CLINICAL REVIEW

Application Type	NDA
Submission Number	(b) (4)
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Letter Date	June, 12, 2006
Stamp Date	June 12, 2006
PDUFA Goal Date	December 10, 2007
Reviewer Name	Dragos Roman
Review Completion Date	December 3, 2007
Established Name	Testosterone gel 1 %
(Proposed) Trade Name	AndroGel
Therapeutic Class	Testosterone (androgen)
Applicant	Solvay Pharmaceuticals
Priority Designation	P
Formulation	Metered-dose pump (1.25 g per actuation) and individual packets (2.5 g and 5 g, respectively)
Dosing Regimen	Dosing Regimen 0.5 g, 1.5 g or 2.5 g daily

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

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1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

None at this point.

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1.2.2 Required Phase 4 Commitments

None at this point.

1.2.3 Other Phase 4 Requests

None at this point.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

AndroGel® is 1 % testosterone manufactured as a hydroalcoholic gel for cutaneous administration. Approved in 2000 under NDA 21-015 for the treatment of primary and secondary hypogonadism in adults, AndroGel is to be administered once daily in doses of 5 g, 7.5 g, or 10 g (which contain 50 mg, 75 mg, and 100 mf of testosterone, respectively) and is supplied as metered-dose pump[2] and individual unit-dose packets[3].

On June 21, 2002 the Division of Endocrinology and Metabolism Products (DMEP) issued a Written Request (WR) to Unimed Pharmaceuticals Inc. for the indication of delayed puberty in boys. The final version of the WR (dated May 24, 2007) requested the following two studies:

- Study 1: a pharmacokinetic (PK) study of testosterone 1% gel in boys with delayed puberty.
- Study 2: a dose titration and safety study of testosterone 1% gel in boys with delayed puberty.

In response to the WR, the applicant conducted studies UMD-01-080 and UMD-01-090.

Study UMD-01-080 (Study 1 of the WR) was a multicenter, open-label, escalating-dose study conducted in 17 boys with delayed puberty due to hypogonadism or constitutional delay of growth and puberty[4]. The study evaluated the pharmacokinetic profile of three (b) (4) pediatric AndroGel doses: 0.5 g, 1.5 g, and 2.5 g (containing 5 mg, 15 mg, and 25 mg of testosterone, respectively).

Study UMD-01-090 (Study 2 of the WR) was a single-arm, open-label, multicenter, 6-month, observational study of AndroGel treatment that was conducted in 86 males aged 13-18 years

[2] A metered-dose pump contains 75 g of of AndroGel (or 60 metered 1.25 g doses).
[3] Individual packets are supplied as 2.5 g and 5 g packets, respectively.
[4] Of the 17 patients enrolled, 6 patients (35.3%) had a diagnosis of primary hypogonadism, 7 patients (41.2%) had a diagnosis of secondary hypogonadism and 4 patients (23.5%) had a diagnosis of CDGP. Approximately two-thirds of all patients were naive to androgen therapy prior to entering the study (11 patients or 64.7%). Patients received a single AndroGel dose for 4 days prior to PK evaluation; after an approximately 14 day washout the next ascending dose was applied.

with a diagnosis of delayed puberty due to primary or secondary hypogonadism, or CDGP[5]. Study treatment began with a 3-week titration period aimed at bringing serum testosterone concentrations in a range deemed appropriate for each patient's Tanner stage[6], followed by a maintenance phase wherein the AndroGel dose was kept more or less constant. The daily AndroGel doses were the same three doses that were evaluated pharmacokinetically in Study 1 (i.e. 0.5 g, 1.5 g, and 2.5 g). The starting dose was 0.5 g daily; dose escalation was based on measured serum testosterone concentrations at steady state. The goal of this study, as stated in the WR, was "to establish a dose regimen that can be safely used for initiating or for progressing puberty". To this end, this study was not designed to evaluate the efficacy of AndroGel whose active ingredient (testosterone) is well characterized and understood in both physiologic and non-physiologic states, but rather to evaluate a starting dose of AndroGel in adolescents, gather information on serum testosterone levels (b) (4) and assess safety (in particular the advancement of bone age relative to that of chronological age).

1.3.2 Efficacy

As mentioned above, Study UMD-01-090 was not an efficacy study (the WR defined it as a"dose titration and safety study") and did not include a control group. Consequently the efficacy assessments collected in Study UMD-01-090 provided very limited information. In addition, even the efficacy analyses performed were largely noninformative due to the heterogeneity[7] of the patient population enrolled in the study and to multiple protocol violations (for instance 19/86 or 22.1% patients were enrolled despite not meeting the inclusion criteria for testosterone level and/or testicular volume).

Study UMD-01-090, however, collected extensive dose-exposure data (specifically, serum testosterone levels in over 70 patients for up to 6 months over the whole range of doses administered), thus expanding considerably the information provided in the pharmacokinetic Study UMD-01-080. The significance of these data is discussed in the Dosage and Administration Section.

[5] Of the 86 patients enrolled, 59 (69%) had a diagnosis of primary or secondary hypogonadism and 27 (31%) had a diagnosis of CDGP. Of the hypogonadal patients 61% had primary hypogonadism and 39% had secondary hypogonadism; 49% of the hypogonadal patients were naïve to testosterone treatment.
[6] The initial titration goal was 100-200 ng/dL. Following an amendment (Amendment 6) this goal was abandoned.
[7] Part of the basis for heterogeneity was that the study included both testosterone-naïve and non-naïve patients. More importantly, however, many patients were already in puberty at baseline: 79 % of hypogonadal patients and 52 % of CDGP patients were ≥ Tanner II and, across diagnostic groups, 19 patients or 22% were already Tanner IV or V (prepubertal and pubertal patients have different initial titration goals). In addition, since some hypogonadal and CDGP patients had endogenous testosterone production (as indicated by high screening and/or baseline total testosterone serum concentrations), it is impossible to differentiate the clinical effects of AndroGel from those due to the endogenous testosterone. Finally, unusually high testosterone levels at baseline observed in some patients may have been due to incomplete washout of prior testosterone treatment in non-naïve patients; as this was an uncontrolled study, reliable baseline information is critical for drawing efficacy conclusions.

1.3.3 Safety

The safety information collected from 86 patients treated for 6 months with AndroGel during trial UMD-01-090 does not identify any new safety signals specific to the pediatric population. This should not be surprising since the active ingredient in AndroGel is testosterone, a compound well characterized in both adults and adolescents. In addition, it should be recognized that, at least for hypogonadal patients, testosterone treatment with AndroGel is not pharmacological but rather replacement therapy aimed at reaching serum testosterone levels appropriate for various normal stages of puberty.

There were no patient deaths in either study. There were four serious adverse events, all in Study UMD-01-090[8]. Only one of them (slipped femoral epiphysis head) was considered possibly related to study medication. Only one patient discontinued the trial for an adverse event (depression).

There was no specific pattern of treatment-emergent adverse events in any of the two studies. The adverse events encountered were mostly manifestations of childhood illnesses. Most adverse events were mild in intensity, some moderate and very few were severe[9]. Although as many as 48 patients (55.8%) experienced a TEAE that was judged "related" to study medication, acne is the only adverse event that can be mechanistically attributed with a reasonable degree of certainty to the study drug. Firm conclusions are difficult to draw due to the absence of a control group.

Standard clinical laboratory and vital signs evaluations did not show any clinically meaningful changes on AndroGel treatment.

Dosing Regimen and Administration

The studies submitted with this NDA evaluate three pediatric AndroGel doses: 0.5 g/day, 1.5 g/day, and 2.5 g/day, respectively. These three doses were selected with the goal of providing serum testosterone concentrations that cover the whole range of testosterone values expected during adolescence. Since serum testosterone concentrations are not uniform throughout puberty but rather increase gradually as the hypothalamic-pituitary- gonadal axis matures, AndroGel treatment is to be started with the low dose (0.5 g/day) and escalated as needed to higher doses (1 g/day and 2.5 g/day) toward adult doses at the end of puberty (5 g/day through 10 g/day). Thus, it is reasonable to assume that, once a safe starting dose of AndroGel is established, given the availability of intermediary pediatric doses, as well as the currently approved adult doses, testosterone titration can be achieved safely with periodic monitoring of serum testosterone, bone age advancement, Tanner stage progression, and growth velocity[10]. It is for these reasons that

[8] Severe adjustment disorder with depressed mood, appendicitis, slipped femoral epiphysis head, and severe depression.
[9] All severe adverse events were in study UMD-01-090 and all were captured as serious adverse events, described above.
[10] Generally speaking, a starting dose of AndroGel is expected to be low enough to generate serum testosterone

this review places particular emphasis on the starting AndroGel dose of 0.5 g/day. It should be emphasized that the 0.5 g dose was in fact the most widely used AndroGel dose in the trial, with approximately 30-40 % of patients receiving it at any given time.

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levels that do not exceed those associated with the early stages of puberty (e.g. Tanner II) and provide reassurance that it does not accelerate unduly bone age at least short-term (otherwise it would raise the concern of loss in final height)

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Finally, and importantly, a routine, audit of the testosterone data collected in Study UMD-01-090, concluded that there were "significant deficiencies that impact[ed] the integrity of the data generated by (b) (4) the clinical laboratory where the testosterone data were centrally analyzed); these deficiencies concerned both the validation of the assay (accuracy, precision, linearity) and the analytical runs (for a detailed description of these deficiencies, refer to the clinical pharmacology review) [16].

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[16] In addition, since Study UMD-01-080, although not formally evaluated by DSI, utilized the same testosterone assay methods used in Study UMD-01-090, this calls into question the reliability of the data collected in Study UMD-01-080as well.

1.3.5 Drug-Drug Interactions

No drug-drug interaction studies were conducted.

Special Populations

No studies were conducted in patients with hepatic or renal failure.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

AndroGel® (testosterone gel) 1% is a hydroalcoholic gel containing 1% testosterone for daily cutaneous administration. AndroGel was approved in 2000 as testosterone replacement therapy in adult males with testosterone deficiency states (primary and secondary hypogonadism). The approved AndroGel doses for adults are 5 g, 7.5 g, and 10 g. AndroGel is supplied as a multi-dose pump capable of delivering 1.25 g of AndroGel per actuation (equivalent to 11.25 mg of testosterone) and as unit-dose packets containing 2.5 g or 5 g gel per packet (equivalent to 25 mg or 50 mg testosterone, respectively). AndroGel treatment is to be initiated with the 5 g dose and adjusted upward with the goal of bringing the testosterone serum level within the normal range.

The pediatric AndroGel drug product, which is the subject of this NDA supplement, is identical to the already approved adult product. The only difference is a new multi-dose pediatric pump that delivers (b) (4) per actuation (instead of a 1.25 g per actuation for the adult pump). Applicant's Table 2.3.P.1 lists the components of the pediatric AndroGel drug product.

Table 2.3.P.1 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
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2.3 Availability of Proposed Active Ingredient in the United States

Currently there are several testosterone based drug products approved in the US, which are administered via several routes: oral, buccal, injectible, transdermal, or as implants. Table 1 summarizes currently approved products (other than AndroGel) by active ingredient, dosage form, and strength, as currently listed in the Orange Book.

Table 1: Currently approved testosterone products listed in the Orange Book

Active Ingredient	Dosage form/route	Dosage strength	Proprietary name	Maker
Methyltestosterone	Capsule/oral	10 mg	Virilon	Star Pharms Fl
Methyltestosterone	Capsule/oral	10 mg	Testred	Valeant Pharm Intl
Methyltestosterone	Tablet/oral	10 mg, 25 mg	Methyltestosterone	Impax Labs
Methyltestosterone	Tablet/oral	10 mg	Android 10	Valeant Pharm Intl
Methyltestosterone	Tablet/oral	25 mg	Android 25	Valeant Pharm Intl
Testosterone	Film, extended release/transdermal	2.5 mg/24 h	Androderm	Watson Labs
Testosterone	Film, extended release/transdermal	5 mg/24 h	Androderm	Watson Labs
Testosterone	Gel/transdermal	1%	Testim	Auxilium Pharms
Testosterone	Gel/transdermal	1%	Testosterone	Par Pharm
Testosterone	Gel/transdermal	1%	Testosterone	Watson Labs
Testosterone	Injectable/injection	100 mg/ml	Testosterone	Watson Labs
Testosterone	Pellet/implantation		Testosterone	Bartor
Testosterone	Extended release tablet/buccal	30 mg	Striant	Columbia Labe
Testosterone cypionate	Injectable/injection	200 mg/ml	Testosterone cypionate	Paddock
Testosterone cypionate	Injectable/injection	100 mg/ml and 200 mg/ml	Depo-testosterone	Pharmacia and Upjohn
Testosterone cypionate	Injectable/injection	100 mg/ml and 200 mg/ml	Testosterone cypionate	Sandoz
Testosterone cypionate	Injectable/injection	200 mg/ml	Testosterone cypionate	Synerx Pharma
Testosterone cypionate	Injectable/injection	100 mg/ml and 200 mg/ml	Testosterone cypionate	Watson Labs
Testosterone enanthate	Injectable/injection	200 mg/ml	Delatestryl	Indevus Pharms
Testosterone enanthate	Injectable/injection	200 mg/ml	Testosterone enanthate	Paddock
Testosterone enanthate	Injectable/injection	200 mg/ml	Testosterone enanthate	Watson Labs
Testosterone propionate	Injectable/injection	25 mg/ml, 50 mg/ml, 100 mg/ml	Testosterone propionate	Watson Labs

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2.4 Important Issues With Pharmacologically Related Products

Testosterone was first synthesized in 1930. Although well absorbed, oral testosterone is rapidly degraded during its passage through the liver making the oral route of administration difficult for long-term therapy. 17α-derivatives of testosterone (e.g. methyl testosterone) were developed to slow the metabolism but have been associated with hepatotoxicity and are therefore rarely used. 17β-derivatives (enanthate and cypionate) were subsequently developed to extend the duration of action and are widely used forms of testosterone.

The safety profile of testosterone has been, in general, well characterized due to its established physiologic functions and to states of testosterone excess (e.g. testotoxicosis, androgen-secreting tumors, etc). In children, excessive testosterone secretion induces premature manifestations of virilization and short stature due to early epiphyseal maturation and closure.

2.5 Presubmission Regulatory Activity

Both studies submitted in this application were conducted in response to a Written Request that the Division issued on June 21, 2002 to Unimed Pharmaceuticals Inc. Per Written Request, the indication to be studied was that of delayed puberty. Several amendments were issued to the WR; the main purpose of these amendments was to address some of the scientific and logistic problems encountered by the sponsor during the implementation of the requested studies. In addition, the Division provided standard regulatory guidance through several teleconferences held with the applicant.

2.6 Other Relevant Background Information

None.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

See CMC review.

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3.2 Animal Pharmacology/Toxicology

There was no new animal toxicology data submitted with this application.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The main sources of data for this clinical review are the two clinical studies conducted under the WR (studies UMD-01-080 and UMD-01-090) and subsequent submissions made in response to Division's requests for additional data dated September 21, 2007 and October 5, 2007.

4.2 Tables of Clinical Studies

The clinical studies submitted in this NDA are summarized in Table 2:

Table 2: Summary of clinical studies of the AndroGel Written Request

WR Study	Description
UMD-01-080	A multicenter, open-label, escalating-dose study conducted in 17 prepubertal adolescent boys aimed at evaluating the pharmacokinetic (PK) profile of three AndroGel doses (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.
UMD-01-090	A multicenter, single-arm, open-label, observational study of AndroGel conducted over 6 months in 86 males with delayed puberty due to primary or secondary hypogonadism and constitutional delay of growth and puberty. Patients were titrated to a testosterone serum concentration appropriate to their Tanner stage using three AndroGel escalating daily doses: 0.5 g, 1.5 g, and 2.5 g.

4.3 Review Strategy

The clinical study UMD-01-090 has been the focus of this review, along with the pharmacokinetic information provided by Study UMD-01-80.

4.4 Data Quality and Integrity

The applicant states that quality control measures during the conduct of the studies included the selection of qualified investigators and appropriate study sites, the review of protocol procedures with the investigators and associated personnel prior to the study, and periodic monitoring visits. CRFs were periodically reviewed for accuracy and completeness. Patient records were regularly checked for completeness, accuracy of entries on the CRFs, adherence to the protocol and to

GCP. Study site visits and inspections were made by the sponsor or designee at regular intervals. A total of four audits were conducted at four different study sites. (b) (4) performed all data management activities.

A routine Division of Scientific Investigation (DSI) visit was requested by DMEP for the clinical sites with the largest number of patients enrolled. Four sites were inspected; they contributed a total of 38 patients (44 % of all patients enrolled in study UMD-01-090). The main observations made by the DSI team are summarized next:

Site 124 (enrolled 10 patients):

- Contrary to the study protocol several subjects had evaluations performed by multiple observers (instead of one observer).
- Two subjects with Month 6 bone age data did not have it included in the study report[18].

Site 104 (enrolled 9 patients):

- Four out of nine patients did not meet the inclusion criterion for baseline testosterone level and one additional patient did not meet the inclusion criterion for testicular volume; all five violators were enrolled with waivers from the sponsor.

Site 109 (enrolled 10 patients):

- Two patients did not meet the inclusion criterion for baseline testosterone level but were enrolled with waivers from the sponsor.

Site 103 (enrolled 9 patients):

- Five out of nine patients did not meet the inclusion criterion for baseline testosterone level (and in some cases also for testicular volume) but were enrolled with waivers from the sponsor.
- Three patients were deemed 'non-naïve" by the applicant although they never received androgen therapy (these patients had the following serum testosterone levels at screening: 561 ng/dL, 205 ng/dL, and 426 ng/dL, respectively).

At the request of the clinical pharmacology team, DSI also conducted an audit of the analytical portion of Study UMD-01-090, focusing on the total testosterone, free testosterone, and dehydrotestosterone measurements (all assays were conducted (b) (4)). The DSI report concludes that there were "significant deficiencies that impact the integrity of the data generated (b) (4)". The deficiencies that were identified concerned both the validation of the assay (accuracy, precision and linearity) and the analytical runs. Since Study UMD-01-080 (although not formally evaluated by DSI) utilized the same assay method, the reliability of the data collected in this study comes under question as well. For a detailed description of these deficiencies refer to the clinical pharmacology review.

[18] Patient 3232 had a month 6 bone age of 14.09 years and patient 3233 had a Month 6 bone age of 14.2 yesrs.

4.5 Compliance with Good Clinical Practices

The applicant states that the protocol with its amendments, the informed consent and assent forms, the annual reports and serious adverse events were presented for review to an Institutional Review Board. It is also reported that the study was conducted "in accordance with the Code of Federal Regulations (21 CFR parts 50, 54, 56, 312, 314, and 320) and International Conference on Harmonization Guidelines (E6 and E11), which originate from the ethical principles laid down in the current revision of the Declaration of Helsinki [and that] Good Clinical Practices (GCPs) and (b) (4) policies and procedures were also followed." Signed informed consent and assent forms were obtained from each subject prior to study participation. Protocol changes were done via written protocol amendments that had to be approved by the applicant before implementation. Deviations from the protocol were reportedly permitted only in the event of an emergency and for subjects with minor departures from the inclusion/exclusion criteria.

The DSI inspection, described in the previous section of this review, questions whether the investigators who enrolled patients with inclusion criteria deviations had in fact obtained IRB approval (in addition to sponsor approval) for enrolling them.

4.6 Financial Disclosures

The applicant provided a signed FDA Form 3454 that certifies that Solvay Pharmaceuticals has not entered into any financial agreement with the listed investigators "whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a)". The applicant also certifies that none of the clinical investigators had a proprietary interest in the product or a significant equity in the sponsor as defined in 21CFR 54.2(b) and that no listed investigator was the recipient of significant payments of other sorts as defined in 21CFR 54.2(f). An attached list of investigators includes all the participating sites (6 sites for study UMD-01-080 and 18 sites for study UMD-01-90). Form FDA 3455 was submitted for (b) (6) "reported unspecified types of significant payments of other sorts, the total of which exceeds USD $25,000, excluding the cost of conducting the clinical trial or other clinical trial." (b) (6)

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

The applicant conducted Study UMD-01-080, a multicenter, open-label, escalating-dose study that included 17 prepubertal boys of adolescent age that was aimed at evaluating the

pharmacokinetics (PK) of AndroGel. The study included one treatment group and three treatment periods during which patients applied one of three escalating doses of AndroGel: 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[19]. Each treatment period was separated by a washout period of up to 14 days[20]. The selected daily doses of 0.5 g, 1.5 g, and 2.5 g were based on data collected from previous clinical studies of hypogonadal adult males. The study design is displayed in applicant's Table 1. The study was conducted between August 2, 2002 and April 23, 2006. The batches of AndroGel used in this study were 5265-69, EP-1020, and EP-926.

Table 1 UMD-01-080 Study Scheme

Pharmacokinetic Evaluation Phase							*Extension Phase*		
Screening	Baseline	Treatment Period 1 0.5 g of Testosterone Gel 1%	Washout Period 1 (if needed)	Treatment Period 2 1.5 g of Testosterone Gel 1%	Washout Period 2 (if needed)	Treatment Period 3 2.5 g of Testosterone Gel 1%	*Clinical Dose Assigned by Investigator*		
		Visit 1		Visit 2		Visit 3	*Visit 4*	*Visit 5*	*Visit 6*
Days -14 to –1	Day 0	4 days	no more than 14 days	4 days	no more than 14 days	4 days	*1 week after Visit 3*	*3 months after Visit 3*	*6 months after Visit 3*

Patients were included in the study on the basis of the following criteria:

- signed informed consent/assent according to local laws
- age 13 to 17 years
- male gender
- a diagnosis of primary or secondary hypogonadism, or constitutional delay of growth and puberty (CDGP)
- prepubertal maturation status for testosterone-naive subjects as indicated by a testicular volume of ≤ 3 mL. and a serum testosterone concentration of ≤ 50 ng/dL
- bone age of at least 10.5 years
- hemoglobin of at least 12 g/dL and hematocrit of at least 36%
- baseline growth data of at least six months prior to study drug administration.

