
Medium	271.6	238.13

Table 3.2 Summary of Non-Inferiority Testing

Test Product (A) vs. Reference Product (B)	
N = 39	
Point Estimate $\mu_A - 1.25\mu_B$	Upper Bound of 95% CI
-73.53	-43.46

Sponsor's Conclusions: The results of this study demonstrate that the test product of testosterone gel 1% by Teva Pharmaceuticals USA is non-inferior to that of the reference product of AndroGel® (testosterone gel) 1% for the amount of testosterone remaining on the hands following a hand washing procedure.

Reviewer's comments:

- 1) The design of the hand-washing study did not include measurement of residual testosterone on the subjects' hands after applying the drug product to the application site but before hand-washing. Therefore, it is not possible to measure the percentage of the testosterone removed by the hand washing procedure (a "wash-off percentage"). Sponsor should comment on whether this impacts on the ability to interpret the results of the hand-washing study.*
- 2) An application site washing study has not yet been conducted and is warranted. It would be reasonable to request such a study as a postmarketing requirement.*

Clinical Study 4: BA Transfer Study (Study No. M1FX10001)

This was an open-label, single-dose, randomized, 4-period, 4-treatment crossover study that assessed the relative bioavailability of the new Testosterone 1% gel compared to that of AndroGel® 1% testosterone gel in healthy female subjects following skin-to-skin contact as well as clothed contact with healthy male subjects who received a single topical dose (2 x 5 g of gel for a total of 100 mg testosterone). Potential for transfer was assessed from males to females with a male wearing a T-shirt and not wearing a T-shirt. Product was applied to the arms and shoulders only.

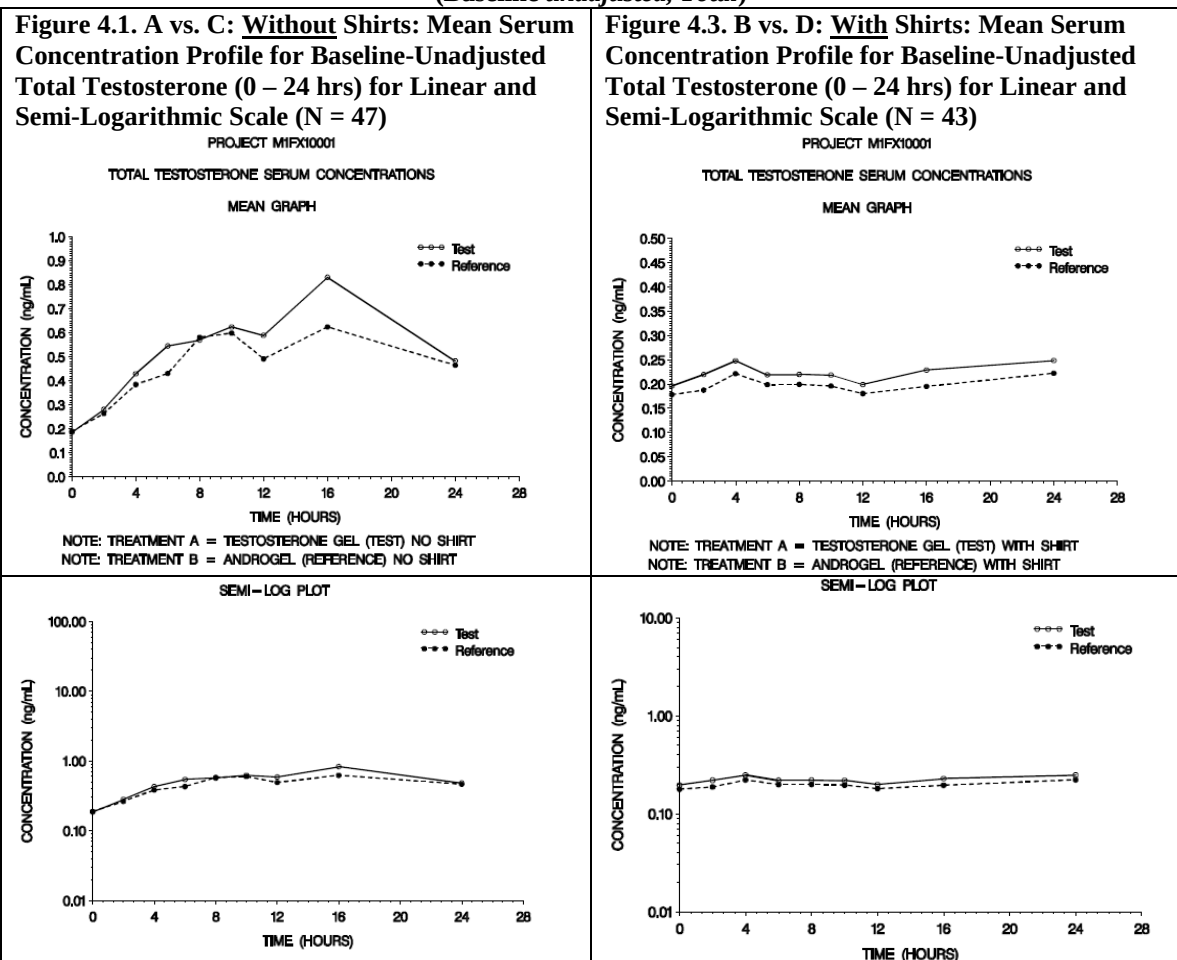
Table 4.1 Summary of Statistical Analysis for Baseline-Unadjusted, Total Testosterone Concentrations in Females

Total Testosterone Concentrations : Baseline- <i>Unadjusted</i> Data					
PK Variable	Geometric Least Squares Means			90% Confidence Interval	Intra-subject variability (%)
	Test	Reference	% Ratio		
Without Shirt (N=47) Testosterone Gel 1% (A) vs. AndroGel 1% (C)					
AUC _{0-t} (ng·h/mL)	13.6987	11.7547	116.54	97.82-135.26	49.4
C _{max} (ng /mL)	1.0112	0.8928	113.26	85.53-141.00	74.2
T _{max} (h)	11.51	12.73	90.43	78.08-102.78	37.0
With Shirt (N=43) Testosterone Gel 1% (B) vs. AndroGel 1% (D)					
AUC _{0-t} (ng·h/mL)	5.3264	4.7808	111.41	97.22-125.60	36.5
C _{max} (ng /mL)	0.2866	0.2452	116.90	101.01-132.79	39.9
T _{max} (h)	13.90	1304	107.23	83.26-131.21	63.0

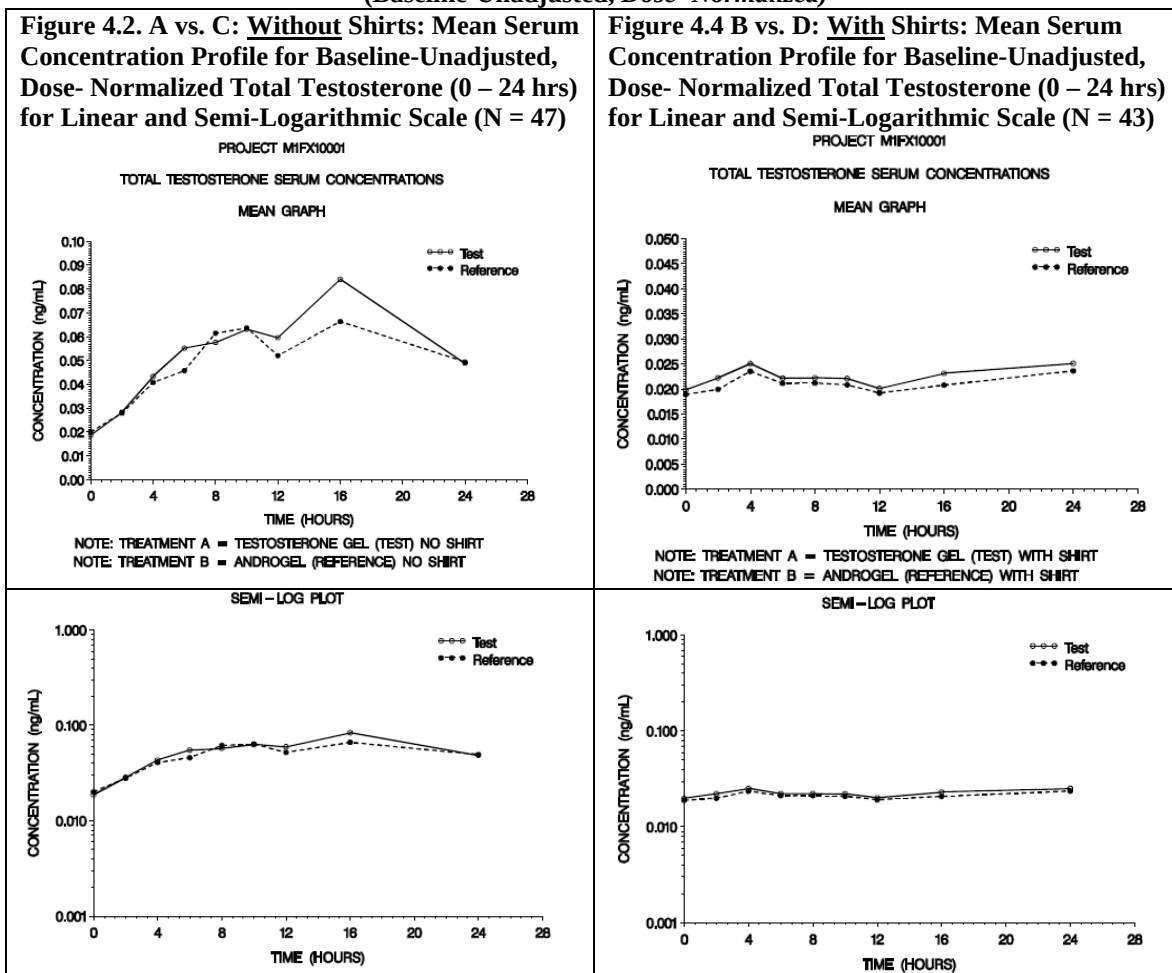
Table 4.2 Summary of Statistical Analysis for Baseline-Unadjusted, Dose-Normalized Total Testosterone

Total Testosterone Concentrations: Baseline- <i>Unadjusted</i> , <u>Dose-Normalized</u> Data					
PK Variable	Geometric Least Squares Means			90% Confidence Interval	Intra-subject variability (%)
	Test	Reference	% Ratio		
Without Shirt (N = 47) Testosterone Gel 1% (A) vs. AndroGel 1% (C)					
AUC _{0-t} (ng·h/mL)	1.3865	1.2486	111.05	92.88-129.22	49.1
C _{max} (ng /mL)	0.1023	0.0947	108.02	81.10-134.94	73.9
T _{max} (h)	11.51	12.73	90.43	78.08-102.78	37.0
With Shirt (N = 43) Testosterone Gel 1% (A) vs. AndroGel 1% (D)					
AUC _{0-t} (ng·h/mL)	0.5384	0.5085	105.89	92.31-119.46	35.9
C _{max} (ng /mL)	0.0290	0.0261	110.90	95.64-126.16	39.4
T _{max} (h)	13.99	13.04	107.23	83.26-131.21	63.0

Figures 4A Without T-Shirt (A and C) vs. With T-Shirt (B and D)
(Baseline unadjusted, Total)



Figures 4B Without Shirts (A and C) vs. With Shirts (B and D)
(Baseline-Unadjusted, Dose- Normalized)



Data from the periods without a T-shirt showed that both products did “transfer” to females:

- AUC_{0-t} (the extent of exposure) determined from baseline testosterone levels accounted for at least 45% of the AUC_{0-t} determined from the total testosterone transferred from males to females for Treatment A and Treatment C.
- C_{max} (the rate of exposure) determined from baseline testosterone levels accounted for at least 44% of the C_{max} determined from the total testosterone transferred from males to females for Treatment A and Treatment C.

Data from periods with a T-shirt showed that “transfer” to females was considerably mitigated:

- AUC_{0-t} (the extent of exposure) determined from baseline testosterone levels (Day –1) accounted for at least 91% of the AUC_{0-t} determined from the total testosterone transferred from males to females for Treatment B and Treatment D.

- $C_{\max}$ (the rate of exposure) determined from baseline testosterone levels (Day –1) accounted for at least 92% of the $C_{\max}$ determined from the total testosterone transferred from males to females for Treatment B and Treatment D.

Reviewer's comments:

- 1. The main purpose of the transfer study is to determine whether the secondary exposure ("transfer") of testosterone to women and children can be effectively mitigated by a t-shirt and this appears to be the case for both products.***
- 2. The study's design, execution and the results appear generally acceptable.***

3. Financial Disclosure

The financial certification and the list of clinical investigators are included in the NDA submission.

4. Pediatric Study Waiver

The sponsor has submitted a pediatric waiver under 21 CFR 314.55(c)(2)(iii) within the NDA submission.

Reviewer's comment: The Clinical review team has been informed that testosterone gel products, such as this new Teva product, do not trigger the Pediatric Research Equity Act (PREA) requirements.

5. Prescription Labeling

The draft labeling and the listed drug labeling both are included in the NDA submission. A Medication Guide is included. An appropriate The Risk Evaluation and Management Plan (REMS) is also included.

6. Clinical Study Site Inspections

For a 505 (b)(2) NDA and a non-NME drug product, considering the nature of the studies that were submitted, this reviewer considers that an audit of clinical sites by Division of Scientific Investigation may not be necessary, except perhaps for the study of bioequivalence, which will be determined by Clinical Pharmacology.

7. Trade Name

No trade was enclosed in the submission, nor is the Sponsor seeking to have one. The Sponsor believes that a tradename is not required and they would like to market the product as "Testosterone Gel (b)(4)".

Reviewer's comment: The lack of a trade name may engender a potential for medication errors. For example, there may be other testosterone transdermal products named "Testosterone (b) (4)" with different application sites compared to the Sponsor's new product, and these could be erroneously dispensed in place of the Sponsor's product. The Sponsor should comment on the potential medication errors that may result from the lack of a tradename.

8. Conclusion and Recommended Regulatory Action

Based on the requirements for filing a 505(b)(2) NDA, the Clinical review team concludes that this NDA is filable.

Several Clinical review issues were noted as part of this filing review and these should be conveyed to the Sponsor in the 74-Day letter, as follows:

1. The bioequivalence study was conducted using the arms/shoulders only as the application site for all 100 mg of testosterone. The current approved labeling for AndroGel 1% calls for application of 100 mg of testosterone to both arms/shoulders and both sides of the abdomen. The Sponsor should comment on whether this difference has any impact on the final determination of bioequivalence to the reference listed drug.
2. The design of the hand-washing study did not include measurement of residual testosterone on the subjects' hands after applying the drug product to the application site but before hand-washing. Therefore, it is not possible to measure the percentage of the testosterone removed by the hand washing procedure (a "wash-off percentage"). Sponsor should comment on whether this impacts on the ability to interpret the results of the hand-washing study.
3. An application-site washing study is needed to assess the degree to which testosterone may be removed from the application site by washing. The study may be conducted as a postmarketing requirement.
4. The lack of a formal trade name may engender a potential for medication errors. For example, there may be other testosterone transdermal products named "Testosterone (b) (4)" with different application sites compared to the Sponsor's new product, and these could be erroneously dispensed in place of the Sponsor's product. The Sponsor should comment on the potential medication errors that may result from the lack of a tradename.

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/s/

GUODONG FANG
02/25/2011

MARK S HIRSCH
02/25/2011
I concur.

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	NDA 202763
Priority or Standard	Standard
Submit Date(s)	2011-01-13
Received Date(s)	2011-01-14
Extended PDUFA Goal Date	2012-02-14
Division / Office	DRUP / ODE 3
Reviewer Name(s)	Guodong Fang
Review Completion Date	2011-12-28 (Final draft)
Established Name	Testosterone Gel
(Proposed) Trade Name	
Therapeutic Class	Topical Steroid Androgen
Applicant	Teva Pharmaceuticals, Inc.
Formulation(s)	C ₁₉ H ₂₈ O ₂ (MW 288.42)
Dosing Regimen	1% Testosterone Gel
Indication(s)	Adult Male Hypogonadism
Intended Population(s)	Adult Men with Hypogonadism

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical perspective, this reviewer recommends that Teva, 1% testosterone transdermal gel, be **approved** for the indication of replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone:

- “Primary hypogonadism (congenital or acquired)” or
- “Hypogonadotropic or secondary hypogonadism (congenital or acquired)”.

The Clinical Review Team and other disciplines through their reviews believe that the results from one bioequivalence study, one irritation and sensitization study, one hand washing study, and one bioavailability transfer study included in this 505(b)(2) NDA submission are acceptable. The results of these studies demonstrate that Teva 1% testosterone gel product is effective and safe for the replacement of testosterone in hypogonadal men.

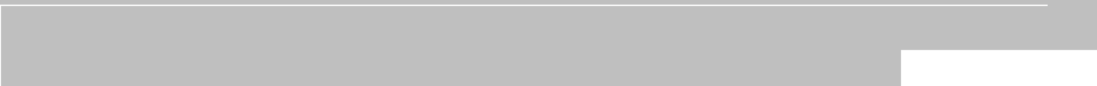
As for all topical testosterone gel products, a Black Box Warning and a Medication Guide addressing the potential for secondary exposure via skin transfer of testosterone to children have been included in labeling and are acceptable.

This Clinical reviewer recommends an Approval action at this time.

1.2 Risk Benefit Assessment Based on Clinical Findings

1.2.1 Brief Overview of the Basis for Submission

The basis for the submission of this NDA, under section 505 (b) 2, is the following:

1.  (b) (4)
 (b) (4) (b) (4)
2. The active ingredients for the proposed drug product are the same as those of the RLD.
3. The route of administration, dosage form and strength of the proposed drug product are the same as those of the RLD.
4. Information demonstrating that the proposed drug product provides sufficiently comparable exposures to the RLD drug is provided in the application.
5. A skin irritation and sensitization study demonstrating acceptable safety, and no more irritation or sensitization than the RLD is provided in this application.

6. Transfer and hand-washing studies have been completed and demonstrate acceptable safety, in addition to comparing the relative bioavailability between the proposed drug product and the RLD in female subjects following direct transfer from healthy male subjects.
7. The labeling for the proposed drug product is the same as that of the reference listed drug, with the exception of information pertaining to the new bioequivalence and transfer studies.

The chart below provides pertinent information regarding the Reference Listed Drug, which is the basis for this NDA 505 (b)(2) submission:

REFERENCE LISTED DRUG	
USP/USAN Drug Name	Testosterone Gel, 1%
Proprietary Name	AndroGel
NDA Holder	Abbott Prods.
NDA number	021015
Dosage Form	Gel
Strength	1%
Rx or OTC	Rx

The following information is relevant to the basis of this submission:



Teva 1% testosterone gel product, supplied in 2.5g and 5g sachets, is a transdermal testosterone preparation indicated for testosterone replacement therapy in adult male hypogonadism associated with a deficiency or absence of endogenous testosterone. The Applicant submitted NDA 202763 on January 13, 2011. During this review cycle, the sponsor sought the same indication (b) (4): testosterone replacement therapy in men with conditions associated with primary or secondary hypogonadism. The main objective of the NDA is to demonstrate bioequivalence to the RLD, and to demonstrate acceptable safety in the special safety studies required by FDA.

1.2.2 Efficacy

Clinical Study 1: Single *in vivo* Bioequivalence study (Study No. 70343): This was a randomized, open-label, 2-way crossover, bioequivalence study of Teva's Testosterone 1% Topical Gel Formulation and Androgel (Reference) following a 100 mg dose in hypogonadal male volunteers. Testosterone concentrations are shown below as baseline corrected values.

**Table 1.1 Summary: Testosterone Concentrations - Baseline Corrected
Re-analysis Dataset Excluding Invalid Samples (N=72)**

Pharmacokinetic Parameters		Test [Testosterone 5 g packet of 1% topical gel (A)]			Reference [Androgel (B)]		
		Mean	SD	CV(%)	Mean	SD	CV (%)
AUC _{0-t}	(ng•h/dL)	6590	3403	51.65	6114	2723	44.53
C _{max}	(ng/dL)	383	248	64.77	322	157	48.73
T _{max}	(h)	19.6	10.7	54.74	19.2	10.5	54.89
T _{max} *	(h)	20.0	4.0	—	20.0	6.0	—

* Medians and inter-quartile ranges are presented.

**Table 1.2 Testosterone Concentrations 5 g packet of 1% topical gel (A) vs Androgel (B)
Baseline Corrected Re-analysis Dataset Excluding Invalid Samples (N=72)**

	AUC _{0-t}	C _{max}
Ratio ¹	105.28%	115.72%
90 % Geometric C.I. ²	95.82 % to 115.67 %	105.95 % to 126.40 %
Intra-Subject CV	34.56 %	32.29 %

¹ Calculated using least-squares means according to the formula:
e^(Testosterone 5 g packet of 1% topical gel [A] - Androgel [B]) X 100.

