OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: (b) (4)	Submission Date: June 12, 2007
Brand Name	AndroGel
Generic Name	Testosterone 1% Gel
Reviewer	Manoj Khurana, Ph.D.
Team Leader	Sally Y. Choe, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	Solvay Pharmaceuticals, Inc.
Submission Type	Supplemental New Drug Application
Formulation; Strength(s)	Testosterone Gel 1%

(b) (4)

1. Executive Summary

AndroGel® (testosterone gel 1%) has been approved for replacement therapy in adult males (> 18 years) for conditions associated with a deficiency or absence of endogenous testosterone (primary and secondary hypogonadism) (NDA 21-015). The current submission is a pediatric supplemental NDA for AndroGel (testosterone gel) 1% CIII that includes two clinical studies, UMD-01-080 and UMD-01-090. These studies were conducted in order to fulfill a Pediatric Written agreement (Pediatric Written Request). (b) (4)

1.1. RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) has reviewed the information provided in the supplement NDA (b) (4) This recommendation and the following comment should be sent to the sponsor as appropriate.

The sponsor should address and provide acceptable resolution of the deficiencies identified by the Division of Scientific Investigation's (DSI) audit on the total and free testosterone and dihydrotestosterone (DHT) data from Study UMD-01-080 and Study UMD-01-090.

1.2. PHASE IV COMMITMENTS

None

1.3. SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

The sponsor has conducted two clinical studies, UMD-01-080 and UMD-01-090.

Study UMD-01-080 was mainly aimed at evaluating the steady-state pharmacokinetics, safety, and tolerability of testosterone in adolescent boys with hypogonadism and CDGP. The following are the key findings of the review of Study UMD-01-080:

- Steady-state pharmacokinetics of total, free and bioavailable testosterone and total DHT was characterized in 17 adolescent boys after once daily application of 0.5 g, 1.5 g and 2.5 g testosterone gel 1% for 4 consecutive days.
- A dose-related increase in exposure ($AUC_{0\text{-}24,ss}$, $C_{max,ss}$, $C_{avg,ss}$) was observed for total and free testosterone with increasing doses of testosterone.

Study UMD-01-090 was conducted with an objective of evaluating the clinical response to testosterone gel 1% for the treatment of delayed puberty due to primary or secondary hypogonadism or CDGP, in boys of adolescent age. The following are the key findings of the review of Study UMD-01-090:

- Increases in serum testosterone concentrations were observed in boys diagnosed with delayed puberty due to primary or secondary hypogonadism or CDGP after treatment with testosterone gel 1% starting at a dose of 0.5 g with upward weekly titration.

- The most frequently used final doses were 0.5 g/day, 1.5 g/day, or 2.5 g/day in the hypogonadal population while the most frequently final dose used was 0.5 g/day in the CDGP population.
- The testosterone concentrations achieved in substantial proportion of subjects using the lowest dose of 0.5 g evaluated in the study exceeded the lower bound of the testosterone levels observed in normal adult males (~ 300 ng/dL).
- Two issues with the reliability of systemic exposure data from Study UMD-01-090 were identified. First, approximately half of subjects (41/86) evaluated in this study had less than 80% compliance for dosing. Secondly, ~50% of subjects (n=43) received doses using the (b) (4) pump that delivered doses in (b) (4) g increments instead of the intended (b) (4) pump that should have delivered doses in (b) (4) increment. It appears that this deficiency was identified very late in the trial (May 2005), where the trial was initiated in June 2002.

(b) (4)

While this review was being compiled, the DSI completed its audit of the analytical portion of the Study UMD-01-090 conducted (b) (4) The DSI audit identified and reported serious deficiencies with the validation and analytical runs for the assay of total testosterone, free testosterone and DHT (See DSI MEMO Dated 20th NOV 2007). Based on the DSI findings, the assay validity is not acceptable unless the sponsor appropriately addresses the deficiencies. Because the UMD-01-080 study utilized the same assay validation and the same (b) (4) laboratory as the UMD-01-090 study, the reliability of data obtained from this study also falls under the same uncertainty.

Therefore, the systemic exposure data of total and free testosterone and DHT from both clinical studies, UMD-01-080 and UMD-01-090, are inconclusive pending an acceptable resolution of the deficiencies identified by DSI and the issues identified with the data resulting from UMD-01-090 study conduct.

2. QBR

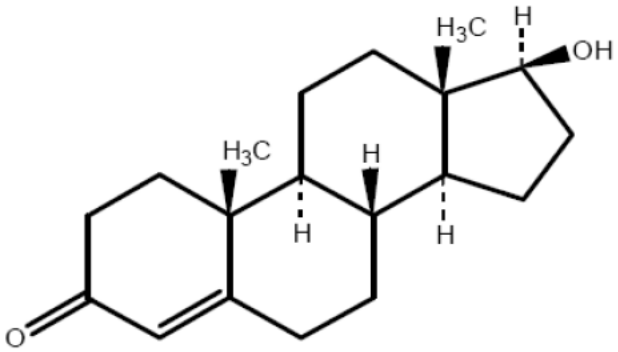
2.1. GENERAL ATTRIBUTES

2.1.1 What relevant regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

In 2000, AndroGel® (testosterone gel) was approved for replacement therapy in adult males (> 18 years) for conditions associated with a deficiency or absence of endogenous testosterone (primary and secondary hypogonadism) (NDA-21-015). Sponsor submitted this supplemental NDA that includes two clinical pharmacology studies, Studies UMD-01-080 and UMD-01-090, which were conducted to fulfill a Pediatric Written agreement (Pediatric Written Request) to gather data on testosterone gel 1% for treatment of delayed puberty in adolescent boys. (b) (4)

2.1.2 What are the description and composition of the drug products?

AndroGel® (testosterone gel) 1% (pediatric) is a clear, colorless hydroalcoholic gel containing 1 % testosterone.
The active pharmacologic ingredient in AndroGel® is testosterone. Testosterone USP is a white to practically white crystalline powder chemically described as 17-beta hydroxyandrost-4-en-3-one.



Testosterone

$C_{19}H_{28}O_2$ MW 288.42

The components and composition information including function and quality of each component for the manufacture of AndroGel® (testosterone gel) 1% CIII for the pediatric population is provided in Table 1(a) and 1(b) below. Excipients used to manufacture the drug product are of USP/NF quality. The pediatric drug product components (b) (4)

(b) (4) are reportedly the same as that currently approved for the adult AndroGel® product.

Table 1(a) Components and Composition of the AndroGel® (testosterone gel) 1% CIII (Pediatric) Formulation-per (b) (4) Grams

Components	Amount	Function	Quality
Testosterone	1.00 g	Active Ingredient	USP
Isopropyl myristate	(b) (4)		NF
(b) (4)			NF
(b) (4) 980 NF			NF
(b) (4) NaOH			NF
Purified water			USP

Table 1(b) Batch Formula For AndroGel® (testosterone gel) 1% CIII (Pediatric) Formulation

Components	Amount per (b) (4) Grams	Amount Per (b) (4) Kg Batch
Testosterone	1.00 g	(b) (4)
Isopropyl myristate	(b) (4	
(b) (4) 980 NF		
(b) (4) NaOH		
Purified water		

Note: The items in italic are the changes made to the tables previously submitted in the NDA.

2.1.3 What are the changes that are being made?

The pediatric drug product which is the subject of this submission is the same as the approved adult AndroGel® drug product (approved NDA 21-015 AndroGel® (testosterone gel) 1% and AndroGel® NDA 21-015, Supplement (b) (4) and the subsequent amendments to Supplement (b) (4)). The key difference between the pediatric Androgel and the Adult Androgel is the use of a (b) (4) actuator for the pediatric population compared to a 1.25 g actuator for the adult population. The container closure system for the pediatric application consists of a multi-dose pump (b) (4)

(b) (4)

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1. What are the pharmacokinetic characteristics of topically applied testosterone?

The following information comes from the AndroGel label:

Absorption:

(b) (4)

The skin serves as a reservoir for the sustained release of testosterone into the systemic circulation. Approximately 10% of the testosterone dose applied on the skin surface from AndroGel is absorbed into systemic circulation. Therefore, (b) (4) 5 g and 10 g of AndroGel systemically deliver approximately 5 mg and 10 mg of testosterone, respectively. In a study with 10 g of AndroGel (b) (4) all patients showed an increase in serum testosterone within 30 minutes, and eight of nine patients had a serum testosterone concentration within normal range by 4 hours after the initial application. Absorption of testosterone into the blood continues for the entire 24-hour dosing interval. Serum concentrations approximate the steady-state level by the end of the first 24 hours and are at steady state by the second or third day of dosing.

Distribution

Circulating testosterone is (b) (4) bound in the serum to sex hormone-binding globulin (SHBG) and albumin. (b) (4)

Approximately 40% of testosterone in plasma is bound to SHBG, 2% remains unbound (free) and the rest is bound to albumin and other proteins.

Metabolism

There is considerable variation in the half-life of testosterone as reported in the literature, ranging from 10 to 100 minutes. Testosterone is metabolized to various 17-keto steroids through two different pathways. The major active metabolites of testosterone are estradiol and dihydrotestosterone (DHT). (b) (4)

Excretion

About 90% of a dose of testosterone given intramuscularly is excreted in the urine as glucuronic and sulfuric acid conjugates of testosterone and its metabolites; about 6% of a

dose is excreted in the feces, mostly in the unconjugated form. Inactivation of testosterone occurs primarily in the liver.

2.2.2. What are the clinical studies used to support dosing or claims and what are their design features?

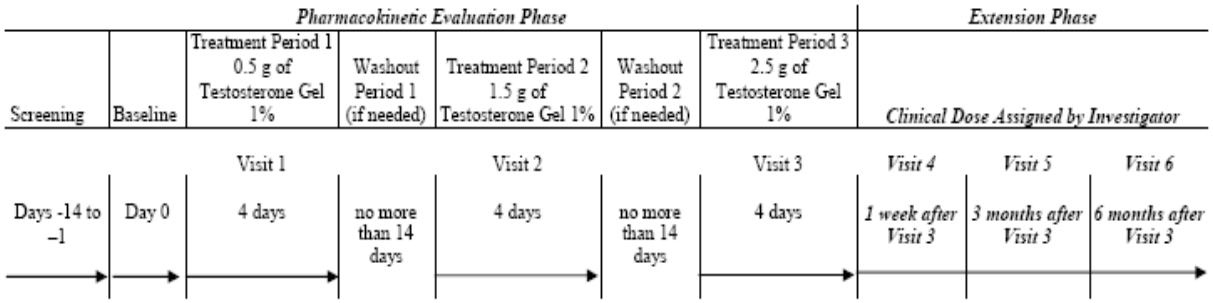
Sponsor conducted two clinical studies; UMD-01-080 and UMD-01-090 to fulfill a Pediatric Written agreement (Pediatric Written Request) to gather data on testosterone gel 1% for treatment of delayed puberty in adolescent boys.

2.2.2.1 Study UMD-01-080

This was a Phase I, open-label, escalating-dose study conducted in adolescent males (aged 13 to 17 years) to evaluate the safety and steady-state serum testosterone concentrations and PK characteristics following daily applications of three different doses of testosterone gel.

The study was conducted in six study centers in the US. Up to 18 subjects were planned and 17 subjects were enrolled and analyzed for safety. Diagnosis and the main criterion for inclusion was delayed puberty in adolescent males due to hypogonadotropic hypogonadism (secondary hypogonadism), hypergonadotropic hypogonadism (primary hypogonadism), or CDGP.

As illustrated in Figure below, there were three treatment periods during which subjects applied one of three escalating doses of testosterone gel 1% (0.5 g, 1.5 g, and 2.5 g containing 5 mg, 15 mg, and 25 mg of testosterone, respectively) for four consecutive days. Each treatment period was separated by a washout period of up to 14 days. A total of 17 subjects were treated with testosterone gel 1% at doses of 0.5 g and 1.5 g. In addition, 13 subjects were also treated with testosterone gel 1% at a dose of 2.5 g. Four subjects did not complete the 2.5g/day dose treatment period due to achieving serum testosterone values > 200 ng/dL, which was a pre-defined upper limit in the protocol for terminating dosing. This upper limit was later eliminated from the study.



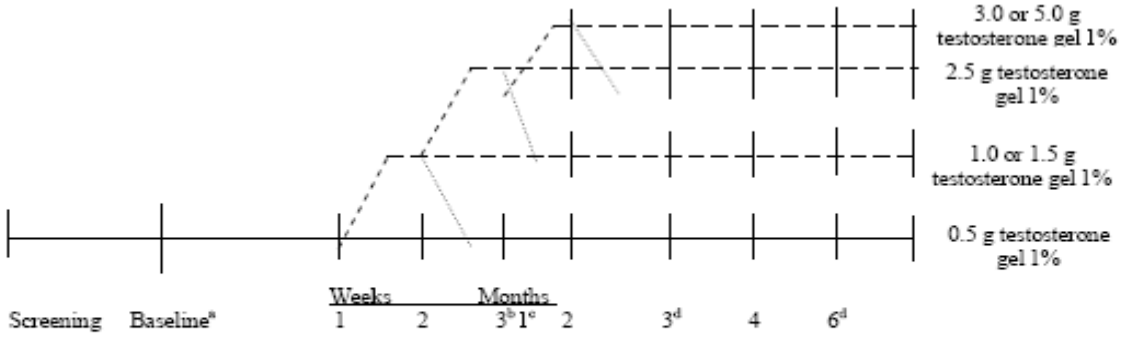
2.2.2.2 Study UMD-01-090

This was a Phase II, open-label, observational study to evaluate the clinical response to testosterone gel 1% for the treatment of delayed puberty in adolescent males (aged 13 to 18 years) with primary or secondary hypogonadism or CDGP.

The study was conducted in 18 study centers in the US. Up to 70 subjects were planned and 86 subjects were enrolled and analyzed for safety. Diagnosis and the main

criterion for inclusion was delayed puberty in adolescent males due to secondary hypogonadism, primary hypogonadism, or adolescent males with CDGP. For all enrolled subjects, whether testosterone naive or testosterone non-naive, the subject's dose of testosterone gel 1% was evaluated by the investigator during the initial three weeks of the study and could be titrated based on the investigator's clinical judgment, with the goal of attaining an appropriate target serum total testosterone range based on the boy's baseline stage of puberty.