Patients were excluded from the study if they met any of the following criteria:

- clinically significant uncontrolled medical condition (e.g., hepatic or renal disease) or psychiatric disorder
- untreated endocrine disorder (endocrine disorders must have been on stable treatment regimens for at least three months)
- generalized skin disease that may affect absorption of testosterone gel 1%
- known skin intolerance to alcohol
- investigational drug use within 30 days prior to enrollment

[19] AndroGel was supplied in multi-dose bottles with attached pumps calibrated to dispense (b) (4) testosterone gel 1%. The 0.5 g dose required one actuation, the 1.5 g required 3 actuations and the 2.5 g required 5 actuations. Subjects were instructed to apply the daily dose of AndroGel in the morning and to wash the application site with soap and water 8-10 hours later.

[20] After the completion of the study 10 patients entered the clinical study UMD-01-090 (Patients 111/2001, 114/2041, 114-2042, 114/2043, 125/2021, 125/2022, 127/2061, 127/2062, 127/2063, and 27/2064).

- history of drug or alcohol abuse
- use of concomitant medications which could interfere with assessments
- Body Mass Index more than one standard deviation (SD) below or three SD above normal for age
- congenital adrenal hyperplasia
- known hypersensitivity or intolerance to soy or soy products.

The baseline characteristics for patients enrolled in this study are presented in Table 8. Six subjects (35.3%) had a diagnosis of primary hypogonadism, seven subjects (41.2%) had a diagnosis of secondary hypogonadism and four subjects (23.5%) had a diagnosis of CDGP. Approximately two-thirds of all subjects were naive to androgen therapy prior to entering the study (11 patients or 64.7%). The mean age at enrollment was 14.8 years (similar for hypogonadal and CDGP patients) and the mean bone age was 14.0 years. The mean serum total testosterone concentration was 70.5 ng/dL, (with a median serum total testosterone concentration of 19.0 ng/dL).

Table 8 Other Baseline Characteristics
All Subjects

Parameter	Statistic	Subject Population		
		CDGP	Hypogonadal	All Subjects
Testicular Volume (mL)	n	4	13	17
	Mean (SD)	6.3 (5.56)	1.8 (1.52)	2.9 (3.35)
	Median	5.0	2.0	2.0
	Range	1.0, 14.0	0.0, 4.0	0.0, 14.0
Tanner Pubic Hair Stage	n	4	12	16
I	n (%)	0	2 (16.7)	2 (12.5)
II	n (%)	1 (25.0)	3 (25.0)	4 (25.0)
III	n (%)	3 (75.0)	3 (25.0)	6 (37.5)
IV	n (%)	0	1 (8.3)	1 (6.3)
V	n (%)	0	3 (25.0)	3 (18.8)
Bone Maturation Age (years)	n	4	13	17
	Mean (SD)	13.5 (0.58)	14.1 (1.25)	14.0 (1.15)
Was the Subject Naive to Androgen Therapy Prior to Entering UMD-01-080				
Yes	n (%)	3 (75.0%)	8 (61.5%)	11 (64.7%)
No	n (%)	1 (25.0%)	5 (38.5%)	6 (35.3%)
Serum Hormone Concentrations				
Total Testosterone (ng/dL)	n	4	13	17
	Mean (SD)	97.3 (97.80)	62.3 (118.90)	70.5 (112.38)
	Median	85.0	17.0	19.0
	Range	3.0, 216.0	3.0, 421.0	3.0, 421.0
Free Testosterone (pg/mL)	n	4	13	17
	Mean (SD)	6.4 (6.17)	7.8 (12.91)	7.5 (11.51)
	Median	5.5	2.5	2.5
	Range	0.5, 14.0	0.7, 38.0	0.5, 38.0
Total DHT (ng/dL)	n	4	13	17
	Mean (SD)	14.9 (13.19)	8.1 (9.71)	9.7 (10.59)
	Median	12.8	4.9	5.4
	Range	2.0, 32.0	2.0, 36.0	2.0, 36.0

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

Compliance with the study medication was evaluated by weighing the AndroGel bottle before the first dose and after the last dose of each treatment period. All subjects were reported to be ≥ 80% compliant with study medication. The mean compliance for all subjects was 108.4% (range: 82-136%).

The pharmacokinetic characteristics of total and free testosterone and total dehydrotestosterone (DHT) generated from Study UMD-01-080 are summarized for all subjects in applicant's Table 2.7.2:1.

Table 2.7.2:1 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%

The baseline-adjusted PK parameters are presented in applicant's Table 11.

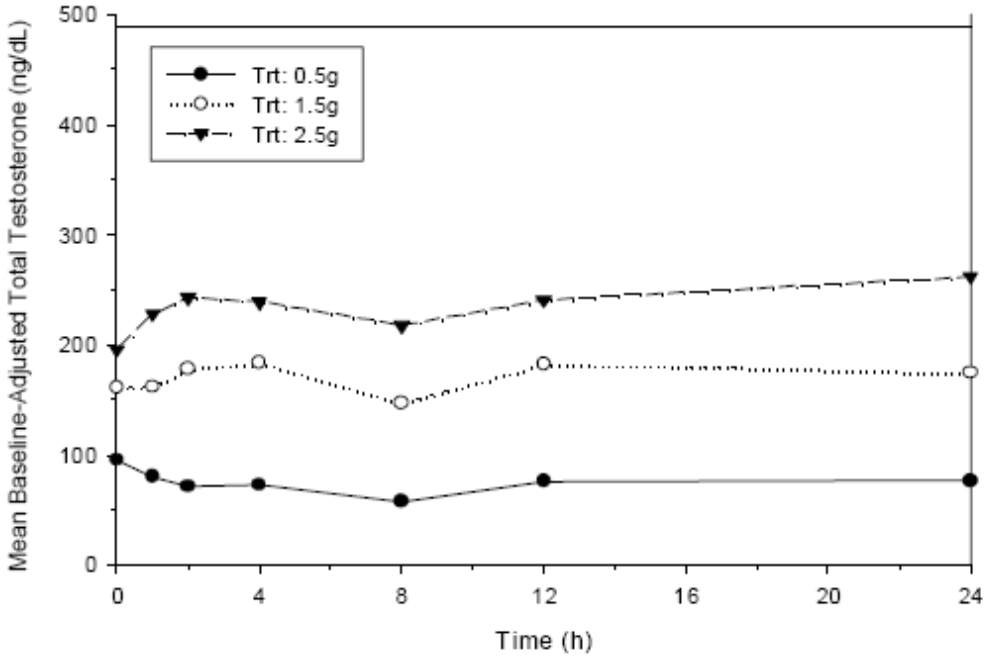
Table 11 Summary of Baseline-Adjusted Pharmacokinetic Parameters in All Subjects

		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)

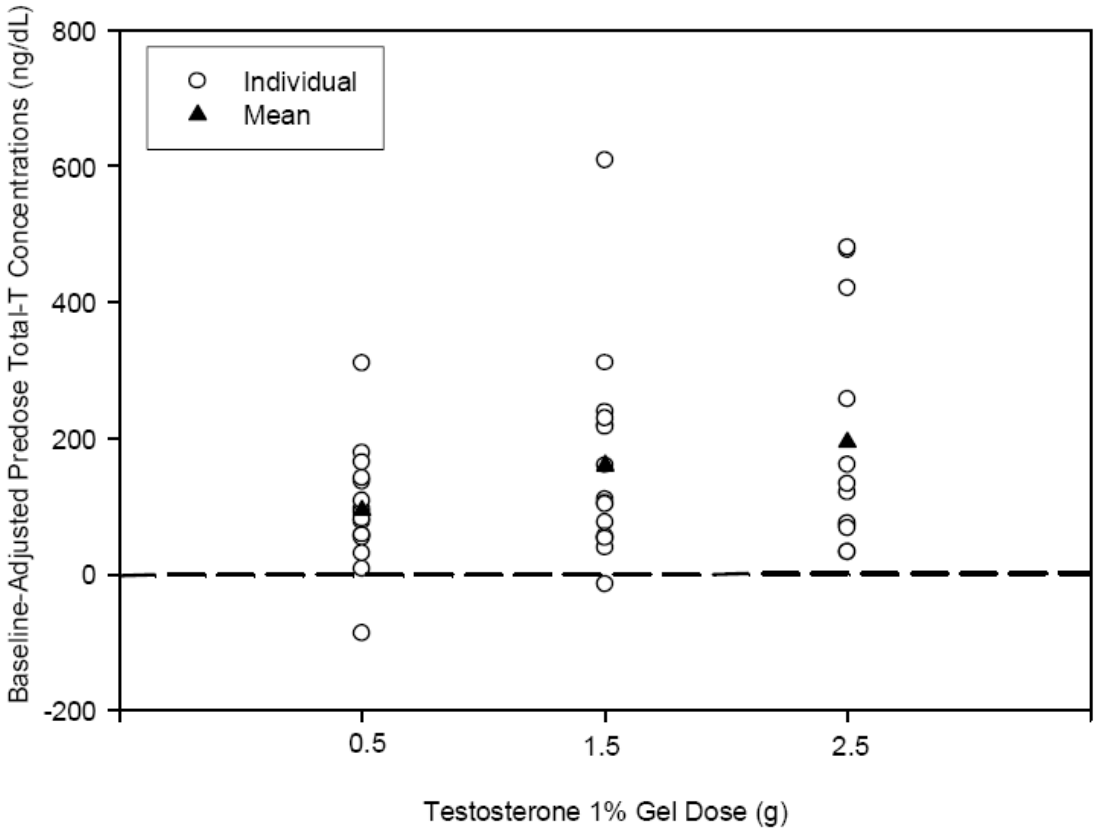
For a critical review of the pharmacodynamic data refer to the Clinical Pharmacology review.

Applicant's figure titled "Baseline-adjusted Total Testosterone" displays the steady-state profile for serum testosterone. Similar profiles are observed for free testosterone and total dehydrotestosterone.

Baseline-adjusted Total Testosterone



The individual and mean levels of total testosterone (baseline adjusted) for all patients and all doses (at steady state) are illustrated in applicant's figure, below.



Importantly, a DSI audit of the pharmacokinetic data from the Study UMD-01-90 (a clinical study that is summarized in the clinical section of this review) found "significant deficiencies that impact the integrity of the data". The deficiencies that were identified concerned both the validation of the testosterone assays (accuracy, precision linearity) and the analytical runs. Although data from Study UMD-01-080 were not audited by DSI, Study UMD-01-080 utilized the same testosterone assay methods as in Study UMD-01-90; therefore, the pharmacokinetic conclusions of Study UMD-01-080 are being called under question as well. For a detailed description of these deficiencies refer to the clinical pharmacology review.

5.2 Pharmacodynamics

The pharmacodynamic information was not reviewed in detail. For Study UMD-01-080 the applicant states that "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. As expected, there was substantial variability in individual serum hormone concentrations." For Study UMD-01-090 the applicant states that "LH, FSH, estradiol (E2), and sex hormone-binding globulin (SHBG) mean serum concentration

results showed small fluctuating changes from Baseline (increases and decreases) throughout [the study]".

5.3 Exposure-Response Relationships

For exposure –response refer to the analysis of bone age advancement in Section 7.1.3.3.

6 INTEGRATED REVIEW OF EFFICACY

(b) (4)

6.1.1 Methods

6.1.2 General Discussion of Endpoints

The efficacy endpoints evaluated in this study (i.e. bone age, bone age advancement, height, growth rate, and Tanner stage) are standard endpoints in statural clinical studies.

6.1.3 Study Design

This was a multi-center (18 centers[21]), single-arm, open-label, 6-month observational study of AndroGel conducted in 86 males with delayed puberty due to hypogonadotropic hypogonadism (secondary hypogonadism), hypergonadotropic hypogonadism (primary hypogonadism), or constitutional delay in growth and puberty. The study included both testosterone naive and non-naïve patients. Patients who participated in the pharmacokinetic study UMD-01-080 were allowed enrollment in this study[22]. During the initial three weeks of the study all the patients enrolled had their testosterone dose titrated by the investigator with the goal of reaching a serum total testosterone concentration that, in the judgment of the investigator, was appropriate for each patient's baseline stage of puberty. All patients started treatment at a dose of 0.5 g of AndroGel once daily, applied at bedtime[23]. Subsequent titration, if necessary, was continued in stepwise fashion with doses of 1.5 g, 2.5 g, or 5.0 g of AndroGel daily until the desired serum testosterone level was reached, at which time no further dose increase was to occur. The trial design is illustrated in applicant's Figure 1. The stated objective of the study was to "evaluate the clinical response to Testosterone-Gel 1% (T-Gel) for the treatment of delayed puberty in boys of adolescent age". AndroGel was supplied as multi-dose bottles with pump-heads that dispensed (b) (4) gel per actuation of the pump, or as individual sachets containing (b) (4) of gel[24]. The

[21] The distribution of patients per site was as follows: sites 109 and 124 (10 patients each); sites 103 and 104 (9 patients each); site 113 (7 patients); sites 114, 121, 123, and 127 (5 patients each); site 124 (4 patients); sites 107, 111, and 124 (3 patients each); sites 110, 117, and 128 (2 patients); sites 108, and 122 (1 patient each).
[22] Since Study UMD-01-080 was a short-term pharmacokinetic study, patients had limited exposure to testosterone.
[23] Five subjects began treatment at a dose > 0.5 g/day (see the Protocol Deviation Section).
[24] Prior to dispensing the first dose of testosterone gel 1% from each bottle of study medication, the pump of the bottle was primed at the investigating site personnel by actuating the pump three times and discarding the delivered testosterone gel 1%. Subjects were instructed to always apply the testosterone gel 1% at bedtime beginning on the evening of the Baseline day, to clean, dry, intact skin, and to avoid exposure of application sites to water for a minimum of five hours following application, but to wash the application sites with soap and water the following morning upon arising. Subjects were to rub the testosterone gel 1% into the skin with a circular motion, and allow the application sites to dry prior to covering with clothing (three to five minutes). Subjects were instructed to wash their hands thoroughly with soap and water following application of gel. A parent supervised the first application of testosterone gel 1%, and the parent determined when the child no longer needed supervision. The instructions emphasized that female and younger male family members were not to have direct skin contact with the testosterone gel 1% or the application sites of the subjects. On the evening before a study visit, the testosterone gel 1% dose had to be applied as usual.

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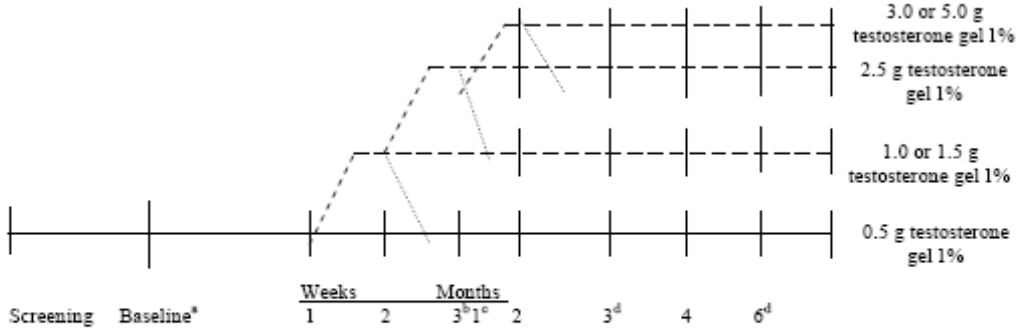
study was conducted between August 15, 2002 and June 19, 2006. The batches used in this study were EP-929, E-840, EG-944, 20046B, EG-1124, EA-1071A, and EA-1098A.

Figure 1 Study Design



[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 initial dose titration scheme for testosterone-naïve patients is summarized in applicant's Table 3[25]. This titration scheme was abandoned with Amendment # 6 (dated February 9, 2004). Following this amendment the titration scheme was described as follows:

> For all enrolled patients, whether testosterone naïve or testosterone-non naïve, the patient's dose of Testosterone gel will be evaluated by the investigator during the initial 3 weeks of the study and may 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.

[25] For non-naïve patients the initial titration scheme was less specific. The protocol states that "all patients will start on the evening of the Baseline visit at a dose of 0.5 g of T-Gel per day. The serum T levels obtained at Weeks 1, 2 and 3 (optional) will provide the basis for adjustment of the patient's T-Gel dose. The T-Gel dose will be adjusted to the appropriate level based upon the investigator's clinical judgment".

Table 3. DOSE TITRATION FOR T-GEL: TESTOSTERONE-NAIVE PATIENTS

Visit	Serum Testosterone Level	Current T-Gel Dose	New T-Gel Dose[a]
Baseline	≤ 30 ng/dL	Not Applicable	0.5 g/day
Week 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 Week 2)[b]
	> 250 ng/dL[c]	0.5 g/day	Discontinue Patient
Week 2 (for those patients titrated up at Week 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[d]
	> 200 ng/dL	1.5 g/day	Decrease to 0.5 g/day

[a] The new dose, if necessary, will begin within 2 to 3 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 Week 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.
[d] A serum testosterone level may be drawn at Week 3 at the investigator's discretion.

Inclusion criteria

The clinical protocol has been amended six times. Amendment # 6 lists the following inclusion criteria:

- signed informed content an assent according to local laws
- age of 13-17 years and a diagnosis of delayed puberty due to primary or secondary hypogonadism or CDGP
- patients could be naïve or non-naive to androgen therapy
- patients naïve to androgen therapy had to have a total testosterone level ≤ 50 mg/dL and a testicular volume ≤ 3 mL or to have completed study UMD-01-080; patients non-naïve to testosterone therapy did not have a minimum testosterone level or testicular volume.
- bone age of at least 10.5 years
- available baseline growth data for at least 6 months prior to receiving testosterone in Study UMD-01-080 or current study.

Exclusion criteria

Amendment # 6 listed the following exclusion criteria:

- skin intolerance to alcohol or allergy to soy products
- generalized skin disease that would affect the absorption of topically applied testosterone
- known contraindications to testosterone or other androgen product
- patients unable to complete the appropriate washout period
- use of medications that may cause interactions with testosterone therapy
- clinically significant, uncontrolled clinical conditions (hepatic, renal, psychiatric)

- untreated endocrine disorders
- history of drug or alcohol abuse
- recent participation in any study other than Study UMD-01-080.

Treatment compliance

For patients who used AndroGel from a bottle, treatment compliance was assessed by weighing the bottle prior to starting the therapy and at each visit (this information was recorded in the CRF). For patients who used unit-dose sachets, compliance was evaluated by counting the unused sachets.

Efficacy and safety assessments

The main efficacy assessments were growth velocity[26], testicular volume[27], Tanner Stage for pubic hair[28], bone maturation[29], and serum hormone concentrations[30]. Safety assessments included adverse events, clinical laboratory[31], vital signs, physical examinations, skin application site assessments, and gynecomastia. The schedule of assessments for this study is summarized in applicant's Table 1.

[26] Height (cm) was measured at screening, baseline (Day 1), Months 1, 2, 3, 4 and 6. Height (without shoes) was measured by the same observer at each visit using a wall-mounted stadiometer (three separate measurements of height were made).
[27] Testicular volume (mL) was measured using a Prader orchidometer at Screening, Baseline (Day 1), Months 1, 3 and 6.
[28] Tanner Stage for pubic hair was assessed at screening, baseline (Day 1), Months 1, 3 and 6.
[29] Bone age (years) was read centrally at screening, Month 6 or at the final visit from an x-ray of the left hand and wrist using the Gruelich & Pyle atlas. The reader was not blinded to the sequence of X-rays or patient ID.
[30] Serum total testosterone concentrations were obtained at the weekly titration visits: Week 1, 2, and 3 (optional). In addition, serum concentrations of total testosterone, free testosterone, bioavailable testosterone, total dihydrotestosterone (DHT), LH, FSH, estradiol (E2), and sex hormone-binding globulin (SHBG) were obtained at baseline (Day 1), Months 1, 2, 3, 4 and 6.
[31] Clinical laboratory included hematology tests (hemoglobin, hematocrit,RBC count, platelet count, and white cell plus differential count), chemistry analytes (alkaline phosphatase, alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT), aspartate aminotransferase/serum glutamic-oxaloacetic transaminase (AST/SGOT), total bilirubin, blood urea nitrogen, creatinine, glucose, electrolytes), urinalysis, and lipid panel (total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides. Clinically significant abnormal laboratory test results were repeated to confirm the results." Hormone assays were performed (b) (4) Wrist and hand radiographs were evaluated (b) (4)

Table 1 Study Flow Chart

Activity[a]	UMD-01-090								UMD-01-090E	
			Week			Month			Month	
	Screening	Baseline Day 1	1	2	3 Optional	1	2	3/ Final Visit	4	6/ Final Visit
Daily testosterone gel 1% Application[b]		+	+	+	+[c]	+	+		+	
Dose Titration			+	+	+[c]					
Informed Consent/Assent	+									
Inclusion/Exclusion Criteria	+									
Medical History	+									
Physical Examination [d]/ Vital Signs	+	+				+	+	+	+	+
Height (without shoes)	+	+				+	+	+	+	+
Tanner Pubic Hair Stage Assessment and Testicular Volume	+	+				+		+		+
AEs		+	+	+	+	+	+	+	+	+
Application Site Assessment	+	+	+	+	+	+	+	+	+	+
Clinical Laboratory Tests	+	+				+		+		+
Concomitant Medications	+	+	+	+	+	+	+	+	+	+
Bone Maturation Age (hand x-ray) [e]	+[f]							+[g]		+
Serum Hormone Concentrations (single a.m. sample) [h, i]	+[i]	+	+[i]	+[i]	+[i]	+	+	+	+	+

[a] Testicular volume, Tanner Pubic Hair Stage, height, and gynecomastia were assessed by the same observer throughout the study.
[b] The initial application of testosterone gel 1% was done in the evening (bedtime) of the Baseline day.
[c] Optional visit for boys who were titrated to 2.5 g at Week 2.
[d] The physical examination included an evaluation for gynecomastia.
[e] Hand x-rays were sent to a central facility for evaluation.
[f] For subjects who participated in Protocol UMD-01-080, Baseline bone maturation age was obtained at the Screening visit for Protocol UMD-01-080.
[g] Bone maturation age was only evaluated at Month 3 for subjects who prematurely terminated from Protocol UMD-01-090 or who were not continuing onto Protocol UMD-01-090E.
[h] Includes total testosterone, free testosterone, bioavailable testosterone, total dihydrotestosterone (DHT), lutenizing hormone (LH), follicle stimulating hormone (FSH), estradiol (E2), and sex hormone-binding globulin (SHBG).
[i] Total testosterone concentration only.