² 90% Geometric Confidence Interval using In-transformed data

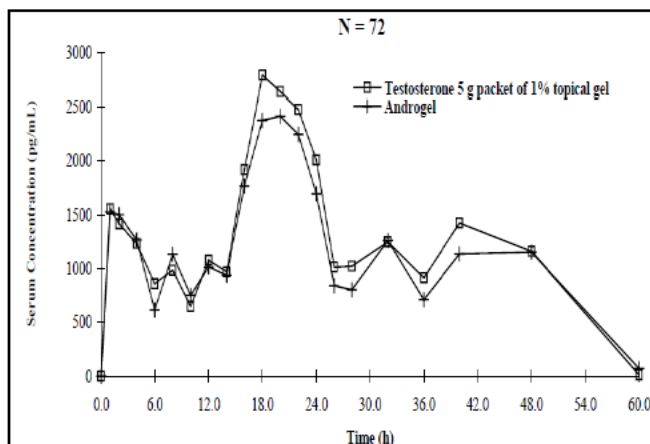


Figure 1.1 Testosterone Baseline Corrected Mean Concentration – Time Profile

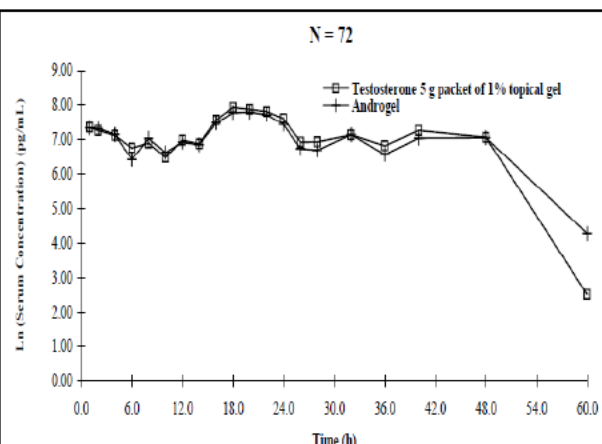


Figure 1.2 Testosterone Baseline Corrected Ln (Mean Concentration) – Time Profile

Sponsor's Conclusion: The test testosterone 5 g packet of 1% topical gel (Treatment A) is bioequivalent to the reference Androgel (Treatment B) following a 100 mg dose in hypogonadal male volunteers.

Reviewer's comments:

The study design and execution, and the results of this BE study are acceptable, even if the baseline corrected C_{max} was not completely bioequivalent. The small increase in maximum C_{max} (126.4% rather than 125%) is not considered to be clinically significant.

1.2.3 Safety

1.2.3.1. Clinical Study 2: Irritation and Sensitization Study (Study No. 10936025)

- 1) Irritation Assessment: During the irritation/induction period, 0.1 ml of gel (or 0.025 ml gel per cm², which is equivalent to 0.25 mg/cm² of testosterone) was applied to an area of 2 cm x 2 cm and replaced once daily to the same application site for a total of 21 days. On Day 22, the Day 21 applications were removed and no new product applied. Signs and symptoms of irritation were evaluated by trained, blinded evaluators daily during the irritation/induction period. Standardized rating scales were utilized. To ensure the integrity of the study blinding, a member of the clinic staff who was not involved in any of the skin irritation grading assessments applied the formulations to each subject according to the randomization schedule. The study subject and staff members performing the irritation assessments were blinded to the treatment allocation.
- 2) Sensitization Assessment: Following Day 22 removal and assessments, subjects underwent a 14 day washout period when no gel was applied. The subjects returned to the clinical facility on Day 36 where the gels were applied to complementary sites on the opposite arm used in the irritation/induction period. These applications were removed on Day 38 after at least 48 hours of application and the sites of application monitored over the next 72 hours (30 minutes, 24, 48, and 72 hours after removal) for signs and symptoms of possible sensitization reactions using the same rating scales as for the induction/irritation period.

A scale of 0-7 was used to evaluate skin irritation (0 = no evidence of irritation, 7 = strong reaction spreading beyond test (i.e. application) site), based upon a previous FDA Draft Guidance. The Sponsor points out that this scale works well when mild irritation is present; however, if irritation is not present at all (e.g., scores of 0) it produces a skewed outcome. To resolve this issue, the mean cumulative total irritation results were "re-scaled" using an adjusted (modified) scale, where 1-8 is the same as 0-7. The original definitions of skin appearance have remained the same (i.e., 1 = no evidence of irritation, 8 = strong reaction spreading beyond test site).

Table 1.3: Mean Cumulative Total Irritation (sum of irritation + “other effects” scores on Days 1 through 22) with the adjusted irritation scale of 1–8

	Product*	N	Mean (SD)	Min.	Median	Max.
Mean Total Irritation Score Day 1 through Day 22	A	233	23.79 (4.12)	22.00	22.00	51.00
	C	233	23.72 (4.39)	22.00	22.00	50.00

* **Test Formulation A:** 0.1 ml of testosterone 1% topical gel (Manufactured by Cipla Ltd. for TEVA Pharmaceuticals USA). Represents one batch (X028).

* **Reference Formulation C:** 0.1 ml of AndroGel® (testosterone gel) 1% (Manufactured by Laboratories Besins International for Unimed Pharmaceuticals, LLC [Unimed]).

Table 1.4: Difference of Means and Locke’s 90% Confidence Intervals of PPPI with the adjusted irritation scale of 1-8.

	Mean Cumulative Total Irritation				
	Mean Test	Mean Ref x 1.25	Difference	Lower CI	Upper CI*
Product A v C	23.79	29.65	-5.85	-6.59	-5.11
Product B v D	26.26	34.13	-7.87	-9.16	-6.57

*If Upper CI is ≤ 0 then test product is considered non-inferior to the reference product.

PPPI = per protocol population irritation phase

Using both of these modified scales, the upper bound of the 95% one-sided CI (upper limit of the 90% two-sided confidence interval) of the difference between the mean cumulative irritation score for test product A minus 1.25 times the mean cumulative irritation score for reference product C was determined to be ≤ 0 , therefore it appears that the Sponsor’s testosterone, 1% topical gel product (A) was no more irritating (non-inferior) to 1% AndroGel® (C).

Sponsor’s Conclusions:

- None of the applications for any subject for any product were halted prematurely for excessive irritation during the study.
- Neither the test nor reference product tested showed any cumulative irritations effects that were of clinical significance.
- No subjects demonstrated any sensitization reaction to the test nor to the reference product.
- There was no significant differences in the number and severity of localized application site reactions reported between the test and reference treatment during the study.

Reviewer’s comments:

1. *Most of the individual scores during the irritation and sensitization phases were either zero or 1.*
2. *The design, execution, and results of this irritation and sensitization study appear acceptable.*

1.2.3.2. Clinical Study 3: Hand Washing Study (Study No. CRI-00018704)

This was an open-label, two-period crossover study in healthy adult male subjects comparing the amount of residual drug remaining on the hands after a hand washing procedure between the Sponsor’s test product Testosterone Gel 1% and AndroGel® (testosterone gel) 1%. The subjects

applied each dose to their arm and shoulder. At five minutes after dose application, the subjects washed their hands as described in the protocol. The subject's hands were wiped with three ethanol dampened gauze per hand (sample for assessment).

Table 1.5 Residual T (µg) from Hand Washing Study (N=39)

	Test Product (A) (Batch # X145)	AndroGel (B) (batch # 31848)
Mean	285	287
Max	593	547
Min	62	99

Table 1.6 Summary of Non-Inferiority Testing

Test Product (A) vs. Reference Product (B) (N = 39)	
Point Estimate $\mu_A - 1.25\mu_B$	Upper Bound of 95% CI
-73.53	-43.46

Sponsor's Conclusions: The results of this study demonstrate that the test product of testosterone gel 1% by Teva Pharmaceuticals USA is non-inferior to that of the reference product of AndroGel® (testosterone gel) 1% for the amount of testosterone remaining on the hands following a hand washing procedure.

Reviewer's comments:

- 1) The design of the hand-washing study did not include measurement of residual testosterone on the subjects' hands after applying the drug product to the application site but before hand-washing. Therefore, it is not possible to measure the percentage of the testosterone removed by the hand washing procedure (a "wash-off percentage"). However, the results of this study shows that a very, very small amount of testosterone remains on the hands after application and these results are clinically acceptable.*
- 2) An application site washing study has not yet been conducted and is warranted. The Sponsor has agreed to conduct such a study as a postmarketing requirement.*

1.2.3.3. Clinical Study 4: BA Transfer Study (Study No. M1FX10001)

This was an open-label, single-dose, randomized, 4-period, 4-treatment crossover study that assessed the relative bioavailability of the new Testosterone 1% gel compared to that of AndroGel® 1% testosterone gel in healthy female subjects following skin-to-skin contact as well as clothed contact with healthy male subjects who received a single topical dose (2 x 5 g of gel for a total of 100 mg testosterone). Potential for transfer was assessed from males to females with a male wearing a T-shirt and not wearing a T-shirt. Product was applied to the arms and shoulders only.

Data from periods without a T-shirt showed that both products did transfer; but data from periods with a T-shirt showed that transfer was minimal (effectively mitigated by a T-shirt).

Table 1.7 % Difference of Testosterone C_{max} and AUC_{0-t} Post-Transfer vs. Pre-Transfer With / Without T-Shirt

Parameter (Mean±SD)	Without T-Shirt (N = 47)			With T-Shirt (N = 45)		
	24-hr Pre-Transfer	24-hr Post-Transfer	% Difference	24-hr Pre-Transfer	24-hr Post-Transfer	% Difference
C _{max} (ng/dL)	27.4±18	102±86	+272	24.5±17	28.3±16	+15.5
AUC _{0-t} (ng•h/dL)	462±184	1378±984	+198	478±275	530±322	+10.8

Reviewer's Comment:

The study's design, execution and the results are acceptable. It was determined through this study that transfer of testosterone to women and children can be effectively mitigated by a t-shirt for both the test and reference products.

1.2.4 Dose Regimen and Administration

The Sponsor originally proposed that testosterone Gel 1% would be supplied as (b) (4) individual packets. Subsequently, the Sponsor withdrew their request to (b) (4). The recommended starting dose of testosterone gel 1% is 5 g once daily (preferably in the morning) to clean, dry, intact skin of the shoulders and upper arms and/or abdomen (area of application should be limited to the area that will be covered by the patient's short sleeve t-shirt). Testosterone gel must not be applied to the genitals. After applying the gel, the application site should be allowed to dry for a few minutes prior to dressing. Avoid fire, flames or smoking until the gel has dried since alcohol based products, including testosterone gel, are flammable. Hands should be washed with soap and water after testosterone gel has been applied.

1.2.5 Special Populations

No new data regarding special populations are included in this re-submission.

1.2.6 Drug Abuse and Dependence

Testosterone Gel 1% is a Schedule III controlled substance because it contains testosterone. The labeling has been reviewed by the Controlled Substances Staff (CSS) and all their comments have been incorporated.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

1.3.1 Black Box Warning

A black box warning has been instituted for the class of topical testosterone gel products due to the risk of adverse outcomes in children who are inadvertently exposed to testosterone by direct

skin contact with the application site of adult males. The TEVA Testosterone Gel 1% label will also contain this black box warning, which reads:

WARNING: SECONDARY EXPOSURE TO TESTOSTERONE

- **Virilization has been reported in children who were secondarily exposed to testosterone gel.**
- **Children should avoid contact with unwashed or unclothed application sites in men using testosterone gel.**
- **Healthcare providers should advise patients to strictly adhere to recommended instructions for use.**

1.3.2 Medication Guide

At the time of instituting the black box warning, the Agency also required manufacturers of topical testosterone products to distribute a Medication Guide to consumers. The Applicant's proposed Medication Guide will be the same as the Medication Guides instituted for the existing approved topical testosterone gel products. The Medication Guide and timetable for assessments constitutes the required Risk Evaluation and Minimization (REMS) program for this product and was submitted in its final form in the (27, January, 2012) submission.

Reviewer's comment:

The Division of Risk Management (DRISK) has concurred with the elements of the proposed REMS. The Patient Labeling Team in the Division of Medical Policy Programs (DMPP) provided comments and recommendations on the Medication Guide and these were all incorporated.

1.4 Recommendations for Postmarket Requirements and Commitments

The sponsor has agreed to conduct a "application site- washoff" study as a postmarketing requirement study in order to demonstrate that Testosterone Gel 1% is effectively removed from the application site by simple washing. The CR submission contains a detailed protocol synopsis for this study.

2 Introduction and Regulatory Background

2.1 Product Information

The Sponsor submitted this NDA under 505b(2) based on its product contains the same active ingredients, but a different inactive ingredient, comparing to reference listed drug (RLD), 1% AndroGel. Table 2.1 compares the components in the two products.

Table 2.1 Comparison Between Teva 1% Testosterone Gel and RLD-505(b)(2)

Manufacturer	Abbott Prods	Teva Pharmaceuticals USA
Drug Name	Androgel® (testosterone gel)	Testosterone Gel
Active Ingredient(s)	Testosterone, USP	Testosterone, USP
Inactive Ingredient(s)	Dehydrated Alcohol, USP Carbopol 980, NF Isopropyl Myristate, NF Sodium Hydroxide, NF Purified Water, USP	Dehydrated Alcohol, USP (b) (4) Isopropyl Palmitate, NF Sodium Hydroxide, NF Purified Water, USP
Route of Administration	Transdermal	Transdermal
Dosage Form Strength	Gel	Gel
	1% (2.5 gm/ Packet) 1% (5 gm/ Packet)	1% (2.5 gm/ Packet) 1% (5 gm/ Packet)

2.2 Currently Available Treatments for Proposed Indications

Testosterone replacement therapy is used to treat conditions associated with a deficiency or absence of endogenous testosterone. FDA-approved testosterone products are shown in Table 2.2, accompanied by their dose and drawbacks/potential risks.

Table 2.2 Currently Available Testosterone Products in the United States

Formulation	Formula / Trade name	Dose [§]	Drawbacks/Potential Risks
Oral	Methyltestosterone Fluoxymesterone	10-50 mg/day	Hepatotoxicity
Parental	T cypionate (Depo-T) # T enanthate (Delatestryl)**	50-400 mg IM (every 2-4 wks)	Supraphysiologic peaks, low trough concentration, mood fluctuations
Transdermal Patch	Testoderm (scrotal) Testoderm TTS Androderm	4-6 mg/day 5 mg/day 5-7.5 mg/day	Can requires skin shaving Application site irritation.
Transdermal Gel	Androgel (1%) Androgel (1.62%) Testim (1%) Axiron (2%)	50-100 mg/day 20.25-81 mg/day 50-100 mg/day 30-120 mg/day	Interpersonal transferability to partners and children
Transbuccal	Straint	30 mg buccal tablet (BID)	Gum or mouth irritation
Implant	Testosterone (Testopel Pellets)*	75 mg pellet; subcutaneous	

* Prescribing information available from Slate: (www.slatepharma.com/wp-content/uploads/2008/12/testopelpi.pdf)

Prescribing information available from Pfizer (www.pfizer.com/files/products/uspi_depo_testosterone.pdf)

** Prescribing information available from Indevus (www.indevus.com/site/images/PDF/delatestryluspi.pdf)

§ Dose information available from Drug Facts and Comparisons, 4.0 (Wolters Kluwer Health, Inc; 2008)

Source: Division's Clinical Reviewer.

Limitations of the currently available products include the following:

- Injectable depot solutions may be associated with pain at the injection site. Mood swings are possible due to large fluctuations in testosterone levels.
- High dose, oral, methyltestosterone formulations have been associated with an increased incidence of liver disease.
- Transdermal patches may be associated with significant application site reactions.
- Pellet implants can be expelled from the insertion site and may result in infection.
- Testosterone gels incur the potential risk of secondary exposure to testosterone of children and women.

Currently, the goal of testosterone replacement therapy in hypogonadal men is to replace testosterone levels at close to physiological concentrations. Clinical guidance from the Endocrine Society indicates that testosterone replacement therapy should aim to achieve testosterone levels in the mid-normal range.

2.3 Important Safety Issues with Consideration to Related Drugs

Labeled risks of testosterone administration in hypogonadal men include worsening of clinical BPH symptoms, polycythemia, induction or exacerbation of sleep apnea, breast tenderness or enlargement, liver toxicity (with methyltestosterone formulations), and acne. Two major areas of

concern in older men are the unknown effects of long-term testosterone administration on the risks of prostate cancer and progression of atherosclerotic heart disease.

Topical testosterone gel preparations, which are applied directly to the skin, have been associated with a small number of events of secondary exposure of testosterone in children. Several exposed children have experienced significant clinical sequelae which prompted the FDA to mandate a Black Box Warning for all topical testosterone products.

2.4 Summary of Presubmission Regulatory Activity Related to Submission

The Sponsor originally submitted an (b) (4) for its product (testosterone Gel, 1%) to the Office of Generic Drug (OGD) on December 29, 2008 and received a Refuse to Receive Letter dated April 7, 2009 from the Agency, based on the fact that the formulation of the product contained different ingredients than those contained in the reference listed drug (RLD) (b) (4)

(b) (4)

(b) (4)

The Sponsor believes that its proposed drug product, Testosterone Gel 1%, is suitable for submission as a NDA under section 505 (b) 2, based on the following:

- 1) A testosterone transdermal gel product in which the formulation contains different inactive ingredients, including but not limited to different penetration enhancers, from those in the RLD can not be submitted as an ANDA. (b) (4)
- 2) The active ingredients for the proposed drug product are otherwise the same as those of the RLD.
- 3) The route of administration, dosage form and strength of the proposed drug product are the same as those of the RLD.
- 4) Information demonstrating that the proposed drug product is bioequivalent to the RLD is provided in the NDA.
- 5) A skin irritation and sensitization study demonstrating that the proposed product will not cause any more irritation or sensitization than the RLD is provided in this NDA.

- 6) A transfer study quantifying and comparing the relative bioavailability between the proposed drug product and the RLD in female subjects following direct transfer from healthy male subjects is provided in the NDA.
 - 7) A hand-washing study quantifying and comparing the residual testosterone following hand washing between the proposed drug product and the RLD is provided in the NDA.
- The labeling for the proposed drug product is the same as that of the reference listed drug, with the exception of those changes annotated in a side-by-side labeling comparison provided in the NDA.

No Pre-NDA meetings were held for this application.

3 Ethics and Good Clinical Practices

No ethics or good clinical practice (GCP) issues have been identified.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls (CMC)

The CMC review team notes during the review cycle, there were several chemistry issues, and after several Information requests, the CMC review team believes the Sponsor has fulfilled all the requests. No remaining CMC issues still exist. The CMC review team recommends an “Approval” action.

4.2 Clinical Microbiology

No microbiology issues have been determined.

4.3 Preclinical Pharmacology/Toxicology

The NDA contains no new nonclinical information, and is relying on published studies of testosterone for approval. The overall toxicological profile of testosterone products is well established and both animals and humans exhibit similar toxicities. There are extensive nonclinical and clinical data with testosterone products including transdermal applications. Nonclinical data support approval of topical testosterone gel 1%. The PharmTox review team stated that Class labeling is appropriate. No significant nonclinical labeling issues were identified nor are significant changes required.

4.4 Clinical Pharmacology

In his final review dated January 19, 2012 , the clinical pharmacology reviewer concluded,

- BE of AUC between T Gel 1% and Androgel® 1% was established.
- BE of $C_{\max}$ was not established but no additional safety concerns were identified
- A small amount of interpersonal transfer of T is still possible with a T-shirt on but wearing a T-shirt helps reducing the interpersonal transfer potential of T from T Gel 1 %
- Hand washing removes the majority of residual T from the hands and also helps reduce the interpersonal transfer potential of T from T Gel 1%
- A study evaluating the effect of washing on removing residual T from the application site is warranted as a PMR

The clinical pharmacology reviewer recommends that the overall clinical pharmacology data submitted to support the approval of this NDA is acceptable provided that a satisfactory agreement is reached regarding the labeling language and the Sponsor agrees to the PMR on conducting an application site washing study.

4.5 Biostatistics

According to their final memo based on the analysis of clinical pharmacology data, the Statistical Review Team recommended approval of this NDA.

4.6 Consults from Other Divisions

4.6.1 Division of Medication Errors Prevention and Analysis (DMEPA)

DMEPA concurred with the final carton/container labeling and final package insert labeling, respectively.

4.6.2 Division of Risk Management (DRISK)

In a final review dated January 20, 2012, DRISK concurred with the elements of the proposed REMS. A final REMS Memorandum was completed by DRUP on January 31, 2012.

In its final review, DRISK stated that the Medication Guide was acceptable with the accompanying recommendations for changes. The applicant made the recommended changes.

4.6.3 Division of Drug Marketing, Advertising and Communications (DDMAC)

DDMAC was asked to review the proposed product labeling (PI), carton labeling and container labeling. All DDMAC comments and recommendations will be addressed in the final labeling.

4.6.4 Division of Scientific Investigation (DSI)

In their final reviews data July 29, 2011, DSI commented upon the Applicant's response to the original FDA Form 483 deficiencies. DSI concluded the following:

- Following our evaluation of (b) (4) response to the Form FDA-483, DBGC's recommendation to DRUP in our July 1, 2011, EIR review remained unchanged.
- DBGC recommends that data from subjects # 60, 61, 62, 92, 93 and 94 and the re-assayed samples in Run #74PQM be excluded from final BE evaluation with the newly re-integrated data. This data was excluded when conducting the Division's final analysis.

4.6.5 Pediatric Review Committee (PeRC)

Pediatric studies are required based on Pediatric Research Equity Act (PREA) for the following reasons:

- 1) New active ingredients;
- 2) New indications;
- 3) New dosage forms;
- 4) New dosing regimens;
- 5) New routes of administration.

None of the above apply to this 1% testosterone gel product, therefore, this testosterone gel 1% is exempt from this requirement.

4.6.6 Controlled Substance Staff (CSS)

In their review dated September 16, 2011, CSS provided recommended labeling for the Drug Abuse and Dependence section of the label, as follows:

9.1 Controlled Substance

Testosterone Gel 1% contains testosterone, a Schedule III controlled substance (b) (4)

9.2 Abuse

Anabolic steroids, such as testosterone, are abused. Abuse is often associated with adverse physical and psychological effects.

9.3 Dependence

Although drug dependence is not documented in individuals using therapeutic doses of anabolic steroids for approved indications, dependence is observed in some individuals abusing high doses of anabolic steroids. In general, anabolic steroid dependence is characterized by any three of the following:

- *Taking more drug than intended*

- *Continued drug use despite medical and social problems*
- *Significant time spent in obtaining adequate amounts of drug*
- *Desire for anabolic steroids when supplies of drug are interrupted*
- *Difficulty in discontinuing use of the drug despite desires and attempts to do so*
- *Experience of withdrawal syndrome upon discontinuation of anabolic steroid use*

5 Sources of Clinical Data

5.1 Size of the clinical trial dataset

The clinical program for NDA 202763 included four clinical studies: a comparative BA & bioequivalence study (Study 70343), an irritation and sensitization study (Study 10936025), a comparative hand washing study (Study CRI-00018704), and a comparative BA transfer study (Study M1FX10001).