All subjects were to begin treatment at a dose of 0.5 g of testosterone gel 1% once daily, applied at bedtime. During the initial three weeks of the study, a subject's dose of testosterone gel 1% could be increased in stepwise fashion to 1.5 g, 2.5 g, or 5.0 g of testosterone gel 1% daily. Once the desired serum testosterone concentration had been attained, no further dose titrations (increase) were to occur. Subjects were treated with testosterone gel 1% at doses of 0.5 g (86 subjects), 1.0 g (18 subjects), 1.5 g (53 subjects), 2.5 g (24 subjects), 3.0 g (1 subject), and 5.0 g (4 subjects), applied topically once daily for six months (the first three months per protocol UMD-01-090 and the subsequent three months per protocol UMD-01-090E).



[a] All subjects were to initially receive testosterone gel 1% 0.5 g daily
[b] Optional visit/dose for testosterone non-naive subjects only
[c] Week 4
[d] Month 3 [Protocol UMD-01-090 (Final Visit)] and Protocol UMD-01-090E (Final Visit) procedures were performed if a subject prematurely discontinued from the study (Early Termination Visit)

Evaluations included measurements of serum total testosterone concentrations and evaluation of achievement and maintenance of pubertal testosterone concentrations. Achievement of pubertal testosterone concentrations was defined as having a serum testosterone value greater than their Baseline value and maintenance of pubertal testosterone concentrations was defined as having two or more post-baseline serum testosterone values greater than their baseline value.

2.2.3 What are the clinical end points and how are they measured?

2.2.3.1 Clinical Outcome Measurements for Study UMD-01-080

Following primary and secondary assessments were done in prepubertal boys of adolescent age with insufficient testosterone production:

Primary:

- The steady-state serum total testosterone concentrations,

- the pharmacokinetic (PK) characteristics based on steady-state PK parameters determined from serum total testosterone concentrations,
- the safety and tolerability of testosterone gel 1%,

Secondary:

- Evaluation of the serum concentrations of free testosterone, bioavailable testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), SHBG, total DHT, and estradiol (E2)
- Evaluation of changes from Baseline in hematocrit, hemoglobin, and blood lipid concentrations;
- appearance of gynecomastia, skin irritation assessment,
- the incidence of treatment-emergent AEs (TEAEs)

2.2.3.2 Clinical Outcome Measurements for Study UMD-01-090

Following were the outcome measurements for this study:

- **Growth Velocity:** Height (cm) was measured at Screening, Baseline (Day 1), Months 1, 2, and 3 (or early termination visit) in Protocol UMD-01-090 and at Months 4 and 6 (or early termination visit) in Protocol UMD-01-090E. Height (without shoes) was measured by the same observer at each visit using a wall-mounted stadiometer. Three separate measurements of height were made.
  Growth velocity (Expressed as cm/year) = (Change in average height between two visits) / # days between the two visits

- **Testicular Volume:** Testicular volume (mL) was measured at Screening, Baseline (Day 1), Month 1, and Month 3 (or early termination visit) in Protocol UMD-01-090 and at Month 6 (or early termination visit) in Protocol UMD-01-090E. All sites were provided with a Prader orchidometer for measurements of testicular volume.

- **Tanner Pubic Hair Stage:** Tanner Pubic Hair Stage was assessed at Screening, Baseline (Day 1), Month 1, and Month 3 (or early termination visit) in Protocol UMD-01-090 and at Month 6 (or early termination visit) in Protocol UMD-01-090E.

- **Bone Maturation Age:** For subjects in Protocol UMD-01-090, bone age (years) was estimated from an x-ray of the left hand and wrist using the Gruelich & Pyle atlas by a central reader at Screening (Protocols UMD-01-080 or UMD-01-090) and at Month 6 in Protocol UMD-01-090E, or at the Final visit if the subject prematurely terminates from Protocol UMD-01-090, or did not continue onto Protocol UMD-01-090E.

- **Serum Hormone Concentrations:**
  Serum total testosterone concentrations (ng/dL) were obtained at the weekly titration visits (Weeks 1, 2, and 3 [optional]).

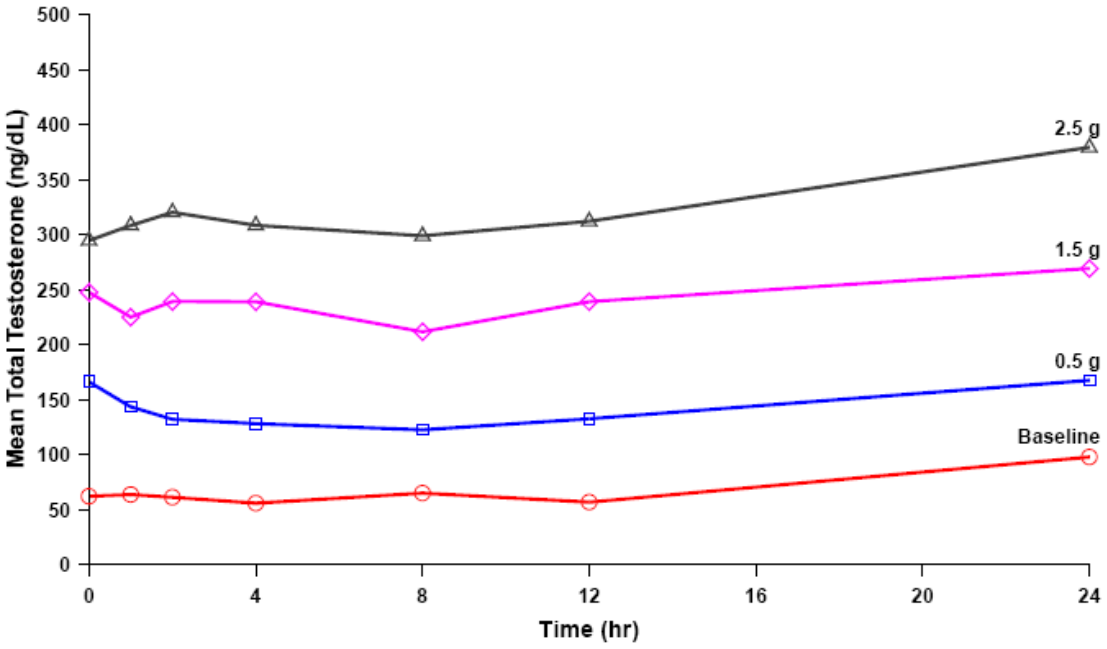
Serum concentrations (ng/dL) of total testosterone, free testosterone, bioavailable testosterone, total DHT, LH, FSH, E2, and SHBG were obtained at Baseline (Day 1), Months 1, 2, and 3 (or early termination visit) in Protocol UMD-01-090 and Months 4 and 6 (or early termination visit) in Protocol UMD-01-090E.

2.2.4 What are the pharmacokinetic characteristics of AndroGel in pediatric subjects?

2.2.4.1 Clinical Study UMD-01-080:

The pharmacokinetic (PK) characteristics of total testosterone, free testosterone and dihydrotestosterone were evaluated in Study UMD-01-080. Exposure was assessed from observed and baseline adjusted area under the curve from 0 to 24 hours ($AUC_{0-24,ss}$), maximum observed concentration over 24-hour dosing interval ($C_{max,ss}$), and the time-averaged concentration over the dosing interval, determined by $AUC_{0-24}/24$ ($C_{avg,ss}$).
The observed mean total testosterone concentrations on Day 4 after 4 days of daily administration of AndroGel (UMD-01-080) are presented in Figure 1 below:

Figure 1. Observed Mean total testosterone concentrations on Day 4 after 4 days of daily administration of AndroGel (UMD-01-080)



Following are the key pharmacokinetic properties of AndroGel observed from this Study:

- Observed median t_{max} for total testosterone ranged from 2 to 12.08 hours across the three treatment groups. Mean (Min, Max) $C_{max,ss}$ was 211.3 (64.0, 558), 361.0 (119, 927), 492.8 (188, 1270) ng/dL, respectively. Mean (Min, Max) $C_{avg,ss}$ was 140.5 (47.3, 450), 241.8 (87.8, 564), 326.0 (110, 692) ng/dL , respectively.

- Total testosterone $AUC_{0\text{-}24,ss}$, $C_{max,ss}$, and $C_{avg,ss}$ showed around 2-fold increase over a 5-fold increase in dose (5 mg to 25 mg) of testosterone, respectively. Similar results were observed for free testosterone.
- For total DHT, the observed median tmax ranged from 8 to 12 hours across the three treatment groups. $AUC_{0\text{-}24,ss}$, $C_{max,ss}$, and $C_{avg,ss}$ showed a 2.5-fold, 2.4-fold and 2.5-fold increase over a 5-fold increase in dose (5 mg to 25 mg) of testosterone, respectively.
- Over a 24 hour period, on average (Min, Max) there was an increase in total testosterone peak exposure of 137.3 (53.4, 333), 288.5 (80.2, 753) and 387.5 (105, 1250) ng/dL from baseline for 0.5, 1.5 and 2.5 g AndroGel dose, respectively.
- On average (Min, Max) there was an increase in total testosterone $C_{avg,ss}$ of 67.9 (-2.9, 129), 166.9 (0, 416) and 227.4 (0, 676) ng/dL from baseline for 0.5, 1.5 and 2.5 g AndroGel dose, respectively.
- A dose-related increase in exposure ($AUC_{0\text{-}24,ss}$, $C_{max,ss}$, $C_{avg,ss}$) was observed for total and free testosterone with increasing doses of testosterone. Although based on the statistical analysis the increase was not dose-proportional, there was no indication of departure from linear pharmacokinetics.
- Short term administration of 0.5 g, 1.5 g and 2.5 g doses of testosterone gel 1% did not change predose serum concentrations of FSH, LH, E2, and SHBG compared to baseline levels.

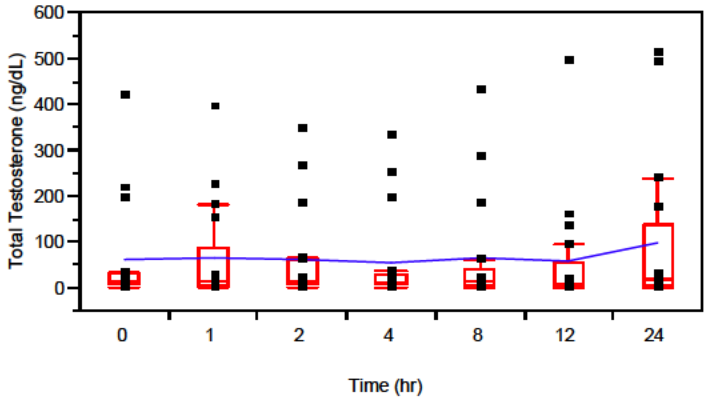
Reviewers Comments:

Although, in this study both subjects with hypogonadism (n=13) and CDGP (n=4) were evaluated and PK data was summarized for the two groups, the number of CDGP subject was small (n=4) to assess any meaningful differences in the PK of AndroGel in the two groups.

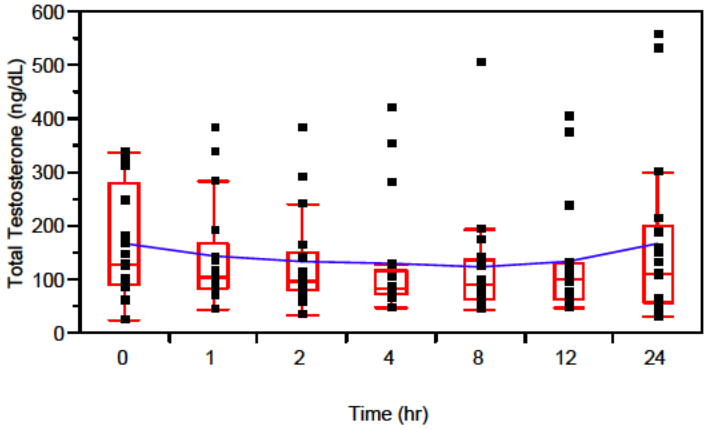
The mean concentration data have to be interpreted with caution as in some cases they are influenced by some extreme values in the data as depicted in the figures below. Figures 2 and 3 below depict the observed testosterone concentrations and baseline adjusted testosterone concentrations, respectively for each dose [Quantiles (box and whiskers) and mean (blue line)].

