DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

| | |
|---|---|
| **NDA/Serial Number:** | (b) (4) |
| **Drug Name:** | AndroGel® PD (testosterone gel) 1% CIII |
| | (b) (4) |
| **Applicant:** | Solvay Pharmaceuticals, Inc., an agent for Unimed Pharmaceuticals, Inc. |
| **Date(s):** | Received 06/13/07; user fee (6 months) 12/13/07 |
| **Review Priority:** | Priority (pediatric exclusivity) |
| **Biometrics Division:** | Division of Biometrics II (HFD-715) |
| **Statistical Reviewer:** | Cynthia Liu, MA |
| **Concurring Reviewer(s):** | Todd Sahlroot, Ph.D., Statistical Team Leader and Deputy Director of Biometrics II |
| **Medical Division:** | Division of Metabolic and Endocrine Products (HFD-510) |
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| **Project manager:** | Jennifer Johnson |
| **Keywords:** | NDA review, clinical study, pediatric exclusivity |

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# 1. EXECUTIVE SUMMARY

## 1.1 Conclusions and Recommendations

Based on the summary statistics (e.g., mean, median, and 95% confidence interval) from the available data, (b) (4) there was no sign of bone age acceleration when compared to chronological age after 6 months.

However, the data were confounded by a number of factors such as free dose titration scheme, no concurrent control group, possible incomplete washout from previous testosterone treatment, very heterogeneous patient population, wide range of serum total testosterone concentration, other than the intended pump-head type for delivering drug, and possible measurement errors for some bone age data. In addition, for the low dose evaluation, only about 50% of the data were available and the number of subjects with excessive changes from baseline in serum total testosterone concentration and bone age concerns the medical reviewer. Moreover, the data from subjects receiving the (b) (4) dose from the (b) (4) pump-head (b) (4) show a mean/median increase from baseline in serum total testosterone concentration at Week 1. The data further suggest that there were improved serum total testosterone concentrations at Months 1-6 and Tanner pubic hair stages at Month 6 in subjects who used the (b) (4) dose from the (b) (4) pump-head.

(b) (4)

## 1.2 Brief Overview of Clinical Studies

The sponsor has submitted (b) (4) in response to the Pediatric Written Request #2, Amendment #1 issued on 05/24/2007 under IND (b) (4) for AndroGel® PD (testosterone gel) 1% CIII.

(b) (4)

There were 2 uncontrolled studies submitted (b) (4)

Study UMD-01-080 corresponded to Study 1 in the Pediatric Written Request (PWR) and was a pharmacokinetic (PK) study. Thus, it is not the focus of this review. Study UMD-01-090 corresponded to Study 2 in the PWR and was a Phase II, 6-month, uncontrolled, open-label, dose-titration, multicenter, USA trial, conducted in 86 adolescent boys aged between 13 and 18 years with a diagnosis of delayed puberty due to either hypogonadism (n = 59) or CDGP (n = 27). The study drug was titrated weekly from a starting dose of 0.5 g/day to 1.0, 1.5, 2.5, 3.0, and 5.0 g/day over a 3-week period until a desired serum total testosterone concentration was reached based on the clinical investigators' discretion.

There were no primary efficacy variables specified in this study. After consulting with the medical reviewer, efficacy evaluation was focused on serum total testosterone concentration and Tanner Pubic Hair Stage in this review. Safety evaluation, particularly whether the 0.5 g/day was a safe starting dose as raised by the reviewing medical officer, was based on serum total testosterone concentration and bone maturation age advancement.

**1.3 Statistical Issues and Findings**

In this reviewer's opinion, the issues that impact the overall conclusions of the study are more related to the study design aspects such as free dose titration scheme, no concurrent control group, possible incomplete washout from previous testosterone treatment (as acknowledged by the sponsor), and many inclusion/exclusion criterion violators. The patient population was very heterogeneous in terms of baseline characteristics (e.g., serum total testosterone concentration, Tanner pubic hair stage, testicular volume, disease diagnosis, and use of prior AndroGel treatment at baseline). The serum total testosterone concentration data were highly variable within and across patients. The pump-head type delivering the study drug was different for some patients during some parts of the study. In addition, there were some clinically implausible decreased on-treatment bone ages when compared to baselines. All of the mentioned facts confound the data and make the interpretation of the results much more difficult.

In general, this reviewer's findings based on the observed data were similar to the sponsor's results based on the observed and last-observation-carried-forward data. The findings for the hypogonadal population were similar to the ones for the CDGP population. The following collective evidence was based on the whole study population.

***Efficacy.*** For subjects using the starting dose, 0.5 g, during the first week of AndroGel treatment (n = 74), the median change in serum total testosterone concentration was 75 ng/dL from baseline to Week 1 and the 95% confidence interval of the mean change was (76.6, 124.4). In addition, for the subgroups defined by prior AndroGel use (naïve, non-naïve), Tanner Pubic Hair Stage (I, > I), disease diagnosis (hypogonadism, CDGP), and pump-head type (b) (4) the mean and median changes from baseline in serum total testosterone concentration at Week 1 and the associated upper bounds of 95% confidence intervals were all well below 200 ng/dL, a threshold that was liberally defined by the reviewing medical officer.

After 6 months of treatment with AndroGel, the patients' serum total testosterone concentrations were still generally increased (mean change = 177.7 ng/dL, median change = 158.3 ng/dL, minimum change = -210 ng/dL, and maximum change = 885 ng/dL). Also, around 60% of the evaluable subjects (= 42/71) had their Tanner pubic hair stages shifted at least 1 stage higher toward puberty and the majority of them were the subjects with early Tanner pubic hair stages (I/II) at baseline. Specifically, for the 39 subjects who had a Tanner Pubic Hair Stage = I or II at baseline, 87% (= 34/39) of them had a progressed stage at Month 6 (Text Table 1).

Text Table 1 – Tanner Pubic Hair Staging at Month 6

| Stage at Baseline | Stage at Month 6 | | | | | |
|---|---|---|---|---|---|---|
| | I | II | III | IV | V | Total |
| I | 3 (15%) | 10 (50%) | 5 (25%) | 2 (10%) | 0 | 20 |
| II | - | 2 (11%) | 8 (42%) | 9 (47%) | 0 | 19 |
| III | - | - | 7 (54%) | 5 (38%) | 1 (8%) | 13 |
| IV | - | - | - | 9 (82%) | 2 (18%) | 11 |
| V | - | - | - | - | 8 (100%) | 8 |
| Total | 3 | 12 | 20 | 25 | 11 | 71 |

The median changes from baseline in serum total testosterone concentration at Month 6 across the 3 cumulative dose groups as defined by low (< 100 g), medium (100 – 240 g), and high (> 240 g) were all slightly greater in subjects with at least 1 progressed stage than in subjects with no change, and also in the naïve subjects than in the non-naïve subjects. The subjects in the low cumulative dose group generally had a smaller change in serum total testosterone concentration at Month 6 when compared to the subjects in the medium and high cumulative dose groups, regardless of Tanner pubic hair stages and prior testosterone treatment use.