Table 5.1. Clinical Studies in NDA 202763

Type of Study (#)	Objectives of the Study	Study Design	Test Product(s)	Numbers of Subjects	Patients / Healthy Subjects	Single / Multi Dose
<u>Bio-equivalence (BE) Study 70343</u>	Determine the BE between Teva drug product and RLD under fasting conditions	Multi-centre, BE, open-label, randomised 2-way crossover study.	Testosterone 1% Topical Gel	93 (90 Completed)	Hypogonadal adult male subject	Single-dose
<u>Irritation & Sensitization Study 10936025</u>	Compare cumulative skin irritation & sensitization potential between 2 test products and 2 marketed RLDs	Multi-sites, multi-application, 2-phase, DB, randomized, irritation & sensitization study	Testosterone 1% Topical Gel	265 (233 included in PPPI and 222 included in PPS)	Healthy adult male subjects	Multiple-dose
<u>Hand-Washing Study CRI-00018704</u>	Quantify and compare the amount of residual drug remaining on the hands between a test product and a marketed RLD.	Open-label, 2-period, crossover, pivotal study on healthy adult male subjects	10 g of Testosterone 1% Topical Gel in each study period, topical	48 (46 Completed)	Healthy adult male subjects	Single dose
<u>Bio-availability (BA) Transfer Study M1FX10001</u>	Quantify and compare the relative BA between a test product and a marketed RLD in female subjects following direct transfer from healthy male subjects	Open-label, randomized, 4-period, 4-treatment crossover study. Test drug: A, B; C, D	Testosterone 1% Topical Gel Without T-Shirt	A vs. C, 48 M and F couples (47 couples completed)	Healthy adult male & female subjects	Single-dose
			Testosterone 1% Topical Gel With T-Shirt	B vs. D, 48 M and F couples (43 couples completed)		

For the Irritation and Sensitization Study, PPPI = Per Protocol Population for Irritation; PPS = Per Protocol Population for Sensitization;

For the Transfer study, Treatment A = Teva testosterone gel without T-shirt; Treatment B = Reference (Androgel) without T-shirt; Treatment C = Teva testosterone gel with T-shirt; Treatment D = Reference (Androgel) with T-shirt.

5.2 Compliance Issues in the BE Study

Following a June 6, 2011, inspection of (b) (4) the contract research organization that conducted bioanalysis of study samples for the bioequivalence study 70343, the Office of

Scientific Investigation (OSI) identified the following deficiencies in their review dated July 1, 2011:

- 1) (b) (4) failed to properly train a laboratory technician who was responsible for sample processing; specifically, repeated long-term freezer stability studies for testosterone failed during the partial validation-6 (5 of 6 runs containing long-term freezer stability data was failed). An investigation of the failures concluded that the technician who processed samples in the failed runs made an error during sample handling. Further, training records ('spiking check' conducted after the investigation) indicated that technician who handled the failed runs could not handle the pipettes properly. A total of 11 validation runs (run # 01SVT, 02SVT, 06SVT, 07SVT, 08SVT, 09SVT, 10SVT, 01FTY, 02FTY, 03FTY and 04FTY), and 4 production runs (run # 58PQM, 67PQM, 71PQM and 74PQM) were affected by this technician's practice.
- 2) (b) (4) failed to provide adequate security for electronic source records, specifically,
(a) A common access procedure is used to access the computer workstation and the 'Analyst' software used for analytical data integration. (b) *Technical writers who do not work in the bioanalytical laboratory were given inappropriate permission to edit chromatograms in 'Analyst' software.*
- 3) Integration parameters from most chromatographic runs in the validation and production were modified and were different from the method SOP. These changed integration parameters were not applied to all samples in the respective runs.

Reviewer's comment: Issue #3 is related to Issue #2.

- 4) (b) (4) failed to use appropriate informed consent forms (ICF) during study # 70343. Specifically, Testosterone ICF dated June 12, 2008 was used in place of ICF dated December 6, 2008 for subjects # 1, 3, 5, 6, 19, 28, 41, 71 and 73.

Based on these deficiencies, OSI concluded in a Form FDA-483 that

- 1) Runs # 58PQM and 71PQM containing plasma sample data from subjects # 60, 61, 62, 92, 93 and 94, and Run # 74PQM containing plasma sample data after repeat analysis is not assured. Therefore, DSI recommended that data from subjects # 60, 61, 62, 92, 93 and 94 and the re-assayed samples in Run #74PQM should be excluded from final BE evaluation
- 2) (b) (4) should re-process all chromatograms for both validation and subject samples using integration parameters established in the method SOP

After evaluating (b) (4) response dated July 11, 2011, OSI concluded that their original deficiency findings and recommendations remained unchanged. The Division of Bioequivalence and GLP Compliance (DBGC) in the Office of Scientific Investigations again recommended that data from subjects # 60, 61, 62, 92, 93 and 94 and the re-assayed samples in Run #74PQM be excluded from final BE evaluation with the newly re-integrated data.

Based on continued concerns related to the Form FDA-483 observations, the Division issued a letter to Sponsor on July 29, 2011 requesting the following:

- To submit a revised study report for Study 70343, to include new bioequivalence (BE) analysis results using data generated from re-integrated chromatograms, but excluding data generated from the 6 subjects in question (Subjects 60, 61, 62, 92, 93, and 94);
- To submit supporting documentation to explain how the chromatograms were re-integrated consistently (e.g., using a standard operating procedure [SOP]).

The Sponsor responded on September 14, 2011 with a major amendment including:

- 1) A revised report for the BE study 70343. This report excluded all samples from the six subjects in question (Subjects #60, #61, #62, #92, #93, and #94) – a total of 22 individual samples excluded from the statistical analysis. This modified study report included only baseline-corrected testosterone data.
- 2) Reintegrated chromatograms as per the (b) (4) standard operating procedure.

The Division responded on October 12, 2011, requesting the Sponsor submit the pharmacokinetics (PK) and statistical results for the baseline *uncorrected* testosterone concentrations.

The Division further requested on October 21, 2011 that the Sponsor submit data for all three testosterone baseline time points (i.e., at -12, -6, and 0 hr before testosterone gel administration) and figures for both baseline corrected and uncorrected testosterone concentration-time profiles for all individual subjects who completed the study. In addition, the Sponsor should submit both the baseline corrected and uncorrected *mean* testosterone concentration-time profiles.

The Division also pointed out that one subject (#96) was excluded, but two subjects (#70 and 88) were included in the most recent analysis compared to the original analysis, and the Sponsor should provide a rationale for this difference.

On November 3, 2011, the Sponsor submitted a re-revised study report for study 70343, in which a PK and statistical analysis was again conducted using the reintegrated chromatograms for the testosterone baseline corrected data. The Sponsor provided data for baseline corrected and baseline uncorrected testosterone concentrations. The Sponsor also provided a rationale for excluding subject #96, and for including Subjects #70 and #88. Therefore, the PK population for this additional analysis was the same as for the original analysis, except that subject No. 70 was not excluded ($N = 77 + 1 = 78$). From this total of 78 subjects, the Sponsor excluded all samples from the 6 subjects in question (Subjects No. 60, 61, 62, 92, 93 and 94). Therefore, 72 subjects were included in the final determination of the bioequivalence criteria for this dataset.

Exclusion in the Original Report (n = 13)	Reasons for exclusion from statistical analysis	Exclusion in the Re-analysis Report (n = 12)
24	This subject samples stability exceeded validation data	24
03, 15, 25, 27, 35, 37, 40, 70, 84, 87, 88, and 89	These subjects had a baseline serum T concentration mean in at least one period that was > 350 ng/dL	03, 15, 25, 27, 35, 37, 40, 84, 87, 89 and 96

Reviewer's comment: The Clinical review team agrees with Clinical Pharmacology (as shown in page 12-13 of their final review) that the final BE dataset is acceptable for analysis.

6 Review of Efficacy

Efficacy Summary

Based on the results from the main analysis, it can be concluded that the test article, Testosterone gel 1% in a 5 g packet (Treatment A) is bioequivalent to the reference Androgel 1% (Treatment B) for AUC, but not for C_{max}, following a 100 mg dose in hypogonadal male volunteers. The reader is referred to Table 6.3 for a clear presentation of the baseline-uncorrected bioequivalence comparisons, which are considered the primary results.

Table 6.1 Summary of Results: Testosterone Baseline Corrected Re-analysis Dataset Excluding Invalid Samples (N=72)

Pharmacokinetic Parameters		Test [Testosterone 5 g packet of 1% topical gel (A)]			Reference [Androgel 1% (B)]		
		Mean	SD	CV(%)	Mean	SD	CV (%)
AUC _{0-t}	(ng•h/dL)	6590	3403	51.65	6114	2723	44.53
C _{max}	(ng/dL)	383	248	64.77	322	157	48.73
T _{max}	(h)	19.6	10.7	54.74	19.2	10.5	54.89
T _{max} *	(h)	20.0	4.0	—	20.0	6.0	—

* Medians and inter-quartile ranges are presented.

**Table 6.2 Summary of Results: Testosterone Baseline *Uncorrected*
Re-analysis Dataset Excluding Invalid Samples (N=72)**

Pharmacokinetic Parameters		Test [Testosterone 5 g packet of 1% topical gel (A)]			Reference [Androgel 1% (B)]		
		Mean	SD	CV(%)	Mean	SD	CV (%)
AUC _{0-t}	(ng•h/dL)	21821	4432	20.31	21062	4359	20.70
C _{max}	(ng/dL)	641	253	39.54	576	180	31.17
T _{max}	(h)	19.6	10.7	54.74	19.2	10.5	54.89
T _{max} *	(h)	20.0	4.0	—	20.0	6.0	—

* Medians and inter-quartile ranges are presented.

**Table 6.3 Testosterone 5 g packet of 1 % topical gel (A) vs Androgel (B)
Baseline Corrected**

	AUC _{0-t}	C _{max}
Ratio ¹	105.28%	115.72%
90 % Geometric C.I. ²	95.82% to 115.67%	105.95 % to 126.40 %
Intra-Subject CV	34.56%	32.29%

¹ Calculated using least-squares means according to the formula:

$$\frac{e^{[\text{Testosterone 5 g packet of 1\% topical gel (A)} - \text{Androgel (B)}]} \times 100.$$

² 90% Geometric Confidence Interval using In-transformed data.

Reviewer's Comment:

Although the C_{max} is not bioequivalent, the upper 90% confidence interval is 126.4%, nominally greater than the 125% acceptable limit, and this does not reflect any clinically meaningful safety risk compared to an upper limit of 125%.

**Table 6.4 Testosterone 5 g packet of 1 % topical gel (A) vs Androgel (B)
Baseline *Uncorrected***

	AUC _{0-t}	C _{max}
Ratio	103.50%	109.58%
90 % Geometric C.I. ²	100.91% to 106.16%	104.53% to 114.88%
Intra-Subject CV	9.07%	16.96%

¹ Calculated using least-squares means according to the formula:

$$\frac{e^{(\text{Testosterone 5 g packet of 1\% topical gel [A]} - \text{Androgel [B]})} \times 100.$$

² 90% Geometric Confidence Interval using In-transformed data

6.1 Review of Study 70343: A Phase 1 Bioequivalence Study

6.1.1 Methods/Patient Disposition

The November 3, 2011, submission includes the revised results from the Phase 1, single dose, bioequivalence study 70343, which constitutes the “pivotal BE study” for this 505(b)(2) NDA.

The primary objective of this study was to compare the rate and extent of absorption of Teva Testosterone gel 1% and Solvay’s Androgel 1% testosterone gel, when applied as a single topical dose of 2 x 5 packets of testosterone gel (each packet corresponding to 50 mg testosterone for a total of 100 mg), under fasting conditions. This was a multi-center, randomized, single-dose, open-label, 2-way crossover bioequivalence study. A total of 96 hypogonadal men signed the study-specific informed consent form and were confined for Period 1; of these 96 subjects, 93 were enrolled and dosed in the study in six groups; 90 of these enrolled subjects completed the study. In each period, subjects reported to the Clinical facility in the morning of Day -1 and remained in the clinical unit until released by the Investigator subsequent to completing the 48.0-hour post-application blood sample draw. Prior to study commencement, subjects were randomly assigned to a treatment in accordance with the randomization scheme . The treatment cases were separated by a washout period of 7 days.

Treatment		
	Test (A)	Reference (B)
Name:	Teva Testosterone gel 1%	testosterone (Androgel® 1%)
Unit dose:	50 mg (1% topical gel)	50 mg (1% topical gel)
Regimen:	single dose of 2 x 5 g packets of 1% topical testosterone gel, corresponding to 50 mg testosterone each packet, for a total of 100 mg testosterone per subject in accordance with the randomization scheme	single dose of 2 x 5 g packets of 1% topical testosterone gel, corresponding to 50 mg testosterone each packet, for a total of 100 mg testosterone per subject in accordance with the randomization scheme
Lot/Batch No.:	Batch No.: X028	Batch No.: 31154
Expiration date:	01/2010	08/2009
Manufacturing date:	02/2008	Not available
Potency	104.8%	100.8%
Company Responsible for Manufacturing:	Manufactured by Cipla Ltd., India for Teva Pharmaceuticals U.S.A.	Manufactured by Laboratoires Besins International, France for Unimed Pharmaceuticals, Inc. a Solvay Pharmaceuticals, Inc. company, U.S.A.
Duration of Treatment: A single topical dose of testosterone as 2 x 5 g packets of 1% testosterone gel (corresponding to 50 mg testosterone each packet, for a total of 100 mg testosterone) was administered in each study period. The treatment phases were separated by a washout period of 7 days.		

Blood Sampling Points:

Blood samples were collected prior to drug application at -12.0, -6.00 and immediately before drug application, and 1.00, 2.00, 4.00, 6.00, 8.00, 10.0, 12.0, 14.0, 16.0, 18.0, 20.0, 22.0, 24.0, 26.0, 28.0, 32.0, 36.0, 40.0, 48.0, and 60.0 (± 0.5) hours post-dose in each period.

Criteria for Evaluation:**Pharmacokinetics:**

The pharmacokinetic parameters are AUC_{0-t} , C_{max} and T_{max} for baseline uncorrected and baseline corrected testosterone. For baseline corrected testosterone, the elimination rate constant could not be properly estimated for all subjects due to physiological fluctuation of endogenous levels of testosterone. Therefore, the AUC_{0-inf} , $AUC_{t/inf}$, $T_{1/2el}$ and K_{el} parameters were not calculated as initially planned in the protocol.

Safety:

Adverse events, vitals signs measurements, physical examination, and standard laboratory evaluations.

Selection of Doses In the Study In this study, two 5g packets of testosterone gel were applied (one packet applied on each shoulder and upper arm) to each hypogonadal subject to ensure a magnitude of post-dose concentrations in relationship to their baseline contribution to allow better discrimination between the endogenous and exogenous source of testosterone. The dose (2 x 5 g packets of 1 % topical gel) was expected to be sufficient to provide measurable levels of study medication and the sampling period was expected to allow good characterization of the concentration time profiles.

Reviewer's comments: *The dose selection was reasonable and acceptable.*

Selection and Timing of Dose for each subject: After a supervised overnight fast of at least 10 hrs, subjects were applied on both shoulders/upper arms with a spatula the test or reference medication (as per the randomization scheme) as a single dose of 2 packets (one 5 g packet per shoulder/upper arm) of 1 % topical gel, each containing 50 mg of testosterone (total dose of 100 mg). Following dosing, subjects fasted for a period of at least 4 hours. Prior to gel application, the shoulders and upper arms of each subject were washed with warm water and mild soap and were rinsed with clean, warm water, and allowed to dry for approximately 1 hour before gel was applied. Any excessive body hair (judged by the Investigator to possibly interfere with drug absorption) on the site of application was to be clipped (not shaved) prior to washing. The application was performed as per procedure described. A separate administration kit (content: 1 weight boat, 1 spatula, and 2 pairs of gloves) was used for each subject and were weighted before and after application of study medication. Within 5 or 10 minutes, before gel application, the topical gel was squeezed out directly onto a weigh boat and approximately 5 g was weighted (in grams out to 2 decimal places). Acceptable range of weight was between 4.70 - 5.00 g. Extra packets of medication could have been used to complete the range. All used packets were placed in a sealed ziplock bag for storage. In each period, using gloved hands and a spatula applicator, the pre-weighted topical gel was applied directly on the application site by the study staff (5 g per shoulder/arm for a total of 10 g) on the designated area predefined with an individual template (outlining a 500 cm² area; each subject was designed his own template) to insure consistent size of the application area between and within subjects. The study staff applied the gel to the upper arms and rubbed into the skin with the spatula so that no visible accumulation of gel remained on the skin. Any gel remaining on the applicator was rubbed into the skin. Study staff responsible for dosing of subjects had to change gloves before drawing blood samples or different study

personnel who had not dosed the subjects had to perform blood draws. The post-dose blood draws and procedures were scheduled taking in account that time "0" is taken as the time of the beginning of the application of the testosterone gel. The time of completion of application was to be recorded. The application site was allowed to dry until after the 30 minutes local irritation evaluation. Subjects were instructed not to touch the application site for at least 4 hours after gel application. After the gel had dried, subjects covered the application site with clothing (e.g., a shirt) (within -30 minutes) to avoid transfer to another person. Subjects were dosed in a separate area of the clinic other than the area designated for drawing pharmacokinetic blood samples. After discharge from the clinic, if direct skin-to-skin contact with another person was anticipated, the subjects were instructed to thoroughly wash the area with soap and water before contact. Subjects were allowed to bath on the evening of Day -1. Washing the treated area was prohibited from 2 hours before until 48 hours after gel application, unless required by study procedures; After the 48.0-hour blood sample collection, subjects had the dosing area washed by clinical staff remove any residual, unabsorbed study drug, and were given the option to shower and wear a clean shirt.

Group No.	Subject No.	Period No.	Date	Time interval
1	01–24	1	March 1, 2008	08:00–09:55
		2	March 8, 2008	08:00–09:55
2	25–36	1	April 5, 2008	08:00–09:55
		2	April.12, 2008	08:00–09:55
3	37–46	1	May 3, 2008	08:00.08:55
		2	May.10, 2008.	08:00–08:45
4	47–56	1	August 23, 2008	08:00–08:45
		2	August 30, 2008	08:01.09:03
5	57–73	1	November 8, 2008	07:00–08:20
		2	November 15, 2008	07:00–08:20
6	77–96	1	November 8, 2008	08:00.09:35
		2	November 15,2008	08:00–09:35

Diagnosis and Main Criteria for Inclusion: Subjects had to be hypogonadal, male subjects, 18 years of age and older; body mass indices ≥ 19.0 and < 35.0 kg/m². All subjects had to be in compliance with the inclusion and exclusion criteria described in the protocol and were judged eligible for enrolment in this study, based on medical and medication histories, demographic data and body measurements (including sex, age, race, ethnicity, body weight [kg], height [cm], and BMI [kg/m²]), vital signs measurements, 12-lead ECG, physical examination (including digital rectal examination), urine drug screen, alcohol breath test, and clinical laboratory tests (hematology, biochemistry, urinalysis, endocrinology [including age adjusted PSA, FSH, LH, and total testosterone*], Human Immunodeficiency Virus [HIV], hepatitis C [HCV] antibodies, and hepatitis B surface antigen [HBsAg]). *Two testosterone tests separated by at least 48 hours were performed on samples obtained between 07:00 and 10:00 AM.

Disposition of Subjects: Enrolled and randomized: 93 hypogonadal males, and all received at least one dose of the study medication, and therefore, comprised the safety population. Ninety

(90) individuals completed both treatment periods. The following subjects were withdrawn or withdrew from the study:

Table 6.5 Subjects Withdrawn from the Study

Subject No. #	Reason for withdrawal	Period	Replaced?	Replaced with
04 (became Stand-by C)	2008-03-01 08:11 / pre-dose / was withdrawn due to difficulty with catheter insertion	Pre-dose	Yes	Stand-by B
12 (became Stand-by B) [†]	2008-02-29 16:41 / pre-dose / was withdrawn due to a high blood pressure	Pre-dose	Yes	Stand-By A
23	2008-03-06 18:45 / test / elected to withdraw due to medication taken as treatment for AEs (pain at buttock left side and infected hematoma on left buttock)	1	No	N/A
42	2008-05-10 06:42 / test / was withdrawn due to positive urine drug screen results for benzodiazepines	1	No	N/A
91	2008-011-14 11:11 / test / was withdrawn since medication was found in baggage during check-in procedures	1	No	N/A

[†] Finally this subject became Subject No. 04 due to withdrawal of another subject.

The following subjects were excluded from the pharmacokinetic and statistical analyses although they completed the study based on the re-analysis reported on 10/18/2011

Exclusion in the Re-analysis Report (n = 12)	Reasons for exclusion from statistical analysis
24	This subject samples stability exceeded validation data
03, 15, 25, 27, 35, 37, 40, 84, 87, 88, and 89	These subjects had a baseline serum T concentration mean in at least one period that was > 350 ng/dL

Subject#	Baseline 1	Baseline 2	Subject#	Baseline1	Baseline 2
3	421	364	40	340	378
15	329	542	84	372	332
25	363	372	87	385	308
27	417	409	88	343	351
35	358	403	89	371	285
37	361	287			

Data set for safety analysis: 93

Data set for statistical analysis: 77 (Subject #04, 23, 42 and 91 were withdrawn, Subject No. 24 was excluded since his samples stability exceeded validation data, and Subjects No. 03, 15, 25, 27, 35, 37, 40, 84, 87, 88, and 89 were excluded since they had a baseline testosterone serum concentration mean in at least one period that was higher than 350 ng/dL), therefore, 77 subjects were included in the determination of the bioequivalence criteria.