Figure 2. Total testosterone concentrations on Day 4 after 4 days of daily administration of AndroGel (UMD-01-080)

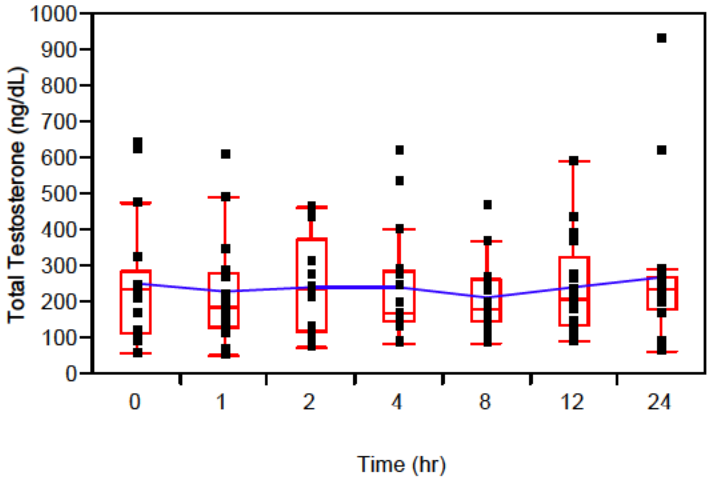
(a) Baseline



(b) 0.5 g dose



(c) 1.5 g dose



(d) 2.5 g dose

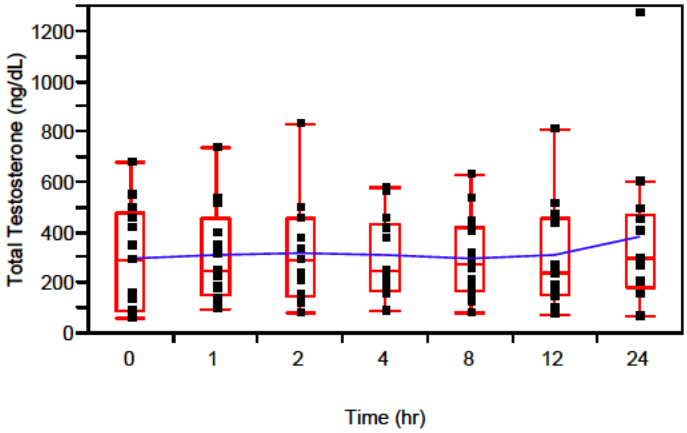
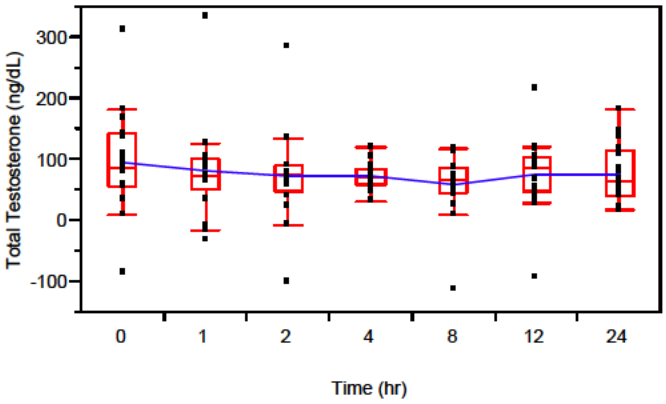
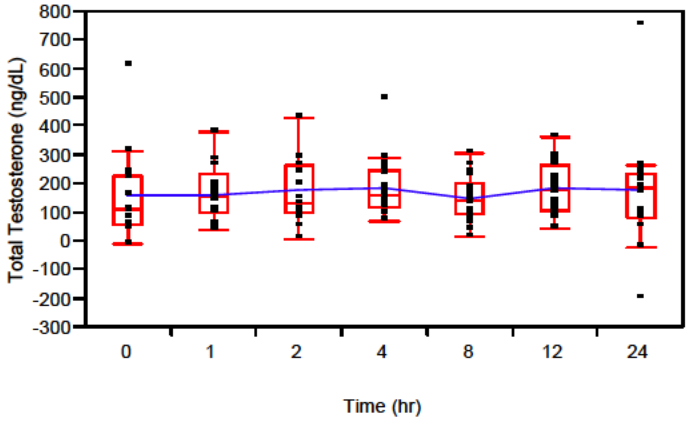


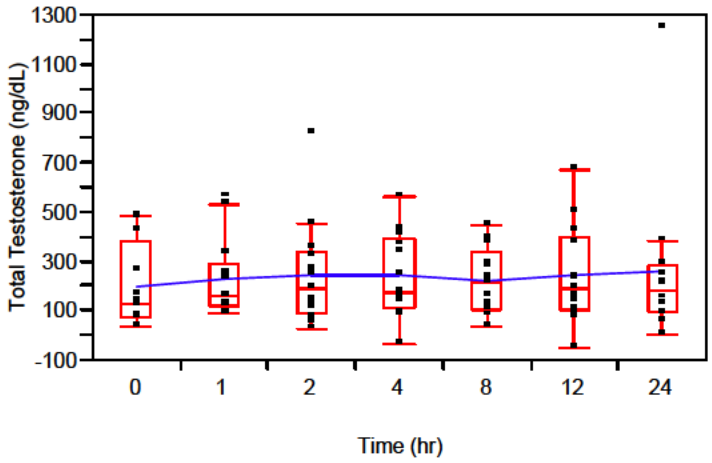
Figure 3. Mean change from baseline in total testosterone concentrations on Day 4 after 4 days of daily administration of AndroGel (UMD-01-080)
(a) 0.5 g dose



(b) 1.5 g dose



(c) 2.5 g dose



Statistical Analysis of Pharmacokinetic Parameters

Dose proportionality was assessed for both observed and Baseline-adjusted PK parameters for total testosterone and free testosterone. Dose-proportionality was evaluated across treatment groups using the power model. In order to assess departures from linear kinetics, a quadratic term was added to the evaluation with the power model. The results of the dose-proportionality are summarized in Table 2 below:

Table 2. Dose-proportionality of AndroGel formulation using observed PK parameters

		Slope			Intercept		
Analyte	Parameter	Estimate	95% Confidence Interval	p-value	Estimate	95% Confidence Interval	p-value
Total T	$AUC_{0\text{-}24,ss}$	0.552	(0.402, 0.702)	<.0001	8.300	(8.043, 8.556)	<.0001
	$C_{max,ss}$	0.545	(0.371, 0.719)	<.0001	5.537	(5.291, 5.783)	<.0001
Free T	$AUC_{0\text{-}24,ss}$	0.605	(0.432, 0.779)	<.0001	6.344	(6.039, 6.648)	<.0001
	$C_{max,ss}$	0.598	(0.391, 0.805)	<.0001	3.618	(3.309, 3.927)	<.0001

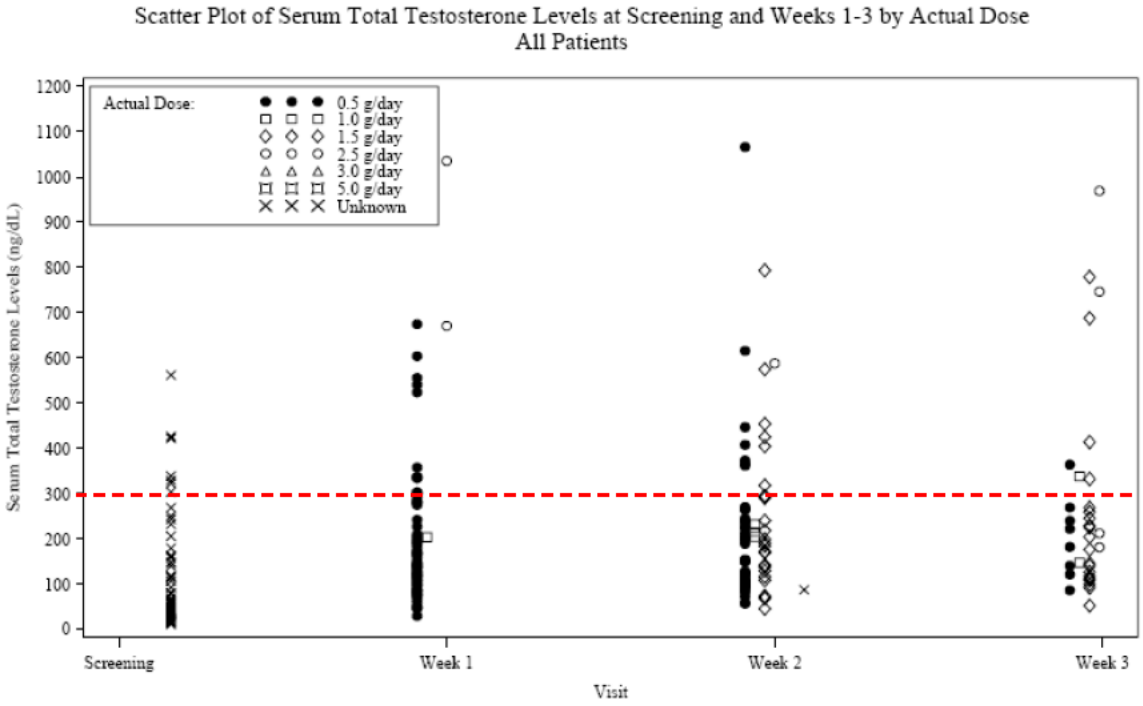
Notes: Estimates are based on model: log(Y) = intercept + slope x log(dose) and estimated using a linear mixed model with log(dose) as a continuousfixed effect and period as a repeated effect. Exponentiation of both sides produces the usual form of the power model: $Y = \exp(\text{intercept}) \times \text{dose}^{\text{slope}}$. p-values were used to evaluate the null hypotheses of slope =1 and intercept = 0.

The results of this analysis indicated that $C_{max,ss}$ and $AUC_{0\text{-}24,ss}$ did not increase in proportion to the administered dose. However, there was no departure from linear kinetics for these two parameters.

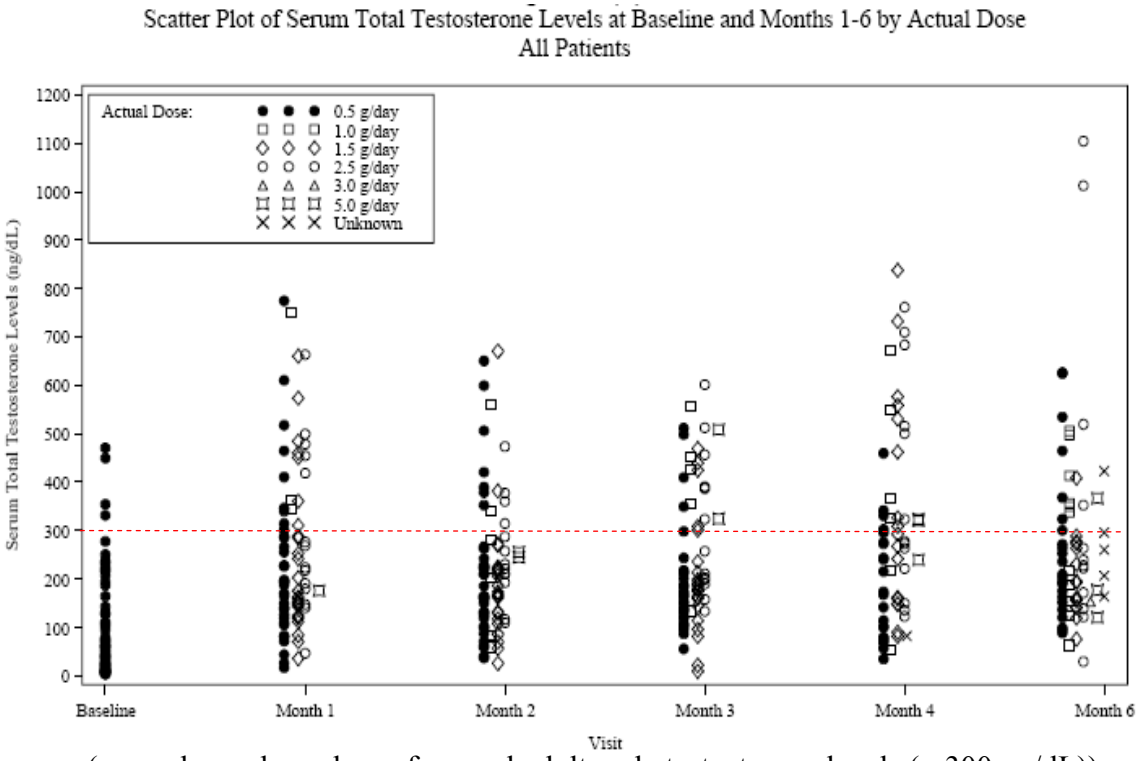
2.2.4.1 Clinical Study UMD-01-090:

Serum total testosterone concentrations were also monitored in the second clinical study UMD-01-090 during the 1 month titration and up to 6 month treatment periods.
The observed serum total testosterone concentrations at Screening, during the titration period (Weeks 1, 2, and 3) and treatment period (Months 1, 2, 3, 4, 5 and 6) are presented for all patients in the figures below:

Figure 4. Observed total testosterone concentrations during titration phase presented by actual dose of AndroGel (UMD-01-090)



(------- lower boundary of normal adult male testosterone levels (~ 300 ng/dL))



(------- lower boundary of normal adult male testosterone levels (~ 300 ng/dL))

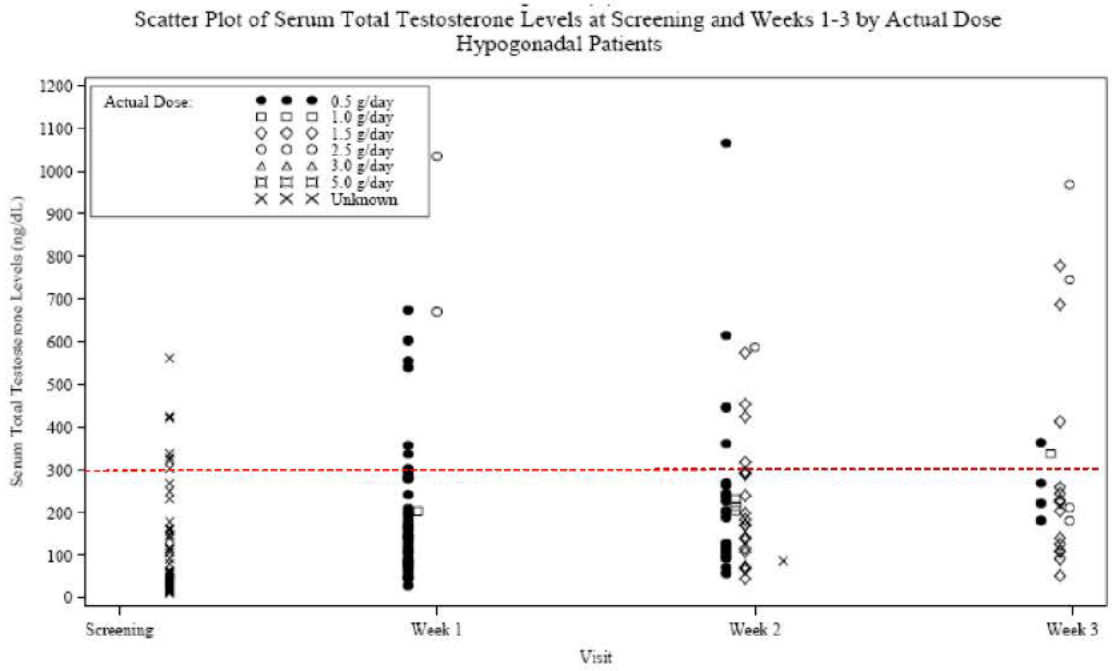
Reviewer's Comment: *Once daily administration, of different dose levels of AndroGel in all subjects resulted in increase in serum Total Testosterone, Free Testosterone and DHT levels from their respective baseline values. However, no dose dependent increase was evident from the graphical evaluation of the trough concentrations measured at various time points during the study.*