***Safety.*** After 6 months of treatment with AndroGel, the mean change from baseline in bone age was 0.4 years and the median change was 0.5 years. In other words, the patients' bone ages were generally advanced about 6 months or so at the end of this 6-month trial (both mean and median ratios of change in bone age to change in chronological age = 0.9). According to the 95% confidence interval of the mean ratio or difference (bone maturation age advancement), the bone age could be advanced more or less than the chronological age by 3 months at the end of the trial. There was a positive dose-response in bone maturation age advancement at 6 months, i.e., patients with higher cumulative doses normally had greater advances in bone age relative to chronological age after 6 months of testosterone treatment. Specifically, while none in the low cumulative dose group, 3 subjects in the medium and 2 subjects in the high cumulative dose groups had their bone ages advanced at least 12 months more than their chronological ages at Month 6. Note that there were 8 out of 62 evaluable subjects with a biologically implausible decreased bone age at Month 6 when compared to baseline and they were all from the medium and high cumulative dose groups. When those negative changes were excluded from the data or replaced with a zero, similar findings to the ones based on the whole evaluable population were also observed.

**To evaluate whether the 0.5 g/day dose is a safe starting dose for adolescent boys with delayed puberty**, the data of subjects with 0.5 g/day dose at any visits during the trial and the data from the low cumulative dose group (< 100 g) were reviewed. It was noted that there were 9 out of 74 evaluable subjects (12%) with a ≥ 200 ng/dL change from baseline in serum total testosterone concentration at Week 1, which was considered excessive by the reviewing medical officer. For the subjects who received the 0.5 g/day dose at a particular visit during Months 1-6, although the mean and median changes in serum total testosterone concentration were all around 100 – 200 ng/dL, there were quite a few subjects showing large changes from baseline which may also be a concern from a safety standpoint. For example, 8/23 subjects with the 0.5 g/day dose at Month 6 had a change ≥ 200 ng/dL from baseline.

In addition, there was an unplanned pump-head type used to deliver drug for some patients during the study, as acknowledged by the sponsor. The unplanned type, (b) (4) pump-head, was designed to deliver (b) (4) testosterone gel 1% per actuation (b) (4) It was found that the median change from baseline in serum total testosterone at Week 1 in patients receiving the (b) (4) dose via the (b) (4) pump-head (114 ng/dL for n = 23) was significantly larger than those in patients receiving the (b) (4) dose via the (b) (4) pump-head (63 ng/dL for n = 39, p = 0.0186 from the Wilcoxon-Mann-Whitney test performed by this reviewer). (b) (4)

Text Table 2 below shows that for subjects receiving the (b) (4) dose from the (b) (4)

pump-head at Week 1, most of them had a progressed Tanner pubic hair stage at Month 6, particularly the ones with a baseline Tanner stage at I, II, or III. Text Table 3 (copied from the sponsor's clinical study report) further shows that for subjects receiving the (b) (4) dose from the (b) (4) pump-head at a particular visit, their serum total testosterone concentrations were generally increased over that at baseline.

Text Table 2 – Tanner Pubic Hair Staging
**for subjects receiving (b) (4) from (b) (4) pump-head at Week 1**

| Stage at Baseline | Stage at Month 6 | | | | | |
|---|---|---|---|---|---|---|
| | I | II | III | IV | V | Total |
| I | 0 | 5 | 2 | 1 | 0 | 8 |
| II | - | 1 | 3 | 7 | 0 | 11 |
| III | - | - | 1 | 4 | 1 | 6 |
| IV | - | - | - | 6 | 2 | 8 |
| V | - | - | - | | 4 | 4 |
| Total | 0 | 6 | 6 | 18 | 7 | 37 |

Text Table 3 – Serum Total Testosterone Concentration (ng/dL)
**for subjects receiving (b) (4) from (b) (4) pump-head**

| Observed | Mean ± SD (n) | Median | Min – Max |
|---|---|---|---|
| Baseline | 93.0 ± 112.0 (42) | 44.5 | 3 – 470 |
| Week 1 | 193.9 ± 147.9 (39) | 143.0 | 28 – 674 |
| Month 1 | 225.1 ± 179.2 (12) | 221.0 | 16 – 610 |
| Month 2 | 215.0 ± 161.1 (13) | 223.0 | 36 – 599 |
| Month 3 | 232.5 ± 162.3 (10) | 208.5 | 55 – 511 |
| Month 4 | 155.3 ± 119.7 (4) | 157.5 | 34 – 272 |
| Month 6 | 318.2 ± 195.9 (6) | 281.5 | 120 – 626 |

There were 27 subjects grouped into the low cumulative dose group (< 100 g) in the study and 21 of them completed the trial. However, only 12 of the completers (57%) had bone maturation age and advancement data at Month 6. Among the 12 evaluable subjects in the low cumulative dose group, 3 subjects had a 12-month advancement in bone age. Their bone maturation age advancement ratios were 2.1, 1.9, and 1.9, respectively, meaning that their bone ages were advanced approximately 6 months more than their chronological ages at the end of the trial.

Similarly, for the 29 subjects who used the 0.5 g/day dose at all times during the trial, as identified by the medical reviewer, 24 of them completed the trial. However, only 15 of the completers (63%) had bone maturation age and advancement data at Month 6. Among the 15 evaluable subjects, 4 subjects had a 12-month advancement in bone age and 1 had a 24-

month. Their bone maturation age advancement ratios were 2.1, 1.9, 1.9, 1.8, and 3.5, respectively, meaning that their bone ages were advanced approximately 6-18 months more than their chronological ages at the end of the trial.

## 2. INTRODUCTION

### 2.1 Overview

The sponsor has submitted (b) (4) in response to the Pediatric Written Request #2, Amendment #1 issued on 05/24/2007 under IND (b) (4) for AndroGel® PD (testosterone gel) 1% CIII.

(b) (4)

There were 2 uncontrolled studies submitted (b) (4)

Study UMD-01-080 corresponded to Study 1 in the Pediatric Written Request (PWR) and was a pharmacokinetic (PK) study. Thus, it is not the focus of this review. Study UMD-01-090 corresponded to Study 2 in the PWR and was mainly a safety study (see the study highlights below).