Statistical plan and populations analyzed

Data were presented using summary statistics. Since this study was an observational study, no statistical testing was performed. Analyses are presented for the following patient groups:

- all subjects (defined as all subjects who received at least one application of AndroGel
- all subjects diagnosed with primary or secondary hypogonadism
- all subjects diagnosed with CDGP.

For each analysis population, patients were grouped with respect to their "overall dose" of Androgel that they received during the study[32]. The schedule of assessments and the window for each visit is presented below[33].

[32] The overall dose (expressed in grams) was calculated as follows: if a subject received 1.0 g/day for 90 days his/her overall dose would be 90 g. Doses were split into three groups (tertiles) for summarization: "low" (< 100 g), "medium" (100-240 g), and "high" (>240g).

Visit	Target Study Day	Lower Limit (study days)	Upper Limit (study days)
Screening	-1	N/A	0
Baseline	1	1	1
Week 1	8	2	12
Week 2	15	13	19
Week 3	22	20	26
Month 1	29	27	44
Month 2	57	45	72
Month 3	85	73	100
Month 4	113	101	128
Month 6	169	129	Not applicable

Note: Study day is defined as (assessment date – date of first dose of study medication +1)

Changes in the conduct of the study

The original protocol, finalized on February 15, 2002, was amended 6 times. Table 3 summarizes the protocol amendments. In addition to the protocol changes listed below, the applicant made some minor changes to the statistical plan that consisted in the addition of two analyses recommended by the Agency and the removal of two subgroup analyses. These were minor changes to the statistical plan.

Table 3: Protocol amendments to Study UMD-01-090

Amendment # (Date)	Summary of major changes
Amendment # 1 (April 1, 2002)	Provided clarifications to the protocol and added hepatic/renal disease as an exclusion criterion.
Amendment # 2 (April 22, 2002)	Added a study visit at Week 2 Added an exclusion criterion that prohibited the discontinuation of a medication used to treat another condition or illness for the purpose of qualifying a subject for this study. Added information about the timing of dose adjustments and the handling of subjects with serum testosterone concentrations above the target range.
Amendment # 3 (July 5, 2002)	Changed the inclusion/exclusion criteria: included subjects diagnosed with primary or secondary hypogonadism and excluded patients with CDGP; included subjects currently being treated with testosterone and excluded those with untreated growth hormone deficiency; extended the allowable age from 13 to 16 years of age to 13 to 17 years of age; required a bone age of < 10.5 years and baseline growth data for ≥ 6 months before study medication; allowed subjects from Protocol UMD-01-080 to be enrolled.
Amendment # 4 (August	Deleted the inclusion criterion that made Tanner Stage I for pubic hair a part of the

[33] Baseline value was defined as the value taken at Day 1 in Protocol UMD-01-090 (if the Day 1 value was missing, the last non-missing value prior to the first testosterone gel 1% application was used as the Baseline value). For subjects who had participated in Study UMD-01-080, baseline value was defined as the baseline value in Protocol UMD-01-080. The Final Visit value was defined as "the last, non-missing, post-Baseline Visit value collected prior to termination in Protocol UMD-01-090E for subjects who entered Protocol UMD-01-090E. If a subject did not enter Protocol UMD-01-090E, the Final Visit value was defined as the last, non-missing, post-Baseline Visit value collected prior to termination in Protocol UMD-01-090".
The applicant states that "if multiple assessments occurred within the same visit window, the assessment closest to the target date [was] included in by-visit data summaries; if there [were] two assessments in the same window equally close to the target date but on different dates, the assessment with the later date [was] used in the by-visit data summaries". The window for each visit assessment is presented below.

21, 2002)	definition of prepubertal status.
Amendment # 5 (March 27, 2003)	Included minor administrative changes.
Amendment # 6 (February 9, 2004)	The study inclusion/exclusion criteria were changed as follows: CDGP patients were allowed in the study, the baseline testosterone level for testosterone-naive boys was changed from from < 30 ng/dL to < 50 ng/dL, the upper testosterone treatment concentration of 200 ng/dL for testosterone naive boys was removed, and the instructions to discontinue patients who exceeded a serum testosterone concentration of 250 ng/dL were removed.

Study disposition

Eighty-six patients were enrolled in the clinical trial and 78 (90.7%) completed the study. Eight patients discontinued the study for the following reasons: adverse event (one patient)[34], serum testosterone > 250 ng/dL at Week 2 (two patients)[35], protocol violation (two patients)[36], investigator's decision (two patients), and "other" (1 patient). Applicant's Table 4 summarizes the subject disposition information.

Table 4 Subject Disposition

	Statistic	Subject Population Group		
		Hypogonadal	CDGP	All Subjects
Number of Subjects Enrolled	n	59	27	86
Number of Subjects Who Received Study Medication	n	59	27	86
End of Study Status				
Completed Study	n (%)	52 (88.1)	26 (96.3)	78 (90.7)
Discontinued Study	n (%)	7 (11.9)	1 (3.7)	8 (9.3)
Premature Termination Reason				
Adverse Event	n (%)	1 (1.7)	0	1 (1.2)
Serum Testosterone Concentration > 250 ng/dL at Week 2	n (%)	2 (3.4)	0	2 (2.3)
Protocol Violation	n (%)	1 (1.7)	1 (3.7)	2 (2.3)
Discontinued by Investigator	n (%)	2 (3.4)	0	2 (2.3)
Other	n (%)	1 (1.7)	0	1 (1.2)

Note: Percentages are based on the number of subjects who received study medication.
Data Source: Table 10.1.1(A), Table 10.1.1(B), and Table 10.1.1(C).

Protocol deviations

The applicant lists the following protocol deviations:

- Five patients who had participated in Study UMD-01-080 started Study UMD-01-090 on a dose higher than the protocol specified dose of 0.5 g/day (three patients started on 1.0 g/day and two subjects on 2.5 g/day).

[34] Depression.
[35] In early versions of the protocol patients were to be discontinued if testosterone level was > 250 ng/dL. This was changed with Amendment # 6.
[36] One patient was noncompliant with study medication; the violation for the second subject was not recorded.

- Several patients were dosed using the wrong pump-head. (b) (4)

Applicant's Listing 12.2.2 titled "Protocol deviations/violations" details multiple protocol deviations. Although only one was considered "major" by the applicant[38], there were multiple deviations of inclusion criteria regarding the baseline testosterone level and the testicular volume as well as deviations concerning bone age assessments. Most other protocol deviations were related to visits completed outside scheduled 'windows", missing doses, use of extradoses, minor irregularities of signing study participation documents, down titrations, titrations not being done according to protocol. Table 4 summarizes the deviations and violations of the inclusion criteria regarding testicular volume and testosterone level from Listing 12.2.2 .

Table 4 Deviations and violations of the inclusion criteria regarding testicular volume and testosterone level.

Patient ID	Protocol Deviation
1025	Klinefelter pt allowed to enter as non-naïve; T-level 561
1027	T-Level = 480
1028	CDGP w/ TL = 68
1029	Klinefelter pt allowed to enter as non-naïve; T-level 344
3021	TV=4mL; T-level = 77
1036	Klinefelter pt allowed to enter as non-naïve; T-level114
1037	CDGP w/ TL = 63
1040	CDGP w/ TL = 54
3032	CDGP w/ TL =60
3033	CDGP w/TL=35; TV=5mL
1062	TV=12mL: pt has panhypopituitarism d/t sx resection (pt was reviewed for entry between Sep-Dec 2002)
1084	SH w/TL= 39
1088	CDGP w/TL= 57
1093	Screen TL = 31 (BL =22)
1103	CDGP w/TL= 60: TV=8mL
1124	Klinefelters w/ TL=56
1127	CDGP w/TL=117 (per waiver request) ; TV=20mL
1135	Klinefelters w/TL=221 entered as non-naïve
1203	Panhypopit d/t cranium rads - pt entered as non-naïve;T-level= 159; TV=4mL

[37] (b) (4)

Patient 1092 was entered as having secondary hypogonadism and was later determined to be CDGP; although at that time CDGP patients were excluded, following Amendment # 6 CDGP patients were allowed participation in the trial and this major deviation became inconsequential.

Medium	Klinefelters w/TL=53 entered as non-naïve; TV = 6mL
1223	Klinefelter pt allowed to enter as non-naïve; T-level 112

Source: Listing 12.2.2. Comments in the Protocol Deviation column belong to the applicant.

A review of Listing 12.4.19 and Listing 12.4.7 (checked against JMP-[CV_VOL]) confirms that, in spite of the fact that per inclusion criteria testosterone-naïve patients had to have a serum testosterone level ≤ 50 ng/dL and a testicular volume of ≤ 3 mls, there were multiple violators[39], summarized in Table 5. Information from Table 4 and 5 overlaps to a large extent. A total of 19/86 (22.1%) patients were entered despite not meeting the inclusion criteria for testosterone level and/or testicular volume.

Table 5: Violators of the inclusion criterion that specified that testosterone-naïve patients had to have had a total testosterone level ≤ 50 ng/dL and a testicular volume ≤3 mL[40]

Patient ID (Diagnosis)	Comment
Testosterone level inclusion criterion violation	
1028 (CDGP)	Had a screening T. level of 68 ng/dL and a baseline T level of 65 ng/dl.
1029 (CDGP)	Had a screening T. level of 426 ng/dL and a baseline T level of 449 ng/dl.
3021 (CDGP)	Had a screening T. level of 77 ng/dL and a baseline T level of 73 ng/dl.
1036 (Hypogonadism)	Had a screening T. level of 114 ng/dL and a baseline T level of 107 ng/dl.
1037 (Hypogonadism)	Had a screening T. level of 63 ng/dL and a baseline T level of 79 ng/dl.
1038 (CDGP)	Had a screening T. level of 41 ng/dL and a baseline T level of 62 ng/dl.
1040 (CDGP)	Had a screening T. level of 54 ng/dL and a baseline T level of 13 ng/dl.
3031(CDGP)	Had a screening T. level of 36 ng/dL and a baseline T level of 58 ng/dl.
1092 (Hypogonadism)	Had a screening T. level of 58 ng/dL and a baseline T level of 12 ng/dl.
1103 (CDGP)	Had a screening T. level of 60 ng/dL and a baseline T level of 29 ng/dl.
1124(Hypogonadism)	Had screening T. levels of 30 and 56 ng/dL, respectively, and a baseline T level of 61 ng/dl
1127(CDGP)	Had screening T. levels of 55 and 117 ng/dL, respectively, and a baseline T level of 186 ng/dl
1135 (Hypogonadism)	Had a screening T. level of 178 ng/dL and a baseline T level of 236 ng/dl.
1203 (Hypogonadism)	Had a screening T. level of 159 ng/dL and a baseline T level of 129 ng/dl.
1204 (Hypogonadism)	Had a screening T. level of 53 ng/dL and a baseline T level of 26 ng/dl.
1206 (Hypogonadism)	Had screening T. levels of 26 and 147 ng/dL, respectively, and a baseline T level of 8.9 ng/dl
1223 (Hypogonadism)	Had a screening T. level of 112 ng/dL and a baseline T level of 49 ng/dl.
Testicular volume inclusion criterion	
3021 (CDGP)	Had a screening/baseline testicular volume of 4 cm.
1036 (Hypogonadism)	Had a screening/baseline testicular volume of 4 cm.
1062 (Hypogonadism)	Had a screening/baseline testicular volume of 12 cm.
1092 (Hypogonadism)	Had a screening/baseline testicular volume of 8 cm.
1093 (Hypogonadism)	Had a screening/baseline testicular volume of 6 cm.
1103 (CDGP)	Had a screening/baseline testicular volume of 8 cm

[39] Of the 50 testosterone-naïve patients, 39 (78%) had baseline total testosterone serum concentrations ≤ 50 ng/dL. Eleven patients (22%) had levels > 50 mg/dL: 6 patients with hypogonadism (all completers) and 5 patients with CDGP (3 completers).
Of the 50 testosterone-naïve patients 36 patients had a baseline testicular volume ≤ 3 mL, 13 patients had testicular volume > 3 ml, and 1 patient did not have a measured baseline testicular volume (Listing 12.4.17 and 12.4.7). Of the 13 patients with testicular volume > 3 ml, five had CDGP and 8 had hypogonadism (2/5 with CDGP and 7/13 with CGGP were completers).
[40] Per protocol, patients who participated in Study UMD-01-080 had to have been considered testosterone naive on entry into UMD-01-080.

1124 (Hypogonadism)	Had a screening/baseline testicular volume of 8 cm.
1127 (CDGP)	Had a screening/baseline testicular volume of 15 cm.
1135 (Hypogonadism)	Had a screening/baseline testicular volume of 6 cm.
1203 (Hypogonadism)	Had a screening/baseline testicular volume of 4 cm.
1204 (Hypogonadism)	Had a screening/baseline testicular volume of 5 cm.

Source: Listing 12.4.19 and Listing 12.4.7 (checked against JMP-[CV_VOL]).

The deviations related to the collection and analysis of bone age radiographs are summarized in Table 6.

Table 6: Deviations regarding bone age radiographs

Patient ID	Protocol Deviation
1024	Final radiograph not obtained/read
1062	Final radiograph not readable [redacted]
1081	Per log, an exception was granted to use radiograph done [redacted] to determine bone age needed for inclusioncriteria at screen visit [redacted]
1084	Screen film obtained by another facility one month prior to screening visit
1085	Screen Bone film obtained by study institution 4 months prior to screen
1103	Screen Bone film submitted by site was deemed Not Readible [redacted] waiver granted as site radiologistverified Bone age as >10.5 years for entry purposes;apparently a readable film was submitted later.
1121	Final Radiograph not readable [redacted]
1122	Parent was unable to have radiograph done on day of the screening visit d/t time constraints
1123	Final Radiograph not readable [redacted] Screen Radiograph not readable [redacted]
1124	Screen Radiograph not readable [redacted] Final Radiograph not readable [redacted]
1127	Final Radiograph not readable [redacted]
1161	Final radiograph not obtained/read
1206	Final radiograph not obtained/read
1221	PI wanted to use bone age film done in [redacted] Screen film
1252	[redacted] deemed 6 month film not readable; Solvay requested [redacted] do what they can with the film, or if not sufficient quality, treat as missing data point
1254	Early Term radiograph not obtained as the PI did not see the need since last done [redacted]
1284	Bone rad. results were not received in time for baseline visits, so waiver provided to allow localradiologist to read film.

Source: Listing 12.2.2. Comments in the Protocol Deviation column belong to the applicant
[redacted] central radiography lab that was responsible for reading the X-ray films.
T = testosterone.

In response to inquiries sent to the applicant following the Filing Meeting regarding the enrollment of such a large number of patients with testosterone and testicular volume violations, the applicant provided comments and expert written testimony that can be summarized as follows:

1) for some of the patients with testicular volume > 3 ml "other baseline data such as Tanner Pubic Hair staging and baseline testosterone values indicate that these subjects may have been prepubertal or in very early stages of puberty".

2) as the treatment of CDGP includes "initiation, maintenance and in some cases acceleration of pubertal development" [..] treatment is still provided if the rate of progression is less than clinically desired".
3) "parameters that mark changes in development such as Tanner staging, testicular volume, height, and testosterone levels do not always develop in synchronous manner"
4) it is possible that some patients who were non-naïve to treatment did not complete a satisfactory washout period
5) it is not uncommon for boys with hypogonadism to produce some amounts of circulating testosterone (e.g. patients 1204, 1223 and Klinefelter patients).

6.1.4 Efficacy Findings

Demographics and baseline characteristics

The baseline patient characteristics are summarized in Table 7. The mean age of all subjects was 14.3 years (range 12 to 18 years) and the mean bone age was 13.7 years. The mean bone age and mean chronological age were concordant for hypogonadal patients and was delayed by one years for CDGP patients. Of the 86 patients enrolled, 59 (69%) had a diagnosis of primary or secondary hypogonadism and 27 (31%) had a diagnosis of CDGP.

Of the hypogonadal patients 61% had primary hypogonadism and 39% had secondary hypogonadism; overall, 49% of the hypogonadal patients were naïve to testosterone treatment. The underlying diagnosis for patients with primary hypogonadism was Klinefelter's Syndrome (21 patients), gonadal failure (2), cryptorchidism, (1), anorchia (3) and "other" (9). The underlying diagnosis for patients with secondary hypogonadism was CNS disorder (4), Kallman's syndrome (1), and "other" (18). Only approximately 20% of hypogonadal patients were prepubertal (Tanner stage I) and the mean total testosterone level was 81.1 (range 3 to 470) which indicates that some of these patients were capable of testosterone secretion or were improperly washed out of prior testosterone therapies, or both. All 7 patients Tanner stage V had Klinefelter syndrome.

Patients with CDGP were mostly naïve to testosterone treatment (78%); on average, they were shorter, had a small delay in bone age (one year), and had a mean testicular volume of 4.4 mls (range 1 to 15 mls), consistent with early puberty. Only about half (48%) were Tanner stage I for pubic hair, with most Tanner stage II and III.

Ten patients (11.6%) participated in the pharmacokinetic Study UMD-01-080; 8/10 were testosterone naïve at the initiation of the PK study. The 75 patients who were enrolled directly in Study UMD-01-90 were approximately evenly distributed between testosterone-naïve (42 patients or 56%) and non-naive (33 or 44%).

The race distribution included the following: Caucasians (74 patients or 86%), African American (5 patients or 5.8%), American-Indian or Alaska Native (2 patients or 2.3%), Asian (2 patients or 2.3%), and "unknown (3 patients or 3.5%).

It is worth mentioning that 13 hypogonadal patients and three CDGP patients were receiving somatropin at baseline.

Table 7: Baseline patient characteristics

Variable	Hypogonadal (N = 59)	CDGP (N = 27)	Total (N=86)
Chronological Age (years)			
mean (SD)	14.3 (1.46)	14.1 (1.17)	14.3 (1.37)
range	12.0, 18.0	13.0, 17.0	12.0, 18.0
Bone Age (years)			
mean (SD)	14.0 (1.26)	13.1 (1.09)	13.7 (1.27)
range	11.0, 17.0	10.5, 16.0	10.5, 17.0
Height (cm)			
mean (SD)	168.4 (11.65)	153.9 (10.72)	163.8 (13.18)
Weight (kg)			
mean (SD)	70.0 (19.94)	50.5 (19.74)	63.9 (21.76)
Testicular Volume (mL)			
mean (SD)	3.2 (2.54)	4.4 (3.52)	3.6 (2.92)
range	0.0, 12.0	1.0, 15.0	0.0, 15.0
Tanner Pubic Hair Stage I			
n (%)	12 (20.7)	13 (48.1)	25 (29.4%)
Tanner Pubic Hair Stage II			
n (%)	19 (32.8)	8 (29.6)	27 (31.8%)
Tanner Pubic Hair Stage III			
n (%)	9 (15.5)	5 (18.5)	14 (16.5%)
Tanner Pubic Hair Stage IV			
n (%)	11 (19.0)	0	11 (12.9%)
Tanner Pubic Hair Stage V			
n (%)	7 (12.1)	1 (3.7)	8 (9.4%)
Total Testosterone (ng/dL)			
mean (SD)	81.1 (108.9)	63.4 (86.1)	75.5 (102.0)
range	3, 470	3, 331	3, 470
Free Testosterone (pg/mL)			
mean (SD)	16.1 (23.2)	9.1 (19.5)	13.9 (22.2)
range	0, 107	0, 94	0, 107
Total DHT (ng/dL)			
mean (SD)	8.99 (9.04)	7.89 (5.58)	8.63 (8.06)
range	2.0, 34.0	2.0, 25.0	2.0, 34.0
LH (mIU/mL)			
mean (SD)	7.86 (11.64)	1.70 (1.67)	5.88 (10.03)
range	0.02, 43.00	0.04, 8.00	0.02, 43.00
FSH (mIU/mL)			
mean (SD)	17.72 (26.79)	2.77 (1.45)	13.096 (23.282)
range	0.02, 134.00	0.88, 5.90	0.02, 134.00
Estradiol (pg/mL)			
mean (SD)	7.88 (6.59)	5.88 (2.36)	7.22 (5.61)

range	5.0, 41.0	5.0, 16.0	5.0, 41.0
Gynecomastia at baseline n (%)	13 (22.0)	5 (18.5)	18 (20.9%)
Normal skin application site n (%)	55 (93.2)	27 (100.0)	82 (95.3%)

Source: Table 10.1.2 (A), Table 10.1.2 (B) and Table 10.1.2 (B).

Compliance

Compliance to the study medication is summarized in applicant's Table 7. Mean compliance was 78% overall (72% in hypogonadal patients and 91% in CDGP patients). Most patients had compliance between 80% and 120% or < 80%.

Table 7 Compliance to Study Medication

		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.

AndroGel dose by visit

Table 8 summarizes the percentage of patients who used each of the various daily doses at Month 1 and beyond (AndroGel titration was completed by Month 1). The most frequently used final dose was 0.5 g/daily (39.5%), followed by the 1.5 g dose (24.4%) and the 2.5 g dose (12.8%). Among hypogonadal patients roughly equal percentages of patients used most frequently the 0.5g dose and the 1.5 g dose (28.8% and 27.1%, respectively) with the 2.5 mg dose closely behind (20.3%); only a few patients used the 3-5 g/day doses. CDGP patients used most frequently the 0.5 g daily dose, followed by the 1.5 g dose (18.5%); none used the 3-5 mg/day doses. In general, the percentage of patients who used each dose remained relatively stable between Month 1 and Month 6.

Table 8: AndroGel dose by visit.