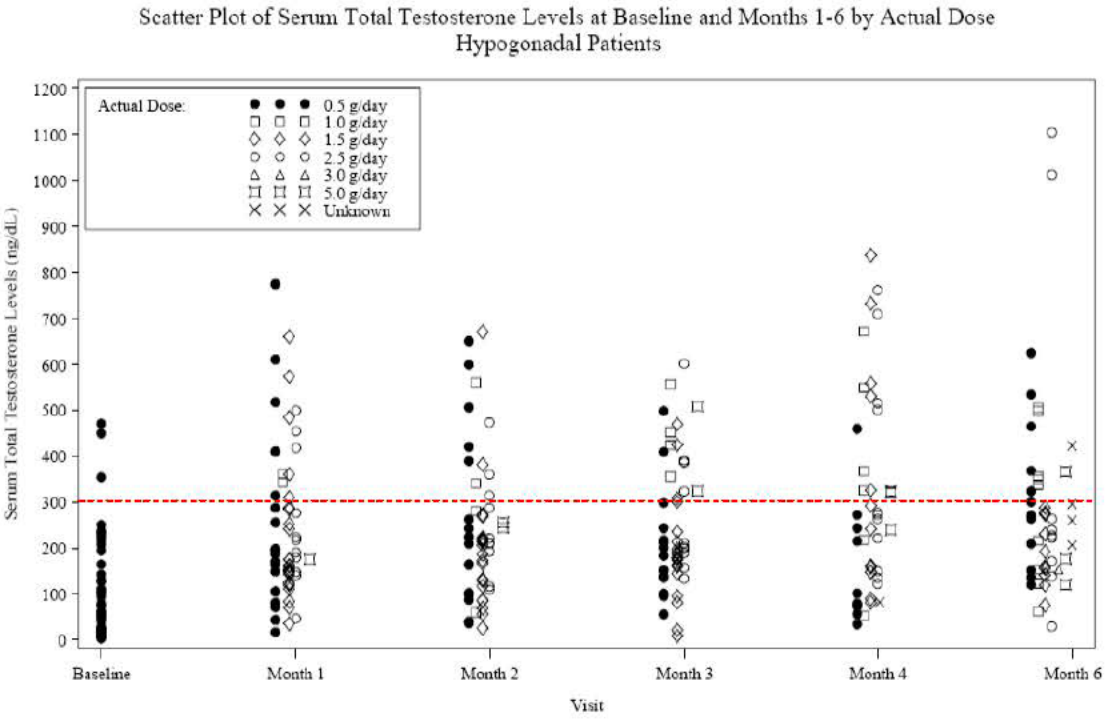
2.3. INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response and what is the impact of any differences in exposure on efficacy or safety responses?

The two clinical studies included hypogonadism and CDGP patients and the PK data was summarized for the two groups. However, in study UMD-01-080, there were only 4 CDGP patients and the meaningful comparison could not be done. In study UMD-01-090, there were 59 subjects with Hypogonadism and 27 subjects with CDGP. Overall, there was a trend towards lower observed total testosterone levels in the CDGP population. However, daily administration of different dose levels of AndroGel, in both the groups as well as collectively, did not exhibit any dose dependent increase in the trough total testosterone concentrations measured in the study. Although overall an increase from baseline in total testosterone was evident. Figures 5 and 6 below depict the observed total testosterone concentrations in hypogonadal and CDGP patients, respectively.

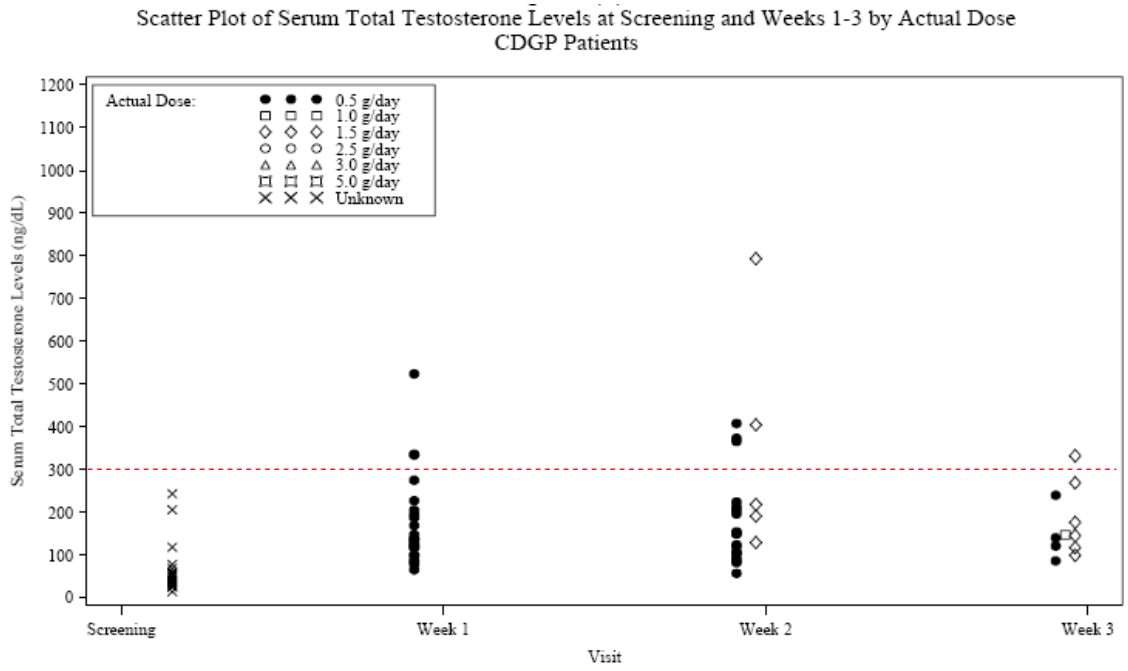
Figure 5. Observed total testosterone concentrations during titration and treatment phases presented by actual dose of AndroGel in Hypogonadal subjects (UMD-01-090)

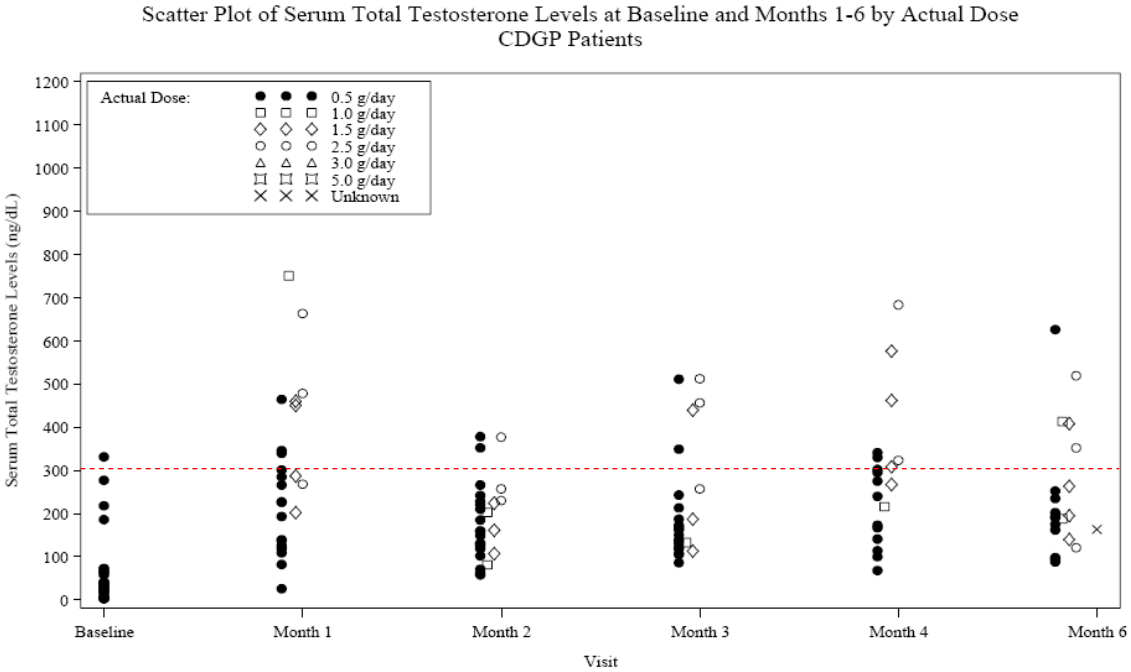




(------ lower boundary of normal adult male testosterone levels (~ 300 ng/dL))

Figure 6. Observed total testosterone concentrations during titration and treatment phases presented by actual dose of AndroGel in CDGP subjects (UMD-01-090)





(------ lower boundary of normal adult male testosterone levels (~ 300 ng/dL))

Reviewer's Comment: *Once daily administration, of different dose levels of AndroGel in all subjects resulted in increase in serum Total Testosterone, Free Testosterone and DHT levels from their respective baseline values in subjects with hypogonadiam as well as*

CDGP. However, no dose dependent increase was evident from the graphical evaluation of the trough concentrations measured at various time points during the study.

2.4. EXTRINSIC FACTORS

2.4.1 Based upon what is known about exposure-response relationships and their variability, and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation?

No exposure-response analysis was conducted under this submission.

2.4.2 What issues, related to dose, dosing regimens or administration, are unresolved and represent significant omissions?

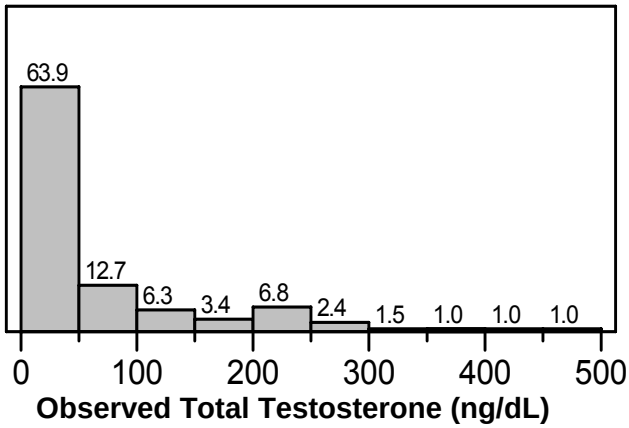
Study UMD-01-090 was initially planned to include subjects with total testosterone baseline values of < 30 ng/dL and titration scheme was planned to achieve total testosterone concentrations in the range of 100-200 ng/dL. However, this criterion was later relaxed to allow easier recruitment and completion of the study, and utilized a titration scheme in which subjects were titrated to individualized target concentrations as deemed appropriate by physicians.

Subsequently the concentration data were analyzed based on a poorly defined criterion of achieving appropriate pubertal testosterone concentrations (not defined anywhere) where, success was judged as achieved if any two concentrations were above the baseline level. In any case, a uniform criterion cannot be utilized with this individualized treatment approach to judge the success of treatment per se and the interpretation of data is difficult.

The study utilized 0.5 g as the lowest starting dose which resulted in total testosterone levels exceeding the lower boundary of normal adult male testosterone concentrations (300 ng/dL) in substantial proportion of subjects by week 1 and this trend continued throughout the study (See Figure 7 below).

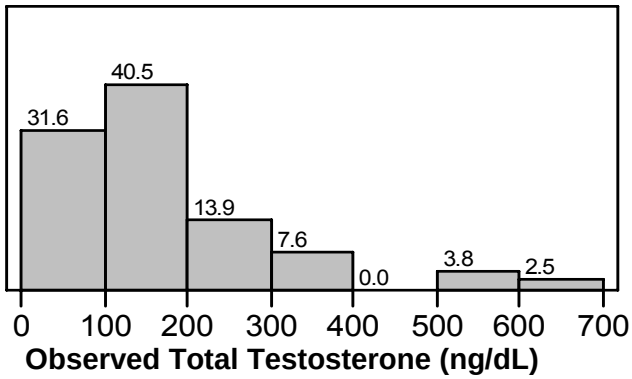
Figure 7. Proportion of Subjects with Total testosterone above 200 ng/dL (upper limit of initial titration scheme) or 300 ng/dL during the titration phase

(a) Baseline, N=79, Week 1



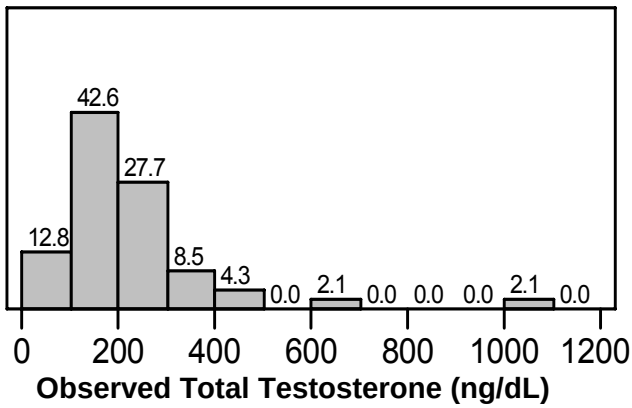
- **4.5% Values above 300 ng/dL**
- **13.7% Values above 200 ng/dL**

(b) Dose 0.5, g, N=79, Week 1



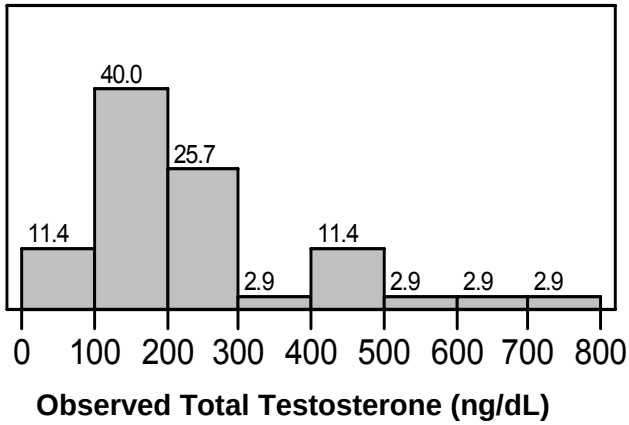
- **13.9% Values above 300 ng/dL**
- **27.8% Values above 200 ng/dL**