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

Abbreviations: CDGP = Constitutional Delay in Growth and Puberty

### 2.2 Data Sources

The study report this reviewer reviewed is located in \\Cdsesub1\nonectd\N22227\N_000\2007-06-12\N21015_S-16\m5\clinstat\permanent-

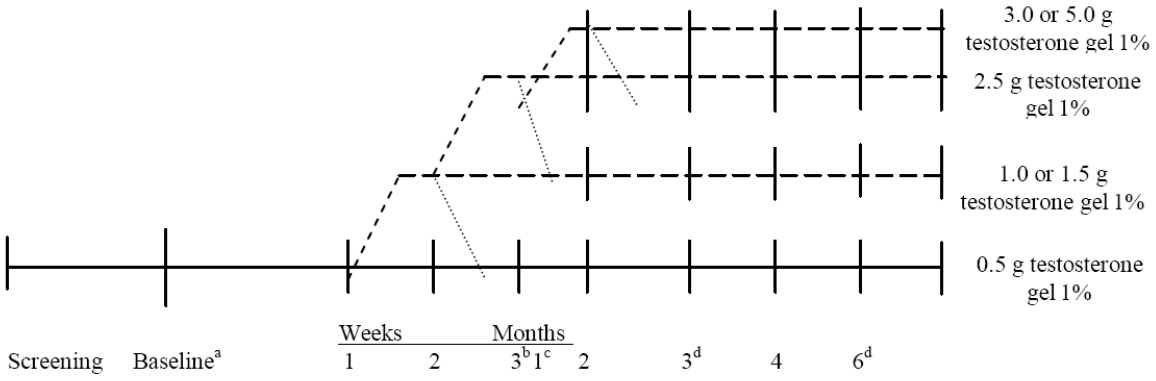
hypogonadism. The electronic data files this reviewer used are located in \\Cdsesub1\nonectd\N22227\N_000\2007-06-12\N21015_S-16\m5\crt\datasets\umd-01-090cv. There were some discrepancies between the electronic data files (e.g., cv_tphs.xpt, cv_bone.xpt, cv_labs.xpt) and study report data listings (e.g., 12.4.17, 12.4.18, 12.4.19). As of 11/26/2007, no explanation regarding this matter was given by the sponsor. Since the quality of electronic data files was poor and the accuracy was doubtful, this reviewer had to use her own best judgment to correct the electronic data sets so that the data were consistent with the listings in the sponsor's clinical study report.

## 3. STATISTICAL EVALUATION

### 3.1 Evaluation of Efficacy

#### 3.1.1 Study Design and Endpoints

Protocols UMD-01-090 and UMD-01-090E combined (08/2002 – 06/2006) was a Phase II, 6-month (3 months for each protocol), open-label, dose-titration, multicenter (in USA) trial, conducted in adolescent boys aged between 13 and 18 years with a diagnosis of delayed puberty due to either primary or secondary hypogonadism or constitutional delay of growth and puberty (CDGP). The study drug was titrated weekly from a starting dose of 0.5 g/day to 1.5 or 2.5 g/day over a 3-week period until a desired serum total testosterone concentration was reached based on the clinical investigators' discretion. The 1.0, 3.0, and 5.0 g/day doses were also added to allow for flexibility in titration to attain a desired clinical response (see the study design below). No control group was included in this study.




[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)

Clinical outcome measurements included growth velocity, testicular volume, Tanner Pubic Hair Stage, bone maturation, and serum hormone concentrations. Pre-treatment growth (height) data were collected retrospectively at least 6 months prior to initiation of the study.

Growth velocity standard deviation score was calculated based on the reference data of Preece (1994). Bone maturation age advancement was defined as the interval change in bone age divided by the interval change in chronological age. The characteristics for each Tanner Pubic Hair Stage were defined by Wheeler (1991) and provided below. There were no primary efficacy variables specified in this study. After consulting with the medical reviewer, efficacy evaluation was focused on serum total testosterone concentration and Tanner Pubic Hair Stage in this review. Safety evaluation, particularly whether the 0.5 g/day was a safe starting dose as raised by the reviewing medical officer, was based on serum total testosterone concentration and bone maturation age advancement.

| Tanner Pubic Hair Stage as Assessed by Pubic Hair Development[1] | |
|---|---|
| **Stage** | **Characteristics** |
| I | Prepubertal; no pubic hair |
| II | Sparse growth of slightly pigmented, slightly curved pubic hair mainly at the base of the penis |
| III | Thicker, curlier hair spread to the mons pubis |
| IV | Adult-type hair that does not yet spread to the medial thighs |
| V | Adult-type hair spread to the medial thighs |

[1] Wheeler MD. Physical changes in puberty. *Endocrinol and Metab Clin N Am;* 1991;20(1): 1-14.

Serum total testosterone concentration was collected at all visits. Tanner Pubic Hair Stage and testicular volume were assessed at Screening, Baseline, and Months 1, 3 and 6 visits. Bone maturation age was mainly evaluated at Screening and Month 6 visits; the evaluation at Month 3 was only performed for subjects who prematurely terminated from Protocol UMD-01-090 or who were not continuing onto Protocol UMD-01-090E. There were 10 subjects from the UMD-01-080 (PK) trial entering the UMD-01-090 trial. For the purpose of statistical analyses, their screening/baseline values from the UMD-01-080 trial were used for the UMD-01-090 trial per the sponsor.

### 3.1.2 Statistical Methods

Since the study was designed to be an observational study, there was no formal statistical testing specified in the Pediatric Written Request and performed by the sponsor. The data were mainly presented in summary statistics and figures in the sponsor's clinical study report by actual dose received as well as by the low (< 100 g), medium (100 to 240 g), and high (> 240 g) tertiles of cumulative dose received during the study. For example, if a subject received 0.5 g for 10 days, 1.5 g for 7 days, and 2.5 g for 150 days, the overall dose for that subject would be 390.5 g. Note that not all subjects who received 0.5 g/day throughout the study or in most part of the study were grouped into the low cumulative dose group.

In the following discussion, unless otherwise stated, the findings were based on this reviewer's calculations using the observed data. This reviewer does not think that it was appropriate to impute data for missing values in this context because of free dose titration scheme (i.e., final dose different from patient to patient), high variability observed in serum total testosterone concentration, and possible incomplete washout of previous testosterone treatment as stated by the sponsor.

### 3.1.3 Subject Disposition

A total of 86 subjects were enrolled in this study. Among them, 59 (69%) were hypogonadal and 27 (31%) were CDGP patients (Table 1, copied from the sponsor's clinical study report). There were 8 subjects withdrawn from the study: 7 with hypogonadism and 1 with CDGP. In other words, at least 25 subjects in each disease diagnosis completed the study, which met the sample size requirement by the Written Request.