Dose	Month 1	Month 2	Month 3	Month 4	Final Dose
	All patients (N=86) n (%)				
0.5 g/day	38 (44.2%)	37 (43.0%)	26 (30.2%)	24 (27.9%)	34 (39.5%)
1 g/day	4 (4.7%)	5 (5.8%)	6 (7.0%)	11 (12.8%)	11 (12.8%)
1.5 g/day	26 (30.2%)	21 (24.4%)	19 (22.1%)	17 (19.8%)	21 (24.4%)
2.5 g/day	14 (16.3%)	15 (17.4%)	15 (17.4%)	14 (16.3%)	15 (17.4%)
3 g/day	0	0	0	1 (1.2%)	1 (1.2%)

5 g/day	1 (1.2%)	2 (2.3%)	3 (3.5%)	4 (4.7%)	4 (4.7%)
Hypogonadal (N=59) n (%)					
0.5 g/day	19 (32.2%)	17 (28.8%)	13 (22.0%)	12 (20.3%)	17 (28.8%)
1 g/day	3 (5.1%)	4 (6.8%)	5 (8.5%)	9 (15.3%)	9 (15.3%)
1.5 g/day	22 (37.3%)	18 (30.5%)	14 (23.7%)	13 (22.0%)	16 (27.1%)
2.5 g/day	11 (18.6%)	12 (20.3%)	12 (20.3%)	11 (18.6%)	12 (20.3%)
3 g/day	0	0	0	1 (1.7%)	1 (1.7%)
5 g/day	1 (1.7%)	2 (3.4%)	3 (5.1%)	4 (6.8%)	4 (6.8%)
CDGP (N=27) n (%)					
0.5 g/day	19 (70.4%)	20 (74.1%)	13 (48.1%)	12 (44.4%)	17 (63.0%)
1 g/day	1 (3.7%)	1 (3.7%)	1 (3.7%)	2 (7.4%)	2 (7.4%)
1.5 g/day	4 (14.8%)	3 (11.1%)	5 (18.5%)	4 (14.8%)	5 (18.5%)
2.5 g/day	3 (11.1%)	3 (11.1%)	3 (11.1%)	3 (11.1%)	3 (11.1%)
3 g/day	0	0	0	0	0
5 g/day	0	0	0	0	0

Source: Tables 10.1.6 (A), 10.1.6 (B), and 10.1.6 (C) in Study UMD-01-090 Study report.

Total testosterone levels during the titration period

Descriptive statistics for serum total testosterone concentrations at screening and during the titration period (Weeks 1, 2, and 3) are presented by actual dose in applicant's Table 10.2.10 (A). At Week 1, almost all patients (75/76) used the 0.5 g dose. At Week 2 only 46 patients used the 0.5 g dose while most of the remainder (24 patients) were titrated to the 1.5 g daily dose (with only a few receiving the 1 g dose) Data for Week 3 are sparse and not representative. By Week 1, the 75 patients who used the 0.5 g dose had testosterone serum concentrations of 184.3 ng/dL (approximately 80 mg over baseline), and were maintained at approximately 100 ng over baseline at Week 2. Patients who were titrated to a daily dose of 1.5 g had serum testosterone levels approximately 150 ng over baseline. It is important to recognize that, as patients had different levels of Tanner stage development at baseline, there was not a single but several "titration goals".

TABLE 10.2.10 (A)
SERUM TOTAL TESTOSTERONE CONCENTRATIONS AT SCREENING AND WEEKLY TITRATION VISITS BY ACTUAL DOSE LEVEL AND VISIT
ALL PATIENTS

Parameter	Statistic	Actual Dose (g/day) Unknown	0.5 (N=86)	1.0 (N=18)	1.5 (N=53)
Total Testosterone (ng/dL)					
Screening	n	74	0	0	0
	Mean (SD)	103.9 (113.9)	- (-)	- (-)	- (-)
	Median	55.0	-	-	-
	Range	10, 561	-, -	-, -	-, -
Week 1	n	0	75	1	0
	Mean (SD)	- (-)	184.3 (134.1)	203.0 (-)	- (-)
	Median	-	140.0	203.0	-
	Range	-, -	28, 674	203, 203	-, -
Week 2	n	1	46	3	24
	Mean (SD)	86.0 (-)	206.0 (173.8)	216.3 (13.7)	241.3 (180.0)
	Median	86.0	150.0	214.0	186.5
	Range	86, 86	56, 1066	204, 231	44, 793
Week 3	n	0	9	2	20
	Mean (SD)	- (-)	192.9 (88.6)	241.5 (135.1)	239.5 (191.3)
	Median	-	181.0	241.5	189.0
	Range	-, -	85, 363	146, 337	51, 778

Note: Actual dose (g/day) represents the actual dose the patient was on at the time of lab collection.
Note: Week 3 was an optional visit that not all patients were required to attend.
Note: Rollover patients from UMD-01-080 did not have Total Testosterone collected at Screening.
Note: N counts in column header represents the total number of patients who received at least one application of study medication at that dose level.

Table 9 summarizes the mean serum levels of total testosterone during the titration period by visit for all patients and for patients with hypogonadism and CDGP separately. In general, the mean serum concentrations of total testosterone increased gradually through Week 3. This was more evident in hypogonadal patients[41].

Table 9: Summary statistics for total testosterone concentrations during the titration period (Weeks 1 through Week 3).

Timepoint	Total testosterone (ng/dL)		
	All patients (N=86)	**Hypogonadism (N=59)**	**CDGP (N=27)**
Screening			
N	74	49	25
Mean (SD)	103.9 (113.9)	122.3 (129.8)	67.7 (60.5)
Range	10, 561	10, 561	13, 242
Week 1			
N	78	53	25
Mean (SD)	201.7 (171.6)	216.8 (194.8)	169.7 (103.4)
Range	28, 1035	28, 1035	64, 523
Week 2			
N	75	49	26
Mean (SD)	221.2 (175.4)	230.8 (185.2)	203.2 (157.2)
Range	44, 1066	44, 1066	56, 793
Week 3			
N	35	23	12

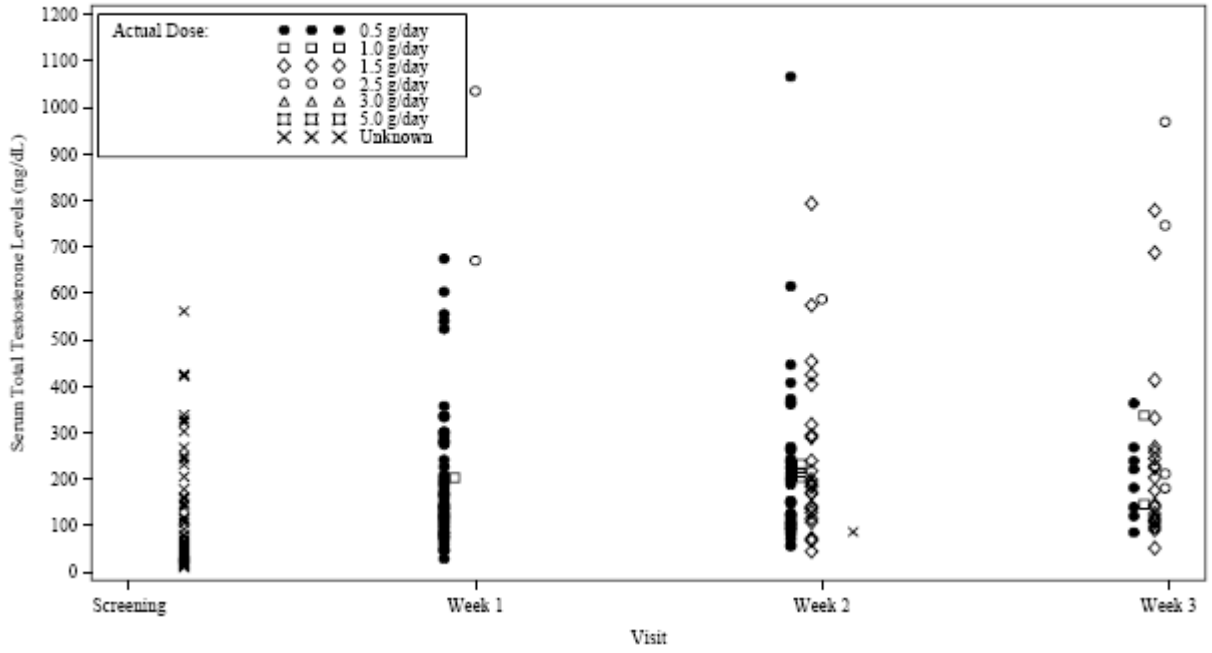
[41] Two patients had exceedingly high testosterone levels: patient 108/1071 (hypogonadism) had a serum total testosterone concentration of 1066 ng/dL at Week 2, and patient 114/2041 had a serum total testosterone concentration of 1035 ng/dL at Week 1. The applicant points out that patient 108/1071 who had received an AndroGel dose of 0.5 g/ 'used four more doses than specified per protocol'. Subject 114/2041 entered this study after completing Study UMD-01-080 and received a dose of 2.5 g at Week 1.

Mean (SD) Range	260.4 (215.1) 51, 969	310.2 (247.3) 51, 969	165.1 (75.4) 85, 331

Source: Tables 10.2.9 (A), 10.2.9 (B), and 10.2.9 (C) in UMD-01-090 Study Report.

A scatterplot of serum concentrations of total testosterone from screening through Week 3 is presented in applicant's Figure 9(A) below. It is noteworthy that, at screening, a remarkable number of patients have testosterone levels above the 50 nd/dL threshold proposed as an inclusion criterion for testosterone naïve-patients. The applicant comments that some hypogonadal patients were still capable of endogenous testosterone secretion or were improperly washed out, while some CDGP patients may have been in the early stages of puberty (refer to the baseline characteristics section and to the protocol deviation section for details). It is remarkable that at Week 1 (the first post-baseline, steady-state testosterone measurement on 0.5 g of AndroGel a large number of individual measurements were in the adult range (300-100 ng/dL)., as were on subsequent measurements.

Figure 9 (A)
Scatter Plot of Serum Total Testosterone Levels at Screening and Weeks 1-3 by Actual Dose
All Patients



Total testosterone levels during the maintenance period

Table 10 summarizes descriptive statistics of serum total testosterone concentrations associated with (b) (4) doses (0.5 g/day, 1.5 g/day, and 2.5 g/day) from Month 1 to Month 6. The 0.5 g/day and the 1 g/day doses were associated with comparable mean serum testosterone concentrations through Month 3; for the next two measurements (Months 4 and 6) there was no consistent pattern. The 2.5 mg AndroGel dose was clearly associated with higher levels throughout the whole study.

Table 10: Total testosterone levels for the (b) (4) pediatric doses of 0.5, 1.5 and 2.5 g

Timepoint and statistic	0.5 g/day	1.5 g/day	2.5 g/day
Month 1			
N	36	28	14
Mean (SD)	228.0 (165.1)	241.8 (158.5)	299.9 (174.4)
Range	16, 774	35, 660	46, 663
Month 2			
N	37	23	14
Mean (SD)	215.8 (147.3)	190.6 (132.6)	329.6 (285.3)
Range	36, 650	25, 670	109, 1259
Month 3			
N	34	22	13
Mean (SD)	191.8 (107.6)	203.0 (121.9)	308.8 (148.8)
Range	55, 511	9, 469	133, 601
Month 4			
N	22	17	13
Mean (SD)	188.8 (115.3)	347.8 (229.4)	379.2 (227.7)
Range	34, 459	81, 837	122, 761
Month 6			
N	23	14	12
Mean (SD)	264.3 (160.0)	208.3 (87.3)	366.4 (345.9)
Range	88, 626	75, 408	29, 1104

Source: Table 10.2.12 (A).

Table 11 summarizes the mean serum levels of total testosterone by visit during the maintenance period (Month 1 through 6) for all patients and for patients with hypogonadism and CDGP separately. In general, the mean testosterone levels either remained constant for the 6 months of the trial (primarily in hypogonadal patients) or changed minimally. As observed during the first month (titration period, Table 9) the mean serum concentrations of total testosterone were higher in hypogonadal patients relative to CDGP patients.

Table 11: Summary statistics for total testosterone concentrations beyond the titration period

Timepoint	Total testosterone (ng/dL)		
	All patients (N=86)	Hypogonadism (N=59)	CDGP (N=27)
Baseline			
N	85	58	27
Mean (SD)	75.5 (102.0)	81.1 (108.9)	63.4 (86.1)
Range	3, 470	3, 470	3, 331
Month 1			
N	82	56	26
Mean (SD)	253.7 (170.6)	242.5 (167.5)	277.7 (178.1)
Range	16, 774	16, 774	26, 750
Month 2			
N	82	55	27
Mean (SD)	231.8 (178.7)	254.9 (205.8)	184.7 (89.8)
Range	25, 1259	25, 1259	58, 378
Month 3			
N	76	50	26

Mean (SD)	233.6 (137.1)	244.4 (141.1)	212.8 (129.0)
Range	9, 601	9, 601	86, 512
Month 4			
N	63	44	19
Mean (SD)	291.4 (199.3)	294.9 (216.5)	283.2 (157.6)
Range	34, 837	34, 837	68, 683
Month 6			
N	69	48	21
Mean (SD)	271.8 (190.6)	284.9 (207.8)	241.8 (143.9)
Range	29, 1104	29, 1104	88, 626
Final Visit			
N	86	59	27
Mean (SD)	259.0 (210.5)	275.3 (237.1)	223.4 (132.3)
Range	16, 1259	16, 1259	88, 626

Source: Tables 10.2.11 (A), 10.2.11 (B), and 10.2.11 (C) in UMD-01-090 Study Report.

Table 12 summarizes the change from baseline in mean total testosterone levels for all patients and for hypogonadal and CDGP patients separately. The mean serum concentrations of total testosterone approximately doubled from baseline to Month 1 and then remained fairly stable throughout the study. The differences between hypogonadal and CDGP patients observed with absolute values were not confirmed when change from baseline measurements were analyzed.

Table 12: Summary statistics for the change from baseline in total testosterone concentrations

Timepoint	**Total testosterone (ng/dL)**		
	All patients (N=86)	**Hypogonadism (N=59)**	**CDGP (N=27)**
Baseline			
N	85	58	27
Mean (SD)	75.5 (102.0)	81.1 (108.9)	63.4 (86.1)
Range	3, 470	3, 470	3, 331
Change from baseline at Month 1			
N	81	55	26
Baseline mean	75.3	80.9	63.6
Mean (SD)	180.9 (165.1)	165.2 (147.4)	214.1 (196.6)
Range	-77, 755	-60, 755	-77, 685
Change from baseline at Month 2			
N	81	54	27
Baseline mean	78.6	86.2	63.4
Mean (SD)	150.2 (169.3)	164.6 (197.2)	121.2 (87.3)
Range	-81, 1256	-81, 1256	-74, 373
Change from baseline at Month 3			
N	75	49	26
Baseline mean	83.0	92.5	65.1
Mean (SD)	145.7 (119.5)	144.7 (132.4)	147.8 (92.7)
Range	-172, 467	-172, 467	24, 405

Change from baseline at Month 4			
N	63	44	19
Baseline mean	81.7	91.1	60.1
Mean (SD)	209.7 (201.6)	203.9 (225.9)	223.1 (133.6)
Range	-198, 834	-198, 834	38, 542
Change from baseline at Month 6			
N	68	47	21
Baseline mean	89.9	97.2	73.7
Mean (SD)	169.6 (161.8)	170.3 (160.9)	168.1 (167.6)
Range	-210, 885	-170, 885	-210, 448
Change from baseline at Final Visit			
N	84	57	27
Baseline mean	75.5	81.1	63.4
Mean (SD)	172.9 (191.0)	179.1 (208.6)	160.0 (149.9)
Range	-210, 1256	-170, 1256	-210, 448

Source: Tables 10.2.13 (A), 10.2.13 (B), and 10.2.13 (C) in UMD-01-090 Study Report.
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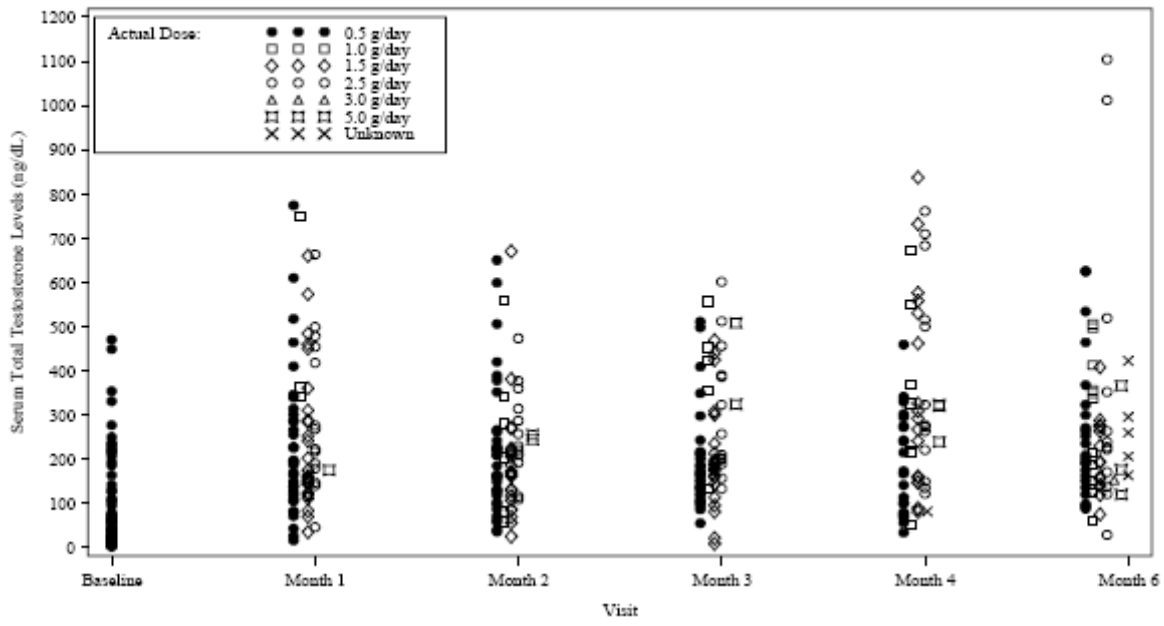
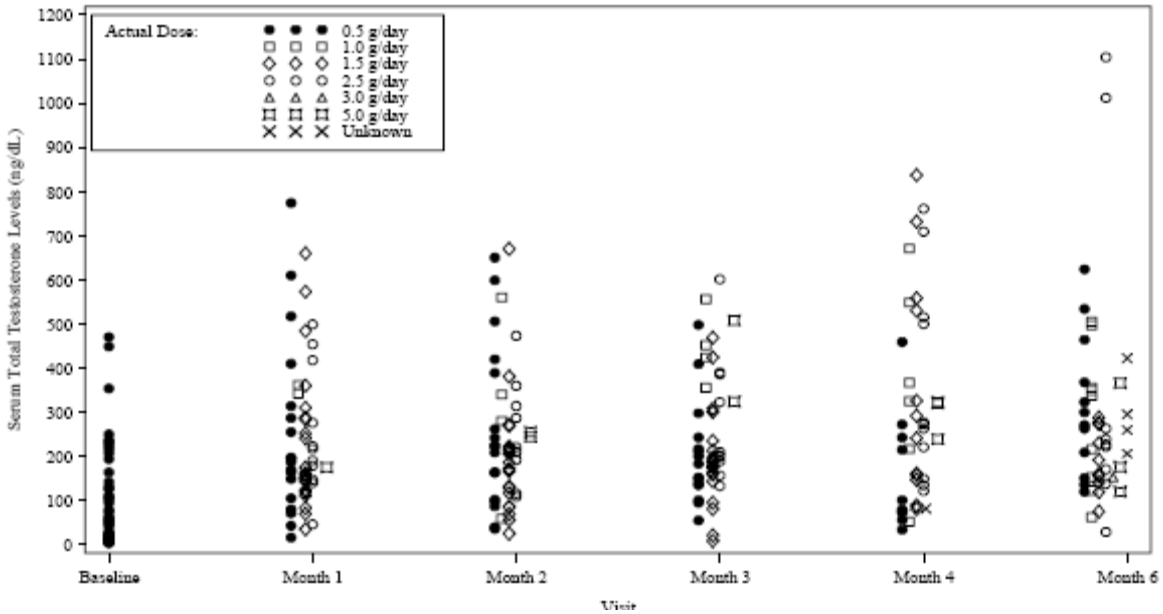
A scatterplot of individual total testosterone values from baseline through Month 6 is presented in applicant's Figure 9.1 (A). In general the distribution of individual values is similar across all timepoints measured from Month 1 through Month 6. As noted during the titration period, absolute total testosterone values in the adult range (300-1000 ng/dL) were observed with all doses including the starting AndroGel dose of 0.5 g/dL.