Protocol Deviations

There were minor protocol deviations reported, as follows:

- At the screening and post-study, it can not be confirmed whether the clinical laboratory samples were collected prior to the physical examinations
- In Periods 1 and 2, the time of completion of gel application was not recorded for all subjects of Groups 1 to 4. This was corrected.
- Some samples were not centrifuged after a minimum of 30 minutes following blood collection.
- Subject #04 was judged eligible to participate in the study although his blood pressure measurements were out of range at screening (highest 142/92 mmHg). A repeat BP measurement was performed on the morning of Day-1 and the value was normal (133/88 mmHg). BP measurements were taken again on the afternoon of Day -1 and were out of range (150/94 mmHg). The values were judged not clinically significant by the Investigator. Due to withdrawal of another subject, this subject had to be put on study.
- Subject #08 was judged eligible to participate in the study although his BMI of 35.4 kg/m² at screening, a waiver was granted from the Sponsor.
- Other sporadic deviations occurred in the blood sampling schedule during the study including pre-dose collections and post-dose collections during confinement sample not collected, samples collected one minute or more from scheduled time or collection time inconclusive; post-dose collection during return visit (60.0 hour post-dose) not collected or collected more than 30 minutes from scheduled time, or collection time considered inconclusive. There is no impact on the statistical analyses due to these time deviations since only the actual collection times were used in the pharmacokinetic calculations.

Treatment Compliance

Measurements of treatment compliance were 100%, as study medication was applied to the subjects by the study staff. Subject identification was verified and cross-checked with the pre-dispensed medication. In each period, subjects reported to the Clinical facility in the morning of clinical unit until released by the Investigator subsequent to obtaining the 48.0-hour post-application blood draw. During the confinement, subjects were under constant surveillance by the clinical staff to ensure that they respected the protocol restrictions.

Demographics

Table 6.6 Demographics for the Subjects Included in the Pharmacokinetic Analyses (n=77):

Parameter	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m ²)
Mean±SD	47 ± 10	175.6 ± 5.6	88.5 ± 12.0	28.6 ± 3.2
Range	21 – 68	159.0 – 191.0	64.0 – 118.8	21.7 – 35.4
Median	47	175.5	88.4	28.6

Reviewer's comment: Descriptive statistics for the subjects were included in the PK re-analysis dated on September 08, 2011, based on the re-integration of the chromatograms for all subjects, but not after exclusion of six subjects requested by the Division.

6.1.2 Pharmacokinetic Analysis

The pharmacokinetic parameters are AUC_{0-t} , C_{max} and T_{max} for baseline uncorrected and baseline corrected testosterone. For baseline corrected testosterone, the elimination rate constant could not be properly estimated for all subjects due to physiological fluctuation of endogenous levels of testosterone. Therefore, the AUC_{0-inf} , $AUC_{t/inf}$, $T_{1/2el}$ and K_{el} parameters were not calculated as initially planned in the protocol.

Pharmacokinetics:

- Parametric ANOVA on AUC_{0-t} , C_{max} and T_{max} ; geometric confidence intervals for AUC_{0-t} and C_{max} ;
- Covariates in the ANOVA model: group, sequence, sequence*group, subject (sequence*group), period (group), treatment and treatment*group;
- Ln-transformed parameters: AUC_{0-t} and C_{max} .

Criteria for Bioequivalence for baseline corrected, non-dose-normalized data:

90% geometric confidence interval of the ratio (A/B) of least-squares means from the ANOVA of the ln-transformed AUC_{0-t} and C_{max} should be within 80.00% to 125.00%.

The Sponsor defined that Baseline Corrected data were presented as primary data and Baseline Uncorrected data were presented as supportive data only.

TESTOSTERONE CONCENTRATIONS – SHOWN AS BASELINE CORRECTED VALUES (N = 72)

Table 6.7 Summary of Results: Testosterone Baseline Corrected Re-analysis Dataset Excluding Invalid Samples (N=72)

Pharmacokinetic Parameters		Test [Testosterone 5 g packet of 1% topical gel (A)]			Reference [Androgel (B)]		
		Mean	SD	CV(%)	Mean	SD	CV (%)
AUC_{0-t}	(ng•h/dL)	6590	3403	51.65	6114	2723	44.53
C_{max}	(ng/dL)	383	248	64.77	322	157	48.73
T_{max}	(h)	19.6	10.7	54.74	19.2	10.5	54.89
T_{max}^*	(h)	20.0	4.0	—	20.0	6.0	—

* Medians and inter-quartile ranges are presented.

Table 6.8 p-values for treatment*group interaction term for AUC_{0-t} and C_{max}

Parameter	p-values (treatment*group) ^a
	Baseline Corrected Testosterone
AUC _{0-t}	0.8515
C _{max}	0.3757

^a: Full ANOVA results kept in file at (b) (4)

Table 6.9 Testosterone 5 g packet of 1% topical gel (A) vs Androgel (B) Baseline Corrected Re-analysis Dataset Excluding Invalid Samples (N=72)

	AUC _{0-t}	C _{max}
Ratio ¹	105.28%	115.72%
90 % Geometric C.I. ²	95.82% to 115.67%	105.95 % to 126.40 %
Intra-Subject CV	34.56%	32.29%

¹ Calculated using least-squares means according to the formula:

$$\frac{e^{[Testosterone\ 5\ g\ packet\ of\ 1\%\ topical\ gel\ (A) - Androgel\ (B)]}}{e} \times 100.$$

² 90% Geometric Confidence Interval using In-transformed data.

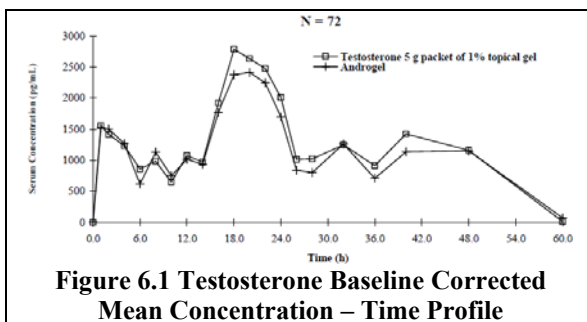


Figure 6.1 Testosterone Baseline Corrected Mean Concentration – Time Profile

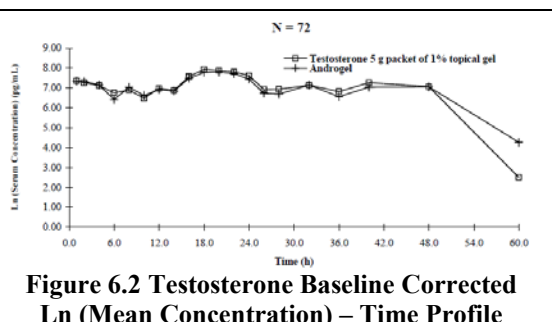


Figure 6.2 Testosterone Baseline Corrected Ln (Mean Concentration) – Time Profile

TESTOSTERONE CONCENTRATIONS – SHOWN AS BASELINE-UNCORRECTED VALUES (N = 72)

Table 6.10 Summary of Results: Testosterone Baseline-Uncorrected Re-analysis Dataset Excluding Invalid Samples (N=72)

Pharmacokinetic Parameters		Test [Testosterone 5 g packet of 1% topical gel (A)]			Reference [Androgel (B)]		
		Mean	SD	CV(%)	Mean	SD	CV (%)
AUC _{0-t}	(ng•h/dL)	21821	4432	20.31	21062	4359	20.70
C _{max}	(ng/dL)	641	253	39.54	576	180	31.17
T _{max}	(h)	19.6	10.7	54.74	19.2	10.5	54.89
T _{max} *	(h)	20.0	4.0	—	20.0	6.0	—

* Medians and inter-quartile ranges are presented.

Table 6.11 Testosterone 5 g packet of 1% topical gel (A) vs Androgel (B) Baseline-Uncorrected Re-analysis Dataset Excluding Invalid Samples (N=72)

	AUC _{0-t}	C _{max}
Ratio ¹	103.50%	109.58%
90 % Geometric C.I. ²	100.91 % to 106.16 %	104.53 % to 114.88 %
Intra-Subject CV	9.07 %	16.96 %

¹ Calculated using least-squares means according to the formula:

$$\frac{e(\text{Testosterone 5 g packet of 1\% topical gel [A]} - \text{Androgel [B]})}{e(\text{Testosterone 5 g packet of 1\% topical gel [A]})} \times 100.$$

² 90% Geometric Confidence Interval using In-transformed data

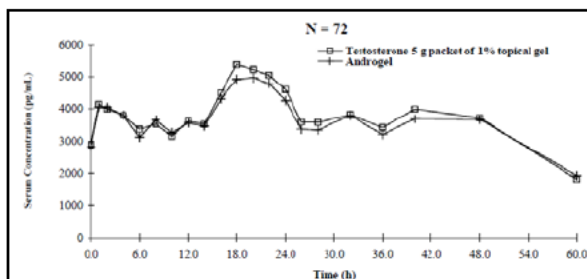


Figure 6.3 Testosterone Baseline Uncorrected Mean Concentration – Time Profile

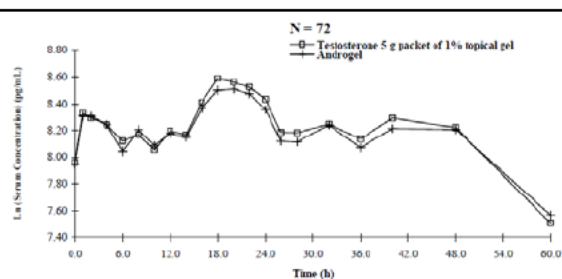


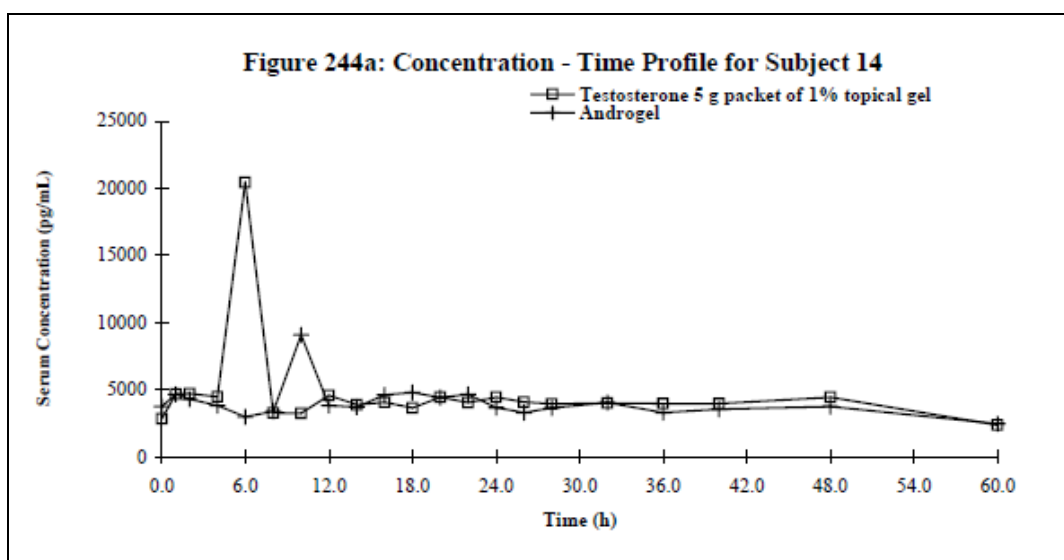
Figure 6.4 Testosterone Baseline Uncorrected Ln (Mean Concentration) – Time Profile

Area under the concentration-time curve (0-t hours) was calculated for each subject and treatment. The baseline-corrected testosterone mean values (%CV) for AUC_{0-t} were 6590 ng•h/dL (52.65 %) for Treatment A and 6114 ng•h/dL (44.53 %) for Treatment B. The baseline-uncorrected testosterone values (% CV) for AUC_{0-t} were 21821 ng h/dL (20.31 %) for Treatment A and 21062 ng•h/mL (20.70 %) for Treatment B.

The peak or maximal serum concentration was calculated for each subject and treatment. The baseline-corrected testosterone mean values (% CV) for C_{max} were 383 ng/dL (64.77 %) for Treatment A and 322 ng/dL (48.73 %) for Treatment B. The baseline-uncorrected testosterone results for C_{max} were 641 ng/dL (39.54 %) for Treatment A and 576 ng/dL (31.17 %) for Treatment B.

The time to reach the peak concentration was determined for each subject and treatment. The baseline-corrected testosterone mean (% CV) T_{max} values were 19.6 h (54.74 %) for Treatment A and 19.2 h (54.89 %) for Treatment B. The baseline-uncorrected testosterone mean (% CV) T_{max} values were 19.6 h (54.74 %) for Treatment A and 19.2 h (54.89 %) for Treatment B.

Reviewer's comment: *This reviewer found there was an outlier in the TEVA T gel treatment group, but there was no single outlier for the RLD treatment group. Subject #14, the 6 hr post dosing the total T reached 2043 ng/dL as C_{max} (baseline uncorrected) and then reduced to 325 ng/dL (baseline uncorrected) at 8 hr post dosing.*



Reviewer's comments on the efficacy of Teva T gel 1%: *Bioequivalence of AUC between Teva T gel 1% and Androgel 1% was established; BE of C_{max} was not completely established, as the 90% CI for the difference between Teva T gel and AndroGel 1% is 126.4%, minimally above the 125% criterion. When assessed using baseline-uncorrected data, the products are bioequivalent.*

6.1.3 Review of Safety for the bioequivalence Study

6.1.3.1. Drug Exposure

On two occasions, subjects received a single topical dose of 2 x 5 g tubes of 1 % topical gel. All subjects who completed the study received two doses of the study medication.

6.1.3.2. Adverse Reactions

Summary of Adverse Events: A total of 208 treatment emergent adverse events (TEAEs) were reported by 80 subjects who received at least one dose of the study medication (safety population). 102 TEAEs were reported by 63.4% (n=59) of the 93 subjects who received treatment A and 106 TEAEs were reported by 67.8% (n=61) of the 90 subjects who received treatment B. The most commonly reported TEAEs were related to study drug application site, with "Application site erythema" and "Application site pruritus" being reported by 63.4% (n=58) and 12.9% (n=12), respectively, of subjects who constituted the safety population. With the exception of "Blood pressure increased" reported by 14.0% (n= 13) of subjects who constituted the safety population, all other TEAEs were reported by no more than 6.5% (n=6) of subjects who constituted the safety population.

Table 6.12 Summary of Treatment Emergent Adverse Events (TEAEs)

MedDRA Preferred Term	A (Teva 1% T gel)	B (AndroGel)
Number of subjects dosed	93	90
Eye disorders	1 (1.1%)	
Conjunctivitis	1 (1.1%)	
Gastrointestinal disorders	2 (2.2%)	1 (1.1%)
Abdominal distension		1 (1.1%)
Diarrhoea		1 (1.1%)
Dyspepsia	1 (1.1%)	
Nausea		1 (1.1%)
Toothache	1 (1.1%)	
General disorders and administration site conditions	43 (46.2%)	45 (50.0%)
Application site erythema	39 (41.9%)	39 (43.3%)
Application site irritation	2 (2.2%)	
Application site papules	2 (2.2%)	1 (1.1%)
Application site pruritus	9 (9.7%)	7 (7.8%)
Application site reaction	2 (2.2%)	1 (1.1%)
Asthenia		1 (1.1%)
Energy increased		1 (1.1%)
Feeling cold	1 (1.1%)	
Peripheral coldness		1 (1.1%)
Pyrexia		1 (1.1%)
Infections and infestations	2 (2.2%)	1 (1.1%)
Folliculitis	1 (1.1%)	1 (1.1%)
Hematoma infection	1 (1.1%)	
Injury, poisoning and procedural complications	8 (8.6%)	11 (12.2%)
Post procedural complication	1 (1.1%)	
Post procedural discomfort	1 (1.1%)	1 (1.1%)
Post procedural hematoma	1 (1.1%)	4 (4.4%)
Post procedural swelling	2 (2.2%)	4 (4.4%)
Procedural pain	1 (1.1%)	4 (4.4%)
Procedural site reaction	3 (3.2%)	
Scratch	1 (1.1%)	1 (1.1%)
Skin laceration	1 (1.1%)	

Wound		1 (1.1%)
Investigations	9 (9.7%)	11 (12.2%)
Blood pressure increased	8 (8.6%)	7 (7.8%)
Gamma-glutamyltransferase increasd		1 (1.1%)
Heart rate increased	1 (1.1%)	3 (3.3%)
Prostatic specific antigen increased		1 (1.1%)
Red blood cells urine positive		1 (1.1%)
Musculoskeletal and connective tissue disorders	3 (3.2%)	1 (1.1%)
Back pain	1 (1.1%)	
Muscle spasms		1 (1.1%)
Musculoskeletal pain	1 (1.1%)	
Pain in extremity	1 (1.1%)	
Nervous system disorders	3 (3.3%)	4(4.4%)
Dizziness		1 (1.1%)
Headache	2 (2.2%)	3 (3.3%)
Somnolence	1 (1.1%)	
Psychiatric disorders		1 (1.1%)
Nervousness		1 (1.1%)
Renal and urinary disorders	1 (1.1%)	1 (1.1%)
Pollakiuria	1 (1.1%)	1 (1.1%)
Reproductive system and breast disorders	1 (1.1%)	
Testicular pain	1 (1.1%)	
Respiratory, thoracic and mediastinal disorders	1 (1.1%)	3 (3.3%)
Cough		1 (1.1%)
Pharngolaryngeal pain		2 (2.2%)
Respiratory tract irritation	1 (1.1%)	
Rhinorrhoea		2 (2.2%)
Skin and subcutaneous tissue disorders	10 (10.8%)	5 (5.6%)
Blister		1 (1.1%)
Dermatitis acneiform	1 (1.1%)	
Dry skin	2 (2.2%)	1 (1.1%)
Eryhema	2 (2.2%)	1 (1.1%)
Pruritus	2 (2.2%)	
Rash	1 (1.1%)	
Rash papular		1 (1.1%)
Skin lesion	4 (4.3%)	1 (1.1%)
Total	59 (63.4%)	61 (67.8%)

The Sponsor did not plan to perform a statistical analysis of adverse events.

6.1.3.3. Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No deaths or serious adverse events were reported during this study. Two significant adverse events "Musculoskeletal pain" and "Hematoma infection" were reported by Subject No. 23.

Narratives of SAE's

Subject No. 23 experienced the significant adverse events "Musculoskeletal pain" (Pain at buttock left side) approximately 1 day prior to first dosing and "Hematoma infection" (Infected hematoma on left buttock) approximately 3 days after study drug administration in Period 1. The subject fell on a sidewalk just before getting inside the Clinical facility. The subject confirmed that he could go on and do all his activities for the study. Approximately 3 days after study drug administration in Period 1, the subject went to the hospital emergency room. He was diagnosed with an infection at left buttock and received medication and a prescription for antibiotic. The subject elected to withdraw from the study due to medication taken as treatment for these events. These adverse events were judged to be unlikely related to study medication and were followed until resolution. The adverse events "Musculoskeletal pain" and "Hematoma infection" experienced by Subject No. 23 were classified as significant because the subject needed medical treatment and not because it posed a significant health risk to the subject. The health of the subject was not at risk during the study.

Reviewer's comments: The musculoskeletal pain and the hematoma infection of the subject #23 were unlikely related to the study medication, and his withdrawal was also unlikely related to the study medication.

6.1.3.4. Clinical Laboratory Evaluations

Some subjects had post-study laboratory results that were repeated in order to confirm the initial out-of range results. If not available for repeat tests, the subject was to be referred to a family physician. All final results were within normal limits or were judged to be not clinically significant by a Medical Sub-Investigator, with the following exception(s) that were judged to be clinically significant:

Subject No.	Test Name (Normal Range)	Initial Result	Repeat Result
16	GGT (8-61 U/L)	173	189*
35	PSA (0.00 - 4.00 µg/L)	6.85	4.42*
58	Red blood cells in urine (Negative/HPF)	5-10	5-10*

*Subject was referred to family physician for follow-up.

6.1.3.5. Vital Signs, Physical findings, and Other Observations Related to Safety

ECGs were performed at the time of screening only. Vital signs measurements and physical examinations (including evaluation of application site irritation) were performed at the times specified in the protocol. All final vital signs measurements were within normal limits (pulse rate: 50-100 bpm; blood pressure: 90-140 mmHg/50-90 mmHg; respiratory rate: 8-20 resp/min; oral temperature: 35.8-37.6°C) or were judged to be not clinically significant by a Medical Sub-Investigator. When judged necessary by the Medical Sub-Investigator, subjects were referred to

their family physician for follow-up. Post-study physical examinations were unchanged from screening with the following exceptions:

Subject Number	Physical Examination	Change
06	Skin	Small papules back of torso; papules on penis (glans).
14	Skin	Erythema under left axilla resolved (was due to a very tight t-shirt).
17	Skin	Superficial left antecubital forearm thrombophlebitis lesion.
23	Skin	Left buttock hematoma, drained. Dressing on it. No cellulitis around.
28	Skin	Recent scarring over chest (subject says he had skin biopsy on 2008-04-09).
31	Skin	Superficial erythema on back at application site + 01 pimple left side.
41	Skin	Mild erythema left lower back superficial
52	Skin	Very few acneiform lesions on upper back
68	Skin	Scratch on 4 th finger of the right hand
70	Skin	Blister on right thumb crusted, not infected

For the reported 13 subjects with “blood pressure increased”, the following are the details of these increased blood pressure as showing in Table 6.13.