Table 1 – 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) |

### 3.1.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics are summarized by disease diagnosis in Table 2 below. All patients were males in this study and 86% of them were White. Although the Written Request calls for recruiting pediatric patients from age 13 to 18 years, there were 3 patients enrolled at 12.3, 12.9, and 18.1 years of age, respectively. The mean chronological age at entry was about 14 years for either disease diagnosis population. The mean bone maturation age was also 14 years for the hypogonadal population, but was 13 years for the CDGP population. Approximately 40% of the enrolled subjects had a Tanner Pubic Hair

Stage ≥ III at baseline, meaning that thicker, curlier pubic hair or adult-type hair as defined by Wheeler (1991) were already seen in those subjects at study entry. In fact, only 20% and 48% of the hypogonadal and CDGP subjects, respectively, were prepubertal at baseline (Tanner Pubic Hair Stage = I). The median serum total testosterone concentration at baseline was 28 ng/dL, but the overall mean was 75.5 ng/dL with a standard deviation of 102, indicating a highly skewed data distribution (maximum concentration = 470 ng/dL). In fact, 25% of the subjects had a serum total testosterone concentration > 100 ng/dL at baseline which was considered as Tanner Pubic Hair Stage III and above. Approximately 51% and 74% of the hypogonadal and CDGP subjects, respectively, were AndroGel treatment naïve prior to entry. Among the 50 AndroGel treatment naïve subjects, there were 11 subjects with a baseline total testosterone > 50 ng/dL even though the inclusion criterion asked for ≤ 50 ng/dL. As expected, a greater percentage of the naïve subjects entered the trial at Tanner Pubic Hair Stage I/II than that of the non-naïve subjects.

Table 2 – Demographic and Baseline Characteristics

| Characteristic | | Hypogonadism | CDGP | Total |
|---|---|---|---|---|
| Age (year): | Mean ± SD (n) | 14.3 ± 1.5 (59) | 14.1 ± 1.2 (27) | 14.3 ± 1.4 (86) |
| | Median | 14.0 | 14.0 | 14.0 |
| | Range | 12 – 18 | 13 – 17 | 12 – 18 |
| Race: White (%) | | 48 (81.4) | 26 (96.3) | 74 (86.0) |
| Black or African-American (%) | | 5 (8.5) | 0 | 5 (5.8) |
| American Indian or Alaska Native (%) | | 1 (1.7) | 1 (3.7) | 2 (2.3) |
| Asian (%) | | 2 (3.4) | 0 | 2 (2.3) |
| Unknown (%) | | 3 (5.1) | 0 | 3 (3.5) |
| Height (cm): | Mean ± SD (n) | 168.4 ± 11.6 (59) | 153.9 ± 10.7 (27) | 163.8 ± 13.2 (86) |
| | Median | 168.7 | 152.2 | 163.6 |
| | Range | 144.5 – 194.1 | 140.2 – 181.9 | 140.2 – 194.1 |
| Weight (kg): | Mean ± SD (n) | 70.0 ± 19.9 (59) | 50.5 ± 19.7 (27) | 63.9 ± 21.8 (86) |
| | Median | 68.0 | 42.2 | 62.4 |
| | Range | 37.9 – 143.3 | 28.5 – 106.1 | 28.5 – 143.3 |
| Bone Maturation Age (year): | | | | |
| Mean ± SD (n) | | 14.0 ± 1.3 (56) | 13.1 ± 1.1 (26) | 13.7 ± 1.3 (82) |
| Median | | 14.0 | 13.0 | 13.6 |
| Range | | 11.0 – 17.0 | 10.5 – 16.0 | 10.5 – 17.0 |
| Tanner Pubic Hair Stage: | | | | |
| I (%) | | 12 (20.3) | 13 (48.1) | 25 (29.1) |
| II (%) | | 19 (32.2) | 8 (29.6) | 27 (31.4) |
| III (%) | | 9 (15.3) | 5 (18.5) | 14 (16.3) |
| IV (%) | | 11 (18.6) | 0 | 11 (12.8) |
| V (%) | | 7 (11.9) | 1 (3.7) | 8 (9.3) |
| Missing (%) | | 1 (1.7) | 0 | 1 (1.2) |

Table 2 – Demographic and Baseline Characteristics (Continued)

| Characteristic | Hypogonadism | CDGP | Total |
|---|---|---|---|
| Serum Total Testosterone (ng/dL): | | | |
| Mean ± SD (n) | 81.1 ± 108.9 (58) | 63.4 ± 86.1 (27) | 75.5 ± 102.0 (85) |
| Median | 25 | 34 | 28 |
| Range | 3 – 470 | 3 – 331 | 3 – 470 |
| ≤ 50 | 35 (60.3) | 18 (66.7) | 53 (62.4) |
| > 50, ≤ 100 | 6 (10.3) | 5 (18.5) | 11 (12.9) |
| > 100, ≤ 200 | 8 (13.8) | 1 (3.7) | 9 (10.6) |
| > 200 | 9 (15.5) | 3 (11.1) | 12 (14.1) |
| AndroGel Treatment Naive: | | | |
| Yes (%) | 30 (50.8) | 20 (74.1) | 50 (58.1) |
| No (%) | 28 (47.5) | 7 (25.9) | 35 (40.7) |
| Missing (%) | 1 (1.7) | 0 | 1 (1.2) |
| Testicular Volume (mL): | | | |
| Mean ± SD (n) | 3.2 ± 2.5 (57) | 4.4 ± 3.5 (27) | 3.6 ± 2.9 (84) |
| Median | 3 | 3 | 3 |
| Range | 0 – 12 | 1 – 15 | 0 – 15 |
| Disease Diagnosis: | | | |
| Primary Hypogonadism (%) | 36 (61.0) | 0 | 36 (41.9) |
| Secondary Hypogonadism (%) | 23 (39.0) | 0 | 23 (26.7) |
| CDGP (%) | 0 | 27 (100) | 27 (31.4) |
| Enrolled in Protocol UMD-01-080: | | | |
| Yes (%) | 9 (15.3) | 1 (3.7) | 10 (11.6) |
| No (%) | 50 (84.7) | 26 (96.3) | 76 (88.4) |

### 3.1.5 Efficacy Results and Discussion

Since the dose titration scheme was based on the clinical investigators' discretion and varied from patient to patient, efficacy evaluation for the intermediate visits in this 6-month trial was less crucial. Therefore, the following evaluation focuses on the baseline and Month 6 values.