Figure 9.1 (A)
Scatter Plot of Serum Total Testosterone Levels at Baseline and Months 1-6 by Actual Dose
All Patients



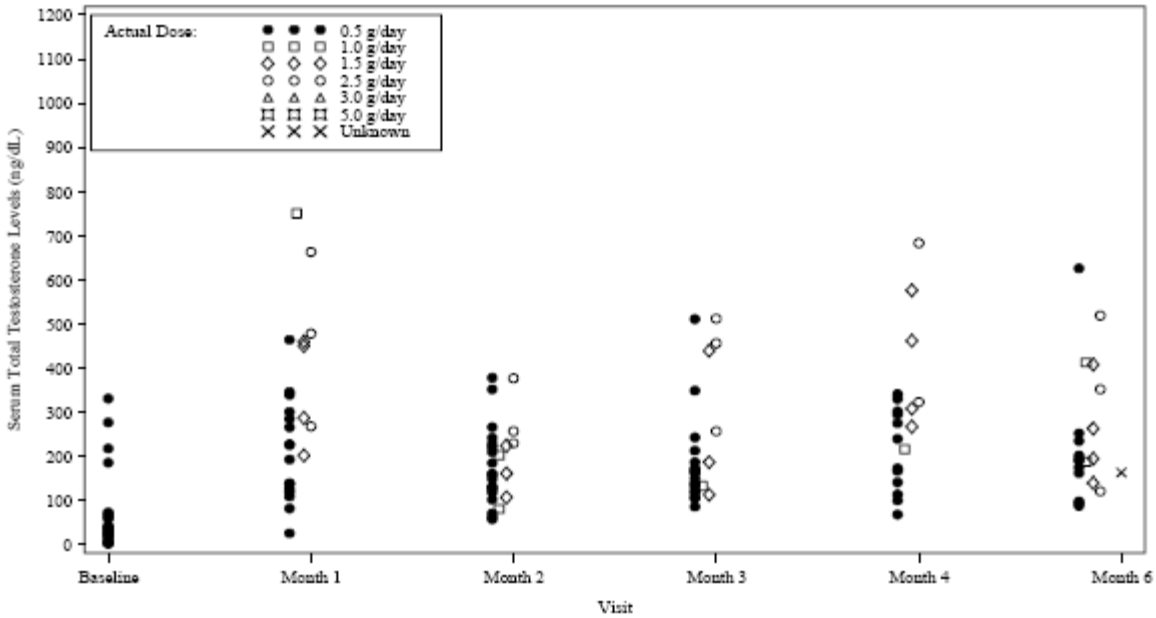
A scatterplot that includes individual serum total testosterone values in hypogonadal patients only is presented by the applicant as Figure 9.1 (B).

Figure 9.1 (B)
Scatter Plot of Serum Total Testosterone Levels at Baseline and Months 1-6 by Actual Dose
Hypogonadal Patients



A similar scatterplot for CDGP patients is presented by the applicant as Figure 9.1 (C).

Figure 9.1 (C)
Scatter Plot of Serum Total Testosterone Levels at Baseline and Months 1-6 by Actual Dose
CDGP Patients



Since during the study it was observed that several patients were dosed using the wrong pump – head the applicant conducted several analyses that compared serum total testosterone concentrations on the (b) (4) pump, and on the mixed use of both pumps. It needs to be recognized, however, that patients were titrated based on serum testosterone levels making the clinical impact of using the inappropriate pump of less importance. Theuse of the

(b) (4)

Total testosterone levels associated with the 0.5 g AndroGel dose

Seventy-five patients had measurements of serum testosterone levels at Week 1 after receiving exclusively 0.5 g/day of Androgel. The Week 1 timepoint is particularly informative because all patients were to have received the starting dose of 0.5 g per day up to this timepoint[42] and the measured testosterone levels were at steady state. Thus, this timepoint provides the largest set of individual testosterone measurements with the 0.5 g AndroGel dose and the serum testosterone levels measured at this time should give the best approximation of the range of levels expected with the starting dose of 0.5 g. The Week 1 mean serum testosterone level was 184.3 ± 134.1 ng/dL and was associated with a wide range of individual values (28 to 674 ng/dL); similar or slightly higher testosterone levels were reached at Week 2 (206.0 ± 173.8; range 56, 1066)[43] and beyond; at Month 1 the mean testosterone serum concentration was 228.0 ± 165.1 ng/dL(range 16, 774), changed minimally at Month 2 (215.8 ±147.3 ng/dL), decreased somewhat at Months 3 and 4 and reached a level of 264.3 (160.0) at Month 6.

Table 13: Serum total testosterone levels in patients receiving the 0.5 g dose throughout the trial

Statistic	Testosterone levels (ng/dL)			
	Baseline	Week 1	Week 2	Month 1
N	74	75	46	36
Mean (SD)	103.9 (113.9)	184.3 (134.1)	206.0 (173.8)	228.0 (165.1)
Range	10, 561	28, 674	56, 1066	16, 774
Statistic	**Testosterone levels (ng/dL) –continued**			
	Month 2	**Month 3**	**Month 4**	**Month 6**
N	37	34	22	23
Mean (SD)	215.8 (147.3)	191.8 (107.6)	188.8 (115.3)	264.3 (160.0)
Range	36, 650	55, 511	34, 459	88, 626

Source: Tables 10.2.10 (A) and 10.2.12 (A).

The change from baseline in serum testosterone concentration at Month 1 was 144.5 ±150.8 (range -77, 755; 95%; CI = 93.5, 195.5), it changed minimally at Month 2 (132.4 ±104.2; range -81, 499, 95% CI (97.7, 167.2)) and declined slightly at Months 3 (102.4 ±80.9; range -172, 293; 95% CI 74.1, 130.6) and Month 4 (98.6 ±120.5; range -198, 313; 95% CI: 45.1, 152.0), only to increase again at Month 6 (154.6 ± 147.6 (range; -170, 527; 95%CI: 90.8, 218.4).

Table 14: Change in serum total testosterone levels relative to baseline for the 0.5 g dose (Month 1 through Month 6)

Statistic	Change from baseline in testosterone levels (ng/dL)				
	Month 1	Month 2	Month 3	Month 4	Month 6
N	36	37	34	22	23
Baseline mean	83.5	83.3	89.4	90.2	109.7
Mean (SD)	144.5 (150.8)	132.4 (104.2)	102.4 (80.9)	98.6 (120.5)	154.6 (147.6)

[42] In fact, according to Table 10.2.10 (A), 75/76 patients received the 0.5 AndroGel dose at Week 1.
[43] A slightly higher mean level in the low 200's was reached by the 1.0 g daily regimen (216.3 ± 13.7ng/dl) and the 1.5 g/day regimen (241.3 ± 180.0) at this timepoint.

Range	-77, 755	-81, 499	-172, 293	-198, 313	-170, 527
95% CI	(93.5, 195.5)	(97.7, 167.2)	(74.1, 130.6)	(45.1, 152.0)	(90.8, 218.4)

Source: Table 10.2.14 (A).

Total testosterone levels associated with the 0.5 g AndroGel dose in a subgroup of patients who were Tanner I at baseline

Twenty five patients, about half with hypogonadism (13/25) and half with CDGP (12/25) were Tanner I at baseline. Changes in serum testosterone levels for the patients who were Tanner I at baseline and received the 0.5 g daily dose of AndroGel on trial are presented in Table 15. There was a trend toward higher baseline-subtracted testosterone levels in this patient subgroup relative to the overall group of patients who used the AndroGel dose of 0.5 g/day.

Table 15: Change in testosterone levels relative to baseline for the patients who were Tanner I at baseline and received the 0.5 g daily dose (Month 1 through Month 6)

Statistic	Change from baseline in testosterone levels (ng/dL)				
	Month 1	Month 2	Month 3	Month 4	Month 6
N	10	13	15	9	10
Baseline mean	20.8	23.8	26.1	29.1	27.0
Mean (SD)	133.3 (72.3)	107.4 (62.2)	122.4 (42.8)	162.1 (99.1)	176.4 (83.1)
Range	20, 272	14, 219	29, 200	55, 313	30, 315
95% CI	(81.6, 185.0)	69.8, 145.0)	(98.7, 146.1)	(85.9, 238.3)	(117.0, 235.8)

Source: FDA Request 13 – Table 2.2 (A).Table 10.2.13 (A).

Serum testosterone levels associated with the 0.5 g/day AndroGel dose at Week 1

Since the main objective of this study was to establish a starting dose of AndroGel in adolescent boys with pubertal delay this reviewer has focused on the serum testosterone concentrations reached at Week 1, the first on-trial evaluation. According to Table 10.2.10(A) titled "Serum total testosterone concentrations at screening and weekly titration visits by actual dose level and visit - all patients", at Week 1, 75/76 measurements were made at a dose of AndroGel of 0.5 g/day (only one measurement was done with the 1 g/day dose). Since AndroGel reaches steady state after approximately 4 days, a measurement at approximately Day 7 is expected to reflect steady-state serum testosterone concentrations. This reviewer re-analyzed the data from the original c.r.t. datasets using screening and Week 1 paired testosterone measurements collected at scheduled visits. The mean serum testosterone level at screening was 96.5 ng/dL; it increased to 175.7 ng/dL at Week 1 thus resulting in a mean baseline subtracted change of 79.3 ng/dL. Importantly, the range of change is quite broad, from -144 ng/dL to 528 ng/dL; the later value would be consistent with a Tanner IV, Tanner V, or even an adult testosterone level[44]. Thus, at

[44] The presence of negative change may reflect variability in measurements but more likely incomplete washout of some patients. The largest negative changes were -85 ng/dL, -85 ng/dL, -112 ng/dL and -144 ng/dL in patients with screening testosterone values of 421 ng/dL, 328 ng/dL, 302 ng/dL amd 322 ng/dL respectively (patients 1211, 1121, 1123, and 1125 respectively.

Week 1, 24/71 patients (33%) had increases of testosterone upward of 100 ng/dL, 13/71 (18%) had increased > 150 ng/dL and 7/71 (10%) had increases greater than 200 ng/dL.

Using baseline testosterone values (instead of screening values), the statistical reviewer has identified 9/74 (= 12.2%) patients who had a baseline subtracted testosterone change ≥ 200 ng/dL at Week 1. They are summarized and highlighted in Table 16:

Table 16: Characteristics of the nine patients who had baseline subtracted Week 1 changes in total testosterone level ≥ 200 mg/dL

Pt Id	Diagnosis	T-naïve at baseline	Baseline T. level (ng/dL)	T. level Week 1 (ng/dL)	Change in T. level to Week 1 (ng/dL)	Baseline Tanner Stage	Baseline bone age	Baseline Testicular volume
1022	Hypogonadism	no	60	290	230	4	13.5	5
1025	Hypogonadism	no	354	674	320	4	NA	3
1027	CDGP	no	277	523	246	5	16	12
1103	CDGP	yes	29	335	306	1	13	8
1122	Hypogonadism	no	225	555	330	4	NA	4
1161	Hypogonadism	yes	3	280	277	2	15	2
1221	Hypogonadism	no	6.8	540	533	4	NA	1
1234	Hypogonadism	no	26	279	253	2	13.5	0
1243	Hypogonadism	yes	9.9	297	287	2	13	NA

T = testosterone
NA = not available

Baseline subtracted serum testosterone levels > 200 ng/dL in hypogonadal patients receiving the 0.5 g/day AndroGel dose at any given time during the trial

In contrast to CDGP patients who, once in puberty, synthesize progressively higher endogenous testosterone levels, hypogonadal patients are expected to have a relatively stable and low endogenous testosterone background. This makes them a very informative subgroup to evaluate baseline subtracted testosterone levels for patients receiving the 0.5 AndroGel dose at any given time during the study. Serum testosterone concentrations > 200 ng/dL were not limited only to Week 1; between 8.3% of patients and 75 % patients had measurements greater than 200 ng/dL while receiving 0.5 g of AndroGel per day (Table 17).

Table 17: Number and percentage of patients with baseline subtracted total testosterone measurements > 200 ng/dL in hypogonadal patients while receiving the 0.5 g/day AndroGel dose

Timepoint	No. patients on 0.5 g/day of AndroGel	N (%) patients with testosterone > 200 ng/dl
Week 1	52	7 (13.5%)
Week 2	25	4 (16%)*
Week 3	4	3 (75%)**
Month 1	19	4 (21%)
Month 2	18	8 (44%)
Month 3	15	2 (13.3%)
Month 4	12	1 (8.3%)
Month 6	13	5 (38.4%)

Source: Listing 12.4.19.
*One patient (1071) may have received additional doses than the 0.5 g dose.
**Measurements at Week 3 were optional.

Serum testosterone levels in patients who used AndroGel 0.5 g daily at all times during the trial

Some patients used the 0.5 g daily dose at all times throughout the trial. These patients constitute a very informative group because they represent patients who either could not be titrated higher or who did not need to be titrated higher in the judgment of the investigator. These 29 patients (14 with hypogonadism and 15 with CDGP) are listed in Tale 18. Testosterone levels and additional information such as diagnosis, Tanner stage, and, whether they were naïve or not to testosterone treatment are included. Highlighted in yellow are observations where baseline-subtracted testosterone levels exceeded 200 ng/dL. Patients who were both naïve to testosterone therapy and Tanner I at baseline are bracketed in the "Patient ID" column (8 patients fell into this category: 3 with hypogonadism and 5 with CDGP). Bolded patient ID numbers represent patients who received AndroGel through the (b) (4) pump head at the beginning of the trial (b) (4) This dataset may be more informative for the hypogonadal patients since, at least theoretically, CDGP patients can augment endogenously their serum testosterone levels once puberty is initiated. This Table indicates that a remarkable number of individual testosterone measurements were above the 200 mg level. This "threshold" was selected somewhat arbitrarily as a testosterone concentration that is consistent with upper range of Tanner II (or above the Tanner II range in some references), closer to the mean for Tanner III and close to the lower end of Tanner V and adult levels; it was also the upper limit of titration goal (100-200 mg) for the better part of Study UMD-01-090. The 200 mg level is a fairly non-conservative "threshold".

Table 18: Listing of patients who used the 0.5 g of AndroGel at all times during the trial*

Patient ID	Diag.	T. at Baseline	T. at Week 1	T. at Week 2	T. at Week 3	T. at Month 1	T. at Month 2	T. at Month 3	T. at Month 4	T. at Month 6	Naive	Tanner stage**
(**1024**)	Hypo	9.7	156.3	228.3	273.3	NA	NA	NA	NA	NA	yes	I-I
1025	Hypo	354	320	7	NA	256	245	144	33	110	no	IV-IV
1029	Hypo	449	154	189	NA	68	201	-40	10	175	yes	V-V
1063	Hypo	111	33	93	NA	38	52	28	-10	40	no	II-III
1081	Hypo	22	83	99	246	292	201	79	12	98	no	II-III
1085	Hypo	74	73	NA	147	213	135	126	NA	198 (231)	no	IV-IV
1092	Hypo	12	82	106	NA	59	90	NA	NA	NA	yes	II-II
(2001)	Hypo	13	196	250	NA	92	NA	NA	NA	NA	yes	I-?
1123	Hypo	470	-280	-226	NA	-60	-81	-172	-198	-170	no	III-IV
1234	Hypo	26	253	200	NA	229	216	217	NA	NA	no	II-II
(3231)	Hypo	6.7	171.3	193.3	NA	163.3	157.3	128.3	70.3	202.3	yes	I-II
1243	Hypo	9.9	287.1	436.1	NA	6.1	NA	NA	NA	NA	yes	II-II
1252	Hypo	55	186	133	NA	-12	-19	NA	-26 (17)	81	no	IV-V

2063	Hypo	194	108	75	NA	3	226	17	21	331 (15) (174)	no	V-V
1026	CDGP	40	153	183	NA	226	145	130	262	#	no	III-IV
1027	CDGP	277	246	130	NA	62	101	72	53	-87	no	V-V
3021	CDGP	73	59	31	166	153	147	64	NA	NA	yes	III-III
1038	CDGP	62	85	133	NA	57	98	24	38	36	yes	II-II
3031	CDGP	58	168	90	NA	NA	152	81	56	30	yes	I-III
3033	CDGP	21	114	69	NA	117	110	NA	NA	NA	yes	II-II
1089	CDGP	218	56	147	NA	128	134	293	NA	290 (408)	no	II-IV
(1102)	CDGP	42	144	170	NA	97	88	121	NA	NA	yes	I-I
(1103)	CDGP	29	306	343	NA	272	96	184	266	223	yes	I-II
1127	CDGP	186	18	18	NA	-77	-37	57	NA	-23	yes	II-III
(1226)	CDGP	39	81	110	NA	87	79	148	236	154	yes	I-II
1239	CDGP	3.7	124.3	77.3	116.3	460 (110)	224.3	169.3	169.3	158.3	yes	II-III
(1240)	CDGP	3	74	115	82	136	59	118	NA	NA	yes	I-II
3233	CDGP	3.2	131.8	88.8	116.8	281	311.8 (262.8)	126.8	126.8	236.8	yes	III-III
(1281)	CDGP	23	145	130	NA	170	219	141	NA	NA	yes	I-II

Source: Listings 12.4.19 and 12.4.17
* Testosterone values post baseline are baseline-subtracted. The Table includes patients who at the last timwepoint on trial the last dose is increased over 0.5 g/day , in which case it is specified as such.
**Tanner stage at the beginning and end of trial.
At rhis timepoint the dose was increased over 0.5 g/day.
Abbreviations: Diag. = diagnosis; Hypo = hypogonadism; CDGP = constitutional delay of growth and puberty. T= total testosterone (ng/dL); NA = not available.

Growth velocity

The change in growth velocity during this study is illustrated in Table 19. The mean growth velocity decreased for the hypogonadal patients by approximately 1.1 cm/yr (from 6.9 cm/yr to 5.7 cm/year) and increased by approximately 2.2 cm/yr for the CDGP patients. A meaningful interpretation of these data without a control group is difficult. Because patients were at various Tanner stages at baseline the data are not informative.

Table 19: Summary statistics for the change from baseline in growth velocity (cm/yr)

Timepoint	**Growth velocity (cm/year)**		
	All patients (N=86)	**Hypogonadism (N=59)**	**CDGP (N=27)**
Baseline			
N	81	58	23
Mean (SD)	6.46 (4.11)	6.90 (4.50)	5.35 (2.68)
Range	-0.5, 31.7	-0.5, 31.7	0.4, 12.7
Final visit			
N	86	59	27
Mean (SD)	6.29 (3.90)	5.73 (3.89)	7.50 (3.69)

Range	-8.2, 17.4	-8.2, 16.0	-0.7, 17.4
Change from baseline to Final visit			
N	81	58	23
Mean (SD)	-0.15 (5.45)	-1.10 (5.67)	2.25 (4.02)
Range	-28.6, 11.9	-28.6, 11.1	-4.0, 11.9
12-month growth velocity SDS			
N	38	25	13
Mean (SD)	0.43 (1.95)	0.57 (2.25)	0.14 (1.23)
Range	-2.2, 9.9	-1.8, 9.9	-2.2, 2.1

Source: Tables 10.2.1 (A), 10.2.1 (B), and 10.2.1 (C) in UMD-01-090 Study Report.

Growth velocity change on study drug is presented, by "overall dose", for the hypogonadism and CDGP populations in applicant's Table 9. Although the number of patients for each dose in each of the study population is small, there does not appear to be a distinct dose-dependent acceleration of height velocity. As mentioned above, interpretation of these data without a control group is daunting.

Table 9 Growth Velocity

		Subject Population Groups					
		Hypogonadal (N = 59)			CDGP (N = 27)		
		Overall Dose (g)					
Parameter	Statistic	< 100 (N = 14)	100 - 240 (N = 20)	> 240 (N = 25)	< 100 (N = 13)	100 – 240 (N = 8)	> 240 (N = 6)
Growth Velocity (cm/y)							
Baseline	n	14	19	25	11	7	5
	Mean (SD)	7.84 (3.29)	5.91 (2.59)	7.13 (5.29)	5.26 (2.32)	5.30 (0.96)	5.61 (4.96)
Final Visit	n	14	20	25	13	8	6
	Mean (SD)	6.46 (4.23)	4.39 (4.18)	6.40 (3.30)	6.89 (4.37)	7.33 (2.29)	9.04 (3.72)
Change in Growth Velocity Rate	n	14	19	25	11	7	5
	Mean (SD)	-1.38 (5.40)	-1.36 (3.68)	-0.74 (7.08)	2.42 (4.17)	1.63 (2.95)	2.73 (5.60)
	95% CI	(-4.50, 1.75)	(-3.13, 0.41)	(-3.66, 2.19)	(-0.38, 5.22)	(-1.10, 4.36)	(-4.22, 9.68)
12-Month Growth Velocity Using SDS	n	6	7	12	6	4	3
	Mean (SD)	0.83 (0.57)	0.07 (1.69)	0.74 (3.01)	0.16 (1.07)	0.13 (0.93)	0.13 (2.21)
	95% CI	(0.23, 1.43)	(-1.50, 1.64)	(-1.17, 2.66)	(-0.96, 1.28)	(-1.35, 1.60)	(-5.35, 5.61)

Data Source: Table 10.2.1(B) and Table 10.2.1(C)..

Testicular volume

Summary statistics for the changes in testicular volume are presented in Table 20. Not surprisingly, the changes from baseline through Month 6 were minimal for the hypogonadal patients. CDGP patients had an average increase in mean testicular volume of approximately 2 ml indicating progression through puberty. As several patients in the CGDP group were already in puberty at baseline it is impossible to differentiate any potential effect of AndroGel from those of the physiologically progressing puberty.

Table 20: Summary statistics for testicular volume (mL):

Timepoint	Testicular volume (mL)		
	All patients (N=86)	**Hypogonadism (N=59)**	**CDGP (N=27)**
Baseline			
N	84	57	27
Mean (SD)	3.6 (2.9)	3.2 (2.5)	4.4 (3.5)
Range	0, 15	0, 12	1, 15
Month 1			
N	82	55	27
Mean (SD)	4.0 (3.1)	3.6 (2.6)	5.0 (3.7)
Range	0, 15	0, 15	1, 15
Change from baseline at Month 1			
N	82	55	27
Baseline mean	3.6	3.2	4.4
Mean (SD)	0.4 (1.2)	0.3 (1.2)	0.6 (1.0)
Range	-4, 5	-4, 5	-1, 4
Month 3			
N	74	47	27
Mean (SD)	4.5 (3.5)	3.8 (2.8)	5.6 (4.2)
Range	0, 20	0, 15	2, 20
Change from baseline at Month 3			
N	74	47	27
Baseline mean	3.7	3.3	4.4
Mean (SD)	0.7 (1.7)	0.4 (1.7)	1.2 (1.6)
Range	-5, 7	-5, 7	0, 5
Month 6			
N	69	48	21
Mean (SD)	4.9 (4.2)	4.3 (4.3)	6.1 (3.7)
Range	0, 25	0, 25	1, 15
Change from baseline at Month 6			
N	68	47	21
Baseline mean	3.6	3.4	4.2
Mean (SD)	1.0 (2.0)	0.6 (1.8)	2.0 (1.9)
Range	-5, 6	-5, 6	-1, 5
Final Visit			
N	84	57	27
Mean (SD)	4.9 (4.2)	4.2 (4.0)	6.4 (4.3)
Range	0, 25	0, 25	1, 20
Change from baseline at at Final Visit			
N	83	56	27
Baseline mean	3.6	3.3	4.4
Mean (SD)	1.0 (1.9)	0.5 (1.7)	2.0 (1.9)
Range	-5, 6	-5, 6	-1, 5

Source: Tables 10.2.2 (A), 10.2.2 (B), 10.2.2 (C), 10.2.3 (A), 10.2.3 (B), and 10.2.3 (C) in UMD-01-090 Study Report.