Table 6.13 Blood Pressure Increased

Table 6.13.1 Non-TEAEs (N=4)

Subj #	AE Descrip.	MedDRA PT	SOC	Date of Onset	Time of Onset	Max Severity	Relationship to Study Drug	Resolution	Date of Resolution	Time of Resolution
04	Blood pressure increased	Blood pressure increased	Inv	2008-02-29	14:33	Mild	Unrelated	Spontaneous	2008-03-02	08:07
18	Blood pressure increased	Blood pressure increased	Inv	2008-03-01	03:36	Mild	Unrelated	Spontaneous	2008-03-01	04:25
79	Blood pressure increased	Blood pressure increased	Inv	2008-11-07	14:05	Mild	Unrelated	Spontaneous	2008-11-09	08:14
89	Blood pressure increased	Blood pressure increased	Inv	2008-11-07	14:34	Mild	Unrelated	Spontaneous	2008-11-07	17:00

Table 6.13.2 TEAEs (N=12)

Subj #	Trtmt. Group	Per	AE Descrip.	MedDRA PT	SOC	Date of Onset	Time of Onset	Max Severity	Relationship to Study Drug	Resolution	Date of Resolution	Time of Resolution
07	A	2	Blood pressure increased	Blood pressure increased	Inv	2008-03-10	08:20	Mild	Possibly	Spontaneous	2008-03-10	20:06
08	B	1	Blood pressure increased	Blood pressure increased	Inv	2008-03-03	20:03	Mild	Possibly	Spontaneous	2008-03-07	15:07
08	A	2	Blood pressure increased	Blood pressure increased	Inv	2008-03-10	20:10	Mild	Possibly	N/AP	Unresolved	Unresolved
15	B	1	Blood pressure increased	Blood pressure increased	Inv	2008-03-03	21:11	Mild	Possibly	Spontaneous	2008-03-07	15:24
15	A	2	Blood pressure increased	Blood pressure increased	Inv	2008-03-10	09:00	Mild	Possibly	Spontaneous	2008-03-10	20:48
16	A	1	Blood pressure increased	Blood pressure increased	Inv	2008-03-03	20:57	Mild	Possibly	Spontaneous	2008-03-07	15:30
18	A	1	Blood pressure increased	Blood pressure increased	Inv	2008-03-03	21:33	Mild	Possibly	Spontaneous	2008-03-07	15:34
40	B	2	Blood pressure increased	Blood pressure increased	Inv	2008-05-12	19:58	Mild	Possibly	N/AP	Unresolved	Unresolved
42	A		Blood pressure increased	Blood pressure increased	Inv	2008-05-05	08:15	Mild	Possibly	Spontaneous	2008-05-09	13:56
42	A	1	Blood pressure increased	Blood pressure increased	Inv	2008-05-10	09:22	Mild	Possibly	N/AP	Unresolved	Unresolved
43	B	1	Increased blood pressure	Blood pressure increased	Inv	2008-05-05	20:15	Mild	Possibly	Spontaneous	2008-05-09	14:01
51	B	1	Increased blood pressure	Blood pressure increased	Inv	2008-08-25	08:53	Mild	Possibly	Spontaneous	2008-08-25	21:07
73	B	2	Blood pressure increased	Blood pressure increased	Inv	2008-11-17	08:10	Mild	Possibly	N/AP	Unresolved	Unresolved
77	B	2	Increased blood pressure	Blood pressure increased	Inv	2008-11-17	19:39	Mid	Unrelated	N/AP	Unresolved	Unresolved
78	A	2	Increased blood pressure	Blood pressure increased	Inv	2008-11-17	19:11	Mild	Possibly	N/AP	Unresolved	Unresolved

Reviewer's comments: The adverse events of "blood pressure increased" from 13 subjects were deemed to mild and temporary and most of the events were resolved spontaneously. Therefore, it should not be considered as a safety issue.

Safety Conclusions: No deaths or serious adverse events were reported during this study. One subject presented two significant adverse events "Musculoskeletal pain" and "Hematoma infection". The health of this subject was not at risk during the study. A total of 208 treatment emergent adverse events (TEAEs) were reported by 80 of the 93 subjects who received at least one dose of the study medication (safety population). The breakdown by treatment group is as follows: 102 TEAEs reported by 63.4% (n=59) of the 93 subjects who received treatment A and 106 TEAEs reported by 67.8% (n=61) of the 90 subjects who received treatment B. The most commonly reported TEAEs were related to application site, with "Application site erythema" and "Application site pruritus" being reported by 63.4% (n=58) and 12.9% (n=12), respectively, of subjects who constituted the safety population. With the exception of "Blood pressure increased" reported by 14.0% (n=13) of subjects who constituted the safety population, all other TEAEs were reported by no more than 6.5% (n=6) of subjects who constituted the safety population. No deaths or serious adverse events were reported during this study. One subject presented two significant adverse events "Musculoskeletal pain" and "Hematoma infection". The health of this subject was not at risk during the study. Upon conclusion of the clinical portion of post-study laboratory tests, vital signs measurements, and physical examination, confirmed the absence of significant changes in the subjects' state of health.

Reviewer's comment: Considering the nature of this bioequivalence study (a single dose study with short-term safety monitoring), this reviewer agrees that no significant safety issues have been determined from this study.

6.1.3 Sponsor's Conclusion for the BE Study:

In accordance with the study protocol, the hypothesis of bioequivalence of the formulations was accepted if the 90% geometric confidence intervals of the ratio of least-squares means of the test to reference product of In-transformed AUC_{0-t} and C_{max} were within the acceptance range of 80.00% to 125.00% for baseline corrected data without dose normalization. Prior to the re-analysis of data, based on a request from the Division to exclude 6 subjects, the Sponsor believed that this study met the bioequivalence criteria as all 90% geometric confidence intervals were within the acceptance range; the test testosterone 5 g packet of 1% topical gel (Treatment A) was deemed bioequivalent to the reference Androgel (Treatment B) following a 100 mg dose in hypogonadal male volunteers.

However, the final re-analysis results (after excluding 6 subjects) showed that the AUC results still satisfied the criteria for BE while the C_{max} results did not, as the 90% CI for the difference between Teva T gel and AndroGel 1% was 126.4%, minimally above the

125% criterion. When assessed using baseline-uncorrected data, the products remained bioequivalent. No additional safety concerns were identified.

6.2 Reviewer's Final Conclusions for Efficacy

The design, procedures and execution, of this study were acceptable. From the baseline corrected results, BE of AUC Teva T gel 1% and RLD Androgel 1% was established; BE of C_{max} was not completely established, as the 90% CI for the difference between Teva T gel and AndroGel 1% was 126.4%, minimally above the 125% criterion. When assessed using baseline-uncorrected data, the products remained bioequivalent. No additional safety concerns were identified.

The efficacy results of this BE results appear still acceptable.

7 Review of Safety

Safety Summary from reviewing the three safety-related clinical studies

- The results of irritation and sensitization study showed neither a cumulative irritation effect nor sensitization reactions occurring in any study subjects.
- The results of the transfer study showed that interpersonal transfer of testosterone was effectively reduced through wearing a T-shirt.
- The results of hand-washing study showed that very little testosterone was left on the hands after application to the sites and handwashing.

7.1. Review of Irritation and Sensitization Study 10936025

7.1.1. Study title and objectives

The title of the study is: “A multiple site study to evaluate the cumulative skin irritation and sensitization potential of two formulations of topical 1% testosterone gel (TEVA) compared to two different already approved formulations; Androgel[®] (Unimed) and Testim[®] (Auxilium) in healthy male subjects.”

The Sponsor planned to demonstrate that their two test formulations of testosterone topical gel 1% when applied for multiple applications over 21 consecutive days do not have the potential to cause more clinically significant local irritation than the currently approved reference products. Additionally, both of the test formulations must be shown to not cause more dermal sensitization when compared to the reference products.

7.1.2. Design and methods of the study

Study Duration: The time from when first subject was dosed to when the last subject completed was approximately 10 weeks.

Study Design: A multiple site, multiple-application, double-blind, randomized, two phase irritation and sensitization study.

Study Objectives: The primary objectives of this study were:

- To compare the cumulative irritation potential of TEVA's two test formulations of testosterone 1% topical gel with the two Orange Book Listed Reference products AndroGel® (testosterone gel), CIII, 1% (Manufactured by Laboratories Besins International for Unimed Pharmaceuticals, LLC) and Testim® 1% (testosterone gel), CIII (Manufactured for Auxilium Pharmaceuticals, Inc. by DPT Laboratories, Ltd.) when applied over a continuous 21 day period.
- To evaluate the incidence of potential sensitization observed with the two test formulations compared to the two reference formulations of testosterone 1% topical gel.

Table 7.1.1 Irritation and Sensitization Study: Formulations Tested

Test Formulations	A	B	C	D
Product	TEVA	TEVA	AndroGel	Testim
Batch #	X028	X045	31618	AIEZ

Reviewer's comment: During the clinical review process, the clinical review requested clarification of the batches used in this study. The Sponsor responded on two occasions (07/29/2011 and 08/15/2011), as follows:

Sponsor's response on 07/29/2011 and 08/15/2011 for the Batch X045

Response from Teva on July 29, 2011	Response from Teva on Aug. 15, 2011
Batch X045 was manufactured using a different formulation of Testosterone Gel (b) (4) (IPP).	Batch X045 is another formulation of Testosterone Gel (b) (4)
The clinical studies were conducted with Batch X028 and X145. No additional batches were used in clinical studies with respect to NDA 202763 for Testosterone Gel, 1%.	In Study No. 10936025 , Batch X028 (Test A) was compared to Reference C - AndroGel®, the RLD for NDA 202763, and Batch X045 (Test B) was compared to Reference D - Testim®.
As such, the formulation and release and stability data for this batch (Batch X045) are not in support of this submission of NDA 202763 for Testosterone Gel, 1%.	Although Batch X045 was included in Study No. 10936025 it does not apply to NDA 202763 as it was not used for comparison to AndroGel®.

This reviewer concludes that the Treatment B with Batch #X045 and its comparison to Treatment D (Testim) are not part of the NDA submission and will not be part of clinical review even if all the related data are presented in this review. The relevant data come from Batch X028 (Treatment A).

Methodology and Assessment: This was a multiple site, multiple-application, randomized, double-blind (subject and irritation assessor), two phase study. 0.1 ml (0.025 ml/cm² of gel which is equivalent to 0.25 mg/cm² of testosterone) of the test and reference formulations was each applied to separate 2 cm x 2 cm (total area 4 cm²) area of the subjects upper arms during the study.

- 1) Irritation Assessment: During the irritation/induction period, the 0.1 ml gels (0.025 ml/cm² of gel which is equivalent to 0.25 mg/cm² of testosterone) were applied on an area of 2 cm x 2 cm and replaced once daily to the same application sites for a total of 21 days. Each of the four application sites was applied to the upper arm at least 1 cm away from each other. The application sites were randomized both by the arm and by vertical site of application. During the 21 day irritation/induction period, half of the subjects had the gels applied to the right arm and the other half to the left arm. During the sensitization period of the study, the opposite arm used in the irritation/induction period was used. After the gels had been applied and the application sites allowed to dry, the application sites were covered by a standardized occlusive patch consisting of a non-woven cotton pad covered by and held securely to the skin on all sides with Cover-Roll® Stretch (BSN Medical), adhesive covering to ensure the integrity of the applications and to keep them clean and dry during the application periods. On Day 22, the Day 21 applications were removed and no new product applied. Signs and symptoms of irritation were evaluated by trained, blinded, validated evaluators daily during the irritation/induction period. Standardized rating scales were utilized. To ensure the integrity of the study blinding, a member of the clinic staff who was not involved in any of the skin irritation grading assessments applied the formulations to each subject according to the randomization schedule. The study subject and staff members performing the irritation assessments were blinded to the treatment allocation.
- 2) Sensitization Assessment: Following Day 22 removal and assessments subjects underwent a 14 day washout period when no gels were applied. The subjects returned to the clinical facility on Day 36 where the gels were applied to complementary sites on the opposite arm used in the irritation/induction period. These applications were removed on Day 38 after at least 48 hours of application and the sites of application monitored over the next 72 hours (30 minutes, 24, 48, and 72 hours after removal) for signs and symptoms of possible sensitization reactions using the same rating scales as for the induction/irritation period.

Statistical analysis was performed to compare the relative irritation and sensitization of the test formulations to the reference formulations.

IRRITATION SCORING

0 = no evidence of irritation

1 = minimal erythema, barely perceptible

2 = definite erythema, readily visible; or minimal edema or minimal papular response

3 = strong erythema; or erythema and papules
4 = definite edema
5 = erythema with edema and papules
6 = vesicular eruption
7 = strong reaction spreading beyond application site

OTHER EFFECTS

Z = no other observations (numerical score = 0)
A = slightly glazed appearance (numerical score = 0)
B = marked glazed appearance (numerical score = 1)
C = glazing with peeling and cracking observed (numerical score = 2)
F = glazing with fissures (numerical score = 3)
G = film of dried serous exudates covering all or part of the application site (numerical score = 3)
H = small petechial erosions and/or scabs (numerical score = 3)

A scale of 0-7 was used to evaluate skin irritation (0 = no evidence of irritation, 7 = strong reaction spreading beyond test (i.e. application) site), based upon previous FDA Guidance. However, the Sponsor points out that this scale works well when mild irritation is present; however, if irritation is not present at all (e.g., scores of 0) it produces a skewed outcome. To resolve this issue, the mean cumulative total irritation results have been adjusted using a modified scale, where 1-8 is the same as 0-7. The original definitions of skin appearance have remained the same (i.e., 1 = no evidence of irritation, 8 = strong reaction spreading beyond test site in one case).

PPPI: Per Protocol Population of Irritation; PPPI was for primary analysis of irritation
ITTI: Intent to Treat Population of Irritation; ITTI was for secondary analysis of irritation

7.1.3. Summary of Results

A total of 265 healthy adult male subjects were entered into this study and were included in the Safety Population (SP) analysis. All subjects who completed the 21-day, cumulative irritation/induction period without significant protocol deviations comprised the Per Protocol Population for Irritation (**PPPI**), and were included in the primary analysis of irritation. All subjects who entered the study and had at least one irritation assessment performed were included in the Intent to Treat Population for Irritation (**ITTI**) population. 233 subjects were included in the Per Protocol Population for Irritation analysis (PPPI) as they completed the 21 day cumulative irritation/induction period without significant protocol deviations. 222 subjects were included in the Per Protocol Population for Sensitization (PPPS) as they completed the entire study without significant protocol deviations. As all subjects who participated in the sensitization period of the study were included in the PPPS, no separate secondary analysis of sensitization utilizing the Intent to Treat Population for Sensitization (ITTS) was performed.

The PPPI was used for the primary analysis of irritation. Cumulative Irritation Analysis: The mean cumulative total irritation results are presented with the more appropriate irritation scale (1-8) modified from traditional scale (0-7).

Part (1) Irritation Study Results: 5,407 individual irritation assessments for each study drug were made during the irritation phase of the study. No applications were halted because of excessive irritation for any subject or any study drug. The percentages of individual observations that had a score > 1 (minimal erythema, barely perceptible) were 2.3% for A, 5.3% for B, 2.1% for C and 7.0% for D.

Part (2) Sensitization Study Results: The PPPS was used for the primary analysis of sensitization. In this protocol, if the total irritation score (irritation + “other effects” scores) was > 1 and greater than the maximum single daily score observed during the irritation phase for the same subject, at either the 48 hour or 72 hour post removal evaluation, then the subject was considered to have demonstrated a potential sensitization response to that specific product(s). No cases of sensitization were observed for any of the four products tested. There were no “other effects” reported during the sensitization period of the study by those subjects included in the PPPS.

Table 7.1.2: Mean Cumulative Total Irritation (sum of irritation + “other effects” scores on Days 1 through 22) with the adjusted irritation scale of 1–8.

	Product*	N	Mean (SD)	Min.	Median	Max.
Mean Total Irritation Score Day 1 through Day 22	A	233	23.79 (4.12)	22.00	22.00	51.00
	B	233	26.26 (7.11)	22.00	23.00	57.00
	C	233	23.72 (4.39)	22.00	22.00	50.00
	D	233	27.30 (7.73)	22.00	24.00	59.00

* **Test Formulation A:** 0.1 ml of testosterone 1% topical gel (Manufactured by Cipla Ltd. (Goa) India for TEVA Pharmaceuticals USA).

* **Test Formulation B:** 0.1 ml of testosterone 1% topical gel (Manufactured by Cipla Ltd. for TEVA Pharmaceuticals USA).

* **Reference Formulation C:** 0.1 ml of Androgel® (testosterone gel) 1% (Manufactured by Laboratories Besins International for Unimed Pharmaceuticals, LLC [Unimed]).

* **Reference Formulation D:** 0.1 ml of Testim® 1% (testosterone gel) (Manufactured by DPT Laboratories, Ltd for Auxilium Pharmaceuticals Inc. [Auxilium]).

Table 7.1.3: Difference of Means and Locke’s 90% Confidence Intervals of PPPI with the adjusted irritation scale of 1-8.

	Mean Cumulative Total Irritation				
	Mean Test	Mean Ref x 1.25	Difference	Lower CI	Upper CI*
Product A v C	23.79	29.65	-5.85	-6.59	-5.11
Product B v D	26.26	34.13	-7.87	-9.16	-6.57

*If Upper CI is ≤ 0 then test product is considered non-inferior to the reference product.

Using both of these modified scales, the upper bound of the 95% one-sided CI (upper limit of the 90% two-sided confidence interval) of the difference between the mean cumulative irritation score for test product A minus 1.25 times the mean cumulative irritation score for reference product C was determined to be ≤ 0 , the difference between

the mean cumulative irritation score for test product B minus 1.25 times the mean cumulative irritation score for reference product D was determined also to be ≤ 0 , therefore it appears that the sponsor's testosterone, 1% topical gel was demonstrated to be no more irritating (non-inferior) to 1% Androgel[®].

The Intent to Treat Population for Irritation (ITTI) was used for the secondary analysis of irritation. Individual observations are presented by subject, by product type. Histograms of irritation score frequencies are included. Descriptive statistics (mean, standard deviation, median, maximum and minimum) and frequency tables of the scores for each product type on each study day (Day 1 through 22 inclusive) are presented below.

Table 7.1.4: Mean Total Irritation (irritation + “other effects”) scores on each day of application

	Product*	N	Mean (SD)	Min.	Median	Max
Mean Total Irritation Score on Day 1	A	265	0.00 (0.00)	0.00	0.00	0.00
	B	265	0.00 (0.00)	0.00	0.00	0.00
	C	265	0.00 (0.00)	0.00	0.00	0.00
	D	265	0.00 (0.00)	0.00	0.00	0.00
Mean Total Irritation Score on Day 2	A	261	0.01 (0.11)	0.00	0.00	1.00
	B	261	0.03 (0.17)	0.00	0.00	1.00
	C	261	0.01 (0.11)	0.00	0.00	1.00
	D	261	0.05 (0.23)	0.00	0.00	2.00
Mean Total Irritation Score on Day 3	A	260	0.01 (0.09)	0.00	0.00	1.00
	B	260	0.03 (0.18)	0.00	0.00	1.00
	C	260	0.02 (0.14)	0.00	0.00	1.00
	D	260	0.07 (0.29)	0.00	0.00	2.00
Mean Total Irritation Score on Day 4	A	257	0.01 (0.09)	0.00	0.00	1.00
	B	257	0.04 (0.18)	0.00	0.00	1.00
	C	257	0.01 (0.09)	0.00	0.00	1.00
	D	257	0.05 (0.23)	0.00	0.00	1.00
Mean Total Irritation Score on Day 5	A	254	0.04 (0.19)	0.00	0.00	1.00
	B	254	0.10 (0.34)	0.00	0.00	2.00
	C	254	0.02 (0.12)	0.00	0.00	1.00
	D	254	0.14 (0.39)	0.00	0.00	2.00
Mean Total Irritation Score on Day 6	A	252	0.04 (0.24)	0.00	0.00	2.00
	B	252	0.09 (0.31)	0.00	0.00	2.00
	C	252	0.03 (0.20)	0.00	0.00	2.00
	D	252	0.11 (0.37)	0.00	0.00	2.00
Mean Total Irritation Score on Day 7	A	251	0.05 (0.29)	0.00	0.00	2.00
	B	251	0.10 (0.37)	0.00	0.00	2.00
	C	251	0.05 (0.26)	0.00	0.00	2.00
	D	251	0.13 (0.43)	0.00	0.00	2.00
Mean Total Irritation Score on Day 8	A	249	0.06 (0.32)	0.00	0.00	2.00
	B	249	0.16 (0.47)	0.00	0.00	2.00
	C	249	0.07 (0.33)	0.00	0.00	2.00
	D	249	0.20 (0.54)	0.00	0.00	2.00
Mean Total Irritation Score on Day 9	A	248	0.06 (0.30)	0.00	0.00	2.00
	B	248	0.15 (0.44)	0.00	0.00	2.00
	C	248	0.07 (0.32)	0.00	0.00	2.00
	D	248	0.18 (0.49)	0.00	0.00	2.00
Mean Total Irritation Score on Day 10	A	248	0.08 (0.33)	0.00	0.00	2.00
	B	248	0.21 (0.58)	0.00	0.00	4.00
	C	248	0.10 (0.39)	0.00	0.00	2.00
	D	248	0.25 (0.63)	0.00	0.00	4.00
Mean Total Irritation Score on Day 11	A	248	0.09 (0.36)	0.00	0.00	2.00
	B	248	0.25 (0.58)	0.00	0.00	2.00
	C	248	0.12 (0.41)	0.00	0.00	2.00
	D	248	0.25 (0.59)	0.00	0.00	2.00
Mean Total Irritation Score on Day 12	A	245	0.11 (0.38)	0.00	0.00	2.00
	B	245	0.24 (0.55)	0.00	0.00	2.00