(c) Dose 0.5 g, N=47, Week 2



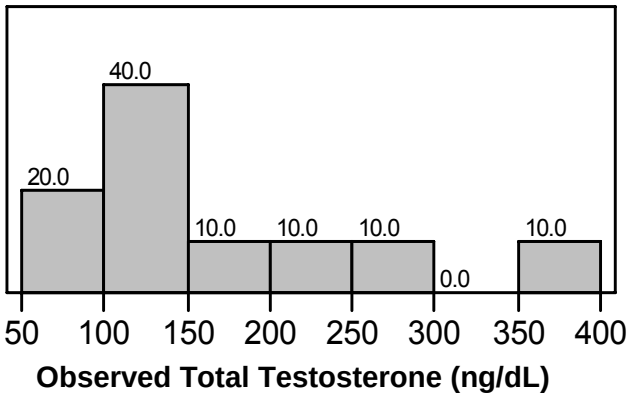
- **17% Values above 300 ng/dL**
- **44.7% Values above 200 ng/dL**

(d) Dose 1.5 g, N=35, Week 2



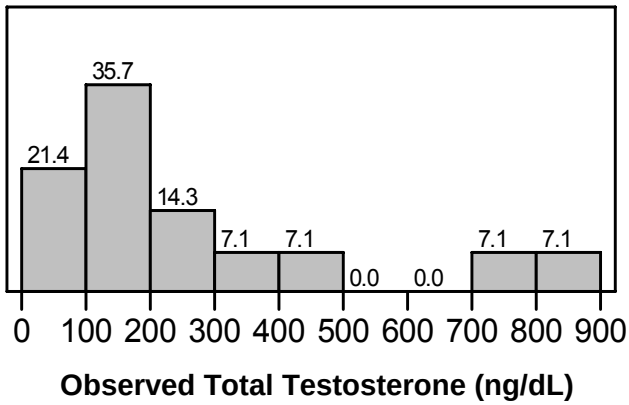
- **23% Values above 300 ng/dL**
- **48.7% Values above 200 ng/dL**

(e) Dose 0.5 g, N=10, Week 3



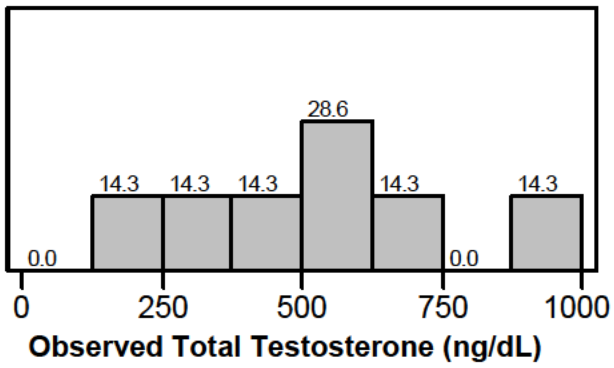
- **10% Values above 300 ng/dL**
- **30% Values above 200 ng/dL**

(f) Dose 1.5 g, N=14, Week 3



- **28.4% Values above 300 ng/dL**
- **42.7% Values above 200 ng/dL**

(g) Dose 2.5 g, N=7, Week 3



- **~80% Values above 300 ng/dL**
- **~90% Values above 200 ng/dL**

2.5. GENERAL BIOPHARMACEUTICS

2.5.1 What data support or do not support the necessary features of (b) (4) AndroGel in pediatric subjects?

The registration batches were tested for their compliance with the content, physicochemical properties and dose uniformity specifications in the acceptance criteria:

Table 3.2.P.7 Results for sNDA Registration Batches for AndroGel Drug Product

Tests	Acceptance criteria	F10001	F10002
Appearance	(b) (4)		
Identity **Testosterone (TLC)** **Ethanol**			
pH			
Viscosity (cps)			
Assay a) Testosterone b) Isopropyl myristate c) Ethanol			
Related Substances Androstenedione Unspecified, each Total			
Pump Performance Dose uniformity (a)			
Number of doses delivered			
Extractable contents			

The formulation batches were found to comply with the specifications.

2.6. ANALYTICAL SECTION

2.6.1 Were relevant parent and metabolite concentrations measured in the clinical pharmacology and biopharmaceutic studies?

Yes, testosterone and its active metabolites; DHT and E2 were measured in human serum in both clinical studies (UMD-01-080 and UMD-01-090).

2.6.3 For all moieties measured, is free, bound or total measured? What is the basis for that decision, if any, and is it appropriate?

Serum concentrations of testosterone were expressed as total, free and bioavailable testosterone. The rationale behind evaluation of total, free and bioavailable testosterone is that circulating testosterone is chiefly bound in the serum to sex hormone-binding globulin (SHBG) and albumin. The albumin-bound fraction of testosterone easily dissociates from albumin and is presumed to be bioactive. The portion of testosterone bound to SHBG is not considered biologically active. The amount of SHBG in the serum and the total testosterone level will determine the distribution of bioactive and non-bioactive androgen. SHBG-binding capacity is high in prepubertal children, declines during puberty and adulthood, and increases again during the later decades of life. Approximately 40% of testosterone in plasma is bound to SHBG, 2% remains unbound (free) and the rest is bound to albumin and other proteins.

2.6.4 What bioanalytical methods are used to assess concentrations in this NDA and are they acceptable?

Reviewer's comment: *DSI audit of the analytical portion of the Study UMD-01-090 conducted* (b) (4) *identified serious deficiencies with the assay validation for testosterone, free testosterone and DHT (See DSI Memorandum dated 20 November 2007). Based on DSI findings the assay validity is not acceptable unless the sponsor provides an acceptable resolution of these deficiencies. Mentioned below are the analytical details submitted by the sponsor with the initial submission.*

2.6.4.1.1 Testosterone

The quantitative determination of testosterone in human serum was done by a validated radioimmunoassay (RIA) after nonpolar solvent extraction and alumina column chromatography. Testosterone is extracted from serum samples (b) (4) Amount of testosterone in each sample is

determined by gamma counting. The method was developed [redacted] (b) (4)

The % cross-reactivity of one of the antiserum lot was determined at a level of 50% bound for significant cross reactants and dihydrotestosterone showed 22% cross-reactivity while other steroidal molecules were 5.5% or below in their cross-reactivity. However, it was also demonstrated that using the alumina column chromatography for sample clean-up does enhances the testosterone specificity of the assay method over the simple extraction method.

The calibration curves were analyzed at testosterone concentrations 2.5, 5.0, 10.0, 25, 50, 75, 100 and 150 pg/100 µL (equivalent to ng/dL). Due to limitation of RIA exhibiting higher relative errors at higher concentrations where the standard curve flattens, the patient values were not determined from area of the curve beyond 100 pg level. Samples were diluted or a smaller aliquot was taken.

The testosterone lower limit of quantitation (LLOQ) was 3.0 pg/ 0.1mL using 0.5 mL human serum. Upper limit of quantitation (ULOQ) was 100.00 pg/0.1 ml in human serum. At or above LLOQ the accuracy, as assessed from %bias, was within the range of -9.0% to 6.5%. Intra-assay precision was within the range of 4.6% to 5.8% for low quality control (LQC) to upper quality control (UQC), and was 23.1% for LLOQ. Inter-assay precision was within the range of 5.4% to 7.8% for LQC to UQC, and was 22.8% for LLOQ.

The stability data presented shows that Testosterone is stable in human serum when stored at -20^{0}C for up to 3 years. Bench-top stability of extract left at room temperature did not show any degradation. Serum samples also showed stability when subjected to 3 freeze-thaw cycles.

2.6.4.2.1 Dihydrotestosterone

The quantitative determination of dihydrotestosterone in human serum was done by a validated radioimmunoassay (RIA) after extraction and oxidation. Samples were extracted [redacted] (b) (4) followed by measurement of DHT by RIA using antiserum raised to a dihydrotestosterone-3-oxime-BSA conjugate in rabbits. Average recovery of DHT after extraction [redacted] (b) (4) was approximately 96%.

The % cross-reactivity of one of the antiserum lot was determined at a level of 50% bound for significant cross reactants and testosterone showed 40% cross-reactivity while other steroidal molecules were 4.8% or below in their cross-reactivity. However, it was also demonstrated that [redacted] (b) (4) removes over 99.5% of the testosterone interference.

Using 0.5 mL sample, the calibration curves were analyzed at dihydrotestosterone concentrations 2.5, 5.0, 10.0, 25, 50, 75, 100 and 150 ng/dL. Due to limitation of RIA exhibiting higher relative errors at higher concentrations where the standard curve flattens, sample readings ≥75 ng/dL were repeated using a smaller sample volume. The LLOQ and ULOQ were 2.00 ng/dL and 75 ng/dL, respectively in human serum using 0.5 mL sample.

The accuracy based on % bias was 13.6% at LOQ QC, 8.9% at LQC, -9.2% at medium quality control (MQC), -2.9% at HQC, and 1.8% at UQC. Intra-batch

precision ranged from 18.1% for the LOQ QC to 4.6% at UQC. Inter-assay precision ranged from14% for the LOQ QC to 7.1% for the HQC.

The stability data presented shows that Long-term storage stability at -20^{0}C for up to 3 years, bench-top stability and freeze-thaw stability was also demonstrated for dihydrotestosterone.

2.6.4.3.1 Miscellaneous Measurement of Estradiol, Free Testosterone, Bioavailable testosterone, SHBG

The quantitative determination of estradiol in human serum was done by a validated radioimmunoassay (RIA) after nonpolar solvent extraction and LH20 column chromatography.

Free testosterone was determined using equilibrium dialysis. The minimum reported fraction using this method was 0.1% free.

Bioavailable testosterone was determined by separation of the SHBG bound steroid from albumin bound and free steroid with ammonium sulfate.

SHBG was measured using an immunoradioactive assay utilizing a monoclonal antibody against human SHBG.

3. (b) (4)

Recommendation:

(b) (4)

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4.2. INDIVIDUAL STUDY REVIEW

4.2.1. Clinical Study UMD-01-080

Clinical Study UMD-01-080

TITLE: Pharmacokinetic Evaluation of Testosterone-Gel (1%) in Prepubertal Boys of Adolescent Age

.

INVESTIGATOR(S) AND STUDY CENTER(S):

Center	Investigator	Study Center(s)
208	Abdullatif, Hussein MD	University of Alabama at Birmingham 1600 7th Avenue South Birmingham, AL 35233
204	Mauras, Nelly MD	Nemours Children's Clinic 807 Children's Way Jacksonville, FL 32207 Nemours Children's Clinic Division of Endocrinology 5153 N. 9th Avenue Jacksonville, FL 32207
201	Moore, Wayne MD	Children's Mercy Hospital 2401 Gilham Road Kansas city, MO 64108
202	Moshang, Thomas MD	Children's Hospital of Philadelphia Division of Endocrinology 34th St. & Civil Center Blvd. Philadelphia, PA 19104
209	Rose, Susan MD	Cincinnati Children's Hospital Medical Center 3333 Burnet Avenue Cincinnati, OH 45229-3039
203	Swerdloff, Ronald MD	Harbor-UCLA Medical Center 1000 West Carson Street Box 446 Torrance, CA 90509-2910

STUDY SPONSOR:

Unimed Pharmaceuticals, Inc., Four Parkway North
Deerfield, IL 60015
847-282-5400

BIOANALYTICAL ANALYSIS:

(b) (4)

STUDY PERIOD: 02 AUG 2002 (First Subject First Visit) – 23 APR 2006 (Last Subject Last Visit)

OBJECTIVE:

The primary objectives of this study were to evaluate the steady-state serum testosterone concentrations, the pharmacokinetic (PK) characteristics, and the safety and tolerability of testosterone gel 1% in prepubertal boys of adolescent age with insufficient testosterone production. The primary evaluation of PK characteristics was based on steady-state PK parameters determined from serum total testosterone concentrations.

The secondary objectives of this study included evaluation of the serum concentrations of free testosterone, bioavailable testosterone, FSH, LH, SHBG, total DHT, and estradiol (E2); changes from baseline in hematocrit, hemoglobin (Hgb), and blood lipid concentrations; appearance of gynecomastia, skin irritation assessment; and the incidence of treatment-emergent AEs (TEAEs).

STUDY DESIGN:

This was a multicenter, open-label, escalating-dose study conducted in up to 18 prepubertal boys of adolescent age to evaluate the safety and steady-state serum testosterone concentrations and PK characteristics following daily applications of testosterone gel 1%. There were three treatment periods (Treatment Period 1, 2, and 3) during which subjects applied one of three escalating doses of testosterone gel 1% (0.5 g, 1.5 g, and 2.5 g containing 5 mg, 15 mg, and 25 mg of testosterone, respectively) for four consecutive days. Each treatment period was separated by a washout period of up to 14 days. Testosterone gel 1% was supplied in multi-dose bottles with attached pumps calibrated to dispense (b) (4) testosterone gel 1%.

BLOOD SAMPLE COLLECTION:

Blood samples for PK measurement of serum concentrations of total, bioavailable, and free testosterone and total DHT were collected five minutes prior to testosterone gel 1% application (predose), and at 1, 2, 4, 8, 12, and 24 hours after application on Day 4 of Treatment Periods 1, 2, and 3. Samples were also collected at the same nominal time points on Day 0, which was the day before the first dose, based on the "projected dosing time" during the treatment periods. Blood samples for measurement of serum concentrations of E2, FSH, LH, and SHBG were collected five minutes prior to

testosterone gel 1% application (predose) on Day 4 of Treatment Periods 1, 2, and 3, and at the corresponding time on Day 0.

SAFETY ASSESSMENT: Safety was evaluated in terms of the incidence of AEs, changes from Baseline in laboratory values, changes from Baseline in vital signs, and shifts or changes from Baseline in the results of the physical examinations, skin application site assessments, and evaluations for presence of gynecomastia. Study medication tolerance was summarized in terms of incidence of AEs by severity and incidence of markedly abnormal laboratory and vital sign values.

SUBJECTS:
Up to 18 patients were planned and 17 patients were enrolled and analyzed. The original study design was to enroll 18 subjects to provide PK data for all three dose levels. Due to slow subject recruitment, an interim analysis of the data was performed after 17 subjects had been enrolled in the study. This analysis demonstrated that sufficient data had been obtained in this subject population to sufficiently characterize the starting dose and pharmacokinetics of testosterone gel for all three dose levels and that further enrollment of subjects would not alter the conclusions from this study. Therefore these 17 subjects are the basis of the analysis in this study report.