***Serum Total Testosterone Concentration.*** According to the sponsor's Listing 12.4.19, 8 subjects at Week 1 did not have any records for dose and serum total testosterone levels and 3 subjects from Protocol UMD-01-080 used dose > 0.5 g during Week 1. Although there were some high serum total testosterone concentrations at baseline and Week 1 (Figure 1), the mean change from baseline for the 74 subjects applying the starting dose, 0.5 g, during Week 1 was 100.5 ng/dL and the median change was 75 ng/dL (Table 3). Figure 2 shows the data distribution of changes in a stem-and-leaf plot. As one can see, 43/74 (= 58.1%) subjects had a change between 0 and 100 ng/dL; 20/74 (= 27.0%) subjects had a change between 100 and 200 ng/dL; 9/74 (= 12.2%) had a change ≥ 200 ng/dL; and 2/74 (= 2.7%)

were below 0. This reviewer could not find any consistent patterns in terms of baseline characteristics that caused the 9 subjects with a change ≥ 200 ng/dL at Week 1 (Appendix I).

The mean and median changes from baseline in serum total testosterone concentration at Week 1 for the various subgroups as shown in Table 3 were also similar to those for the whole population, and their upper bounds of 95% confidence intervals were all well below 200 ng/dL, a threshold that was liberally defined by the reviewing medical officer.

Table 3 – Serum Total Testosterone Concentration (ng/dL) **for subjects with 0.5 g/day during Week 1**

| | Mean ± SD (n) | 95% C.I | Median | Min – Max |
|---|---|---|---|---|
| Baseline | 81.8 ± 105.0 (74) | (57.9, 105.7) | 38 | 3 – 470 |
| Week 1 | 182.3 ± 133.9 (74) | (151.8, 212.8) | 138.5 | 28 – 674 |
| Change from Baseline | 100.5 ± 105.1 (74) | (76.6, 124.4) | 75 | -280 – 533.2 |
| Change from Baseline – Naïve | 99.0 ± 73.1 (41) | (76.6, 121.4) | 81 | 0 – 306 |
| Change from Baseline – Non-naive | 102.3 ± 136.1 (33) | (55.9, 148.7) | 68 | -280 – 533.2 |
| Change from Baseline – Tanner I | 96.8 ± 68.3 (21) | (67.6, 126.0) | 76.4 | 15 – 306 |
| Change from Baseline – Tanner > I | 100.1 ± 117.5 (52) | (68.2, 132.1) | 70.5 | -280 – 533.2 |
| Change from Baseline – Hypogonadal | 99.3 ± 119.9 (49) | (65.7, 132.9) | 68 | -280 – 533.2 |
| Change from Baseline – CDGP | 102.8 ± 69.5 (25) | (75.5, 130.0) | 87 | 2 – 306 |
| Change from Baseline – (b) (4) Pump | 118.7 ± 60.1 (23) | (94.1, 143.3) | 114 | 18 – 306 |
| Change from Baseline – (b) (4) Pump | 94.9 ± 131.9 (39) | (53.5, 136.3) | 63 | -280 – 533.2 |
| Change from Baseline – Mixed | 102.8 ± 79.4 (8) | (47.8, 157.8) | 87.65 | 29 – 246 |
| Change from Baseline – Unknown | 45.0 ± 11.7 (4) | (33.6, 56.4) | 43 | 33 – 61 |

Note that the (b) (4) pump-head designed to deliver (b) (4) testosterone gel 1% per actuation was intended to be used in this study. However, the sponsor found that 43 subjects had received drug via the (b) (4) 9 subjects via both (b) (4) and 4 via unknown pump-head types during the course of the study prior to 07/18/2005. The (b) (4) pump-head was designed to deliver (b) (4) testosterone gel 1% per actuation (b) (4) As shown in Table 3, the mean and median changes from baseline in serum total testosterone at Week 1 in patients receiving drug via the (b) (4) pump-head were both numerically larger than those in patients receiving drug via the (b) (4) pump-head. Results from Wilcoxon-Mann-Whitney test (a non-parametric test), performed by this reviewer, confirmed a significant difference between the 2 pump-head types (p = 0.0186).

Figure 1

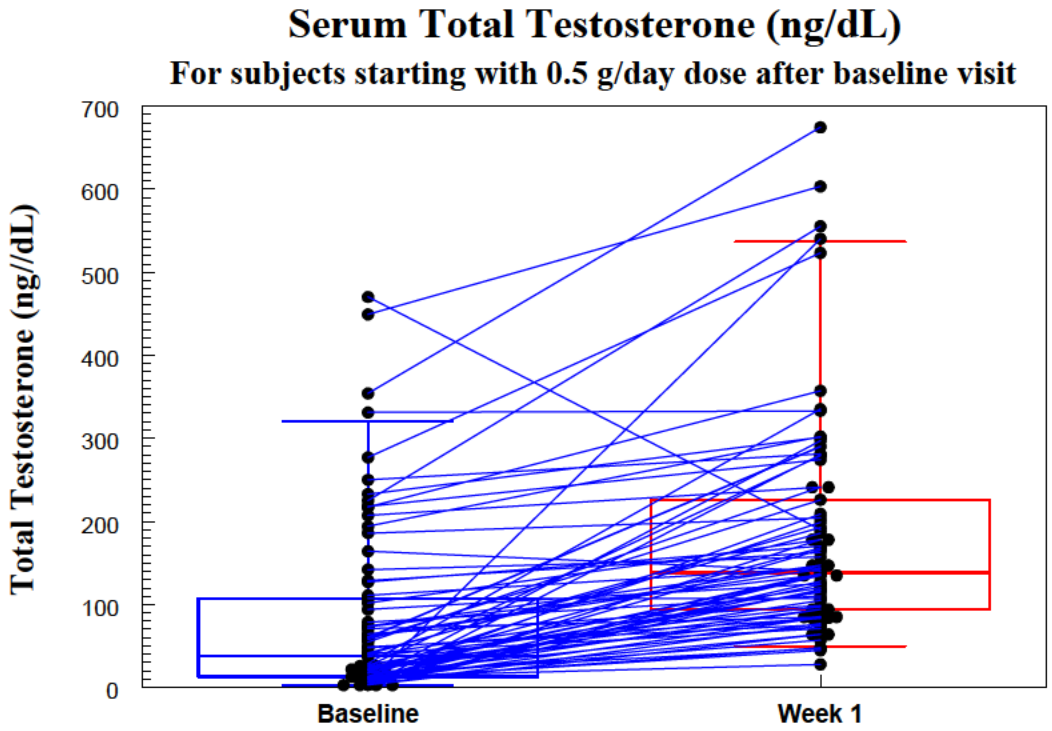



Figure 2
Change from Baseline in Serum Total Testosterone at Week 1

```
Stem Leaf                      #    Boxplot
   5 3                         1       *
   4
   4
   3
   3 123                       3       0          Note: In the stem-and-leaf plot,
   2 5589                      4       |          (Stem.Leaf)*100 shows the response of
   2 03                        2       |          each subject.  In the box pot, the
   1 5567789                   7       |          horizontal line inside the box shows
   1 011222233444             12    +--+--+       the median and + sign shows the mean.
   0 5666666666777788888889   22    *-----*       Any value more than 1.5 interquartile
   0 001222333333333334444    21    +-----+       range (= 75th - 25th percentiles) is
  -0 2                        1       |          marked with a 0 or a *.
  -0
  -1
  -1
  -2
  -2 8                        1       0
     ----+----+----+----+--
 Multiply Stem.Leaf by 10**+2
```