	C	245	0.11 (0.39)	0.00	0.00	2.00
	D	245	0.29 (0.62)	0.00	0.00	2.00
	Product*	N	Mean (SD)	Min.	Median	Max
Mean Total Irritation Score on Day 13	A	243	0.11 (0.40)	0.00	0.00	2.00
	B	243	0.21 (0.56)	0.00	0.00	2.00
	C	243	0.10 (0.38)	0.00	0.00	2.00
	D	243	0.29 (0.64)	0.00	0.00	2.00
Mean Total Irritation Score on Day 14	A	238	0.11 (0.40)	0.00	0.00	2.00
	B	238	0.24 (0.62)	0.00	0.00	4.00
	C	238	0.12 (0.41)	0.00	0.00	2.00
	D	238	0.30 (0.67)	0.00	0.00	2.00
Mean Total Irritation Score on Day 15	A	237	0.12 (0.43)	0.00	0.00	2.00
	B	237	0.28 (0.60)	0.00	0.00	2.00
	C	237	0.12 (0.43)	0.00	0.00	2.00
	D	237	0.32 (0.64)	0.00	0.00	2.00
Mean Total Irritation Score on Day 16	A	237	0.14 (0.45)	0.00	0.00	2.00
	B	237	0.31 (0.64)	0.00	0.00	2.00
	C	237	0.12 (0.43)	0.00	0.00	2.00
	D	237	0.35 (0.65)	0.00	0.00	2.00
Mean Total Irritation Score on Day 17	A	236	0.11 (0.43)	0.00	0.00	2.00
	B	236	0.32 (0.64)	0.00	0.00	2.00
	C	236	0.11 (0.39)	0.00	0.00	2.00
	D	236	0.36 (0.67)	0.00	0.00	2.00
Mean Total Irritation Score on Day 18	A	236	0.12 (0.45)	0.00	0.00	2.00
	B	236	0.30 (0.62)	0.00	0.00	2.00
	C	236	0.10 (0.40)	0.00	0.00	2.00
	D	236	0.33 (0.67)	0.00	0.00	2.00
Mean Total Irritation Score on Day 19	A	236	0.14 (0.44)	0.00	0.00	2.00
	B	236	0.28 (0.61)	0.00	0.00	2.00
	C	236	0.11 (0.40)	0.00	0.00	2.00
	D	236	0.34 (0.66)	0.00	0.00	2.00
Mean Total Irritation Score on Day 20	A	236	0.11 (0.41)	0.00	0.00	2.00
	B	236	0.30 (0.60)	0.00	0.00	2.00
	C	236	0.12 (0.42)	0.00	0.00	2.00
	D	236	0.40 (0.72)	0.00	0.00	2.00
Mean Total Irritation Score on Day 21	A	236	0.12 (0.44)	0.00	0.00	2.00
	B	236	0.31 (0.67)	0.00	0.00	3.00
	C	236	0.12 (0.43)	0.00	0.00	2.00
	D	236	0.39 (0.72)	0.00	0.00	2.00
Mean Total Irritation Score on Day22	A	234	0.12 (0.45)	0.00	0.00	2.00
	B	234	0.28 (0.62)	0.00	0.00	2.00
	C	234	0.10 (0.39)	0.00	0.00	2.00
	D	234	0.41 (0.71)	0.00	0.00	2.00

***Test Formulation A:** 0.1 ml of testosterone, CIII, 1% topical gel (Manufactured by Cipla Ltd. (Goa) India for TEVA Pharmaceuticals USA); **Test Formulation B:** 0.1 ml of testosterone, CIII, 1% topical gel (Manufactured by Cipla Ltd. for TEVA Pharmaceuticals USA); **Reference Formulation C:** 0.1 ml of Androgel® (testosterone gel), CIII, 1% (Manufactured by Laboratoires Besins International for Unimed Pharmaceuticals, LLC [Unimed]); **Reference Formulation D:** 0.1 ml of Testim® 1% (testosterone gel), CIII (Manufactured for Auxilium Pharmaceuticals Inc. (Auxilium) by DPT Laboratories, Ltd.)

Table 7.1.4.1: Frequency of Irritation Scores for Test Formulation A*

Day	N	Irritation Score							
		0 N (%)	1 N (%)	2 N (%)	3 N (%)	4 N (%)	5 N (%)	6 N (%)	7 N (%)
1	265	265 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
2	261	258 (98.85)	3 (1.15)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
3	260	258 (99.23)	2 (0.77)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
4	257	255 (99.22)	2 (0.78)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
5	254	244 (96.06)	10 (3.94)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
6	252	243 (96.43)	7 (2.78)	2 (0.79)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
7	251	242 (96.41)	5 (1.99)	4 (1.59)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
8	249	238 (95.58)	6 (2.41)	5 (2.01)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
9	248	236 (95.16)	8 (3.23)	4 (1.61)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
10	248	234 (94.35)	9 (3.63)	5 (2.02)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
11	248	232 (93.55)	10 (4.03)	6 (2.42)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
12	245	224 (91.43)	15 (6.12)	6 (2.45)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
13	243	223 (91.77)	13 (5.35)	7 (2.88)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
14	238	219 (92.02)	12 (5.04)	7 (2.94)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
15	237	218 (91.98)	10 (4.22)	9 (3.80)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
16	237	215 (90.72)	12 (5.06)	10 (4.22)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
17	236	219 (92.80)	7 (2.97)	10 (4.24)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
18	236	219 (92.80)	6 (2.54)	11 (4.66)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
19	236	212 (89.83)	15 (6.36)	9 (3.81)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
20	236	220 (93.22)	7 (2.97)	9 (3.81)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
21	236	217 (91.95)	9 (3.81)	10 (4.24)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
22	234	216 (92.31)	7 (2.99)	11 (4.70)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

* **Test Formulation A:** 0.1 ml of testosterone, CIII, 1% topical gel (Manufactured by Cipla Ltd. (Goa) India for TEVA Pharmaceuticals USA).

Table 7.1.4.2: Frequency of Irritation Scores for Reference Formulation C*

Day	N	Irritation Score							
		0 N (%)	1 N (%)	2 N (%)	3 N (%)	4 N (%)	5 N (%)	6 N (%)	7 N (%)
1	265	265 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
2	261	258 (98.85)	3 (1.15)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
3	260	255 (98.08)	5 (1.92)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
4	257	255 (99.22)	2 (0.78)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
5	254	250 (98.43)	4 (1.57)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
6	252	245 (97.22)	6 (2.38)	1 (0.40)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
7	251	242 (96.41)	6 (2.39)	3 (1.20)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
8	249	236 (94.78)	8 (3.21)	5 (2.01)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
9	248	234 (94.35)	10 (4.03)	4 (1.61)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
10	248	229 (92.34)	12 (4.84)	7 (2.82)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
11	248	227 (91.53)	13 (5.24)	8 (3.23)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
12	245	225 (91.84)	13 (5.31)	7 (2.86)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
13	243	224 (92.18)	13 (5.35)	6 (2.47)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
14	238	218 (91.60)	12 (5.04)	8 (3.36)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
15	237	218 (91.98)	10 (4.22)	9 (3.80)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
16	237	218 (91.98)	10 (4.22)	9 (3.80)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
17	236	218 (92.37)	11 (4.66)	7 (2.97)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
18	236	220 (93.22)	8 (3.39)	8 (3.39)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
19	236	217 (91.95)	12 (5.08)	7 (2.97)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
20	236	216 (91.53)	12 (5.08)	8 (3.39)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
21	236	217 (91.95)	10 (4.24)	9 (3.81)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
22	234	218 (93.16)	9 (3.85)	7 (2.99)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

* **Reference Formulation C:** 0.1 ml of Androgel[®] (testosterone gel), CIII, 1% (Manufactured by Laboratoires Besins International for Unimed Pharmaceuticals, LLC [Unimed]).

Table 7.1.4.3: Frequency of “Other Effects” Scores for Test Formulation A*

Day	N	Irritation Score			
		0 N (%)	1 N (%)	2 N (%)	3 N (%)
1	265	265 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
2	261	261 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
3	260	260 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
4	257	257 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
5	254	254 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
6	252	252 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
7	251	251 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
8	249	249 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
9	248	248 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
10	248	248 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
11	248	248 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
12	245	245 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
13	243	243 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
14	238	238 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
15	237	237 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
16	237	237 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
17	236	236 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
18	236	236 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
19	236	236 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
20	236	236 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
21	236	236 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
22	234	234 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)

* **Test Formulation A:** 0.1 ml of testosterone, CIII, 1% topical gel (Manufactured by Cipla Ltd. (Goa) India for TEVA Pharmaceuticals USA).

Table 7.1.4.4: Frequency of “Other Effects” Scores for Test Formulation C*

Day	N	Irritation Score			
		0 N (%)	1 N (%)	2 N (%)	3 N (%)
1	265	265 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
2	261	261 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
3	260	260 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
4	257	257 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
5	254	254 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
6	252	252 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
7	251	251 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
8	249	249 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
9	248	248 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
10	248	248 (100.00)	0 (0.00)	1 (0.40)	0 (0.00)
11	248	248 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
12	245	245 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
13	243	243 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
14	238	238 (100.00)	0 (0.00)	1 (0.42)	0 (0.00)
15	237	237 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
16	237	237 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
17	236	236 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
18	236	236 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
19	236	236 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
20	236	236 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)
21	236	236 (100.00)	0 (0.00)	1 (0.42)	0 (0.00)
22	234	234 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)

* **Reference Formulation C:** 0.1 ml of Androgel[®] (testosterone gel), CIII, 1% (Manufactured by Laboratoires Besins International for Unimed Pharmaceuticals, LLC [Unimed]).

Table 7.1.4.5: Frequency of Total Irritation Scores (Irritation + “Other Effects”) for Test Formulation A*

Day	N	Irritation Score										
		0 N (%)	1 N (%)	2 N (%)	3 N (%)	4 N (%)	5 N (%)	6 N (%)	7 N (%)	8 N (%)	9 N (%)	10 N (%)
1	265	265 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
2	261	258 (98.85)	3 (1.15)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
3	260	258 (99.23)	2 (0.77)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
4	257	255 (99.22)	2 (0.78)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
5	254	244 (96.06)	10 (3.94)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
6	252	243 (96.43)	7 (2.78)	2 (0.79)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
7	251	242 (96.41)	5 (1.99)	4 (1.59)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
8	249	238 (95.58)	6 (2.41)	5 (2.01)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
9	248	236 (95.16)	8 (3.23)	4 (1.61)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
10	248	234 (94.35)	9 (3.63)	5 (2.02)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
11	248	232 (93.55)	10 (4.03)	6 (2.42)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
12	245	224 (91.43)	15 (6.12)	6 (2.45)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
13	243	223 (91.77)	13 (5.35)	7 (2.88)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
14	238	219 (92.02)	12 (5.04)	7 (2.94)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
15	237	218 (91.98)	10 (4.22)	9 (3.80)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
16	237	215 (90.72)	12 (5.06)	10 (4.22)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
17	236	219 (92.80)	7 (2.97)	10 (4.24)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
18	236	219 (92.80)	6 (2.54)	11 (4.66)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
19	236	212 (89.83)	15 (6.36)	9 (3.81)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
20	236	220 (93.22)	7 (2.97)	9 (3.81)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
21	236	217 (91.95)	9 (3.81)	10 (4.24)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
22	234	216 (92.31)	7 (2.99)	11 (4.70)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

* Test Formulation A: 0.1 ml of testosterone, CIII, 1% topical gel (Manufactured by Cipla Ltd. (Goa) India for TEVA Pharmaceuticals USA).

Table 7.1.4.6: Frequency of Total Irritation Scores (Irritation + “Other Effects”) for Test Formulation C*

Day	N	Irritation Score										
		0 N (%)	1 N (%)	2 N (%)	3 N (%)	4 N (%)	5 N (%)	6 N (%)	7 N (%)	8 N (%)	9 N (%)	10 N (%)
1	265	265 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
2	261	258 (98.85)	3 (1.15)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
3	260	255 (98.08)	5 (1.92)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
4	257	255 (99.22)	2 (0.78)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
5	254	250 (98.43)	4 (1.57)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
6	252	245 (97.22)	6 (2.38)	1 (0.40)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
7	251	242 (96.41)	6 (2.39)	3 (1.20)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
8	249	236 (94.78)	8 (3.21)	5 (2.01)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
9	248	234 (94.35)	10 (4.03)	4 (1.61)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
10	248	229 (92.34)	12 (4.84)	7 (2.82)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
11	248	227 (91.53)	13 (5.24)	8 (3.23)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
12	245	225 (91.84)	13 (5.31)	7 (2.86)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
13	243	224 (92.18)	13 (5.35)	6 (2.47)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
14	238	218 (91.60)	12 (5.04)	8 (3.36)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
15	237	218 (91.98)	10 (4.22)	9 (3.80)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
16	237	218 (91.98)	10 (4.22)	9 (3.80)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
17	236	218 (92.37)	11 (4.66)	7 (2.97)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
18	236	220 (93.22)	8 (3.39)	8 (3.39)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
19	236	217 (91.95)	12 (5.08)	8 (3.39)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
20	236	216 (91.53)	12 (5.08)	8 (3.39)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
21	236	217 (91.95)	10 (4.24)	9 (3.81)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
22	234	218 (93.16)	9 (3.85)	7 (2.99)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

* Reference Formulation C: 0.1 ml of Androgel[®] (testosterone gel), CIII, 1% (Manufactured by Laboratoires Besins International for Unimed Pharmaceuticals, LLC [Unimed]).

In the ITTI (intent to treat population of irritation) population a total of 21,628 individual irritation assessments, 5,407 for each study drug were made during the irritation phase of the study. No applications were halted because of excessive irritation for any subject or any study drug. The percentage of individual observations that had a score greater than 1 (minimal erythema, barely perceptible) was 2.31% for A, 5.31% for B, 2.09% for C and 6.99% for D. Using Fishers Exact two sided testing the p value for A v C was $p = 0.4710$ and for B v D $p = 0.0003$. There was no statistical difference between the incidence of anything greater than very mild erythema between the Test formulation A and the Reference Formulation C.

Sensitization Analysis

The Per Protocol Population for Sensitization (PPPS) was used for the primary analysis of sensitization. Individual observations are presented by subject, by product type. The results are summarized below. As all subjects who participated in the sensitization period of the study were included in the PPPS, no separate secondary analysis of sensitization utilizing the ITTS was performed.

If at either the 48 hour or 72 hour post removal evaluation on Day 38, the scoring of total irritation (irritation + “other effects” scores) is greater than 1 and is greater than a maximum single daily score observed during the irritation phase of the study for that subject then the subject was considered to have demonstrated a potential sensitization response to that specific product(s). No cases of sensitization were observed for any of the four products tested. There were no “other effects” reported during the sensitization period of the study by those subjects included in the PPPS.

Table 7.1.5: Total Score (mean scores of irritation + “other effects” at 30 min, 24, 48, and 72 hours after product removal on Day 38) of PPPS

	Product*	N	Mean (SD)	Min.	Median	Max.
Mean Total Score – 30 min.	A	222	0.00 (0.07)	0.00	0.00	1.00
	B	222	0.05 (0.26)	0.00	0.00	2.00
	C	222	0.01 (0.12)	0.00	0.00	1.00
	D	222	0.07 (0.33)	0.00	0.00	2.00
Mean Total Score – 24 hr	A	222	0.03 (0.21)	0.00	0.00	2.00
	B	222	0.04 (0.22)	0.00	0.00	2.00
	C	222	0.03 (0.24)	0.00	0.00	2.00
	D	222	0.09 (0.36)	0.00	0.00	2.00
Mean Total Score – 48 hr	A	222	0.00 (0.07)	0.00	0.00	1.00
	B	222	0.02 (0.13)	0.00	0.00	1.00
	C	222	0.00 (0.00)	0.00	0.00	0.00
	D	222	0.01 (0.12)	0.00	0.00	1.00
Mean Total Score – 72 hr	A	220	0.00 (0.00)	0.00	0.00	0.00
	B	220	0.00 (0.00)	0.00	0.00	0.00
	C	220	0.00 (0.00)	0.00	0.00	0.00
	D	220	0.01 (0.10)	0.00	0.00	1.00

*Test Formulations A, B, C, and D (0.1 mL each) as referenced above

Table 7.1.5.1: Frequency of Total Scores (Irritation + “Other Effects”) for Test Formulation A* of PPPS

Time Post Removal	N	Total Score										
		0 N (%)	1 N (%)	2 N (%)	3 N (%)	4 N (%)	5 N (%)	6 N (%)	7 N (%)	8 N (%)	9 N (%)	10 N (%)
30 min.	222	221 (99.55)	1 (0.45)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
24 hour	222	218 (98.20)	2 (0.90)	2 (0.90)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
48 hour	222	221 (99.55)	1 (0.45)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
72 hours	220	220 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

* Test Formulation A: 0.1 ml of testosterone,

Table 7.1.5.2: Frequency of Total Scores (Irritation + “Other Effects”) for Reference Formulation C* of PPPS

Time Post Removal	N	Total Score										
		0 N (%)	1 N (%)	2 N (%)	3 N (%)	4 N (%)	5 N (%)	6 N (%)	7 N (%)	8 N (%)	9 N (%)	10 N (%)
30 min.	222	219 (98.65)	3 (1.35)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
24 hour	222	218 (98.20)	1 (0.45)	3 (1.35)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
48 hour	222	222 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
72 hours	220	220 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

* Reference Formulation C: 0.1 ml of AndroGel[®] (testosterone gel).

7.1.4. Safety Results for Study 10936025:

7.1.4.1. Extend of Exposure:

Two hundred sixty-five (265) subjects participated in the induction/irritation period of the study and had all four products/dressings applied simultaneously on at least one occasion. Two hundred thirty-four (234) subjects had all four products/dressings applied simultaneously for the 21 day irritation/induction period, followed by a 14 day washout period where no products/dressings were applied. Two hundred twenty-two (222) subjects had all four products/dressings applied simultaneously during the 48-hour sensitization period.

7.1.4.2. Adverse Events (AEs):

Overall Safety Results of the Irritation and Sensitization Study:

- A total of 231 AEs were reported by 110/265 subjects who participated in the study.
- A total of 229 AEs were considered “mild” in severity. Of these, 204 AEs resolved spontaneously prior to study completion, 17 resolved with treatment, and 8 had not resolved by the end of the study.
- One (1) AE of a fractured left arm with hospitalization was considered “moderate” and documented as a SAE and resolved spontaneously. This event was judged by the Investigator to be unrelated to the study drug(s);
- One (1) AE of syncope resulting in hospitalization was considered “severe” and documented as a SAE and resolved spontaneously. This event was judged by the Investigator to be unrelated to the study drug(s);
- Of the 231 AEs reported during the study, 160 AEs could not be directly attributed to the application of a specific product and were recorded as “non-localized” adverse events. The most frequently reported “non-localized” AEs were blood pressure increased (22 subjects), open wound (14 subjects), blood pressure decreased (12 subjects), and headache (12 subjects).
- 71 of the reported AEs could be attributed directly to application of a specific product and were considered “localized” adverse events. The most frequently reported “localized” event was application site pruritus: 8 subjects for test product A; 7 subjects for test product B, 8 subjects for AndroGel 1%, and 14 subjects for Testim. There were no statistically significant differences between the number and severity of localized application site reactions reported between the four treatments.

7.1.4.2.1. Narratives of Deaths, Other Serious Adverse Events, and Certain Other Significant Adverse Events

No deaths occurred during the Study. Two SAEs occurred during this study.

Site No. 01 Subject 1028 (COM) reported being hospitalized on (b) (6) Study Day 24 (during the washout period), due to a fractured left arm. This subject underwent medical examination and treatment on both an in-patient and out-patient basis and was discharged from the hospital on (b) (6). The hospital visit was reported to the clinic on 07/16/09, at which time the subject was discontinued from further study participation prior to study drug application on Day 36. It was discovered he was admitted to the hospital and stayed overnight when the clinic received this subject's hospital records on 08/18/09. The following adverse events were not considered an SAE but contributed to the hospitalization of the subject: pain left arm, soft tissue swelling-left upper extremity, and ecchymosis left arm. All adverse events, including the SAE of fractured left arm, resolved spontaneously or with treatment. This subject completed study termination procedures on 07/16/09. The Investigator judged the relationship between this SAE and the study drugs to be "unrelated".

Reviewer's comment: This SAE is judged as not related to the study medication.

Site No. 01, Subject 1048 (MFK) reported being hospitalized on (b) (6), Study Day 41, due to the adverse event of syncope. This subject underwent medical examination and treatment on an in-patient basis and was discharged from the hospital on (b) (6). The hospital visit was reported to the clinic on 07/28/09. This subject was considered to have completed the study since he had at least two post removal assessments (at 30 minutes and at 48 hours) completed within 72 hours of removal. The following adverse events were not considered an SAE but contributed to the hospitalization of the subject: nausea, vomiting, and feeling anxious. All adverse events, including the SAE of syncope, resolved with treatment. This subject completed end of study procedures on 07/29/09. The Investigator judged the relationship between this SAE and the study drugs to be "unrelated".

Reviewer's Comment: This SAE is judged as not related to the study medication.

7.1.4.2.2. Other Adverse Events

Of the 231 AE's reported during the study, 160 AE's could not be directly attributed to the application of a specific product and were recorded as non-localized adverse events. The most frequently reported non-localized AE's were blood pressure increased (22 subjects), open wound (14 subjects), blood pressure decreased (12 subjects), and headache (12 subjects).

Seventy-one (71) of the reported AE's could be attributed directly to application of a specific product and were considered localized adverse events. The most frequently reported localized event was application site pruritus for Test Product A (8 subjects), Test Product B (7 subjects), Reference Product C (8 subjects), and Reference Product D (14 subjects).

Reviewer's Comment: Among the cases of "blood pressure increased", none were above 20 mm Hg systolic increase from baseline. The BP increase occurred at variable times during the study.

7.1.4.2.3. Laboratory Measurements

A urine/saliva test for THC, cocaine and ethanol was performed on all subjects at screening and prior to application on Day 1 and Day 36. All subjects tested negative with the following exceptions: Subjects 1068 (b) (4) and 3082 (b) (4) tested positive for a restricted substance on Study Day 36 and were discontinued from the sensitization period of the study.