Tanner Pubic Hair Stage

This reviewer's analysis of Tanner stage changes from screening/baseline to endpoint derived from Listing 12.4.17 indicates that, overall, 48/86 patients (56%) experienced a Tanner stage shift; 29/86 patients (34%) had a shift of one Tanner stage, 17/86 patients (20%) had a shift of two Tanner stages and 2/86 patients (2%) had a shift of three Tanner stages.

For patients with hypogonadism 31/59 patients (52%) had advancement in Tanner stages from baseline to the end of trial: 19/59 patients (32%) had a shift of one Tanner stage, 10/59 patients (17%) had a shift of two Tanner stages, and 2/59 (3%) patients had a shift of three Tanner stages. Of the 10 patients who experienced a shift of two Tanner stages, all received either the "medium" AndroGel dose (3 patients) or the "high" AndroGel dose (7 patients). Both patients who advanced by 3 Tanner stages received the high overall AndroGel dose (>240 mg).

For patients with CDGP, 17/27 patients (63%) experienced advancement in Tanner stages: 10/27 patients (37%) had a shift of one Tanner stage, 7/27 (26%) had a shift of two Tanner stages and none had a shift of three or more Tanner stages. Among the 7 patients who experienced a shift of two Tanner stages, one patient received the "low" dose (i.e. <100g) of AndroGel, three received the medium dose (i.e. 100-240 g) and three others received the high dose (> 240 g). Since it is expected that patients with CDGP will have pubertal progression, the absence of a concurrent control group precludes attributing the progression through Tanner stages exclusively to treatment with Androgel.

6.1.5 Clinical Microbiology

Not applicable.

6.1.6 Efficacy Conclusions

Since Study UMD-01-090 was not an efficacy study (the WR defined it as a"dose titration and safety study") and did not include a control group, the efficacy assessments collected provided very limited information. In addition, even the efficacy analyses performed were largely noninformative due to the heterogeneity of the patient population enrolled in the study and to multiple protocol violations. The main contribution of Study UMD-01-090 was that it collected extensive dose-exposure data (i.e. serum testosterone levels in over 70 patients for up to 6 months over the whole range of doses evaluated), thus expanding considerably the information provided in the pharmacokinetic Study UMD-01-080. The significance of these data is discussed in the Dosage and Administration Section (b) (4)

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

No deaths occurred during any of the two studies.

7.1.2 Other Serious Adverse Events

There were only four serious adverse events, all in Study UMD-01-090. They are summarized in Table 21. One of them (slipped femoral epiphysis head0 was consider possibly related to study medication; all others were considered unlikely to be related or unrelated. There were no SAEs recorded in Study UMD-01-080.

Table 21: Serious adverse events in Study UMD-01-090

Patient ID	Adverse event and summary narrative
103/1029	**Severe adjustment disorder with depressed mood**: a 14-year old with Klinefelter's syndrome who had been receiving 0.5 g of AndroGel for 169 days developed depression which lasted for 14 days, required hospitalization and was considered unlikely related to study medication.
104/1036	**Appendicitis**: 13-year old with Klinefelter's syndrome, who developed appendicitis after receiving AndroGel at a dose of 1.5 g/day for 115 days; the appendicitis lasted for nine days, resolved after surgical intervention and was considered unrelated to study medication.
123/1224	**Slipped femoral epiphysis**: 15-year old who experienced a severe slipped femoral epiphysis after receiving AndroGel at a dose of 1.5 g/day for 104 days (the patient was 172 cm tall and weight 64.8 kg at baseline); the event was considered possibly related to study medication and required hospitalization.
124/1233	**Severe depression**: 13-year old with a history of depression, attention hyperactivity disorder, and primary hypogonadism due to secondary testicular irradiation experienced severe depression after receiving AndroGel at a dose of 1.5 g/day for 38 days. The depression was considered unlikely related to study medication, lasted for seven days, and resolved. The patient however discontinued the study.

Source: text

7.1.3 Dropouts and Other Significant Adverse Events

One patient discontinued trial UMD-01-090 due to an adverse event of severe depression (Patient 124/1233, see description in the SAE section).

7.1.3.1 Overall profile of dropouts

Refer to Section 7.1.3.

7.1.3.2 Adverse events associated with dropouts

Refer to Section 7.1.3. There was only one dropout in this study making further interpretation of the data difficult. It should be recognized that depression is oftentimes a comorbid condition that in patients with delayed puberty.

7.1.3.3 Other significant adverse events

Bone age advancement

Table 22 summarizes the bone age changes from baseline to the 6-month endpoint by testosterone exposure across all doses in Study UMD-01-090[45]. According to the data presented in this Table, over 6 months (0.5 years) of AndroGel treatment the mean bone age advanced by 0.3 years for the low dose, 0.5 for the medium dose and 0.5 for the high dose; across all exposures it advanced by 0.4 years (95% CI: 0.2, 0.6). This data would indicate that, on average, bone age did not advance in excess of chronological age. However, this conclusion is not supported by the evaluation of individual values (see following scatterplot).

Table 22: Bone age advancement in Study UMD-01-090

Parameter	Overall dose			Across all doses N=86
	Low (<100 g) N=27	Medium (100-240) N=28	High (>240) N=31	
Baseline bone age (years)				
n	25	26	31	82
Mean (SD)	13.4 (1.0)	13.5 (1.4)	14.0 (1.4)	13.7 (1.3)
Range	12, 16	11, 17	11, 17	11, 17
Change in bone age at final visit (years)				
N	19	24	26	69
Baseline mean	13.5	13.5	13.6	13.6
Mean (SD)	0.3 (0.7)	0.4 (0.7)	0.5 (0.7)	0.4 (0.7)
Range	-1, 1	-1, 2	-2, 2	-2, 2
95% CI	(-0.1, 0.6)	(0.1, 0.7)	(0.2, 0.8)	(0.2, 0.6)
Bone Maturation Age Advancement (years)* (ΔBA/ΔCA)				
n	19	24	26	69
Mean (SD)	0.0 (0.3)	0.1 (0.1)	0.1 (0.1)	0.1 (0.2)
Range	-1, 1	-0, 0	-0, 0	-1, 1
95% CI	(-0.1, 0.2)	(0.0, 0.1)	(0.0, 0.1)	(0.0, 0.1)

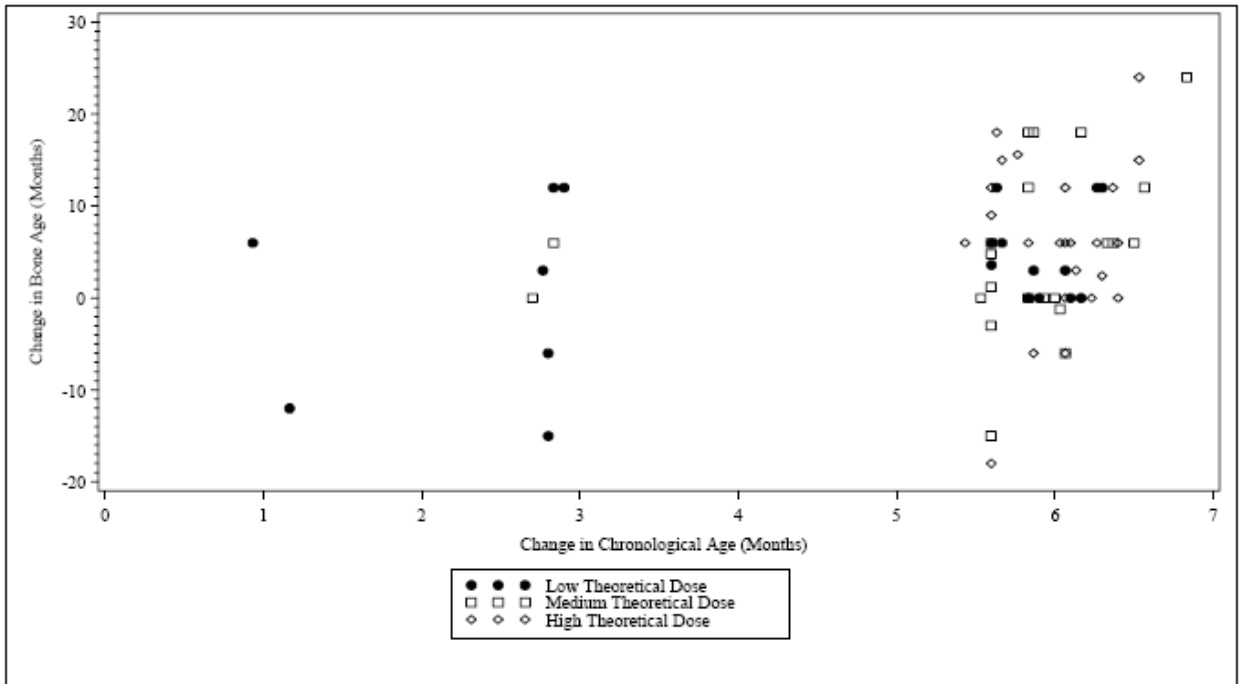
Source: Table 10.2.8A
* Defined as: "Bone maturation age advancement is calculated as the interval change in bone age divided by the interval change in chronological age".

A scatterplot of the change in bone age vs. change in chronological age in the All Subjects Population is presented in applicant's Figure 4. Two observations stand out:

[45] The applicant states that bone age readings were made centrally by a single radiologist who was not masked to the Patient ID or the sequence of X-rays. Four readings were provided by an alternate radiologist.

- Although the duration of the trial was approximately 6 months for most patients, a sizable number of patients had advances in bone age in excess of 6 months, some as high as two years.
- Several patients had reductions in bone age (i.e. negative baseline subtracted values at the end of trial), which is biologically implausible.

Figure 4 **Scatter Plot of Change in Bone Age vs. Change in Chronological Age - All Patients**



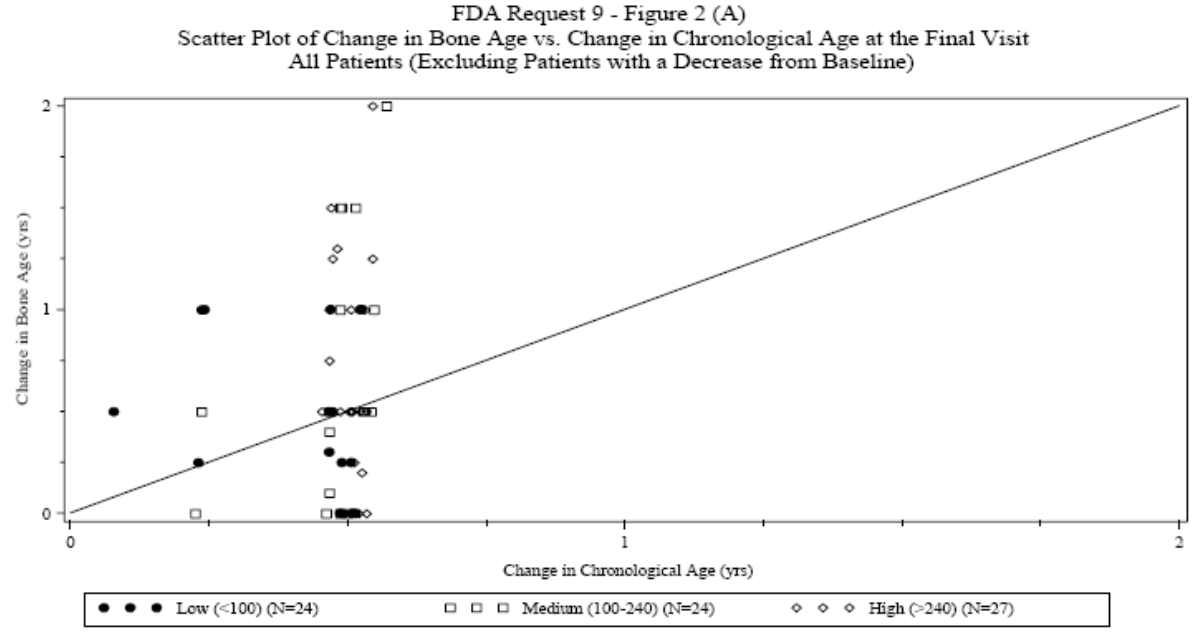
As the above described scatterplot indicates that several patients had a decrease in bone age which is biologically impossible, an analysis of bone age advancement excluding there values was requested from the applicant. This analysis excluded 3 patients in the low dose group, 4 patients in the medium dose group, and 4 patients in the high dose group. This information is summarized in Table 23. The mean change in bone age at final visit showed a discrete dose response (0.47 for low dose, 0.58 for medium dose and 0.65 for high dose). The bone age advancement was highest with the low dose and greater with the high dose relative to the medium dose.

Table 23: Bone age advancement in Study UMD-01-090 excluding patients with decrease from baseline

Parameter	Overall dose			Across all doses N=75
	Low (<100 g) N=24	Medium (100-240) N=24	High (>240) N=27	
Baseline bone age (years)				
n	22	22	27	71
Mean (SD)	13.50 (1.02)	13.60 (1.39)	13.82 (1.34)	13.65 (1.26)
Range	11.5, 16.0	10.5, 17.0	11.0, 17.0	10.5, 17.0
Change in bone age at final visit (years)				
N	16	20	23	59
Baseline mean	13.6	13.6	13.4	13.5
Mean (SD)	0.47 (0.41)	0.58 (0.63)	0.65 (0.55)	0.58 (0.54)
Range	0.0, 1.0	0.0, 2.0	0.0, 2.0	0.0, 2.0
95% CI	(0.26, 0.69)	(0.28, 0.87)	(0.41, 0.89)	(0.44, 0.72)
Change in chronological age at final visit (years)				
N	17	22	23	62
Mean (SD)	0.42 (0.14)	0.44 (0.13)	0.50 (0.03)	0.46 (0.11)
Range	0.1, 0.5	0.0, 0.6	0.5, 0.5	0.0, 0.6
95% CI	(0.35, 0.49)	(0.38, 0.50)	(0.49, 0.52)	(0.43, 0.49)
Bone Maturation Age Advancement (years) (ΔBA/ΔCA)*				
n	16	20	23	59
Mean (SD)	1.60 (1.85)	1.18 (1.23)	1.30 (1.09)	1.34 (1.37)
Range	0.0, 6.4	0.0, 3.5	0.0, 3.7	0.0, 6.4
95% CI	(0.61, 2.59)	(0.60, 1.75)	(0.83, 1.78)	(0.99, 1.70)

Source:: FDA Request 9 – Table 10.2.8 (A)
* Defined as "the interval change in bone age divided by the interval change in chronological age".

A scatterplot of bone age vs. chronological age changes after removing the biologically implausible values was re-submitted by the applicant at my request and reproduced below. It indicates that some patients had bone age changes < 6 months, others had concordant chronological and bone age changes, while others had maturation in bone age that exceeded chronological age (with some observations of 1-2 years for a 6-month period). Although there were 24 observations recorded in the graph for the 0.5 g dose, only 12 were paired (i.e. baseline and postbaseline observations in the same patient). This limits significantly the usefulness of this dataset.



Reference: FDA REQUEST 9 - TABLE 10.2.8 (A)

Gynecomastia

Although 10 subjects (12%) developed gynecomastia during the trial, this finding has limited significance since gynecomastia is a common occurrence in boys during puberty. Breast volumes were not measured; instead, the horizontal diameter of the breast was assessed at baseline in 18 patients (21%) and was on average 6.7 cm. Fourteen patients had measurements at both baseline and final visit; for this subgroup the mean diameter decreased by 0.6 cm.

Application site (skin) assessment

The applicant reports that three patients had developed transient abnormalities at the application site:

- Patient 123/1222 had a fine popular rash in skin folds in his abdomen and flank at Week 3 that returned to normal at Month 1.
- Patient 124/1239 had a slightly pink, dry and itchy abdomen at Month 2 that normalized at Month 3.
- Patient 126/1251 had a mild "acne burn" on his left arm at Month 2 that normalized at Month 3.

7.1.4 Other Search Strategies

Only standard analyses of adverse events were conducted.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Safety assessments included adverse events, clinical laboratory[46], vital signs, physical examinations, skin application site assessments, and gynecomastia. Both physical exams and clinical laboratory evaluations (other than hormonal assessments) were performed at baseline, and almost monthly between the Month 1 and Month 6 timepoints. Bone age was measured at baseline and Month 6 (or Month 3 for patients who terminated early).

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were categorized using the MedDRA dictionary, Version 5.0. Visual inspection of Listing 12.4.20 found concordance between the verbatim and the preferred terms.

7.1.5.3 Incidence of common adverse events

In study UMD-01-080, 12 subjects (70.6%) experienced TEAEs: 6 subjects (35.3%) 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. Treatment-emergent AEs reported for more than one subject included headache NOS (3 patients or 17.6%), vomiting NOS (2 patients or 11.8%), and hemoglobin decreased (2 patients or 11.8%). Most of the adverse events reported were mild in intensity; a few were moderate in intensity (constipation, decreased hemoglobin, and convulsion NOS aggravated); none was severe. The only adverse events that were considered "related" to the study medication by the investigators (included "unlikely", "possible", "probable", and "unknown) were upper abdominal pain, constipation, nausea, vomiting, headache, and petechiae.

In Study UMD-01-090, 74 patients (86.0%) experienced a treatment-emergent adverse event. Applicant's Table 17 presents TEAEs that occurred with a frequency ≥ 5%. Headache, a common symptom in general, was the most frequent TEAE (23.3%). Most other adverse events represent common childhood and adolescence conditions (e.g. respiratory infections). The only adverse events listed in this table that could be mechanistically associated with the study drug, are acne and contact dermatitis (absence of a control group make causality assignment difficult).

[46] Clinical laboratory included hematology tests (hemoglobin, hematocrit,RBC count, platelet count, and white cell plus differential count), chemistry analytes (alkaline phosphatase, alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT), aspartate aminotransferase/serum glutamic-oxaloacetic transaminase (AST/SGOT), total bilirubin, blood urea nitrogen, creatinine, glucose, electrolytes), urinalysis, and lipid panel (total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides. Clinically significant abnormal laboratory test results were repeated to confirm the results. Hormone assays were performed (b) (4) Wrist and hand radiographs were evaluated (b) (4)

Most TEAEs were reported as mild in severity. The only severe TEAEs were those that were also reported as serious adverse events (appendicitis, slipped femoral epiphysis, adjustment disorder with depressed mood, and depression). A total of 26 TEAE were reported as moderate in severity (19 reported in patients with hypogonadism and seven in patients with CDGP). Most "moderate" TEAE were reported by only one patient; exceptions were upper respiratory tract infection NOS (4 patients), cough (3 patients), viral infection NOS (3 patients), pyrexia (2 patients) and arthralgia (2 patients).

Table 17 Incidence of Treatment-emergent Adverse Events Occurring in ≥ 5% of the All Subjects Population

		Subject Population Group		
System Organ Class Preferred Term	Statistic	Hypogonadal (N = 59)	CDGP (N = 27)	All Subjects (N = 86)
Subjects with ≥ 1 TEAE	n (%)	48 (81.4)	26 (96.3)	74 (86.0)
Infections and Infestations				
Nasopharyngitis	n (%)	7 (11.9)	2 (7.4)	9 (10.5)
Upper Respiratory Tract Infection NOS	n (%)	8 (13.6)	2 (7.4)	10 (11.6)
Viral Infection NOS	n (%)	6 (10.2)	1 (3.7)	7 (8.1)
Nervous System Disorders				
Headache NOS	n (%)	10 (16.9)	10 (37.0)	20 (23.3)
Respiratory, Thoracic and Mediastinal Disorders				
Cough	n (%)	8 (13.6)	3 (11.1)	11 (12.8)
Nasal Congestion	n (%)	3 (5.1)	6 (22.2)	9 (10.5)
Pharyngitis	n (%)	5 (8.5)	3 (11.1)	8 (9.3)
Skin and Subcutaneous Tissue Disorders				
Acne NOS	n (%)	8 (13.6)	0	8 (9.3)
Dermatitis Contact	n (%)	2 (3.4)	3 (11.1)	5 (5.8)

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

Forty eight patients (55.8%) experienced a TEAE "related" to study medication[47]. Applicant' Table 18 lists such TEAEs that occurred with a frequency ≥ 5%. The only such TEAEs that could not be ascribed to intercurrent illnesses were arthralgia and acne. Headache was the most frequent TEAE (14%).

[47] Includes relationships of "possible", "probable", and "unknown".

Table 18 Treatment-Emergent Adverse Events Related to Study Medication Occurring in ≥ 5% of Subjects in Either the Hypogonadal or CDGP Population Groups

System Organ Class Preferred Term	Statistic	Subject Population Group Hypogonadal (N = 59)	 CDGP (N = 27)	 All Subjects (N = 86)
Subjects with ≥ 1 Related TEAE	n (%)	32 (54.2)	16 (59.3)	48 (55.8)
Infections and Infestations				
Viral Infection NOS	n (%)	3 (5.1)	0	3 (3.5)
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	n (%)	2 (3.4)	2 (7.4)	4 (4.7)
Nervous System Disorders				
Headache NOS	n (%)	5 (8.5)	7 (25.9)	12 (14.0)
Respiratory, Thoracic and Mediastinal Disorders				
Nasal Congestion	n (%)	0	3 (11.1)	3 (3.5)
Skin and Subcutaneous Tissue Disorders				
Acne NOS	n (%)	6 (10.2)	0	6 (7.0)

Note: Relationships of unlikely, possible, probable, and unknown are counted as related.
Data Source: Table 10.3.4(A), Table 10.3.4(B), and Table 10.3.4(C).