The overall mean change from baseline in serum total testosterone concentration at Month 6 was 177.7 ng/dL and the median change was 158.3 ng/dL. Although greater changes were

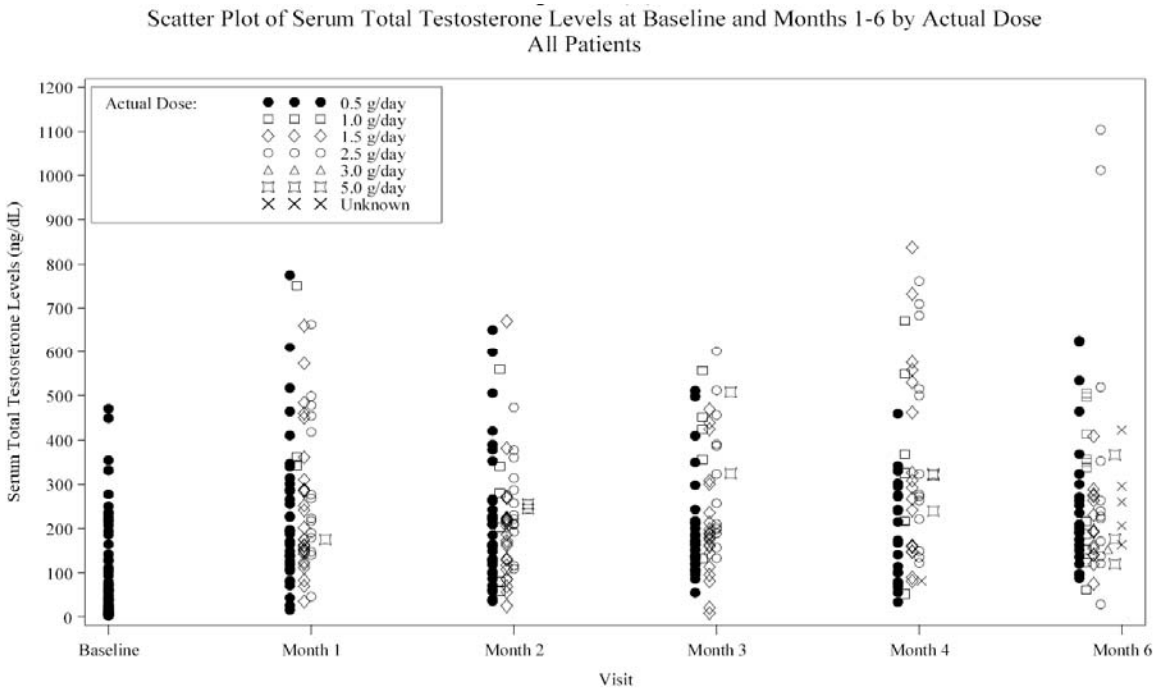
observed in higher dose groups, there was no positive linear dose-response in mean or median change from baseline at Month 6. In fact, for patients in the medium cumulative dose group, their serum total testosterone changes from baseline to Month 6 were generally greater than those in the low and high cumulative dose groups. Similar findings were also observed for both naïve and non-naïve patient populations, as shown in Table 4. However, there were quantitative differences between the naïve and non-naïve populations, as the naïve patients consistently showing greater changes from baseline at 6 months across the 3 cumulative dose groups.

Table 4 – Serum Total Testosterone Concentration (ng/dL) at Month 6

| | Low Dose (< 100 g) (n = 27) | Medium Dose (100 – 240 g) (n = 28) | High Dose (> 240 g) (n = 31) | Total (n = 86) |
|---|---|---|---|---|
| **Baseline** | | | | |
| Mean ± SD (n) | 165.0 ± 164.9 (14) | 52.1 ± 70.0 (25) | 82.7 ± 86.5 (28) | 88.5 ± 109.3 (67) |
| Median | 92.5 | 23 | 48.5 | 40 |
| Min – Max | 3.7 – 470 | 3 – 236 | 3 – 331 | 3 – 470 |
| **Month 6** | | | | |
| Mean ± SD (n) | 289.4 ± 173.2 (14) | 270.9 ± 155.0 (25) | 250.3 ± 182.3 (28) | 266.1 ± 168.8 (67) |
| Median | 230.5 | 235 | 216.5 | 227 |
| Min – Max | 98 – 626 | 62 – 662 | 29 – 1012 | 29 – 1012 |
| **Change from Baseline at Month 6** | | | | |
| Mean ± SD (n) | 124.5 ± 141.1 (14) | 218.8 ± 145.3 (25) | 167.5 ± 189.1 (28) | 177.7 ± 165.9 (67) |
| 95% C.I. | (50.4, 198.5) | (161.9, 275.8) | (97.5, 237.6) | (138.0, 217.4) |
| Median | 156.2 | 189 | 157.5 | 158.3 |
| Min – Max | -170 – 408 | 30 – 526.5 | -210 – 885 | -210 – 885 |
| **Change from Baseline at Month 6 – Naïve Patients** | | | | |
| Mean ± SD (n) | 158.1 ± 65.4 (6) | 226.9 ± 149.4 (17) | 172.7 ± 92.5 (13) | 195.9 ± 121.1 (36) |
| 95% C.I. | (105.8, 210.4) | (155.9, 297.9) | (122.4, 223.0) | (156.3, 235.4) |
| Median | 166.7 | 213 | 178 | 187 |
| Min – Max | 36 – 223 | 30 – 526.5 | 20.1 – 347.5 | 20.1 – 526.5 |
| **Change from Baseline at Month 6 – Non-Naïve Patients** | | | | |
| Mean ± SD (n) | 99.3 ± 179.9 (8) | 201.7 ± 144.3 (8) | 163.1 ± 248.2 (15) | 156.6 ± 206.4 (31) |
| 95% C.I. | (-25.4, 223.9) | (101.7, 301.6) | (37.5, 288.6) | (83.9, 229.2) |
| Median | 104 | 131 | 96 | 112.2 |
| Min – Max | -170 – 408 | 81 – 474 | -210 – 885 | -210 – 885 |

The scatter plot of serum total testosterone levels at baseline and Month 1-6, copied from the sponsor's clinical study report, is provided below (Figure 3).

Figure 3




The mean plot of serum total testosterone levels at baseline and Month 1-6, copied from the sponsor's clinical study report, is provided below (Figure 4). It depicts that regardless of dose level used, the serum total testosterone concentrations during the treatment period were generally improved over that at baseline.