Table 7.1.6 Non-Localized Adverse Events by MedDRA System Organ Class (SOC)

MedDRA SOC	MedDRA Preferred Term	N ¹ = 265	
		n ²	% ³
Gastrointestinal disorders	Abdominal pain upper	1	.38
Gastrointestinal disorders	Dyspepsia	1	.38
Gastrointestinal disorders	Nausea	1	.38
Gastrointestinal disorders	Stomach discomfort	2	.75
Gastrointestinal disorders	Vomiting	1	.38
General disorders & administration site conditions	Energy increased	2	.75
General disorders & administration site conditions	Inflammation	1	.38
General disorders & administration site conditions	Oedema peripheral	1	.38
General disorders & administration site conditions	Pain	1	.38
Injury, poisoning & procedural complications	Face injury	1	.38
Injury, poisoning & procedural complications	Open wound	14	5.28
Injury, poisoning & procedural complications	Scratch	1	.38
Injury, poisoning & procedural complications	Skin laceration	5	1.89
Injury, poisoning & procedural complications	Upper limb fracture	1	.38
Investigations	ALT increased	1	.38
Investigations	AST increased	2	.75
Investigations	Blood ALKP increased	1	.38
Investigations	Blood ALKP increased	1	.38
Investigations	Blood bilirubin increased	1	.38
Investigations	Blood glucose abnormal	4	1.51
Investigations	Blood glucose increased	3	1.13
Investigations	Blood pressure decreased	12	4.53
Investigations	Blood pressure increased	22	8.30
Investigations	Heart rate increased	1	.38
Musculoskeletal & connective tissue disorders	Arthralgia	1	.38
Musculoskeletal & connective tissue disorders	Musculoskeletal stiffness	1	.38
Musculoskeletal & connective tissue disorders	Pain in extremity	2	.75
Nervous system disorders	Dizziness	1	.38
Nervous system disorders	Headache	12	4.53
Nervous system disorders	Insomnia	1	.38
Psychiatric disorders	Anxiety	2	.75

Renal and urinary disorders	Pollakiuria	1	.38
Reproductive system & breast disorders	Spontaneous penile erection	1	.38
Respiratory, thoracic and mediastinal disorders	Nasal congestion	4	1.51
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	3	1.13
Respiratory, thoracic and mediastinal disorders	Sneezing	2	.75
Respiratory, thoracic and mediastinal disorders	Throat irritation	1	.38
Skin and subcutaneous tissue disorders	Acne	1	.38
Skin and subcutaneous tissue disorders	Ecchymosis	1	.38
Skin and subcutaneous tissue disorders	Erythema	1	.38
Skin and subcutaneous tissue disorders	Excoriation	4	1.51
Skin and subcutaneous tissue disorders	Pruritus	10	3.77
Skin and subcutaneous tissue disorders	Skin erosion	2	.75
Surgical and medical procedures	Wound drainage	1	.38
Vascular disorders	Hypotension	1	.38
Vascular disorders	Syncope	2	.75

¹ N = Number of subjects who dosed with respective treatment

² n = number of subjects reporting Adverse Event

³ % calculated as (number of subjects reporting Adverse Event / Number of subjects who dosed with respective treatment) times 100

Table 7.1.7 Localized Adverse Events by MedDRA System Organ Class (SOC)

MedDRA SOC	MedDRA Preferred Term	N ¹ = 265		N = 265		N = 265		N = 265	
		A ⁴	A	B	B	C	C	D	D
		n ²	% ³	n	n	n	%	n	%
General disorders & administration site conditions	Application site pain	7	2.64	4	1.51	6	2.26	6	2.26
General disorders & administration site conditions	Application site paraesthesia	2	0.75	1	0.38	0	0	1	0.38
General disorders & administration site conditions	Application site pruritus	8	3.02	7	2.64	8	3.02	14	5.28

¹ N = Number of subjects who dosed with respective treatment

² n = number of subjects reporting Adverse Event

³ % calculated as (number of subjects reporting Adverse Event / Number of subjects who dosed with respective treatment) times 100

⁴ Treatment: *Test Formulation A*: 0.1 ml of testosterone, CIII, 1% topical gel (Manufactured by Cipla Ltd. (Goa) India for TEVA Pharmaceuticals USA). *Test Formulation B*: 0.1 ml of testosterone, CIII, 1% topical gel (Manufactured by Cipla Ltd. for TEVA Pharmaceuticals USA). *Reference Formulation C*: 0.1 ml of AndroGel® (testosterone gel), CIII, 1% (Manufactured by Laboratoires Besins International for Unimed Pharmaceuticals, LLC (Unimed)). *Reference Formulation D*: 0.1 ml of Testim® 1% (testosterone gel), CIII (Manufactured for Auxilium Pharmaceuticals Inc. (Auxilium) by DPT Laboratories, Ltd.).

7.1.4.3 Summary of Overall Safety Results of the Irritation and Sensitization Study:

- A total of 231 AEs were reported by 110/265 subjects.
- A total of 229 AEs were considered “mild” in severity. Of these, 204 AEs resolved spontaneously prior to study completion, 17 resolved with treatment, and 8 had not resolved by the end of the study.

- One (1) AE of a fractured left arm with hospitalization was considered “moderate” and documented as a SAE and resolved spontaneously. This event was judged to be unrelated to the study drug(s);
- One (1) AE of syncope resulting in hospitalization was considered “severe” and documented as a SAE and resolved spontaneously. This event was judged to be unrelated to the study drug(s);
- Of the 231 AEs reported during the study, 160 AEs could not be directly attributed to the application of a specific product and were recorded as “non-localized” adverse events. The most frequently reported “non-localized” AEs were blood pressure increased (22 subjects), open wound (14 subjects), blood pressure decreased (12 subjects), and headache (12 subjects). None of the cases of “blood pressure increased” were > 20 mm Hg systolic increase from baseline. The increases occurred at variable times in the study.
- 71 of the reported AEs could be attributed directly to application of a specific product and were considered “localized” adverse events. The most frequently reported “localized” event was application site pruritus: 8 subjects for test product A; 7 subjects for test product B, 8 subjects for AndroGel 1%, and 14 subjects for Testim. There were no significant differences between the number and severity of localized application site reactions reported between the four treatments.

7.1.5 Sponsor’s Conclusions:

- None of the applications for any subject for any product were halted prematurely for excessive irritation during the study.
- None of the four products tested showed any cumulative irritations effects that were of clinical significance.
- No subjects demonstrated any sensitization reaction to the four products.
- There was no significant difference between the number and severity of localized application site reactions reported between the four treatments during the study.

7.1.6 Reviewer’s conclusion for the Study of Irritation and Sensitization:

- **Most of the individual scores during the irritation and sensitization phases were either zero or 1.**
- **The design, execution, and results of this irritation and sensitization study appear acceptable.**
- **No cumulative irritation effect of clinical significance was determined for the test product.**
- **No subjects demonstrated any sensitization reaction to the test product.**
- **Almost all AEs were considered “mild” in severity. The most frequently reported “non-localized” AEs were blood pressure changes (all in minor range and at variable times during the study) and headache.**
- **The most frequently reported “localized” event was application site pruritus.**
- **There were no significant differences between the number and severity of localized application site reactions reported between the testing and RLD treatments.**

7.2. Review of Hand Washing Study (Study No. CRI-00018704)

7.2.1. Study Title

A Pivotal Study to Evaluate the Residual Amount of Topically Delivered Testosterone Gel 1% Present on Normal Skin of the Hand, in Healthy Adult Male Subjects Following Hand Washing Procedures

7.2.2. Study design

7.2.2.1. Study Objectives: To quantify and compare the amount of residual drug remaining on the hands between Testosterone Gel 1% manufactured by Cipla Ltd. for Teva Pharmaceuticals USA and AndroGel® (testosterone gel) 1% manufactured by Solvay Pharmaceuticals, Inc., following a hand washing procedure.

7.2.2.2. Study Methodology: This was an open-label, two-period crossover, pivotal study on healthy adult male subjects. This study compared the amount of the residual drug product remaining on the hands between Teva's testosterone Gel, 1% and AndroGel®, 1% following a hand-washing procedure. The dosing product randomization scheme was determined prior to study initiation by the investigator's statistical staff. On study days 1 (Period I) and 15 (Period II), subjects entered the clinic, had their hands washed and wiped each with three ethanol dampened gauze (blank control sample). Subsequently, each subject had 10 grams of testosterone gel (2 x 5 gram doses, total 100 mg testosterone) applied to their dominate hand. The subject distributed each 5 gram dose to areas of the upper arm and posterior and anterior shoulder. The subjects were then required to follow the below handwashing procedure:

- The subjects wet their hands with warm tap water ($35^{\circ}\text{C} \pm 5^{\circ}\text{C}$) for 10 seconds.
- 2 mL of liquid soap was dispensed to the hands (same brand of soap was used throughout the study)
- Subjects washed their hands with a controlled hand scrubbing procedure for 20 seconds
- Subjects rinsed their hands with warm tap water for 20 seconds
- Subjects dried their hands with a dry cotton towel for 30 seconds

The subjects performed this hand-washing procedure following the application of both products evaluated in this study, Teva's Testosterone Gel, 1% and AndroGel®, 1%. Each dosing was separated by a 14 day washout period. Samples taken following the hand-washing procedure were evaluated for testosterone content. Following the hand wash, the subject's hands were wiped with three ethanol dampened gauze per hand (sample for assessment), the palm, fingers, and back of each hand were wiped with gauze (2" x 2") dampened with approximately 2 mL of ethanol (1 to palm, 1 to fingers, and 1 to back of hand) to collect any residual testosterone left on the skin surface. The three gauze wipes per hand were combined into one vial, with a second vial for the three gauze wipes from the other hand. This process was repeated 14 days later with the other test article. The gauze was retained for analytical quantification of recovered testosterone.

Table 7.2.1 Identity of Products

Product	Test	Reference
Treatment ID	A	B
Product Name	Testosterone gel 1% w/w	AndroGel® 1%
Manufacturer	CIPLA, LTD.	Solvay Pharmaceuticals, Inc.
Batch/Lot No.	X145	31848
Manufacture Date	05/2010	N/A
Expiration Date	N/A	03/12
Strength	1%	1%
Dosage Form	Gel	Gel
Dose Administered	5 grams x 2	5 grams x 2
Route of Administration	Topical	Topical

7.2.2.3. Study Sample Size: The total sample size for this study was 48 subjects. This sample size was based on clinical judgment and was believed to be sufficient to satisfy the objectives. Sufficient numbers of volunteers were screened to enroll 48 subjects. Data from a total of 39 subjects were included in the statistical analysis.

7.2.2.4. Main Criteria for Inclusion: All subjects were asymptomatic, non-smoking (fourteen [14] day abstinence from smoking prior to dosing was required), non-obese adult male volunteers between the ages of 18 and 65 inclusive, who met the requirements for BMI (between 18 and 34 kg/m²), and who were demonstrated to be generally healthy by screening medical and medication history.

7.2.2.5. Study Procedures

Table 7.2.2 Study Flow sheet

	Screening	Day 1 Predose	Day 1	Day 15 Predose	Day 15	Exit ^h
Informed Consent	X			X ^g		
Inclusion/Exclusion	X			X ^g		
Medical History	X			X ^g		
Concurrent Medications	X	X	X	X	X	X
Urine Drug Screen	X	X		X		
Dose Application			X	X	X	
Pre-Dose Hand Washing		X ^c		X ^c		X ^h
Dose Removal Hand Washing			X ^a		X ^a	
Site Evaluation	X ^b	X ^b	X ^b	X ^b	X ^b	
Hand Wipe Sample Collection		X ^d	X ^e	X ^d	X ^e	
Shower			X ^f		X ^f	X ^f
Query for AEs	X	X	X	X	X	X

- a Dose removal occurred by hand washing at 5 minute following study drug application
- b Skin on the hands was evaluated for any skin problems
- c Hand washing occurred approximately 30 minutes prior to dosing
- d Pre-dose hand wipe with three ethanol dampened gauze (per hand) and was collected 15 minutes prior to dose application
- e Five minutes after dose application and hand washing, three ethanol dampened gauze (per hand) were used to collect any residual study drug
- f Subjects were to shower prior to leaving the clinic on study day 1 and 15 or at early exit if dose was applied to arm and shoulder
- g Confirmation that no changes occurred that affected eligibility for continuation in the study
- h Exit procedures in the event that a subject withdrew or early termination (hand washing occurred if a dose had been applied)

7.2.2.6. Statistical Methods: The primary statistical analysis was a non-inferiority analysis to show that the amount of residual drug for the test product was not greater than that for the reference product. The data was the amount recovered from the hand swabs (fingers, palm, dorsal hand) as the total sum across parts and hands. The relevant hypotheses are:

$$H_0: \mu_T / \mu_R > 1.25 \text{ or } \mu_T - 1.25\mu_R > 0$$

$$H_1: \mu_T / \mu_R \leq 1.25 \text{ or } \mu_T - 1.25\mu_R \leq 0$$

where μ_T is the expected value of the mean amount recovered for the test and μ_R is the expected value of the mean amount recovered for the reference.

Reviewer's comment: The study design, sample size, and inclusion criteria are acceptable. The focus of our review was Teva's product itself, not the comparison to the RLD.

7.2.3. Study Results

Table 7.2.3 Discontinued Subjects

Subject No.	Reason	Gender	Age	Race*
21	Subject withdrew consent prior to Period II check-in due to schedule conflict	Male	25	W
40	Subject withdrew consent prior to Period II check-in due to schedule conflict	Male	19	W

Table 7.2.4 Summary of Subject Disposition by Sequence

	Sequence		Total
	AB	BA	
Subjects Randomized	24	24	48
Subjects Who Successfully Completed the Study	22	24	46
Subjects Who Withdrew Consent	2	0	2
Subjects Discontinued by the Sponsor	0	0	0
Subjects Excluded from Statistical Analysis	5	4	9

Table 7.2.5 Summary of Subject Disposition by Study Period

	Total	Period I	Period II
Number of Subjects Randomized	48	48	46
Number of Subjects Who Completed the Period/Study	46	48	46
Number of Subjects Discontinued by Medical Investigator	0	0	0
Number of Subjects Discontinued by the Sponsor	0	0	0
Number of Subjects Who Withdrew Consent	2	0	2

Table 7.2.6 Summary of Demographic Data

Parameters	All Subjects N = 39
Age	28.3 (18 – 57)
Weight (lbs)	187.3 (116.0 – 276.0)
Height (in.)	70.8 (64.1 – 77.2)
BMI	26.2 (19.1 – 33.5)
Race	
Asian	--
African American:	--
Native Hawaiian or Other Pacific Islander	--
American Indian or Alaskan Native	--
White	39 (100.0 %)

Wash-off Results

The results of this study demonstrated that Teva's Testosterone Gel, 1% is statistically non-inferior to Androgel®, 1% with regard to the amount of residual testosterone remaining on the hands following a hand-washing procedure. The current product monograph of RLD Androgel® instructs patients to wash their hands immediately with soap and water after applying Androgel® in order to minimize the potential for secondary exposure to testosterone.

Table 7.2.7 Summary of Non-Inferiority Testing

Test Product (A) vs. Reference Product (B) (N = 39)	
Point Estimate $\mu_A - 1.25\mu_B$	Upper Bound of 95% CI
-73.53	-43.46

Reviewer's comments: For the TEVA product and for AndroGel 1%, a total of 285 µg and 287 µg (<0.3 mg) of testosterone, respectively, remained on the hands following application of 100 mg testosterone to the arms/shoulders and then hand-washing. This demonstrates that very little testosterone is left on the hands after application to the sites and hand-washing.

Table 7.2.8 Residual T (µg) from Hand Washing Study (N=39)

	Test Product (A) (Batch # X145)	AndroGel (B) (batch # 31848)
Mean	285	287
Max	593	547
Min	62	99
Medium	272	238

Safety Results:

Table 7.2.9 Extent of Exposure for All Dosed Subjects

Subjects Who Completed the Study			
Subject No.	Total Number Doses Taken	Treatment Dose	Total Exposure
01 – 20, 22 – 39, 41 – 48	4 (2 in each period)	5 grams per application for a total of 10 grams per period	20 grams
Discontinued Subjects			
Subject No.	Total Number Doses Taken	Treatment Dose	Total Exposure
21, 40	2 (2 in each period)	5 grams per application for a total of 10 grams per period	10 grams

Table 7.2.10 Disposition of All Dosed Subjects by Treatment

	Treatment	
	A	B
Number of subjects who received study treatment	48	46
Number of subjects who withdrew consent*	2	0
Number of subjects who withdrew due to AEs*	0	0
Number of subjects who were discontinued per investigator and/or sponsor due to AEs	0	0
Number of subjects with AEs	0	1
Total number of AEs	0	1

* AEs and discontinuations are classified by the last treatment the subject received. For example, the subject could enter Period II and discontinue *before dosing in that period*; the treatment under which this instance is recorded would be that which was administered in Period I. Totals represent all subjects dosed with the specific treatment.

Treatment A: Testosterone gel 1% w/w (Batch #: X145); Treatment B: AndroGel® 1% (Lot #: 31848)

No serious adverse events (SAEs) were reported over the course of this study. One (1) subject experienced one AE over the course of the study. The adverse event was moderate in intensity. Subject #23 experienced a joint sprain prior to Period II activities that was deemed as having no reasonable possibility of being related to the administration of study drug. No subject was discontinued due to an AE.

Reviewer's Additional Comments:

- 1) **The optimal primary endpoint of a hand washing study would be the comparison between the residual testosterone amount on the hands after application but prior to hand-washing and after hand-washing. However, the design of the hand-washing study did not include measurement of residual testosterone on the subjects' hands after applying the drug product to the application site but before hand-washing. Therefore, it is not possible to measure the percentage of the testosterone removed by the hand washing procedure (a "wash-off percentage").**
- 2) **From both the Sponsor's non-inferior analysis comparing test product with RLD, and the measurements of absolute amount of wash-off testosterone, it may be concluded that the Sponsor's test product appeared sufficiently removed from the hands since very little testosterone was left on the hands following applying the test product to the site and then a hand washing procedure.**
- 3) **Although very little product remained on the hands after washing, it is not known if the same result would occur after washing the application site. A "wash-off percentage" washing study to assess the degree to which testosterone may be removed from the application site by washing is not considered necessary prior to approval. However, the "wash-off percentage" washing study at application sites should be conducted as a postmarketing requirement (PMR).**

7.3. Review of Bioavailability Transfer Study (Study No. M1FX10001)

7.3.1. Study Title

A Study Comparing The Transfer Of Testosterone Gel 1% Manufactured By Cipla Ltd. For TEVA Pharmaceuticals USA To Androgel® 1% By Solvay Pharmaceuticals From A Male Subject To A Female Subject

7.3.2. Study Design

7.3.2.1. Study Objectives: This study assessed the relative bioavailability of Testosterone 1% gel by TEVA Pharmaceuticals USA compared to that of AndroGel® 1% testosterone gel by Solvay Pharmaceuticals in healthy female subjects following direct transfer from healthy male subjects who received a single topical dose (2 x 5 g of gel for a total of 100 mg testosterone). Transfer from males with a T-shirt and without a T-shirt was assessed.

7.3.2.2. Study Methodology:

This was an open-label, single-dose, randomized, 4-period, 4-treatment crossover study. The total duration of the study, screening through study exit, was approximately 12 weeks with at least a 7-day washout period between doses. At study check-in, female subjects reported to the

clinical site on Day -2 at least 48 hours prior to dosing and stayed for 26 hours after dosing of the male subjects (i.e. Day 2, 24 hours after dose transfer). Male subjects reported to the clinical site on Day -1 at least 10 hours prior to Day 1 dosing and stayed for at least 4 hours after dosing (Day 1). Male subjects were to be unclothed from the waist up (without T-shirts) except for Treatments B and D. For Treatments B and D (with T-shirts), male subjects were to be given a 100% cotton long-sleeved T-shirt (heavy weight 6.1 oz) provided by the site to wear that fully covered the application sites. Starting at 2 hours after dosing, each couple was to engage in total of 15 minutes of contact in a vertical position. Blood sample collections were obtained on Day -1 from female subjects at pre-dose, 2, 4, 6, 8, 10, 12, 16 and 24 hours. These sampling times were relative to the time of dose transfer on Day 1 such that the sampling schedule on Day -1 was parallel to the sampling schedule on Day 1. On Day 1 blood samples were collected from females subjects within 10 minutes prior to dose transfer (0 hour) and after dose transfer at 2, 4, 6, 8, 10, 12, 16 and 24 hours. One single sample was to be collected to represent both the Day -1, 24 hour sample and the Day 1, 0 hour sample. A total of 17 blood samples were collected per period x 4 study periods for a total of 68 samples or 408 mL total volume.

Table 7.3.1 Identity of Products and Treatment

Product	Test	Reference
Treatment ID	A and C	B and D
Product Name	Testosterone gel 1% w/w	AndroGel® 1%
Batch/Lot No.	X145	31848
Dose Administered	5 grams x 2	5 grams x 2

7.3.2.2. Number of Subjects (Planned and Analyzed): The total sample size for this study was 96 subjects (48 couples: 48 males and 48 females). Sufficient numbers of volunteers were screened to enroll 96 subjects. Serum concentration data from a total of 47 female subjects were included in the statistical analysis for A vs. C, and 43 female subjects were included in the statistical analysis for B vs. D.

7.3.2.3. Main Criteria for Inclusion: All subjects were volunteers between the ages of 18 and 65, who met the requirements for BMI and testosterone levels, who were demonstrated to be generally healthy by screening medical and medication history, physical examinations, 12-lead electrocardiogram, and clinical laboratory testing. Volunteers were also willing to refrain from excessive consumption of sodium in food or beverages and caffeine/xanthine 48 hours prior to dosing and throughout the study, as well as willing to shower with standard soaps/cleansers provided by the clinic during the confinement periods.

7.3.2.4. Duration of Treatment: The male subjects received 1 topical application of test or reference drug over an 8-week period with a 7-day washout period between dosing periods. Total study participation, exclusive of screening, was 8 weeks.