A display of adverse events with a frequency ≥ 2% by dose (0.5, 1.0, 1.5, or 2.5 g/day) is included in applicant's Table 19; it does not indicate any clear dose response with the exception of nasopharyngitis, upper respiratory tract infection, pharyngitis, headache, and possibly acne and contact dermatitis. It should be recognized that exposure was not balanced between the different doses (for instance more patients were exposed to the 0.5 g daily dose than any other dose).

Table 19 Treatment-Emergent Adverse Events by Study Medication Dose Occurring in ≥ 2 Subjects in the 0.5, 1.0, 1.5, or 2.5 g/day Dose Groups in Either the Hypogonadal or CDGP Population

	Subject Population Groups							
	Hypogonadal (N = 59)				CDGP (N = 27)			
	Actual Dose (g/day)							
System Organ Class Preferred Term	0.5 (N = 59)	1.0 (N = 15)	1.5 (N = 41)	2.5 (N = 21)	0.5 (N = 27)	1.0 (N = 3)	1.5 (N = 12)	2.5 (N = 3)
Subjects with ≥ 1 TEAE	28 (47.5)	6 (40.0)	19 (46.3)	14 (66.7)	21 (77.8)	2 (66.7)	5 (41.7)	3 (100)
Gastrointestinal Disorders								
Abdominal Pain Upper	0	0	1 (2.4)	0	2 (7.4)	0	0	0
Dyspepsia	2 (3.4)	0	0	0	0	0	0	0
Vomiting NOS	0	0	0	1 (4.8)	2 (7.4)	0	0	0
General Disorders & Administration Site Conditions								
Pyrexia	2 (3.4)	1 (6.7)	1 (2.4)	0	0	0	0	0
Infections & Infestations								
Nasopharyngitis	2 (3.4)	1 (6.7)	4 (9.8)	0	2 (7.4)	0	0	0
Upper Respiratory Tract Infection NOS	2 (3.4)	0	2 (4.9)	3 (14.3)	1 (3.7)	0	1 (8.3)	0
Viral Infection NOS	4 (6.8)	0	2 (4.9)	0	0	0	1 (8.3)	0
Investigations								
Blood Triglycerides Increased	2 (3.4)	0	0	0	0	0	0	0
Nervous System Disorders								
Headache NOS	4 (6.8)	0	3 (7.3)	4 (19.0)	6 (22.2)	1 (33.3)	2 (16.7)	2 (66.7)
Respiratory, Thoracic, & Mediastinal Disorders								
Cough	5 (8.5)	0	2 (4.9)	2 (9.5)	2 (7.4)	0	1 (8.3)	0
Pharyngitis	1 (1.7)	0	2 (4.9)	2 (9.5)	3 (11.1)	0	0	0
Skin & Subcutaneous Tissue Disorders								
Acne NOS	3 (5.1)	0	2 (4.9)	3 (14.3)	0	0	0	0
Dermatitis Contact	1 (1.7)	0	0	1 (4.8)	3 (11.1)	0	0	0
Rash NOS	0	2 (13.3)	1 (2.4)	0	0	0	0	0

Incidence of Acne

Nine patients (10.5%) had a TEAE of acne. Six of the nine patients developed acne during the first two months of treatment, four patients (4.7%) developed it at Month 1 and two patients (2.3%) developed it at Month 2. One patient who had worsened acne at Month 2 also had another adverse event of acne at Month 3.

7.1.5.4 Common adverse event tables

Refer to Section 7.1.5.3.

7.1.5.5 Identifying common and drug-related adverse events

Absence of a control group makes interpretation of the safety data in this clinical trial difficult. It is important to recognize that most adverse events observed are common childhood illnesses or symptoms. Of the TEAEs that were considered treatment-related by the investigators, acne was the only one that could be mechanistically related to study drug; this is, however, an anticipated finding for testosterone replacement in adolescents.

7.1.5.6 Additional analyses and explorations

None.

7.1.6 Less Common Adverse Events

Adverse events occurring in only one patient (5.9%) in study UMD-01-080 were: upper abdominal pain, constipation, nausea, seasonal allergy, viral gastroenteritis NOS, abrasion NOS, convulsion NOS aggravated, rhinorrhea, upper respiratory tract infection, acanthosis nigricans, and petechiae.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Clinical laboratory evaluations included hematology tests (hemoglobin, hematocrit, RBC count, platelet count, and white cell count plus differential), chemistry analytes (alkaline phosphatase, alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT), aspartate aminotransferase/serum glutamic-oxaloacetic transaminase (AST/SGOT), total bilirubin, blood urea nitrogen, creatinine, glucose, electrolytes, urinalysis, and lipid panel (total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides. Hormone assays were performed (b) (4) Clinical laboratory evaluations (other than hormonal assessments) were performed at baseline, and almost monthly between the Month 1 and Month 6 timepoints.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Unless otherwise specified, the laboratory data are presented only for study UMD-01-090.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

Table 24 summarizes the hematology changes on trial by testosterone exposure (low, medium, and high dose) and across all doses. There were no clinically meaningful changes by Month 6 in any of the tests analyzed.

Table 24: Summary of hematology changes by overall dose

Parameter	Overall dose			Across all doses N=86
	Low (<100 g) N=27	Medium (100-240) N=28	High (>240) N=31	
Hemoglobin (g/dL)				
Baseline				
n	27	28	31	86
Mean (SD)	13.73 (0.85)	13.30 (1.17)	13.80 (1.14)	13.62 (1.08)
Range	12.5, 15.8	10.7, 15.9	11.6, 16.4	10.7, 16.4
Change to Month 6				
n	14	25	30	69
Mean (SD)	0.36 (0.62)	0.40 (0.84)	0.05 (0.68)	0.24 (0.74)
Range	-1.1, 1.1	-1.0, 2.5	-1.4, 1.2	-1.4, 2.5
Hematocrit (%)				
Baseline				
n	27	28	31	86
Mean (SD)	40.44 (2.71)	39.14 (3.44)	40.29 (3.20)	39.96 (3.16)
Range	36.4, 46.1	31.2, 46.6	34.8, 48.0	31.2, 48.0
Change to Month 6				
n	14	25	30	69
Mean (SD)	0.39 (2.59)	1.29 (2.52)	0.35 (1.75)	0.70 (2.24)
Range	-4.7, 3.5	-2.3, 7.6	-3.5, 4.3	-4.7, 7.6
Platelet Count (x10E3/µL)				
Baseline				
n	27	28	31	86
Mean (SD)	272.3 (53.0)	272.4 (74.5)	267.9 (58.7)	270.8 (62.0)
Range	166, 410	136, 478	151, 380	136, 478
Change to Month 6				
n	14	25	30	69
Mean (SD)	3.1 (39.2)	-2.9 (53.3)	-11.6 (31.5)	-5.5 (41.9)
Range	-62, 59	-169, 97	-75, 55	(-15.5, 4.6)
WBC Count (x10E3/µL)				
Baseline				
n	27	28	31	86
Mean (SD)	6.06 (1.48)	6.55 (1.79)	5.81 (1.60)	6.13 (1.64)
Range	3.7, 8.9	3.9, 12.5	3.2, 8.8	3.2, 12.5
Change to Month 6				
n	14	25	30	69
Mean (SD)	-0.24 (1.15)	-0.34 (1.23)	-0.16 (1.06)	-0.24 (1.13)
Range	-2.4, 1.3	-3.5, 2.5	-2.5, 2.4	-3.5, 2.5
Neutrophils (%)				
Baseline				
n	27	28	31	86
Mean (SD)	52.02 (7.73)	48.01 (10.58)	51.75 (8.80)	50.62 (9.19)
Range	39.5, 72.5	23.2, 70.1	32.3, 67.4	23.2, 72.5
Change to Month 6				
n	14	25	30	69
Mean (SD)	-1.17 (7.02)	0.43 (7.87)	-2.57 (7.74)	-1.20 (7.66)
Range	-17.7, 7.7	-24.6, 12.0	-22.2, 13.0	-24.6, 13.0
Lymphocytes (%)				

Baseline				
n	27	28	31	86
Mean (SD)	36.66 (6.72)	40.97 (10.87)	36.88 (7.76)	38.14 (8.75)
Range	19.5, 45.4	22.8, 67.2	23.4, 49.7	19.5, 67.2
Change to Month 6				
n	14	25	30	69
Mean (SD)	0.91 (7.11)	-0.57 (5.85)	3.08 (7.11)	1.32 (6.78)
Range	-9.1, 17.1	-11.1, 12.5	-9.4, 20.2	-11.1, 20.2
Monocytes (%)				
Baseline				
n	27	28	31	86
Mean (SD)	5.89 (2.09)	6.44 (2.73)	7.10 (1.99)	6.51 (2.31)
Range	0.9, 10.0	2.7, 16.5	3.1, 14.4	0.9, 16.5
Change to Month 6				
n	14	25	30	69
Mean (SD)	0.61 (3.53)	0.00 (2.73)	-0.37 (1.67)	-0.04 (2.52)
Range	-4.7, 8.0	-8.8, 5.8	-4.3, 2.7	-8.8, 8.0
Eosinophils (%)				
Baseline				
n	27	28	31	86
Mean (SD)	4.99 (3.85)	4.16 (2.72)	3.83 (2.71)	4.30 (3.12)
Range	1.5, 14.9	1.4, 14.9	0.9, 11.4	0.9, 14.9
Change to Month 6				
n	14	25	30	69
Mean (SD)	-0.27 (2.24)	-0.09 (2.19)	-0.11 (1.83)	-0.13 (2.02)
Range	-4.9, 3.1	-4.9, 6.1	-5.4, 2.9	-5.4, 6.1
Basophils (%)				
Baseline				
n	27	28	31	86
Mean (SD)	0.44 (0.31)	0.37 (0.30)	0.44 (0.20)	0.42 (0.27)
Range	0.0, 1.2	0.0, 1.4	0.1, 0.9	0.0, 1.4
Change to Month 6				
n	14	25	30	69
Mean (SD)	-0.08 (0.34)	0.03 (0.26)	-0.04 (0.27)	-0.02 (0.28)
Range	-0.7, 0.7	-0.5, 0.5	-0.7, 0.7	-0.7, 0.7

Source: Table 1.3 11(A)

Table 25 summarizes the chemistry changes on trial by testosterone exposure (low, medium, and high dose) and across all doses. There were no clinically meaningful changes by Month 6 in any of the tests analyzed.

Table 25: Summary of chemistry analyte changes by overall dose

Parameter	**Overall dose**			**Across all doses N=86**
	Low (<100 g) N=27	**Medium** (100-240) N=28	**High** (>240) N=31	
Sodium (mEq/L)				
Baseline				
n	27	28	31	86
Mean (SD)	141.37 (2.50)	141.96 (2.08)	141.90 (2.57)	141.76 (2.39)
Range	136.0, 146.0	137.0, 146.0	136.0, 149.0	136.0, 149.0

Change to Month 6				
n	15	25	30	70
Mean (SD)	0.80 (3.73)	-0.64 (2.36)	0.17 (3.71)	0.01 (3.29)
Range	-4.0, 8.0	-5.0, 4.0	-10.0, 8.0	-10.0, 8.0
Potassium (mEq/L)				
Baseline				
n	27	28	31	86
Mean (SD)	4.47 (0.33)	4.43 (0.30)	4.42 (0.29)	4.43 (0.30)
Range	3.9, 5.1	3.8, 4.9	4.0, 5.3	3.8, 5.3
Change to Month 6				
n	15	25	30	70
Mean (SD)	-0.04 (0.31)	0.03 (0.41)	-0.00 (0.32)	0.00 (0.35)
Range	-0.6, 0.5	-0.5, 1.0	-0.7, 0.6	-0.7, 1.0
Chloride (mEq/L)				
Baseline				
n	27	28	31	86
Mean (SD)	105.1 (2.6)	105.3 (2.8)	105.7 (2.2)	105.4 (2.5)
Range	101, 112	100, 110	102, 111	100, 112
Change to Month 6				
n	15	25	30	70
Mean (SD)	-0.7 (2.9)	-0.6 (2.6)	-0.4 (2.8)	-0.5 (2.7)
Range	-5, 4	-4, 6	-7, 5	-7, 6
Bicarbonate (mEq/L)				
Baseline				
n	27	28	31	86
Mean (SD)	24.0 (2.6)	24.7 (3.1)	25.0 (2.3)	24.6 (2.7)
Range	19, 30	21, 32	20, 30	19, 32
Change to Month 6				
n	15	25	30	70
Mean (SD)	1.3 (3.8)	0.3 (3.6)	-0.7 (3.4)	0.1 (3.6)
Range	-5, 8	-6, 6	-8, 7	-8, 8
Calcium (mg/dL)				
Baseline				
n	27	28	31	86
Mean (SD)	9.50 (0.37)	9.50 (0.42)	9.46 (0.37)	9.48 (0.38)
Range	8.8, 10.4	8.9, 10.4	8.1, 10.1	8.1, 10.4
Change to Month 6				
n	15	25	30	70
Mean (SD)	0.06 (0.37)	0.04 (0.39)	0.03 (0.47)	0.04 (0.41)
Range	-0.6, 0.7	-0.7, 0.8	-0.8, 1.7	-0.8, 1.7
Phosphorus (mg/dL)				
Baseline				
n	27	28	31	86
Mean (SD)	4.85 (0.48)	4.82 (0.58)	4.80 (0.61)	4.82 (0.56)
Range	3.9, 5.8	3.6, 6.2	3.6, 6.5	3.6, 6.5
Change to Month 6				
n	15	25	30	70
Mean (SD)	0.00 (0.62)	0.04 (0.72)	0.22 (0.60)	0.11 (0.65)
Range	-0.8, 1.2	-1.4, 1.4	-1.0, 1.3	-1.4, 1.4
Alkaline Phosphatase (IU/L)				
Baseline				
n	27	28	31	86

Mean (SD)	277.1 (81.5)	280.5 (112.5)	287.1 (94.2)	281.8 (95.9)
Range	162, 500	121, 554	154, 516	121, 554
Change to Month 6				
n	15	25	30	70
Mean (SD)	-12.0 (82.7)	44.3 (74.5)	10.0 (78.3)	17.5 (79.8)
Range	-138, 152	-114, 168	-145, 183	-145, 183
ALT (SGPT) (IU/L)				
Baseline				
n	27	28	31	86
Mean (SD)	21.1 (12.9)	23.4 (15.3)	18.5 (7.8)	20.9 (12.3)
Range	8, 62	8, 78	7, 46	7, 78
Change to Month 6				
n	15	25	30	70
Mean (SD)	0.5 (8.7)	0.5 (10.3)	-0.1 (6.7)	0.2 (8.4)
Range	-23, 18	-31, 15	-17, 12	-31, 18
AST (SGOT) (IU/L)				
Baseline				
n	27	28	31	86
Mean (SD)	26.4 (7.2)	27.1 (12.4)	22.3 (4.2)	25.2 (8.7)
Range	16, 42	14, 72	17, 37	14, 72
Change to Month 6				
n	15	25	30	70
Mean (SD)	-0.7 (6.0)	0.6 (9.2)	1.0 (5.2)	0.5 (6.9)
Range	-11, 12	-35, 18	-7, 18	-35, 18
Total Bilirubin (mg/dL)				
Baseline				
n	27	28	31	86
Mean (SD)	0.59 (0.46)	0.44 (0.20)	0.50 (0.32)	0.51 (0.34)
Range	0.2, 2.1	0.2, 1.0	0.2, 1.6	0.2, 2.1
Change to Month 6				
n	15	25	30	70
Mean (SD)	0.19 (0.56)	0.04 (0.17)	-0.01 (0.29)	0.05 (0.34)
Range	-0.7, 1.7	-0.2, 0.5	-1.0, 0.6	-1.0, 1.7
BUN (mg/dL)				
Baseline				
n	27	28	31	86
Mean (SD)	13.2 (4.2)	14.0 (3.6)	12.0 (2.7)	13.0 (3.6)
Range	6, 22	9, 24	7, 19	6, 24
Change to Month 6				
n	15	25	30	70
Mean (SD)	-0.5 (3.0)	-0.3 (3.3)	0.2 (3.2)	-0.1 (3.1)
Range	-6, 5	-6, 5	-6, 8	-6, 8
Creatinine (mg/dL)				
Baseline				
n	27	28	31	86
Mean (SD)	0.64 (0.18)	0.61 (0.14)	0.61 (0.13)	0.62 (0.15)
Range	0.3, 1.3	0.3, 0.9	0.4, 0.9	0.3, 1.3
Change to Month 6				
n	15	25	30	70
Mean (SD)	0.07 (0.12)	0.04 (0.11)	0.05 (0.08)	0.05 (0.10)
Range	-0.1, 0.2	-0.2, 0.2	-0.1, 0.2	-0.2, 0.2
Fasting Glucose (mg/dL)				

Baseline				
n	25	24	31	80
Mean (SD)	87.4 (6.6)	86.3 (6.6)	86.1 (7.0)	86.6 (6.7)
Range	76, 105	72, 97	68, 100	68, 105
Change to Month 6				
n	14	20	27	61
Mean (SD)	0.8 (8.6)	1.2 (7.8)	2.0 (12.6)	1.4 (10.2)
Range	-13, 17	-20, 14	-20, 53	-20, 53

Source: Table 10.3. 12(A)

Table 26 summarizes the changes in urinalysis on trial by testosterone exposure (low, medium, and high dose) and across all doses. There were no clinically meaningful changes by Month 6.

Table 26: Summary of urinalysis changes by overall dose

Parameter	**Overall dose**			**Across all doses N=86**
	Low (<100 g) N=27	**Medium** (100-240) N=28	**High** (>240) N=31	
pH				
Baseline				
n	27	28	31	86
Mean (SD)	5.78 (0.66)	5.80 (0.70)	5.69 (0.70)	5.76 (0.68)
Range	5.0, 7.0	5.0, 7.5	5.0, 8.0	5.0, 8.0
Change to Month 6				
n	15	24	28	67
Mean (SD)	-0.10 (0.43)	-0.27 (0.86)	-0.16 (0.75)	-0.19 (0.73)
Range	-1.0, 0.5	-2.5, 1.5	-2.0, 1.0	-2.5, 1.5
Specific Gravity				
Baseline				
n	27	28	31	86
Mean (SD)	1.025 (0.005)	1.027 (0.007)	1.023 (0.006)	1.025 (0.006)
Range	1.01, 1.04	1.01, 1.04	1.01, 1.04	1.01, 1.04
Change to Month 6				
n	15	24	28	67
Mean (SD)	0.001 (0.007)	-0.002 (0.008)	0.003 (0.009)	0.001 (0.009)
Range	-0.01, 0.02	-0.02, 0.02	-0.03, 0.02	-0.03, 0.02

Source: Table 10.3. 13(A)

Table 27 summarizes the changes in lipid metabolism analytes on trial by testosterone exposure (low, medium, and high dose) and across all doses. There were no clinically meaningful changes by Month 6 for any of the tests analyzed.

Table 27: Summary of lipid analytes changes on trial by overall dose

Parameter	**Overall dose**			**Across all doses N=86**
	Low (<100 g) N=27	**Medium** (100-240) N=28	**High** (>240) N=31	
Total Cholesterol (mg/dL)				

Baseline				
n	27	28	31	86
Mean (SD)	167.2 (33.2)	169.1 (32.7)	173.4 (28.5)	170.1 (31.1)
Range	80, 241	125, 241	121, 224	80, 241
Change to Month 6				
n	15	25	30	70
Mean (SD)	-6.5 (19.6)	1.8 (22.4)	-7.9 (20.5)	-4.1 (21.2)
Range	-58, 18	-38, 55	-42, 28	-58, 55
Triglycerides (mg/dL)				
Baseline				
n	27	28	31	86
Mean (SD)	97.0 (61.4)	112.0 (63.3)	121.5 (65.1)	110.7 (63.5)
Range	20, 248	43, 319	35, 283	20, 319
Change to Month 6				
n	15	25	30	70
Mean (SD)	-3.1 (65.5)	-12.0 (49.2)	-1.1 (66.3)	-5.4 (59.9)
Range	-97, 184	-174, 63	-115, 234	-174, 234
HDL Cholesterol (mg/dL)				
Baseline				
n	27	28	31	86
Mean (SD)	51.9 (11.1)	46.3 (10.4)	48.9 (13.3)	49.0 (11.8)
Range	34, 75	24, 68	28, 81	24, 81
Change to Month 6				
n	15	25	30	70
Mean (SD)	-1.9 (6.6)	1.5 (7.7)	-1.8 (7.0)	-0.6 (7.3)
Range	-17, 5	-11, 18	-17, 11	-17, 18
LDL Cholesterol (mg/dL)				
Baseline				
n	27	28	31	86
Mean (SD)	96.0 (27.8)	100.4 (29.1)	100.1 (21.6)	-1.9 (18.4)
Range	28, 168	63, 170	57, 146	-46, 56
Change to Month 6				
n	15	25	30	70
Mean (SD)	-4.0 (11.5)	2.7 (18.6)	-5.8 (17.1)	-2.4 (16.9)
Range	-27, 12	-31, 44	-42, 20	-42, 44

Source: Table 10.3.14 (A).

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

In Study UMD-01-080 one patient had a laboratory value that met the criterion for an abnormal result (elevated serum alkaline phosphatase); this elevated level, however, was similar to that measured at screening and baseline. Two patients had a mild decrease of hemoglobin concentration listed as a TEAE but none was of any clinical consequence)[48].

Table 28 summarizes the out-of-range hematology values recorded in study UMD-01-090 that were judged "markedly abnormal" by protocol prespecified criteria. Most of these observations

[48] Patient 2044 had a hemoglobin measurement which decreased from 12.3 g/dL at baseline to 11.5 g/dL (normal range 12.3 to 17 g/dL; threshold for abnormal" value: <9 g/dL). Patient 2064 had a hemoglobin concentration of 11.6 g/dL at baseline and 10.4 on trial.

were minimal deviations from the normal range and of no clinical significance; some of them were only present at screening or baseline.