Figure 4

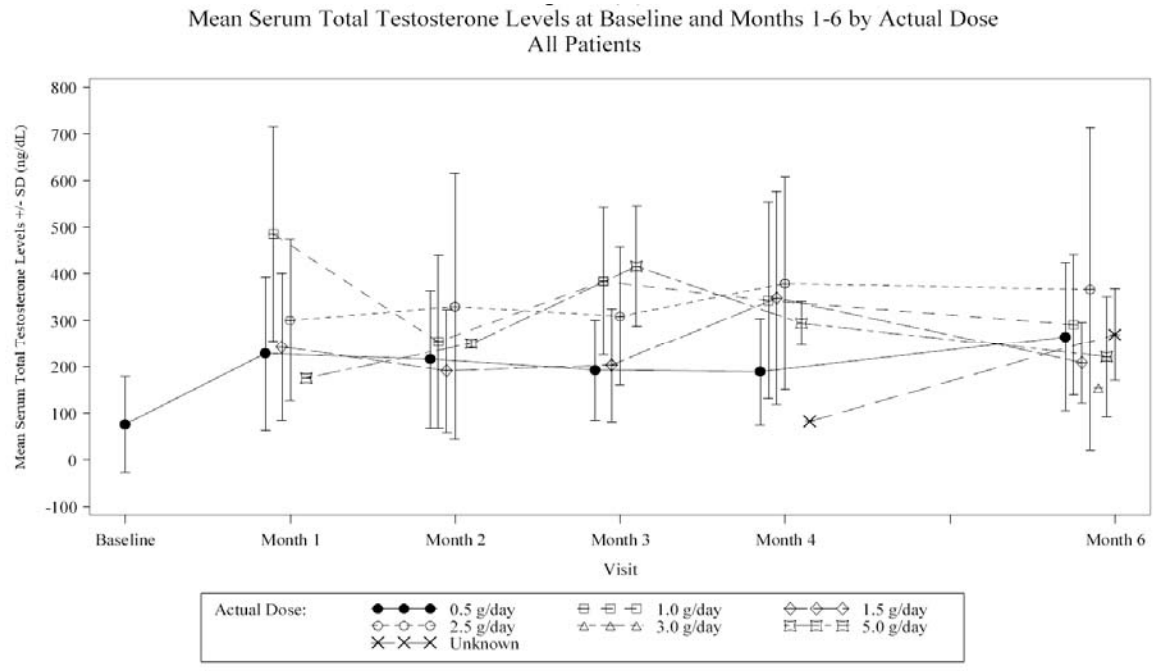


Table 5 below, also copied from the sponsor's clinical study report, showed that for subjects who received the lowest dose (0.5 g/day) at a particular visit, despite that the mean and median changes were around 100 – 200 ng/dL, there were quite a few subjects having large changes from baseline which may be a concern from a safety standpoint. For example, 8/23 subjects at Month 6 had a change ≥ 200 ng/dL from baseline.

Table 5 – Serum Total Testosterone Concentration (ng/dL) **for subjects with 0.5 g/day at Months 1-6**

| | Mean ± SD (n) | 95% C.I | Median | Min – Max |
|---|---|---|---|---|
| Change from Baseline at Month 1 | 144.5 ± 150.8 (36) | (93.5, 195.5) | 125.5 | -77 – 755 |
| Change from Baseline at Month 2 | 132.4 ± 104.2 (37) | (97.7, 167.2) | 131.0 | -81 – 499 |
| Change from Baseline at Month 3 | 102.4 ± 80.9 (34) | (74.1, 130.6) | 119.5 | -172 – 293 |
| Change from Baseline at Month 4 | 98.6 ± 120.5 (22) | (45.1, 152.0) | 63.2 | -198 – 313 |
| Change from Baseline at Month 6 | 154.6 ± 147.6 (23) | (90.8, 218.4) | 158.3 | -170 – 527 |

***Tanner Pubic Hair Stage.*** Numbers and percentages of subjects by baseline and Month 6 Tanner pubic hair stages are summarized in Table 6. For the 39 subjects who had a Tanner Pubic Hair Stage = I or II at baseline, 87% (= 34/39) of them had a progressed Tanner pubic hair stage at Month 6. For the subjects who had a Tanner Pubic Hair Stage ≥ III at baseline, not much of improvement in the sexual characteristics was seen after 6 months.

Table 6 – Tanner Pubic Hair Staging at Month 6

| Stage at Baseline | Stage at Month 6 | | | | | |
|---|---|---|---|---|---|---|
| | I | II | III | IV | V | Total |
| I | 3 (15%) | 10 (50%) | 5 (25%) | 2 (10%) | 0 | 20 |
| II | - | 2 (11%) | 8 (42%) | 9 (47%) | 0 | 19 |
| III | - | - | 7 (54%) | 5 (38%) | 1 (8%) | 13 |
| IV | - | - | - | 9 (82%) | 2 (18%) | 11 |
| V | - | - | - | - | 8 (100%) | 8 |
| Total | 3 | 12 | 20 | 25 | 11 | 71 |

Similar findings were also observed for both naïve and non-naïve patient populations, as shown in Table 7, except for the non-naïve subjects entering the trial at Tanner Pubic Hair Stage III, in which case most of the subjects had a progressed Tanner pubic hair stage at Month 6.

Table 7 – Tanner Pubic Hair Staging at Month 6 by Prior AndroGel Treatment

| | Stage at Month 6 | | | |
|---|---|---|---|---|
| | Naïve Patients | | None-Naïve Patients | |
| Stage at Baseline | No Change | At Least 1 Stage Higher | No Change | At Least 1 Stage Higher |
| I | 3 (16%) | 16 (84%) | 0 | 1 (100%) |
| II | 1 (9%) | 10 (91%) | 1 (13%) | 7 (88%) |
| III | 5 (100%) | 0 | 2 (25%) | 6 (75%) |
| IV | 2 (100%) | 0 | 7 (78%) | 2 (22%) |
| V | 1 (100%) | 0 | 6 (100%) | 0 |
| Total | 12 | 26 | 16 | 16 |

Whether Patient 1211 was naïve to prior AndroGel treatment or not was unknown, but his baseline and Month 6 Tanner Pubic Hair Stages were both at V.

After 6 months of treatment with AndroGel, the number of subjects with an improved Tanner pubic hair stage in each of the 3 cumulative dose groups was larger than that of subjects with no changed stages (Table 8). The median changes from baseline in serum total testosterone concentration across the 3 dose groups as well as the overall were all slightly higher in subjects with at least 1 progressed stage than in subjects with no change. The subjects in the low cumulative dose group generally had a smaller change in serum total testosterone concentration at Month 6 when compared to the subjects in the medium and high cumulative dose groups, regardless whether their Tanner pubic hair stages were improved or not.