ANALYTICAL METHOD:
Measurements of total, free, and bioavailable testosterone, as well as total DHT, E2, FSH, LH, and SHBG were performed (b) (4)

PHARMACOKINETICS

Pharmacokinetic parameters were evaluated in any subjects who provided sufficient samples for PK assessment. Pharmacokinetic parameters were calculated for both 'observed' and 'Baseline adjusted' data. Baseline-adjusted data were computed for each treatment by subtracting the Baseline data (Day 0) from the time-matched concentration data of each treatment period (Day 4 concentrations minus Day 0 concentrations). For the purpose of computation of Baseline-adjusted data, as well as for pharmacokinetic analysis and computation of descriptive statistics (observed and Baseline-adjusted data), serum concentrations that fell below the limit of quantification for the assay (BLQ) were assigned a value of zero. For observed data, if a concentration was not reported for a sample time point, then it was assigned a value of missing. In the case of Baseline-adjusted data, if the Baseline or treatment concentration was missing for a sample time point, then the corresponding Baseline-adjusted value was not calculated. Actual collection times were used for computation of PK parameters for 'observed' data and actual collection times of the treatment samples were used in the case of Baseline-adjusted data. Serum concentrations (ie, observed concentrations) for total, free, and bioavailable testosterone, and total DHT were summarized descriptively (n, mean, SD, CV%, minimum, maximum, median and geometric mean) for each serial sampling time at Baseline (Day 0) and for each treatment period (on Day 4 of Treatment Periods 1, 2 and 3). Additionally, Baseline-adjusted concentrations for each treatment period for total, free, and bioavailable testosterone, and total DHT were also summarized descriptively.

The summary data was presented for all subjects (N = 17), subjects with hypogonadism (N = 13) and subjects with CDGP (N = 4) separately.

Pharmacokinetic parameters were estimated for total, free, and bioavailable testosterone, and total DHT after multiple dosing of each treatment (on Day 4 of Treatment Periods 1, 2, and 3) for both 'observed' and 'Baseline-adjusted' data.

Pharmacokinetic parameters included the following:

- $AUC_{0\text{-}24,ss}$: area under the curve from 0 to 24 hours, determined using the linear trapezoidal rule; a minimum of four data points were required for the calculation of AUC; otherwise AUC was set to missing;
- $C_{max.ss}$: maximum observed concentration over 24-hour dosing interval;
- $t_{max,ss}$: time at which C_{max} occurred;
- $C_{min,ss}$: lowest concentration observed during the 24-hour dosing interval;
- $t_{min,ss}$: time at which C_{min} occurred;
- $C_{avg,ss}$: the time-averaged concentration over the dosing interval, calculated as $AUC_{0\text{-}24}/24$;
- Fluctuation Index: the extent of variation in the serum concentration over the course of a single day, calculated as $(C_{max}\text{-}C_{min})/C_{avg}$;

Descriptive statistics (n, mean, SD, CV%, median, minimum, maximum and geometric mean) for the PK parameters are provided for each treatment group. The PK parameters, $C_{max,ss}$, $C_{avg,ss}$, and $AUC_{0\text{-}24,ss}$, were displayed using Box and Whiskers plots.

An exploratory analysis of dose proportionality of the PK parameters, $AUC_{0\text{-}24}$ and $C_{max,ss}$, was performed using a power model to determine whether the PK was proportional over the dose range tested in all subjects. To assess departures from linear kinetics, a quadratic term was added to the power model. This additional term was added to assess the evidence for curvilinearity in the dose-exposure relationship to yield a more complete characterization. In addition, dose proportionality was assessed by visual examination of plots of $C_{max,ss}$ and $AUC_{0\text{-}24,ss}$ versus dose and by summary statistics. Predose serum concentrations (observed and Baseline-adjusted) for FSH, LH, E2, and SHBG were summarized for all treatment periods using descriptive statistics (n, mean, SD, median, minimum, maximum, CV%).

Results:

All subjects were ≥ 80% compliant with study medication. Half of the subjects were ≥112% compliant (median) and the mean compliance for all subjects was 108.4%, in range of 82-136%, based on bottle weight.

The PK characteristics of total testosterone, free testosterone and DHT were evaluated in Study UMD-01-080. Results from Study UMD-01-080 showed a dose-related increase in exposure for total and free testosterone and total DHT with increasing doses of testosterone administration. In this case, exposure refers to observed and baseline adjusted area under the curve from 0 to 24 hours ($AUC_{0\text{-}24,ss}$), maximum observed concentration over 24-hour dosing interval ($C_{max,ss}$), and the time-averaged

concentration over the dosing interval, determined by $AUC_{0-24}/24$ ($C_{avg,ss}$). The increase was not dose-proportional, though there was no indication of departure from linear PK.

Summary of Observed Pharmacokinetic Parameters in All Subjects

		Arithmetic Mean (SD)		
Analyte	**Parameter**	**0.5 g (n = 17)**	**1.5 g (n = 17)**	**2.5 g (n = 13)**
Total Testosterone	$C_{max,ss}$ (ng/dL)	211.3 (147.2)	361.0 (217.8)	492.8 (291.7)
	$C_{avg,\ ss}$ (ng/dL)	140.5 (111.7)	241.8 (133.70)	326.0 (188.0)
	$t_{max,ss}$ (h)[a]	2.00 (0.0 - 24.03)	4.00 (0.00 – 24.25)	12.08 (0.0 – 24.0)
	$AUC_{0-24,ss}$ (ng*h/dL)	3372 (2683)	5808 (3220)	7853 (4511)
Free Testosterone	$C_{max,ss}$ (pg/mL)	31.80 (22.47)	53.94 (29.47)	86.31 (62.44)
	$C_{avg,\ ss}$ (pg/mL)	19.67 (15.01)	34.93 (15.68)	53.73 (42.76)
	$t_{max,ss}$ (h) [a]	2.00 (0.0 - 24.03)	4.00 (0.00 – 24.25)	12.00 (0.0 – 24.0)
	$AUC_{0-24,ss}$ (pg*h/mL)	472.4 (361.0)	839.2 (376.8)	1294 (1027)
Total DHT	$C_{max,ss}$ (ng/dL)	31.71 (17.15)	53.29 (38.78)	76.31 (43.58)
	$C_{avg,\ ss}$ (ng/dL)	21.94 (12.20)	40.50 (26.34)	54.03 (33.87)
	$t_{max,ss}$ (h) [a]	8.00 (0.0 – 25.00)	12.00 (0.00 – 24.25)	12.00 (0.0 – 24.0)
	$AUC_{0-24,ss}$ (ng*h/dL)	527.2 (293.3)	974.4 (637.8)	1301 (813)

[a] The estimate is the median value and range for the PK parameter.
0.5 g = 5 mg of testosterone gel 1%
1.5 g = 15mg of testosterone gel 1%
2.5 g = 25 mg of testosterone gel 1%

- Observed median t_{max} for total testosterone ranged from 2 to 12.08 hours across the three treatment groups
- Total testosterone $AUC_{0-24,ss}$, $C_{max,ss}$, and $C_{avg,ss}$ showed around 2-fold increase over a 5-fold increase in dose (5 mg to 25 mg) of testosterone, respectively. Similar results were observed for free testosterone
- For total DHT, the observed median tmax ranged from 8 to 12 hours across the three treatment groups. $AUC_{0-24,ss}$, $C_{max,ss}$, and $C_{avg,ss}$ showed a 2.5-fold, 2.4-fold and 2.5-fold increase over a 5-fold increase in dose (5 mg to 25 mg) of testosterone, respectively.

Summary of Baseline-Adjusted Pharmacokinetic Parameters in All Subjects

		Arithmetic Mean (SD)		
Analyte	Parameter	0.5 g (n = 17)	1.5 g (n = 17)	2.5 g (n = 13)
Total-T	$C_{max,ss}$ (ng/dL)	137.3 (66.6)	288.5 (177.8)	387.5 (311.3)
	$C_{avg,\ ss}$ (ng/dL)	67.85 (36.61)	166.9 (98.5)	227.4 (189.1)
	$t_{max,ss}$ (h)[a]	2.0 (0.0 – 24.03)	4.00 (0.00 – 24.25)	8.08 (0.00 – 24.00)
	$AUC_{0-24,ss}$ (ng*h/dL)	1634 (883)	4014 (2382)	5482 (4539)
Free-T	$C_{max,ss}$ (pg/mL)	22.72 (13.17)	44.47 (28.63)	75.02 (64.14)
	$C_{avg,\ ss}$ (pg/mL)	10.94 (6.69)	25.70 (16.64)	41.41 (42.24)
	$t_{max,ss}$ (h) [a]	12.0 (0.0 – 24.03)	4.00 (0.00 – 24.25)	12.03 (0.00 – 24.00)
	$AUC_{0-24,ss}$ (pg*h/mL)	263.1 (160.4)	617.8 (400.5)	999.5 (1019.2)
Total DHT	$C_{max,ss}$ (ng/dL)	23.86 (12.60)	45.01 (36.36)	67.15 (43.87)
	$C_{avg,\ ss}$ (ng/dL)	14.77 (8.50)	33.36 (24.76)	45.28 (32.69)
	$t_{max,ss}$ (h) [a]	7.98 (0.00 – 24.00)	12.00 (0.00 – 24.25)	12.00 (0.00 – 24.00)
	$AUC_{0-24,ss}$ (ng*h/dL)	355.3 (204.8)	802.5 (599.8)	1090 (785)

[a] The estimate is the median value and range for the PK parameter.
0.5 g = 5 mg of testosterone gel 1%
1.5 g = 15mg of testosterone gel 1%
2.5 g = 25 mg of testosterone gel 1%
Total T = total testosterone
Free T = free testosterone
Bioavailable T = bioavailable testosterone
Total DHT= dihydrotestosterone

- Median t_{max} for baseline-adjusted total testosterone ranged from 2 to 8 hours across the three treatment groups
- Baseline-adjusted total testosterone $AUC_{0-24,ss}$, $C_{max,ss}$, and $C_{avg,ss}$ showed a 2 to 3-fold increase over a 5-fold increase in dose (5 mg to 25 mg) of testosterone, respectively. Similar results were observed for free testosterone.
- For total DHT, the observed median tmax ranged from 8 to 12 hours across the three treatment groups. The baseline adjusted parameters $AUC_{0-24,ss}$, $C_{max,ss}$, and $C_{avg,ss}$ showed a 2 to 3-fold increase over a 5-fold increase in dose (5 mg to 25 mg) of testosterone.

Dose proportionality was assessed for both observed and Baseline-adjusted PK parameters for total testosterone and free testosterone. Dose-proportionality was evaluated across treatment groups using the power model. In order to assess departures from linear kinetics, a quadratic term was added to the evaluation with the power model.

Based on Observed PK Parameters:

Analyte	Parameter	Slope Estimate	Slope 95% Confidence Interval	Slope p-value	Intercept Estimate	Intercept 95% Confidence Interval	Intercept p-value
Total T	$AUC_{0-24,ss}$	0.552	(0.402, 0.702)	<.0001	8.300	(8.043, 8.556)	<.0001
	$C_{max,ss}$	0.545	(0.371, 0.719)	<.0001	5.537	(5.291, 5.783)	<.0001
Free T	$AUC_{0-24,ss}$	0.605	(0.432, 0.779)	<.0001	6.344	(6.039, 6.648)	<.0001
	$C_{max,ss}$	0.598	(0.391, 0.805)	<.0001	3.618	(3.309, 3.927)	<.0001

Notes: Estimates are based on model: log(Y) = intercept + slope x log(dose) and estimated using a linear mixed model with log(dose) as a continuousfixed effect and period as a repeated effect. Exponentiation of both sides produces the usual form of the power model: $Y = \exp(\text{intercept}) \times \text{dose}^{\text{slope}}$. p-values were used to evaluate the null hypotheses of slope =1 and intercept = 0.

Based on Baseline Adjusted PK Parameters;

Analyte	Parameter	Slope Estimate	Slope 95% Confidence Interval	Slope p-value	Intercept Estimate	Intercept 95% Confidence Interval	Intercept p-value
Total T	AUC(0-24),ss	0.625	(0.351, 0.898)	<.0001	7.897	(7.658, 8.136)	<.0001
	Cmax,ss	0.568	(0.315, 0.821)	<.0001	5.231	(5.033, 5.428)	<.0001
Free T	AUC(0-24),ss	0.780	(0.540, 1.021)	<.0001	6.018	(5.714, 6.321)	<.0001
	Cmax,ss	0.630	(0.366, 0.894)	<.0001	3.373	(3.082, 3.663)	<.0001

Notes: Estimates are based on model: log(Y) = intercept + slope x log(dose) and estimated using a linear mixed model with log(dose) as a continuousfixed effect and period as a repeated effect. Exponentiation of both sides produces the usual form of the power model: $Y = \exp(\text{intercept}) \times \text{dose}^{\text{slope}}$. p-values were used to evaluate the null hypotheses of slope =1 and intercept = 0.

The results of these analysis indicated that $C_{max,ss}$ and $AUC_{0-24,ss}$ did not increase in proportion to the administered dose. However, there was no departure from linear kinetics for these two parameters.

SAFETY ASSESSMENT

A total of 12 subjects (70.6%) experienced TEAEs during the study. Based on dose level, at onset 6 subjects (35.3%) experienced a TEAE with onset at the 0.5 g/day dose level, 5 subjects (29.4%) at 1.5 g/day, and 4 subjects (30.8%) at 2.5 g/day. The most frequently reported system organ classes were nervous system disorders (N = 4, 23.5%) and gastrointestinal disorders (N = 3, 17.6%). TEAEs reported for more than one subject included headache (N = 3, 17.6%), vomiting (N = 2, 11.8%), and hemoglobin decreased (N = 2, 11.8%).