Table 28: Out of range hematology values

Patient ID	Comment
104/1031	Had minimally out of range lymphocyte concentration of 71% (upper limit of normal = 70%) and neutrophil concentration of 18% (lower limit of normal = 20%) at screening followed by normal values at baseline and throughout Month 6.
114/2041	Had an increased monocyte concentration of 18% at baseline (upper limit of normal 15%) but normal subsequent monocyte concentrations through Month 6.
123/1222	Had a minimally out of range hematocrit value of 0.31 at screening (lower limit of normal = 0.32) and normal hematocrit values throughout the trial.
127/2062	Had a minimally out of range hematocrit value of 0.31 at baseline in Study UMD-01-080 (lower limit of normal = 0.32) and normal hematocrit values at baseline in Study UMD-01-090 and throughout the trial. Also had a minimally elevated monocyte concentration of 16.5% (normal upper value =15%) at baseline in Study UMD-01-080 with subsequent normal values at baseline in Study UMD-01-090 and throughout the trial.
127/2064	Had a reduced neutrophil concentration of 11% at baseline (lower limit of normal =20%) followed by normal values throughout the trial. Had a reduced WBC count at baseline of 1.6 (lower limit of normal <3) followed by normal values throughout the trial.

Source: Table 10.3.15 and text.

Eight patients experienced TEAEs involving hematology analytes; reportedly, none resulted in discontinuation of study medication and all events resolved. They are summarized in Table 29. Most were mild, transient and of limited clinical significance, and only a few were judged possibly related to the study medication.

Table 29: Abnormal hematology values that were recorded as TEAEs

Patient ID	TEAE	Comments
104/1039	mild neutropenia	Neutrophil values of 2.02 $x10^9$/L and 2.18 $x10^9$/L at baseline and Month 1, respectively, were slightly below the normal lower limit of 2.3 $x10^9$/L. Normal neutrophil counts at Months 3 and 6.
104/1040	mild neutropenia	Noted at Month 1 (2.16$x10^9$/L) returned to normal at Month 3 and remained normal at Month 6. Judged unlikely related to study medication.
113/1122	mild eosinophilia, mild neutropenia, and mild lymphocytosis	Had eosinophilia throughout the study (5.7% at screening, 6.7% at Week 1, 6.7% at Month 1, 7.7% at Month 3, and 8.5% at Month 6 (upper limit of normal range: 4.8%). Had neutropenia throughout the study (2.05$x10^9$/L at Screening, .61$x10^9$/L at Week 1, 1.43$x10^9$/L at Month 1, 1.57x109/L at Month 3, and 1.60$x10^9$/L at Month 6 (normal range: 2.3-11.1x109/L). Had mild lymphocytosis throughout the study: 52.8% at Week 1, 47.2% at Month 1, and 48.2% at Month 6 (normal range: 15.5-46.6%). Each of the events was considered unrelated to study medication.
114/1135	mild eosinophilia	Had eosinophilia at baseline (5.5%), that returned to normal at Month 2 but was present at Month 4 (4.9%) and Month 6 (7.8%) (upper limit of normal: 4.8%). It was considered possibly related to study medication.
114/2041	mild eosinophilia	Had mild eosinophilia at Month 3 (7.8%), Month 4 (6.7%) and Month 6 (6.9%); it was considered possibly related to study medication.
114/2042	moderate microcytic anemia	Had low hematocrit (35 % at baseline and Month 1; lower limit of normal = 37%) and Hb concentration (119 g/L at baseline and

		113 g/L at Month 1; lower normal value: 123 g/L). Both Hct and Hb concentrations were normal at Month 3 and Month 6. Judged possibly related to study medication.
114/2043	mild eosinophilia	Had mild eosinophilia at baseline and throughout the study. Judged unrelated to study medication.
125/2022	mild neutropenia	Had mild neutropenia at Month 2 (1.23x109/L) and Month 3 (2.19x109/L) which returned to normal at Months 4 and 6. Judged unrelated to study medication

Source: Text.

Table 30 summarizes the out-of-range chemistry values recorded in study UMO-01-090 that were judged abnormal by protocol prespecified criteria. Most observations were transient; some occurred at baseline or screening.

Table 30: Out of range chemistry values

Patient ID	Comment
103/1029	Had elevated total bilirubin at screening of 41µmol/L and 36 µmol/L (normal <34.2). Had elevation of 48 µmol/L at Month 1 and normal bilirubin concentrations at baseline, Month 3 and Month 6.
109/1083	Had low serum sodium concentration at screening of 128 mmol/L (lower normal limit: 130) and normal concentrations at baseline and throughout the trial.
113/1121*	Had an elevated ALT of 285 IU/L at Month 1 (upper limit of normal: 45) and normal values at baseline and at all post-Month 1 timepoints (Month 3 and Month 6).
113/1123	Had an elevated total bilirubin at baseline and throughout the whole trial: 46 µmol/L at screening, 36 µmol/L at baseline, 50 µmol/L at Month 1, 38 µmol/L at Month 3, and 65 µmol/L at Month 6 (upper limit of normal 34.2 µmol/L).
127/2063	Had an elevated serum sodium of 154 mmol/L at Month 3 (upper limit of normal =150 mmol/L) and normal values preceding it (at baseline, and Month 1) and following it (Month 6).

Source: Table 10.3.15 and text.
*Also reported as an adverse event.

Table 31 summarizes abnormal chemistry values that were associated with adverse events at baseline or during the trial (treatment-emergent). All events, reportedly, resolved.

Table 31: Abnormal chemistry values that were recorded as adverse events

Patient ID	TEAE	Comments
107/1061	Elevated ALT/AST	Had a mild elevation of ALT/SGOT (84 IU/L; upper limit of normal = 45 IU/L) and AST/SGPT (70 IU/L; upper limit of normal 45 IU/L) at screening (judged unrelated to study medication). The ALT/SGPT and AST/SGOT concentrations remained elevated at Month 1 (65 IU/L and 55 IU/L, respectively), but returned to normal at Month 3. The events were not considered treatment-emergent.
113/1121	Elevated ALT/AST	Had a treatment-emergent increase in ALT/SGPT concentration of 285 IU/L (upper limit of normal = 45 IU/L) and AST/SGOT concentration of 125 IU/L (upper limit of normal = 45 IU/L) at Month 1 that returned to normal at Month 3 and remained normal at Month 6. It was judged not related to study medication.
113/1123	Elevation in total bilirubin	At screening had an elevation of total bilirubin concentration (46 mcmol/L; upper limit of normal = 21 mcmol/L) and a mildly increased indirect bilirubin (41 mcmol/L; upper limit of normal: 17 mcmol/L). The total bilirubin concentration remained elevated throughout the study at baseline (36 mcmol/L), Month 1 (50 mcmol/L), Month 3 (38

		mcmol/L), and Month 6 (65 mcmol/L). Indirect bilirubin results were only reported at screening and Month 6 (62 mcmol/L). The events were not treatment-emergent and considered unlikely related to study medication.

Source: Text.

One patient (107/1062) experienced mild hematuria at baseline (absent at Months 1, 3, and 6) and another patient (113/1123) had mild proteinuria at screening, Month 1, and Month 6 but not at Month 3.

Out of range lipid metabolism measurements are presented in Table 32. None was of clinical significance.

Table 32: Out of range lipid metabolism values

Patient ID	TEAE	Comments
113/1121	elevated triglycerides and decreased HDL cholesterol	Had an elevation in triglyceride concentration of 3.2 mmol/L (upper limit of normal =2.06 mmol/L) at baseline and lasted for 32 days (judged possibly related to study drug) and a decreased HDL cholesterol concentration (0.73 mmol/L; lower limit of normal: 1.04 mmol/L) that started at Month 1 and lasted for 27 days (judged unrelated to study medication).
113/1124	elevated triglycerides	Had a mild elevation triglyceride concentration (2.01 mmol/L; upper limit of normal = 1.9 mmol/L) that started at Month 1 and lasted for 59 days and was judged possibly related to study medication.
114/1135	decreased HDL cholesterol	Had a decreased HDL cholesterol concentration (0.93 mmol/L; lower limit of normal range: 1.04mmol/L) that started at baseline, remained low at Month 2 (0.98 mmol/L) and Month 4 (0.83 mmol/L) and returned to normal at Month 6 (1.04 mmol/L); it was judged unrelated to study medication.

Source: Text.

7.1.3.3.3 Marked outliers and dropouts for laboratory abnormalities

There were no marked outliers in laboratory measurements.

7.1.7.4 Additional analyses and explorations

None done.

7.1.7.5 Special assessments

None.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

In Study UMD-01-090 vital signs were measured at baseline, Month 1, Month 2, Month 3, Month 4, and Month 6 and included blood pressure, pulse, respiratory rate, and body temperature.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Not applicable (there was no control group in study UMD-01-090).

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Table 33 summarizes the descriptive statistics from baseline to Month 6 for vital signs by testosterone dose. There were no clinically significant changes from baseline to Month 6 in vital signs.

Table 33: Summary of vital sign changes by overall dose

Parameter	Overall dose			Across all doses N=86
	Low (<100 g) N=27	**Medium** (100-240) N=28	**High** (>240) N=31	
Systolic Blood Pressure (mm Hg)				
Baseline				
n	27	28	31	86
Mean (SD)	111.5 (14.5)	113.1 (13.6)	111.6 (10.1)	112.1 (12.6)
Range	86, 156	86, 144	88, 130	86, 156
Change to Month 6				
n	16	25	31	72
Mean (SD)	-3.7 (15.4)	-4.3 (10.5)	0.6 (8.1)	-2.0 (11.0)
Range	-33, 25	-22, 19	-18, 13	-33, 25
Diastolic Blood Pressure (mmHg)				
Baseline				
n	27	28	31	86
Mean (SD)	64.8 (8.6)	67.5 (9.4)	66.5 (7.8)	66.3 (8.6)
Range	50, 90	45, 85	50, 88	45, 90
Change to Month 6				
n	16	25	31	72
Mean (SD)	1.1 (9.8)	-3.1 (8.5)	-0.5 (7.3)	-1.0 (8.4)
Range	-21, 17	-24, 12	-19, 12	-24, 17

Pulse Rate (beats/min)				
Baseline				
n	27	28	31	86
Mean (SD)	72.3 (14.0)	73.9 (13.2)	72.4 (10.9)	72.8 (12.6)
Range	55, 109	50, 103	56, 94	50, 109
Change to Month 6				
n	16	25	31	72
Mean (SD)	4.2 (14.7)	0.4 (13.6)	-0.4 (9.9)	0.9 (12.3)
Range	-16, 42	-35, 23	-22, 26	-35, 42
Respiratory Rate (breaths/min)				
Baseline				
n	27	28	31	86
Mean (SD)	18.8 (2.4)	19.2 (3.1)	18.7 (2.9)	18.9 (2.8)
Range	12, 22	12, 24	12, 24	12, 24
Change to Month 6				
n	16	25	31	72
Mean (SD)	-0.3 (2.4)	-1.0 (5.0)	-0.3 (3.9)	-0.5 (4.0)
Range	-4, 4	-12, 14	-6, 12	-12, 14
Temperature (°C)				
Baseline				
n	27	28	30	85
Mean (SD)	36.3 (0.4)	36.3 (0.4)	36.5 (0.5)	36.4 (0.4)
Range	35, 37	36, 37	35, 37	35, 37
Change to Month 6				
n	16	25	30	71
Mean (SD)	0.1 (0.4)	0.0 (0.5)	-0.0 (0.5)	0.0 (0.5)
Range	-1, 1	-1, 1	-1, 1	-1, 1

Source: Table 10.3. 16(A)

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

In study 01-UMD-080 there were 6 patients (35.3%) who met the criterion of diastolic pressure < 60 mmHg and change from baseline ≥-10 mm (the lowest were 38 and 41 mm Hg, respectively, and most were in the 50's) . Sixteen patients (84%) had temperatures recorded < 36.5 degrees Celsius and one patient (5.9%) with greater than 38 degrees Celsius.

In Study UMD-01-090, seventy-seven patients (90%) had one or more abnormal vital signs parameter. The most frequently reported was a temperature of < 36.5 °C (75 patients or 87%); none was reported as a TEAE. Four patients (5%) experienced TEAEs of fever, in three cases associated with symptoms of infection, and one subject (1%) experienced a treatment-emergent increase in heart rate. The applicant reports that none of these five events were serious or resulted in discontinuation of study medication and that all events resolved and occurred between scheduled visits.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

There no marked outliers or dropouts due to vital sign abnormalities.

7.1.8.4 Additional analyses and explorations

None conducted.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

AndroGel is an approved drug product. Refer to the review for NDA 21-015.

No ECG reports/analyses were identified in the study reports for Study UMD-01-080 and study UMD-01-090, respectively.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Refer to Section 7.1.9.1.

7.1.9.3 Standard analyses and explorations of ECG data

Refer to Section 7.1.9.1.

7.1.9.3.1 Analyses focused on measures of central tendency

Refer to Section 7.1.9.1.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

Refer to Section 7.1.9.1.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities
Refer to Section 7.1.9.1.

7.1.9.4 Additional analyses and explorations

None done.

7.1.10 Immunogenicity

AndroGel is not a protein therapeutic. Immunogenicity (other than allergy) is not anticipated to be a safety concern. There were no allergic reactions reported in this pediatric clinical trial.

7.1.11 Human Carcinogenicity

Refer to the existing AndroGel label.

7.1.12 Special Safety Studies

No special safety studies were conducted in children.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Since AndroGel contains testosterone as an active ingredient (a Schedule III controlled substance) there is a potential for abuse as an anabolic agent. (b) (4)

7.1.14 Human Reproduction and Pregnancy Data

AndroGel was tested only in male patients.

7.1.15 Assessment of Effect on Growth

Refer to the efficacy section.

7.1.16 Overdose Experience

There were no cases of accidental overdose in the clinical program.

7.1.17 Postmarketing Experience

(b) (4)

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Refer to Section 6.1.3.

7.2.1.2 Demographics

Refer to Section 6.1.4.

7.2.1.3 Extent of exposure (dose/duration)

In Study UMD-01-080, 13 of the 17 subjects enrolled received all three doses of AndroGel (0.5 g/day, 1.5 g/day and 2.5 g//day, respectively) once. The remaining four subjects received only the 0.5 g/day and 1.5 g/day AndroGel doses once.

The mean (SD) duration of patient exposure to AndroGel in Study UMD-01-090 was 161.2 (43.5) days. Approximately 83% of subjects were exposed to study medication for ≥ 151 days. The patient exposure in this study is summarized in applicant's Table 15.

Table 15 Exposure to Study Medication

		Subject Population Group		
	Statistic	Hypogonadal (N = 59)	CDGP (N = 27)	All Subjects (N = 86)
Duration of Exposure (Days)	Mean (SD)	162.7 (45.3)	158.0 (40.0)	161.2 (43.5)
Exposure (Days Categorized)	n	59	27	86
1-30 Days	n (%)	1 (1.7)	0	1 (1.2)
31-60 Days	n (%)	3 (5.1)	0	3 (3.5)
61-90 Days	n (%)	5 (8.5)	5 (18.5)	10 (11.6)
91-120 Days	n (%)	0	1 (3.7)	1 (1.2)
121-150 Days	n (%)	0	0	0
151-180 Days	n (%)	22 (37.3)	11 (40.7)	33 (38.4)
> 180 Days	n (%)	28 (47.5)	10 (37.0)	38 (44.2)
Unknown	n (%)	0	0	0

Note: Duration of exposure is calculated as the number of days from the first application to the last application of study medication.
Data Source: Table 10.1.4(A), Table 10.1.4(B), and Table 10.1.4(C).

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

There were no secondary sources used in the review of this supplement.

7.2.2.1 Other studies

There were no other studies reviewed than those included in the supplement.

7.2.2.2 Postmarketing experience

There is no postmatketing experience with AndroGel in children.

7.2.2.3 Literature

There are no clinical trials of AndroGel in children.

7.2.3 Adequacy of Overall Clinical Experience

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

AndroGel is an approved drug product (refer to the original approval of NDA 21-015).

7.2.5 Adequacy of Routine Clinical Testing

The clinical testing in trials UMD-01-80 and UMD-01-09 was standard and adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Refer to the current AndroGel label.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

AndroGel has is an approved drug product (refer to NDA 21-015).

7.2.8 Assessment of Quality and Completeness of Data

Study UMD-01-90 had multiple protocol violations/deviations. Many of them were related to the inclusion criterion that specified a serum testosterone level ≤ 50 ng/dL and testicular volume ≤ 3 mls in testosterone-naïve patients (refer to Section 6.1.3 for details). Although most violations were minor elevations above the prespecified criteria, some were not (for instance some testosterone-naïve patients were enrolled with testosterone levels of 178 and 426 ng/dL, respectively or with testicular volumes of 8-15 mls). In addition, several non-naïve patients were enrolled with high baseline testosterone levels and some of the hypogonadal patients had residual testosterone secretion (or may have not have been washed out properly of the pre-existing dose of testosterone), while several CDGP patients were clearly already in puberty. Although the

latter were not formal protocol violations, they reduced considerably the chance to obtain an interpretable dataset at the end of the study and should have been anticipated by the applicant. Paying limited attention to enrolling patients with quality baseline data in a study that does not include a control arm and for which the baseline data are the only internal control, doomed any sustained attempt to extract meaningful efficacy information from this study. Even more regrettable, is the fact that the bone age data, critical for interpreting the effect of AndroGel on bone age maturation, was incomplete and consequently inconclusive.

Finally, and importantly, a routine, audit of the testosterone data collected in Study UMD-01-090, concluded that there were "significant deficiencies that impact[ed] the integrity of the data generated (b) (4)".[49] These deficiencies concerned both the validation of the assay (accuracy, precision, linearity) and the analytical runs (for a detailed description of these deficiencies, refer to the clinical pharmacology review).

7.2.9 Additional Submissions, Including Safety Update

The application does not include a safety update.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

There were no adverse events that could have been clearly associated with AndroGel with the exception of acne. The small size of the dataset and the absence of a control group limit the ability to draw further conclusions. It should be recognized however that the active ingredient in AndroGel is testosterone and that the safety profile of testosterone, in general, is well known due to its established physiologic functions and to states of testosterone excess (e.g. testotoxicosis, androgen-secreting tumors, etc).

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Not applicable. There was a single clinical study.

7.4.1.2 Combining data

Refer to Section 7.4.11.

[49] (b) (4), was the clinical laboratory where the testosterone data were centrally analyzed)

7.4.2 Explorations for Predictive Factors

None done.

7.4.2.1 Explorations for dose dependency for adverse findings

None done due to the small size of the dataset.

7.4.2.2 Explorations for time dependency for adverse findings

None done due to the small size of the dataset.

7.4.2.3 Explorations for drug-demographic interactions

None done due to the small size of the dataset.

7.4.2.4 Explorations for drug-disease interactions

None done due to the small size of the dataset.

7.4.2.5 Explorations for drug-drug interactions

None done due to the small size of the dataset.

7.4.3 Causality Determination

There were no adverse events that could have been clearly associated with the AndroGel with the exception of acne. The small size of the dataset and the absence of a control group do not allow further conclusions.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The studies submitted with this NDA evaluate three pediatric AndroGel doses: 0.5 g/day, 1.5 g/day, and 2.5 g/day, respectively. These three doses were selected with the goal of providing serum testosterone concentrations that cover the whole range of testosterone values expected during adolescence. Since serum testosterone concentrations are not uniform throughout puberty but rather increase gradually as the hypothalamic-pituitary- gonadal axis matures, AndroGel treatment is to be started with the low dose (0.5 g/day) and escalated as needed to higher doses (1

g/day and 2.5 g/day) toward adult doses at the end of puberty (5 g/day through 10 g/day). Thus, it is reasonable to assume that once a safe starting dose of AndroGel is established, given the availability of intermediary pediatric doses, as well as the currently approved adult doses, testosterone titration can be achieved safely with periodic monitoring of serum testosterone, bone age advancement, Tanner stage progression, and growth velocity[50]. It is for these reasons that this review placed particular emphasis on the starting AndroGel dose of 0.5 g/day. It should be emphasized that the 0.5 g dose was in fact the most widely used AndroGel dose in the trial with approximately 30-40 % of patients receiving it at any given time.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

The execution of the study (inclusion of a very heterogeneous patient population, multiple protocol violations, and shortcomings in the quality of bone age data) complicates further the interpretation of an already limited dataset. Finally, and importantly, a routine, audit of the testosterone data collected in Study UMD-01-090, concluded that there were "significant deficiencies that impact[ed] the integrity of the data generated by (b) (4) the clinical laboratory where the testosterone data were centrally analyzed); these deficiencies concerned both the validation of the assay (accuracy, precision, linearity) and the analytical runs (for a detailed description of these deficiencies, refer to the clinical pharmacology review) [52].

8.2 Drug-Drug Interactions

No drug-drug interaction studies were conducted.

8.3 Special Populations

No studies were conducted in patients with hepatic or renal failure.

8.4 Pediatrics

This NDA supplement included studies conducted exclusively in children. Studiers of AndroGel in prepubertal children (< 13 years of age) should be waived under PREA.

8.5 Advisory Committee Meeting

There were no Advisory Committee meetings for this application.

8.6 Literature Review

There are no published pediatric studies with AndroGel in children.

8.7 Postmarketing Risk Management Plan

None at this point.

[52] In addition, since Study UMD-01-080, although not formally evaluated by DSI, utilized the same testosterone assay methods used in Study UMD-01-090, this calls into question the reliability of the data collected in Study UMD-01-080as well.

8.8 Other Relevant Materials

None.

9 OVERALL ASSESSMENT

9.1 Conclusions

(b) (4)

9.2 Recommendation on Regulatory Action

(b) (4)

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

None.

9.3.2 Required Phase 4 Commitments

None.

9.3.3 Other Phase 4 Requests

None.

(b) (4)

(b) (4)

10 APPENDICES

10.1 Review of Individual Study Reports

Refer to the body of the clinical review.

(b) (4)

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Dragos Roman
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Mary Parks
12/5/2007 07:29:44 PM
MEDICAL OFFICER