7.3.2.5. Criteria for Evaluation: Comparison of transfer from males to females. The primary pharmacokinetic parameters of the unadjusted C_{max} and AUC_{0-t} were transformed to their natural logarithms. To be considered comparable, transfer from the Test formulation should be within

20% of the transfer from the Reference formulation. Criteria for transfer comparability were met if the test/reference ratio of geometric means of $C_{\max}$ and AUC_{0-t} , and their 90% confidence intervals were all contained in the interval 80.00 to 125.00% for total testosterone. Ratios were derived to compare Treatment A/Treatment C and Treatment B/Treatment D. Additionally, from a safety point of view, transfer from the Test formulation that was less than the transfer from the Reference formulation was acceptable.

7.3.2.6. Safety: All subjects were monitored throughout the confinement portions of the study. Seated blood pressure, heart rate, respiratory rate, and temperature were measured at screening and at study exit. Seated blood pressure and pulse were measured prior to dosing at check-in and 1 (± 0.5), 2 (± 0.5), and 4 (± 0.5) hours after each dose for males. While dose application was present on the male, vitals were taken from the contra-lateral arm. For females, seated blood pressure and heart rate were measured prior to dosing at check-in and 1 (± 0.5), 2 (± 0.5), 5 (± 0.5), 12 (± 1) and 24 (± 1) hours after the start of contact with the male subject. Volunteers were queried for problems prior to dosing (*i.e.* conditions which would not have prevented them from study participation, but could have potentially been exacerbated by the test or reference products) at screening and check-in; and, as subjects they were queried for adverse events at check-in for each period, during the confinement portions of the study, and at study exit (or early termination). All subjects underwent clinical laboratory testing at screening, including hematology, biochemistry, urinalysis, urine drug screen, ethyl alcohol, testosterone, and for females only, a FSH (if necessary to document post-menopausal status) and serum pregnancy test. Male subjects underwent PSA testing at screening and at study exit/early termination. Urine drug, serum pregnancy (females only) and testosterone testing were repeated at check-in of each period. Clinical laboratory testing (hematology, biochemistry, and urinalysis) was repeated at study exit/early termination. Additionally, physical examinations were performed at Period I check-in if not done at screening and at study exit/early termination.

7.3.2.8. Statistical Methods: The analytical data were used to calculate the pharmacokinetic parameters: AUC_{0-t} , $C_{\max}$ and $T_{\max}$. Statistical analyses were to be performed for baseline-unadjusted and baseline-adjusted total testosterone serum concentration data. Additionally, statistical analyses were performed for dose-normalized total testosterone serum concentration. An Analysis of Variance was used to evaluate the pharmacokinetic parameters for differences due to group, sequence, period within group, formulation and formulation by group interaction as a fixed effect and subjects within group by sequence as a random effect. The statistical analyses were completed using the SAS® appropriate procedure

Reviewer's comment: The study design, sample size, inclusion criteria, duration of treatment appeared to be acceptable. The DRUP review focused on the comparison of PK parameters between subjects wearing T-shirts vs. subjects without T-shirt for the test product itself, not the comparison between the test product vs. RLD.

7.3.3. Study Results

7.3.3.1. Demographic Results:

Table 7.3.2 Summary of Demographic Data: Treatment Groups

		Study Subject			
		Treatment Groups (A vs. C)		Treatment Groups (B vs. D)	
		Test Product N=47 ¹	Reference Product N=47 ¹	Test Product N=43 ¹	Reference Product N=43 ¹
Age (years)	Mean ± SD Range	40.4±8.5 26-60	40.4±8.5 26-60	41.0±8.3 27-60	41.0±8.3 27-60
Age Groups	< 18	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	18 – 39	23 (48.9%)	23 (48.9%)	20 (46.5%)	20 (46.5%)
	40 – 64	24 (51.1%)	24 (51.1%)	23 (53.5%)	23 (53.5%)
	65 – 75	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	> 75	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Sex	Male	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Female	47 (100%)	47 (100%)	43 (100%)	43 (100%)
Hispanic or Latino Race	N	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	A	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	B	1 (2.1%)	1 (2.1%)	1 (2.3%)	1 (2.3%)
	I	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	W	45 (95.7%)	45 (95.7%)	41 (95.3%)	41 (95.3%)
Not Hispanic or Latino Race	N	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	A	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	B	1 (2.1%)	1 (2.1%)	1 (2.3%)	1 (2.3%)
	I	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	W	0 (0%)	0 (0%)	0 (0%)	0 (0%)
BMI	Mean ± SD	26.9±3.5	26.9±3.5	27.2±3.3	27.2±3.3
	Range	18.5-33.8	18.5-33.8	20.6-33.8	20.6-33.8

¹Subjects used in final statistical report. RACE: American Indian or Alaskan Native N; Asian A; Black or African American B; Native Hawaiian or Other Pacific Islander I; White W.

7.3.3.2. Pharmacokinetic Results:

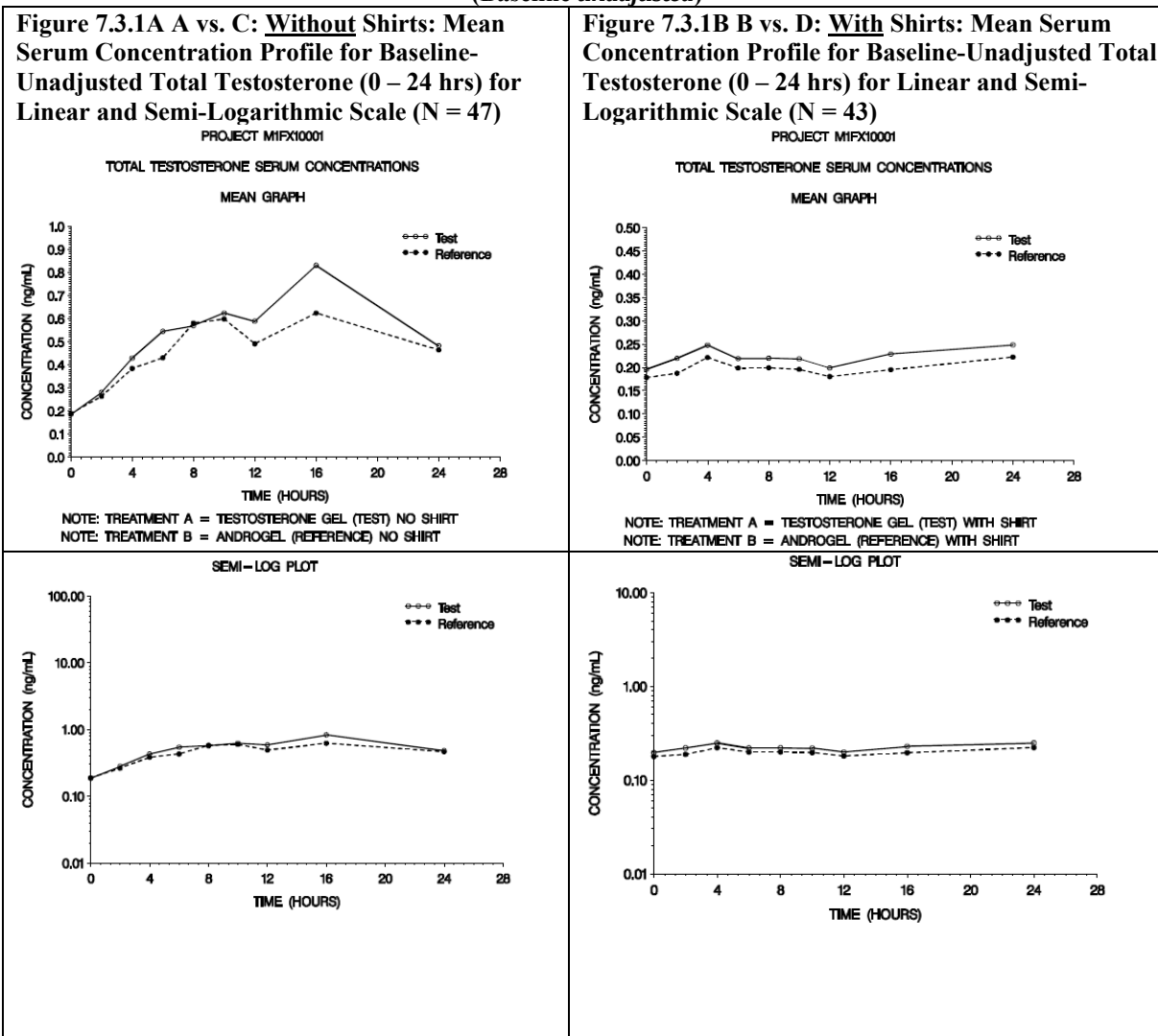
**Table 7.3.3 Summary of Statistical Analysis for Baseline-*Unadjusted*,
Total Testosterone Concentrations in Females**

Non-Transformed Total Testosterone Concentrations : Baseline- <i>Unadjusted</i> Data					
PK Variable	Geometric Least Squares Means			90% Confidence Interval	Intra-subject variability (%)
	Test	Reference	% Ratio		
Without Shirt (N=47) Testosterone Gel 1% (A) vs. AndroGel 1% (C)					
AUC _{0-t} (ng·h/dL)	1370	1175	116.54	97.82-135.26	49.4
C _{max} (ng /dL)	101	89.28	113.26	85.53-141.00	74.2
T _{max} (h)	11.51	12.73	90.43	78.08-102.78	37.0
With Shirt (N=43) Testosterone Gel 1% (B) vs. AndroGel 1% (D)					
AUC _{0-t} (ng·h/dL)	533	478	111.41	97.22-125.60	36.5
C _{max} (ng /dL)	28.7	24.5	116.90	101.01-132.79	39.9
T _{max} (h)	13.90	1304	107.23	83.26-131.21	63.0

**Table 7.3.4 Summary of Statistical Analysis for Baseline-*Unadjusted*, Dose-
Normalized Total Testosterone**

Non-Transformed Total Testosterone Concentrations: Baseline- <i>Unadjusted</i> , <u>Dose-</u> <u>Normalized</u> Data					
PK Variable	Geometric Least Squares Means			90% Confidence Interval	Intra-subject variability (%)
	Test	Reference	% Ratio		
Without Shirt (N = 47) Testosterone Gel 1% (A) vs. AndroGel 1% (C)					
AUC _{0-t} (ng·h/dL)	139	125	111.05	92.88-129.22	49.1
C _{max} (ng /dL)	10.2	9.5	108.02	81.10-134.94	73.9
T _{max} (h)	11.51	12.73	90.43	78.08-102.78	37.0
With Shirt (N = 43) Testosterone Gel 1% (A) vs. AndroGel 1% (C)					
AUC _{0-t} (ng·h/dL)	53.8	50.9	105.89	92.31-119.46	35.9
C _{max} (ng /dL)	2.9	2.6	110.90	95.64-126.16	39.4
T _{max} (h)	13.99	13.04	107.23	83.26-131.21	63.0

Figures 7.3.1 Without T-Shirt (A and C) vs. With T-Shirt (B and D)
(Baseline *unadjusted*)



Figures 7.3.2 Without Shirts (A and C) vs. With Shirts (B and D)
(Baseline-Unadjusted, Dose- Normalized)

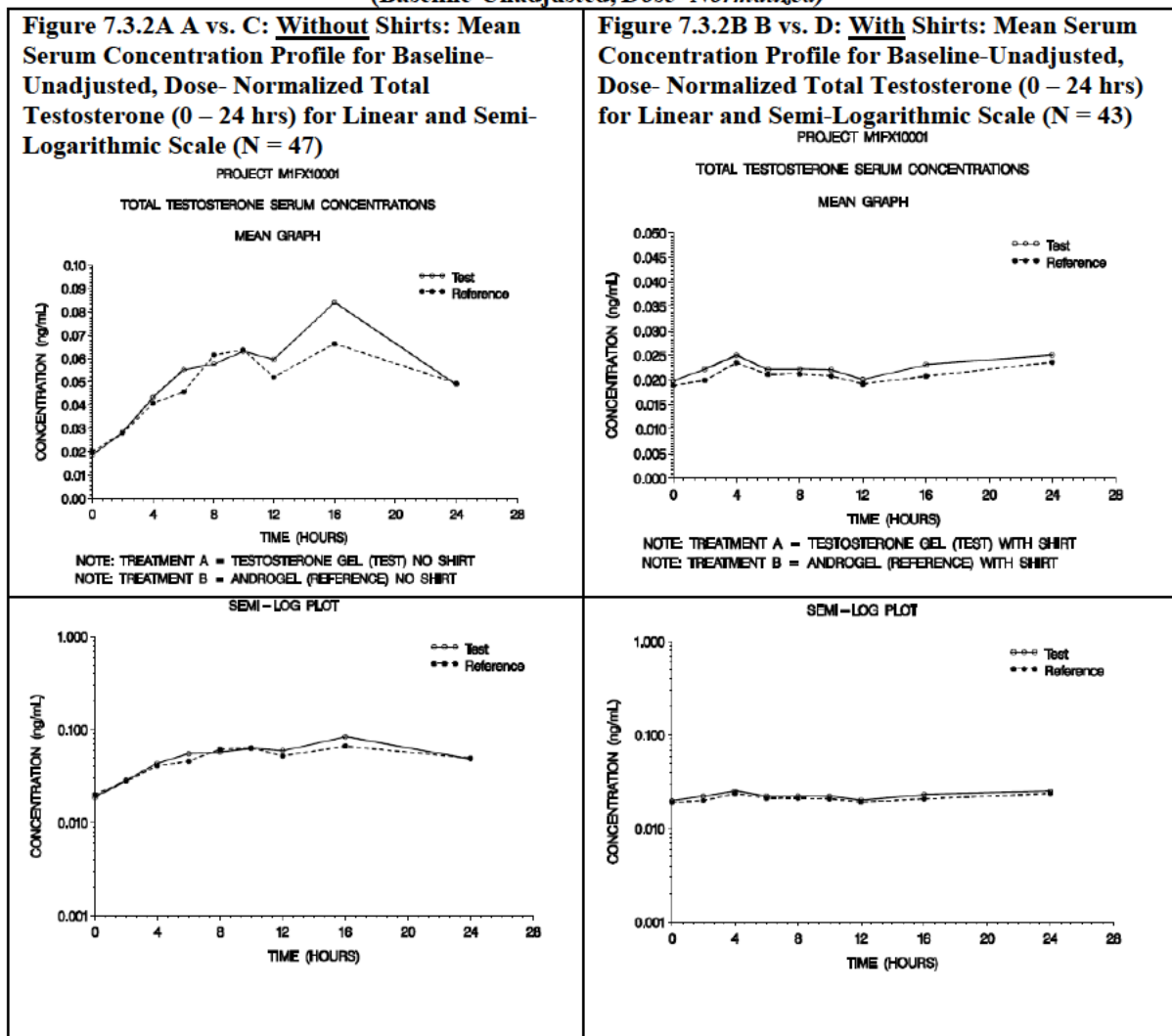


Table 7.3.5 Teva Testosterone Gel (Test Products A and C) - % Difference of Testosterone C_{max} and AUC_{0-t} Post-Transfer vs. Pre-Transfer With / Without T-Shirt

Parameter (Mean±SD)	Without T-Shirt (N = 47)			With T-Shirt (N = 43)		
	24-hr Pre-Transfer	24-hr Post-Transfer	% Difference	24-hr Pre-Transfer	24-hr Post-Transfer	% Difference
C_{max} (ng/dL)	27.4±18	102±86	+272	24.5±17	28.3±16	+15.5
AUC_{0-t} (ng•h/dL)	462±184	1378±984	+198	478±275	530±322	+10.8

Without T-shirt study showed that both products did “transfer” to females. For Teva testosterone gel:

- AUC_{0-t} (the extent of exposure) determined that when comparing at post-rubbing to at baseline, the AUC_{0-t} increased almost 200%.
- C_{max} (the rate of exposure) determined that when comparing at post-rubbing to at baseline, the C_{max} increased 272%.

With T-shirt study showed that “transfer” to females was considerably mitigated for both products. For Teva testosterone gel:

- AUC_{0-t} (the extent of exposure) determined that when comparing at post-rubbing to at baseline, the AUC_{0-t} increased by approximately 11%.
- C_{max} (the rate of exposure) determined that when comparing at post-rubbing to at baseline, the C_{max} increased by 15.5%.

Reviewer’s comment: The study’s design, execution and the results appear generally acceptable. It was determined through this study that the transfer of testosterone from the test product T gel to women and children can be effectively mitigated by use of a T-shirt, and this appears to be the case for both test product and RLD product.

7.3.3.3. Safety Results:

7.3.3.3.1. Extent of Exposure

Table 7.3.6 Extent of Exposure for All Dosed Subjects

Subjects Who Completed the Study			
Subject No.	Total Number Doses Taken	Treatment Dose	Total Exposure
Treatments A and C			
01 – 23, 25 – 48	2	2 × 5 g gel	20 g
Treatment B and D			
01, 03 – 19, 21 – 23, 25 – 37, 39 – 46, 48	2	2 × 5 g gel	20 g
Discontinued Subjects			
Subject No.	Total Number Doses Taken	Treatment Dose	Total Exposure
24	1	2 × 5 g gel	10 g
38, 47	2	2 × 5 g gel	20 g
02, 20	3	2 × 5 g gel	30 g

Table 7.3.7 Disposition of All Dosed Subjects by Treatment

	Treatment			
	A	B	C	D
Number of subjects who received study treatment	94	92	94	86
Number of subjects who withdrew consent*	0	0	0	0
Number of subjects who withdrew due to AEs*	0	0	0	0
Number of subjects who were discontinued per investigator and/or sponsor due to AEs	0	1	0	0
Number of subjects with AE	5	3	3	2
Total number of AEs	6	3	4	3

*AEs and discontinuations are classified by the last treatment the subject received. For example, the subject could enter Period II and discontinue *before dosing in that period*; the treatment under which this instance is recorded would be that which was administered in Period I. Totals represent all subjects dosed with the specific treatment.

Treatment A: 2 x 5 g of Testosterone Gel 1% without a T-shirt (Lot #: X145);

Treatment B: 2 x 5 g of Testosterone Gel 1% with a T-shirt (Lot #: X145);

Treatment C: 2 x 5 g of Androgel® 1% without a T-shirt (Lot #: 31848);

Treatment D: 2 x 5 g of Androgel® 1% with a T-shirt (Lot #: 31848).

7.3.3.2. Adverse Events

12 subjects experienced a total of 16 AEs across all treatments over the course of the study. The AEs were all mild in severity, with the exception of pregnancy experienced by Subject #24; the severity of this AE is not applicable. No SAEs were reported. A total of 6 mild AEs occurred in subjects after they received Treatment A. A total of 3 AEs occurred in subjects after they received Treatment B, with the exception of pregnancy experienced by Subject #24, the other 2 AEs were mild in severity. There were no reported complications of the pregnancy. A total of 4 mild AEs occurred in subjects after they received Treatment C. A total of 3 mild AEs occurred in subjects after they received Treatment D.

Overall, the most common AE reported was headache. Headache occurred on at least one occasion in four subjects (4.17%) and generally was considered by the investigator to be probably related to the treatment. Headache was reported by three subjects (3.19%) after administration of Treatment A, one subject (1.09%) after administration of Treatment B, and one (1.06%) subject after administration of Treatment C.

Table 7.3.8 Frequently Reported Adverse Events by Treatment Arm

Adverse Event (AE) MedDRA SOC / Preferred Term	Treatment Arm			
	Treatment A (N=94)	Treatment B (N=92)	Treatment C (N=94)	Treatment D (N=86)
Nervous system disorders				
Headache	3 (3.19%)	1 (1.09%)	1 (1.06%)	0

7.3.4. Study Conclusions

The data showed that overall percent difference of the PK parameters for female subjects was much lower when male subjects were wearing a T-shirt during the rubbing procedure than without a T-shirt, indicating that there is significantly less exposure to testosterone when a T-shirt is covering the application site.

Reviewer's Comments: Data from periods without a T-shirt showed that both products did "transfer"; but data from periods with a T-shirt showed that "transfer" was minimal (effectively mitigated by a T-shirt).

7.4 Overall Safety Conclusions

This reviewer concludes that

- No irritation effects of clinical significance and sensitization reactions were determined from subjects who applied testing Teva T gel 1% in the submitted irritation and sensitization study.
- The results from the enclosed hand washing study demonstrates that hand washing removed the majority of residual testosterone from the hands that involved in applying Teva T gel 1%, and helped reducing the potential interpersonal transfer of testosterone from this product.
- Through the enclosed transfer study it was determined that the transfer of testosterone gel product to women and children can be effectively mitigated by wearing a T-shirt for the Teva T gel (b) (4) product.

8 Postmarket Requirement

While the handwashing study in this NDA showed that only a minimal amount of residual T remains after hand washing, the review team believes that a study evaluating the effect of washing on removing residual T from the application site is necessary in addition to the handwashing study. The application site washing study will be useful to provide additional support for labeling indicating that washing the application site will limit the potential for interpersonal transfer. Therefore, a postmarketing requirement to conduct a handwashing study will be part of the action on this NDA.

The tentative dates for the proposed study are as following:

- Final Protocol Submission: 03/2012
- Study/Trial Completion: 08/2012
- Final Report Submission: 11/2012

9 Labeling

Labeling discussions were held with the entire review team from November 2011 through January 2012. Since this is a 505 (b)(2) application, the Sponsor has adapted the entire labeling from AndroGel 1%. Issues addressed during labeling discussions included, but were not limited to: presentation of the tradename (or lack of tradename), presentation of product strength and dose, presentation of the bioavailability and transfer study data, and reducing the risks of medication errors and interchanging Teva's testosterone gel with testosterone gels other than AndroGel 1%. Final draft FDA-editted labeling (PI and PPI) was conveyed to Sponsor on January 20, 2012 and January 24, 2012, respectively. Labeling discussions will continue.

10 Appendices

There are no Appendices in this review.

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

/s/

GUODONG FANG
01/26/2012

MARK S HIRSCH
01/26/2012
I concur.