CONCLUSION

- Pharmacokinetics of total, free and bioavailable testosterone and total DHT was characterized in pediatric population after the application of 0.5 g, 1.5 g and 2.5 g testosterone gel 1%
- Steady-state concentration-time profiles were relatively flat for all analytes, indicating that concentrations of these analytes remained at fairly stable levels throughout the dosing interval
- A dose-related increase in exposure ($AUC_{0\text{-}24,ss}$, $C_{max,ss}$, $C_{avg,ss}$) was observed for total and free testosterone with increasing doses of testosterone. Although the increase was not dose-proportional, there was no indication of departure from linear pharmacokinetics

4.2.2. Clinical Study UMD-01-090

Clinical Study UMD-01-090

TITLE: A Multi-Center, Open-Label, Observational Study of Testosterone Gel (1%) in the treatment of Adolescent Boys with Hypogonadism

INVESTIGATOR:

Study Center	Investigator	Study Center(s)
103	Boston, Bruce MD	Oregon Health & Science University Doernbecher Children's Hospital 3181 Sam Jackson Park Rd. Portland, OR 97239
104	Cohen, Allen Jay MD	The Endocrine Clinic, PC 5659 South Rex Road Memphis, TN 38119
123	Fennoy, Ilene MD, MPH	General Clinical Research Center College of Physicians and Surgeons, Columbia University Children's Hospital of NY Presbyterian 3959 Broadway New York, NY 10032
107	Geffner, Mitchell MD	Childrens Hospital Los Angeles 4650 Sunset Boulevard Los Angeles, CA 90027
108	Kumar, Anil MD	VCU Medical Center The Children's Pavillion 1001 E. marshall Street Richmond, VA 23298
109	Lee, Peter A. MD, PhD	Penn State Children's Hospital Hershey Medical Center Department of Pediatrics, H0-85 500 University Drive Hershey, PA 17033
110	Linarelli, Louie G. MD	Louie G. Linarelli, MD, Inc. 7930 Frost Street, Suite 401 San Diego, CA 92123
127	Mauras, Nelly MD	Nemours Children's Clinic 807 Children's Way Jacksonville, FL 32207 Nemours Children's Clinic Division of Endocrinology 5153 N. 9th Avenue Jacksonville, FL 32207
111	Moore, Wayne MD	Children's Mercy Hospital 2401 Gilham Road Kansas city, MO 64108

Study Center	Investigator	Study Center(s)
125	Moshang, Thomas	Children's Hospital of Philadelphia Division of Endocrinology 34th St. & Civil Center Blvd. Philadelphia, PA 19104
122	Perelman, Alvin H. MD, MBA	Southwest Pediatric Endocrinology, PLC 10900 N. Scottsdale Road, Suite 504 Scottsdale, AZ 85254
126	Ross, Judith MD	Thomas Jefferson University Department of Pediatrics 1025 Walnut Street Suite 726 Philadelphia, PA 19107
128	Silverman, Lawrence A. MD	Morristown Memorial Hospital 100 Madison Avenue Morristown, NJ 07962
121	Silverstein, Janet H. MD	Shands Medical Plaza 2000 SW Archer Rd. Gainesville, FL 32610 University of Florida 1600 SW Archer Rd. Gainesville, FL 32610
113	Styne, Dennis MD	UC Davis Medical Center Department of Pediatrics 2516 Stockton Blvd. Sacramento, CA 95817 UC Davis Medical Center Pediatric Specialty Clinic 2521 Stockton Blvd. Sacramento, CA 95817 UC Davis Medical Center Investigational Drug Pharmacy DT 0726 2315 Stockton Blvd. Sacramento, CA 95817 UC Davis Medical Center Ambulatory Care Center Imaging Department 4860 Y St. Sacramento, Ca 95817

Study Center	Investigator	Study Center(s)
114	Swerdloff, Ronald MD	Harbor-UCLA Medical Center 1000 West Carson Street Box 446 Torrance, CA 90509-2910
117	Walvoord, Emily MD	Riley Hospital for Children 702 Barnhill Drive, Room 5960 Indianapolis, IN 46202
124	Wetterau, Lawrence MD	Children's Hospital c/o Pediatric Clinical Trials, Intl. 555 South 18th Street, Ste. 6E Columbus, OH 43205-2696 Children's Hospital c/o Pediatric Clinical Trials, Intl. 700 Children's Drive Columbus, OH 43205-2696

STUDY CENTER: (b) (4)

PHARMACOKINETIC and STATISTICAL ANALYSIS: (b) (4)

BIOANALYTICAL ANALYSIS: (b) (4)

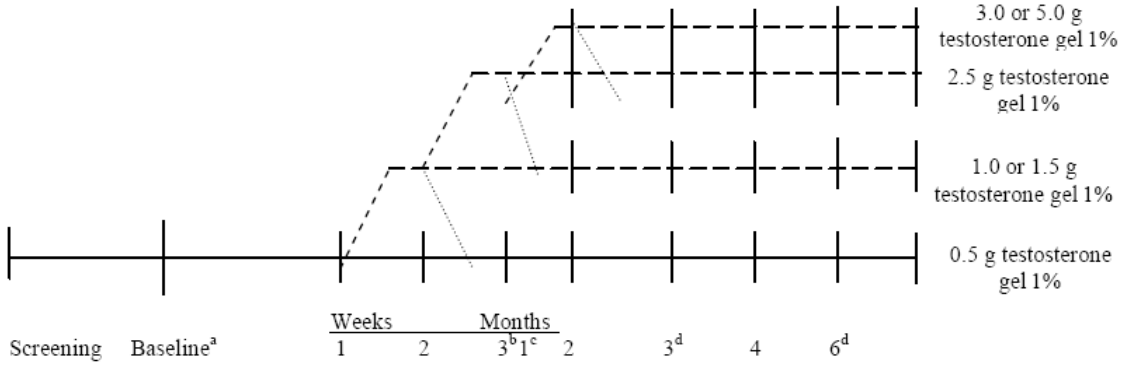
STUDY PERIOD:

First Subject First Visit: 15 AUG 2002, **Last Subject Last Visit:** 19 JUN 2006

OBJECTIVE:
The objective of this study was to evaluate the clinical response to testosterone gel 1% for the treatment of delayed puberty due to primary or secondary hypogonadism or CDGP, in boys of adolescent age.

STUDY DESIGN:
This was a multi-center, open-label, observational study of the clinical response to testosterone gel 1% as treatment for delayed puberty. Up to 70 adolescent males, 13 to 17 years of age, diagnosed with delayed puberty due to primary or secondary hypogonadism or CDGP were enrolled into this study. The total observational period was six months. The first three months of observation were under Protocol UMD-01-090 and the last

three months of observation were included in the extension, Protocol UMD-01-090E. This Clinical Study Report (CSR) presents results from the two protocols combined. Both testosterone naive subjects (subjects who were naive to androgen therapy) and testosterone non-naïve subjects were enrolled. Subjects could be enrolled after completed participation in the UMD-01-080 protocol (since UMD-01-080 was a short-term pharmacokinetic study which provided limited exposure to the study drug, subjects who were considered to be testosterone naïve on entry in to the UMD-01-080 protocol were considered testosterone naïve for the purposes of this protocol). For all enrolled subjects, whether testosterone naive or testosterone non-naive, the subject's dose of testosterone gel 1% was evaluated by the investigator during the initial three weeks of the study and could be titrated based on the investigator's clinical judgment, with the goal of attaining an appropriate target serum total testosterone range based on the boy's Baseline stage of puberty. All of these subjects were to begin treatment at a dose of 0.5 g of testosterone gel 1% once daily, applied at bedtime (five subjects began treatment at a dose > 0.5 g/day. During the initial three weeks of the study, a subject's dose of testosterone gel 1% could be increased in stepwise fashion to 1.5 g, 2.5 g, or 5.0 g of testosterone gel 1% daily. Once the desired serum testosterone level had been attained, no further dose titration (increase) was to occur. Subjects were evaluated at Screening, Baseline, Week 1, Week 2, Month 1, Month 2, and Month 3 (UMD-01-090); and Month 4 and Month 6 (UMD-01-090E). The Week 3 visit was an optional titration visit for boys who were titrated to 2.5 g at Week 2. The overall design is illustrated in figure below:



[a] All subjects were to initially receive testosterone gel 1% 0.5 g daily
[b] Optional visit/dose for testosterone non-naive subjects only
[c] Week 4
[d] Month 3 [Protocol UMD-01-090 (Final Visit)] and Protocol UMD-01-090E (Final Visit) procedures were performed if a subject prematurely discontinued from the study (Early Termination Visit)

The final dose-titration scheme used in the study was as follows:

Revised Table 3: Dose Titration for T-Gel:

Visit	Serum Testosterone Level	Current Testosterone-Gel Dose	New Testosterone-Gel Dose[a]
Baseline	≤ 30 ng/dL	Not Applicable	0.5 g/day
Month 1	100-200 ng/dL	0.5 g/day	Continue 0.5 g/day
	< 100 ng/dL	0.5 g/day	Increase to 1.5 g/day
	201-250 ng/dL	0.5 g/day	Continue 0.5 g day (Repeat at Month 2)[b]
	> 250 ng/dL[c]	0.5 g/day	Discontinue Patient
Month 2 (for those patients titrated up at Month 1)	100-200 ng/dL	1.5 g/day	Continue 1.5 g/day
	< 100 ng/dL	1.5 g/day	Increase to 2.5 g/day
	> 200 ng/dL	1.5 g/day	Decrease to 0.5 g/day
Month 3 (for those patients titrated up at Month 2)	100-200 ng/dL	2.5 g/day	Continue 2.5 g/day
	< 100 ng/dL	2.5 g/day	Continue 2.5 g/day
	> 200 ng/dL	2.5 g/day	Decrease to 1.5 g/day

a The new dose, if necessary, will begin within 5 to 10 days of the scheduled visit, when the site personnel have been notified by the sponsor or designee of the need to make a dosing adjustment.
b If still 201-250 ng/dL at Month 2, investigator will confer with sponsor or designee about the patient's continued participation in the study.
c A patient will also be discontinued if his serum testosterone level at Week 2 is > 250 ng/dL.

BLOOD SAMPLE COLLECTION: Serum total testosterone concentrations (ng/dL) were obtained at the weekly titration visits (Weeks 1, 2, and 3 [optional]). Serum concentrations (ng/dL) of total testosterone, free testosterone, bioavailable testosterone, total DHT, LH, FSH, estradiol (E2), and SHBG were obtained at Baseline (Day 1), Months 1, 2, and 3 (or early termination visit) in Protocol UMD-01-090 and Months 4 and 6 (or early termination visit) in Protocol UMD-01-090E.

SAFETY ASSESSMENT: Safety of the subjects was monitored prior to, during, and at the conclusion of the study using the following assessments: AEs, clinical laboratory parameters, vital signs, physical examinations, skin application site assessments, gynecomastia.

SUBJECTS:
Of the 86 subjects, 59 subjects had a diagnosis of primary or secondary hypogonadism and 27 subjects had a diagnosis of CDGP. The mean age of all subjects was 14.3 years. Most subjects were White (N = 74, 86%) and of non-Hispanic and non-Latino ethnicity (N = 74, 86%). The mean height and weight for the Hypogonadal Population were 168.4 cm and 70.0 kg, respectively; for the CDGP Population the mean height and weight were 153.9 cm and 50.5 kg, respectively. 90% of the subjects completed the study. Table below summarizes the baseline characteristics of the subjects evaluated in this study:

		Subject Population Group	
	Statistic	Hypogonadal (N = 59)	CDGP (N = 27)
Testicular Volume (mL)	n	57	27
	Mean (SD)	3.2 (2.54)	4.4 (3.52)
Tanner Pubic Hair Stage	n	58	27
I	n (%)	12 (20.7)	13 (48.1)
II	n (%)	19 (32.8)	8 (29.6)
III	n (%)	9 (15.5)	5 (18.5)
IV	n (%)	11 (19.0)	0
V	n (%)	7 (12.1)	1 (3.7)
Bone Maturation Age (years)	n	56	26
	Mean (SD)	14.0 (1.26)	13.1 (1.09)
Serum Hormone Concentrations			
Total Testosterone (ng/dL)	n	58	27
	Mean (SD)	81.1 (108.9)	63.4 (86.1)
	Median	25	34
	Range	3, 470	3, 331
Free Testosterone (pg/mL)	n	58	27
	Mean (SD)	16.1 (23.2)	9.1 (19.5)
	Median	5	2
	Range	0, 107	0, 94
Total DHT (ng/dL)	n	56	27
	Mean (SD)	8.99 (9.04)	7.89 (5.58)
	Median	5.0	6.2
	Range	2.0, 34.0	2.0, 25.0
Gynecomastia Status	n	59	27
Present	n (%)	13 (22.0)	5 (18.5)
If Present, Horizontal Diameter (cm)	n	13	5
	Mean (SD)	7.4 (5.81)	4.8 (3.77)
Skin Application Site Status	n	59	27
Normal	n (%)	55 (93.2)	27 (100.0)
Abnormal	n (%)	4 (6.8)	0

Note: Percentages are based on the number of subjects who received study medication.

ANALYTICAL METHOD:

Validated RIA methods were employed for the analysis of total testosterone, free testosterone, DHT, estradiol and bioavilable testosterone in human serum. Serum samples were frozen and stored at -20°C prior to analysis (b) (4)

PHARMACOKINETIC ASSESSMENT:

Summary statistics for serum total testosterone concentrations at screening and the weekly titration visit (Weeks 1, 2, and 3 [optional]) are provided. Summary statistics for serum concentrations (ng/dL) of total testosterone, free testosterone, bioavailable testosterone, total DHT, LH, FSH, E2, and SHBG are provided for observed values at Baseline, Months 1, 2, 3, 4, and 6 and at the Final Visit. Summary statistics are presented for change from Baseline values at Months 1, 2, 3, 4, 6, and Final Visit.

RESULTS:

The summary of the treatment compliance is given in the following table:

		Subject Population Group		
	Statistic	Hypogonadal (N = 59)	CDGP (N = 27)	All Subjects (N = 86)
Compliance (%)	n	56	27	83
	Mean (SD)	72.3 (20.5)	90.7 (19.3)	78.3 (21.7)
Compliance (Categorized)				
< 80%	n (%)	34 (57.6)	7 (25.9)	41 (47.7)
80-120%	n (%)	22 (37.3)	19 (70.4)	41 (47.7)
> 120%	n (%)	0	1 (3.7)	1 (1.2)
Unknown	n (%)	3 (5.1)	0	3 (3.5)

Note: Compliance is calculated as (the number of grams of study medication used by a subject) divided by (the subject's overall dose estimate), multiplied by 100.

Approximately half of subjects (41/86) evaluated in this study had less than 80% compliance for dosing.

Following table summarizes the study medication dose received at Month 1 and final dose received by subjects in the Hypogonadal and CDGP population groups:

		Subject Population Group	
Average Medication Dose (g/day)	Statistic	Hypogonadal (N = 59)	CDGP (N = 27)
Month 1	n	56	27
0.5	n (%)	19 (32.2)	19 (70.4)
1.0	n (%)	3 (5.1)	1 (3.7)
1.5	n (%)	22 (37.3)	4 (14.8)
2.5	n (%)	11 (18.6)	3 (11.1)
3.0	n (%)	0	0
5.0	n (%)	1 (1.7)	0
Final Dose	n	59	27
0.5	n (%)	17 (28.8)	17 (63.0)
1.0	n (%)	9 (15.3)	2 (7.4)
1.5	n (%)	16 (27.1)	5 (18.5)
2.5	n (%)	12 (20.3)	3 (11.1)
3.0	n (%)	1 (1.7)	0
5.0	n (%)	4 (6.8)	0

Note: For subjects who received multiple doses of study medication between two visits, only the first dose received after attending the visit is presented.

In the hypogonadal population, most subjects used a study medication dose of either 0.5 g/day (32%) or 1.5 g/day (37%) at Month 1. A shift to higher final doses was observed: a final dose of either 0.5 g/day, 1.5 g/day, or 2.5 g/day were the most used (29%, 27%, and 20%, respectively). Most subjects in the CDGP Population were using a study medication dose of 0.5 g/day at Month 1 (70%) and as a final dose (63%). A final dose of 1.5 g/day or 2.5 g/day was only used by 30% of subjects in the CDGP Population.

The pharmacokinetic results in terms of observed total testosterone and free testosterone serum concentrations resulting from different treatments in hypogonadal and CDGP subjects are summarized by the actual AndroGel Dose in the Tables below:

Total Testosterone:

		SubjectPopulationGroups							
		Hypogonadal (N=59)				CDGP (N=27)			
		Actual Dose (g/day)							
Parameter	Statistic	0.5	1.0	1.5	2.5	0.5	1.0	1.5	2.5
Serum Total testosterone (ng/dL)									
Baseline	n	58	0	0	0	27	0	0	0
	Mean (SD)	81.1 (108.9)	- (-)	- (-)	- (-)	63.4 (86.1)	- (-)	- (-)	- (-)
	Median	24.5	-	-	-	34.0	-	-	-
	Range	3,470	-,-	-,-	-,-	3,331	-,-	-,-	-,-
Month 1	n	18	2	24	11	18	1	4	3
	Mean (SD)	252.4 (205.8)	352.0 (14.1)	223.8 (158.2)	253.5 (143.9)	203.5 (111.9)	750.0 (-)	349.8 (126.5)	469.7 (197.6)
	Median	191.0	352.0	161.0	217.0	166.0	750.0	368.5	478.0
	Range	16,774	342,362	35,660	46,499	26,464	750,750	202,460	268,663
Month 3	n	15	4	19	10	19	1	3	3
	Mean (SD)	205.7 (119.1)	446.8 (83.5)	196.1 (117.2)	278.9 (145.7)	180.8 (99.5)	133.0 (-)	246.3 (170.9)	408.3 (134.0)
	Median	183.0	438.0	179.0	206.0	163.0	133.0	187.0	456.0
	Range	55,498	355,556	9,469	133,601	86,511	133,133	113,439	257,512
Month 6	n	12	9	10	9	11	2	4	3
	Mean (SD)	313.6 (160.0)	288.7 (159.4)	191.0 (73.4)	378.3 (392.3)	210.5 (148.5)	300.5 (159.1)	251.5 (115.8)	330.7 (199.9)
	Median	285.5	338.0	176.0	227.0	190.0	300.5	229.0	352.0
	Range	120,624	62,505	75,288	29,1104	88,626	188,413	140,408	121,519
Final Visit	n	17	9	14	11	17	2	4	3
	Mean (SD)	262.8 (163.0)	288.7 (159.4)	169.9 (75.4)	436.3 (450.4)	192.4 (122.5)	300.5 (159.1)	251.5 (115.8)	330.7 (199.9)
	Median	243.0	338.0	159.0	227.0	164.0	300.5	229.0	352.0
	Range	16,624	62,505	56,288	29,1259	88,626	188,413	140,408	121,519

Free Testosterone:

		SubjectPopulationGroups							
		Hypogonadal (N=59)				CDGP (N=27)			
		Actual Dose (g/day)							
Parameter	Statistic	0.5	1.0	1.5	2.5	0.5	1.0	1.5	2.5
Free Testosterone (pg/mL)									
Baseline	n	58	0	0	0	27	0	0	0
	Mean (SD)	16.09 (23.23)	- (-)	- (-)	- (-)	9.12 (19.50)	- (-)	- (-)	- (-)
	Median	5.20	-	-	-	2.00	-	-	-
	Range	0.4,107.0	-,-	-,-	-,-	0.2,94.0	-,-	-,-	-,-
Month 1	n	18	2	24	11	18	1	4	3
	Mean (SD)	44.03 (49.88)	63.00 (16.97)	44.00 (44.75)	54.11 (42.00)	23.90 (24.31)	68.00 (-)	44.50 (18.12)	67.33 (47.01)
	Median	22.50	63.00	25.50	38.00	15.50	68.00	41.50	66.00
	Range	1.8,201.0	51.0,75.0	6.3,185.0	9.2,132.0	3.6,98.0	68.0,68.0	26.0,69.0	21.0,115.0
Month 3	n	15	4	19	9	19	1	3	3
	Mean (SD)	32.79 (17.71)	65.25 (13.94)	35.69 (30.33)	56.89 (24.82)	23.07 (28.32)	25.00 (-)	27.00 (14.73)	40.00 (14.93)
	Median	33.00	64.00	29.00	50.00	12.00	25.00	35.00	46.00
	Range	9.9,65.0	50.0,83.0	1.4,136.0	24.0,104.0	4.1,102.0	25.0,25.0	10.0,36.0	23.0,51.0
Month 6	n	12	9	10	9	11	2	4	3
	Mean (SD)	45.42 (24.04)	64.89 (53.92)	36.03 (21.73)	92.18 (126.25)	30.81 (45.77)	34.50 (2.12)	37.95 (27.14)	60.00 (58.13)
	Median	37.00	52.00	24.00	41.00	15.00	34.50	37.00	42.00
	Range	15.0,100.0	17.0,164.0	8.3,71.0	2.6,354.0	6.9,163.0	33.0,36.0	9.8,68.0	13.0,125.0
Final Visit	n	16	9	14	11	17	2	4	3
	Mean (SD)	36.52 (26.31)	64.89 (53.92)	32.16 (20.48)	108.60 (141.07)	25.56 (37.64)	34.50 (2.12)	37.95 (27.14)	60.00 (58.13)
	Median	33.50	52.00	22.50	41.00	15.00	34.50	37.00	42.00
	Range	1.8,100.0	17.0,164.0	8.3,71.0	2.6,354.0	4.1,163.0	33.0,36.0	9.8,68.0	13.0,125.0

SAFETY ASSESSMENT

A total of 74 subjects (86.0%) experienced TEAEs during the study; 48 subjects experienced a TEAE that was considered related to study medication. Most TEAEs were

considered mild; 4 subjects (4.7%) experienced a TEAE that was considered severe. Headache was the most frequent TEAE and was experienced by 23.3% of subjects in the All Subjects Population, followed by cough (12.8%), and upper respiratory infection (11.6%). A total of eight subjects experienced acne. Neither the overall incidence of TEAEs, nor the incidence of specific TEAEs appears to be related to the dose of study medication. Four subjects experienced treatment-emergent severe adverse events (SAEs) (severe adjustment disorder with depressed mood, appendicitis, slipped femoral epiphysis, and depression). One subject permanently discontinued study medication due to the SAE of depression. No deaths occurred in this study. There were no clinically meaningful changes from Baseline to Final Visit for any hematology, blood chemistry, urinalysis, or lipid parameters, vital sign parameter, or physical examination results.

CONCLUSION

- Increases in serum testosterone concentrations were observed in boys diagnosed with delayed puberty due to primary or secondary hypogonadism or CDGP after treatment with testosterone gel 1% starting at a dose of 0.5 g with upward weekly titration.
- The most frequently used final doses were 0.5 g/day, 1.5 g/day, or 2.5 g/day in the Hypogonadal Population while the most frequently final dose used was 0.5 g/day in the CDGP Population.

4.3. FILING REVIEW FORM

Office of Clinical Pharmacology *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		Information
NDA	(b) (4)	Brand Name	ANDROGEL®
OCP Division	2	Generic Name	Testosterone
Medical Division	DMEP, HFD-510	Drug Class	Steroid Hormone
OCP Reviewer	S.W. Johnny Lau		(b) (4)
OCP Team Leader (Acting)	Sally Y. Choe	Dosage Form	Topical Gel
Date of Submission	12-Jun -2007	Dosing Regimen	0.5 g/day
Estimated Due Date of OCP Review	16-NOV-2007	Route of Administration	Transdermal
PDUFA Due Date (Action)	13-DEC-2007	Sponsor	Solvay Pharmaceuticals
Division Due Date	28-NOV-2007	Priority Classification	Standard

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Comments (Study number)
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary				
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Metabolism in different species:				
Isozyme characterization:				
Metabolite Identity				
Metabolism inhibition:				
Plasma protein binding:				
Blood/plasma ratio:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Cancer Patients (bone metastases)-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	2		Study UMD-01-080 (Phase 1): Study UMD-01-090 (Phase 2)
Phase 3 clinical trial:				
Population Analyses -				

Meta-analysis:				
NONMEM:				
II. Biopharmaceutics				
Absolute bioavailability:				
Bioequivalence				
Relative bioavailability				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
QT prolongation assessment				
Total Number of Studies	x	2		

Filability and QBR comments

	"X" if yes	Comments
Application filable?	X	
Comments to be sent to firm?	X	Please provide individual patient's concentration-time and respective pharmacokinetic parameters data for serum total and unbound testosterone as well as serum total dihydrotestosterone for Studies UMD-01-080 and UMD-01-090 via SAS transport files.
QBR questions (key issues to be considered)		
Other comments or information not included above	Since the serum testosterone concentrations are used as a primary efficacy measurement, a DSI inspection on the pivotal clinical study's (UMD-01-090) bioanalytical work to measure serum testosterone concentrations (about 1000 samples) is in order. Study UMD-01-090 A Multi-Center, Open-Label, Observational Study of Testosterone Gel (1%) in the Treatment of Adolescent Boys with Hypogonadism Bioanalytical Site: (b) (4)	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

Timeline:
Receipt date: June 13, 2007
Filing date: August 12, 2007
Pediatric Exclusivity Board meeting: August 22, 2007
74 Day letter must issue: on or before **August 24, 2007**
Day 90: September 11, 2007 (Exclusivity Board decision due)
Date to Division Director: November 28, 2007
Day 175: December 5, 2007 (reviews must be posted on pediatric website)
PDUFA Goal Date: December 13, 2007

Filing Memo

CLINICAL PHARMACOLOGY

NDA:	(b) (4)
Compound:	Testosterone 1% (ANDROGEL®)
Sponsor:	Solvay Pharmaceuticals
Submission Date:	June 12, 2007
From:	S.W. Johnny Lau, R.Ph., Ph.D.

Background

The sponsor markets testosterone topical gel 1% (ANDROGEL®) for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone:

- Primary hypogonadism (congenital or acquired)
- Hypogonadotropic hypogonadism (congenital or acquired)

The sponsor submitted NDA (b) (4) (b) (4)

Findings

To support NDA (b) (4) the sponsor submitted the following information:

Major:

- Reports of the Phase I Study UMD-01-080 and Phase II Study UMD-01-090 (See Attachment)
- Bioanalytical reports with validation data for Studies UMD-01-080 and UMD-01-090 for the determination of bioavailable, total, and free testosterone as well as total dihydrotestosterone
- The sponsor claimed to use (b) (4) in clinical Studies UMD-01-080 and UMD-01-090. Quality Assurance reviewer will verify (b) (4)
- (b) (4)

Minor:

- The last amended Pediatric Study Written Request
- Accomplishment to meet the conditions of the Pediatric Study Written Request

Attachment starts here.

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK, safety	UMD-01-080 (United States)	Evaluate the steady-state serum testosterone concentrations, the pharmacokinetic (PK) characteristics, and the safety and tolerability of testosterone gel 1%.	Multi-center, open-label escalating-dose	Testosterone gel 1% 0.5 g, 1.5 g, 2.5 g each dose was applied topically once daily at bedtime for four consecutive days.	13; 4 17 total	Primary or secondary hypogonadism; CDGP	Up to 12 days	Complete; Full
Safety	UMD-01-090 (United States)	Evaluate the clinical response to testosterone gel 1%	Multi-center, open-label	Testosterone gel 1% 0.5 g, 1.0 g, 1.5 g, 2.5 g, 3.0 g, and 5.0 g was applied topically once daily at bedtime.	59; 27 86 total	Primary or secondary hypogonadism; CDGP	Six months	Complete; Full

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/s/

S.W. Johnny Lau
8/22/2007 02:22:41 PM
BIOPHARMACEUTICS

Sally Choe
8/22/2007 03:32:09 PM
BIOPHARMACEUTICS

4.4. DIVISION OF SCIENTIFIC INVESTIGATION REVIEW

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 20, 2007

TO: Mary H. Parks, MD
Director
Division of Anesthesia, Analgesia, and
Rheumatology Products (HFD-510)

FROM: Nilufer M. Tampal, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. 11/20/07
Associate Director – Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA (b) (4)
Androgel PD (testosterone) Gel 1%, Sponsored by Solvay Pharmaceuticals,
Agent for Unimed Pharmaceuticals, Inc.

At the request of HFD-510, the Division of Scientific Investigations conducted an audit of the analytical portion of the following observational study:

Protocol UMD-01-090: A Multi-Center, Open-Label, Observational Study of Testosterone Gel (1%) in the Treatment of Adolescent Boys with) Constitutional Delay of Growth and Puberty (CDGP) ((b) (4) Project UN1009).

The inspection focused only on total testosterone (TT), free testosterone (FT) and dihydrotestosterone (DHT) measurements as requested by the review division in the email dated 10/24/07. The analytical portions of the study were conducted (b) (4) Following the inspection (11/01-09/07) Form FDA 483 was issued (attachment 1). Our evaluation of the significant findings is as follows:

(b) (4)

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/s/

Manoj Khurana
12/6/2007 05:21:02 PM
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Sally Choe
12/7/2007 04:07:21 PM
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