Table 8 – Mean and Median Change from Baseline in Total Testosterone by Tanner Staging at Month 6

| Tanner Pubic Hair Stage: from baseline to Month 6 | Low Dose (< 100 g) (n = 27) | Medium Dose (100 – 240 g) (n = 28) | High Dose (> 240 g) (n = 31) | Total (n = 86) |
|---|---|---|---|---|
| No Change | 104.8 ± 113.8 (6)<br>Median = 142.0 | 236.5 ± 150.1 (8)<br>Median = 175.5 | 166.5 ± 260.7 (12)<br>Median = 144.0 | 173.8 ± 203.1 (26)<br>Median = 148.0 |
| At Least 1 Stage Higher | 139.2 ± 165.2 (8)<br>Median = 156.2 | 210.5 ± 146.8 (17)<br>Median = 189.0 | 168.3 ± 120.5 (16)<br>Median = 159.0 | 180.1 ± 140.1 (41)<br>Median = 161.0 |

***Bone Maturation Age and Advancement.*** As shown in Table 9, after 6 months of treatment with AndroGel, the mean change from baseline in bone age was 0.4 years and the median change was 0.5 years. There were 8 out of 62 evaluable subjects with a decreased (clinically implausible) bone age at Month 6 when compared to baseline (Figure 5) and they were all from the medium and high cumulative dose groups. The mean and median ratios of change in bone age from baseline to Month 6 to change in chronological age for the same interval (bone maturation age advancement) were both 0.9, indicating that the advancements in bone

age after 6 months of treatment were close to the advancements in chronological age in general. However, as depicted in Figure 6, 12 out of 59 evaluable subjects had a ratio > 2, meaning that 20% of the subjects had their bone ages advanced at least 6 months more than their chronological ages at the end of the trial and except for 1 subject, they were all also from the medium and high cumulative dose groups. Nevertheless, the 95% confidence interval of the mean ratio (bone maturation age advancement) was between 0.5 and 1.2, implying that the average baseline adjusted bone age at 6 months could be simply 3 months behind or 1-2 month more than the chronological age. In addition, there was a positive dose-response in bone maturation age advancement, i.e., patients with higher cumulative doses normally had greater advances in bone age relative to chronological age. Figure 7 presents a scatter plot of change in bone age vs. change in chronological age for all patients including dropouts (copied from the sponsor's clinical study report). Similar findings were also observed when the negative changes in bone age from baseline at 6 months were excluded or replaced with a 0 (sensitivity analyses, Table 9).

Table 9 – Bone Maturation Age and Advancement at Month 6

| | Low Dose (< 100 g) (n = 27) | Medium Dose (100 – 240 g) (n = 28) | High Dose (> 240 g) (n = 31) | Total (n = 86) |
|---|---|---|---|---|
| **Bone Age (in years) at Baseline** | | | | |
| Mean ± SD (n) | 14.0 ± 1.0 (12) | 13.5 ± 1.5 (22) | 13.8 ± 1.3 (28) | 13.7 ± 1.3 (62) |
| Median | 14.0 | 13.6 | 14.0 | 14.0 |
| Min – Max | 12.5 – 16.0 | 10.5 – 17.0 | 11.0 – 17.0 | 10.5 – 17.0 |
| **Bone Age (in years) at Month 6** | | | | |
| Mean ± SD (n) | 14.4 ± 1.3 (12) | 13.9 ± 1.5 (22) | 14.2 ± 1.1 (28) | 14.1 ± 1.3 (62) |
| Median | 14.0 | 14.0 | 14.0 | 14.0 |
| Min – Max | 12.8 – 17.0 | 11.0 – 17.0 | 12.5 – 17.5 | 11.0 – 17.5 |
| **Change from Baseline in Bone Age (in years) at Month 6** | | | | |
| Mean ± SD (n) | 0.4 ± 0.4 (12) | 0.4 ± 0.8 (22) | 0.4 ± 0.8 (28) | 0.4 ± 0.7 (62) |
| 95% C.I. | (0.2, 0.6) | (0.1, 0.7) | (0.2, 0.7) | (0.3, 0.6) |
| Median | 0.3 | 0.5 | 0.5 | 0.5 |
| Min – Max | 0 – 1.0 | -1.3 – 2.0 | -1.5 – 2.0 | -1.5 – 2.0 |
| **Bone Maturation Age Advancement (change in BA/change in CA)** | | | | |
| Mean ± SD (n) | 0.8 ± 0.8 (12) | 0.8 ± 1.5 (21) | 1.0 ± 1.5 (26) | 0.9 ± 1.4 (59) |
| 95% C.I. | (0.4, 1.3) | (0.2, 1.5) | (0.4, 1.5) | (0.5, 1.2) |
| Median | 0.6 | 0.9 | 1.0 | 0.9 |
| Min – Max | 0 – 2.1 | -2.7 – 3.5 | -3.2 – 3.7 | -3.2 – 3.7 |

Table 9 – Bone Maturation Age and Advancement at Month 6 (Continued)

| | Low Dose (< 100 g) (n = 27) | Medium Dose (100 – 240 g) (n = 28) | High Dose (> 240 g) (n = 31) | Total (n = 86) |
|---|---|---|---|---|
| **Bone Maturation Age Advancement – Excluding Negative Changes in Bone Age at Month 6** | | | | |
| Mean ± SD (n) | 0.8 ± 0.8 (12) | 1.3 ± 1.2 (17) | 1.3 ± 1.1 (23) | 1.2 ± 1.1 (52) |
| 95% C.I. | (0.4, 1.3) | (0.7, 1.9) | (0.9, 1.8) | (0.9, 1.5) |
| Median | 0.6 | 0.9 | 1.0 | 1.0 |
| Min – Max | 0 – 2.1 | 0 – 3.5 | 0 – 3.7 | 0 – 3.7 |
| **Bone Maturation Age Advancement – Replacing Negative Changes in Bone Age at Month 6 with 0** | | | | |
| Mean ± SD (n) | 0.8 ± 0.8 (12) | 1.0 ± 1.2 (21) | 1.2 ± 1.1 (26) | 1.0 ± 1.1 (59) |
| 95% C.I. | (0.4, 1.3) | (0.5, 1.5) | (0.7, 1.6) | (0.8, 1.3) |
| Median | 0.6 | 0.9 | 1.0 | 0.9 |
| Min – Max | 0 – 2.1 | 0 – 3.5 | 0 – 3.7 | 0 – 3.7 |

Bone maturation age advancement was calculated by the sponsor as the interval change in bone age (in months) divided by the interval change in chronological age (in months).

Figure 5

Change from Baseline in Bone Age at Month 6

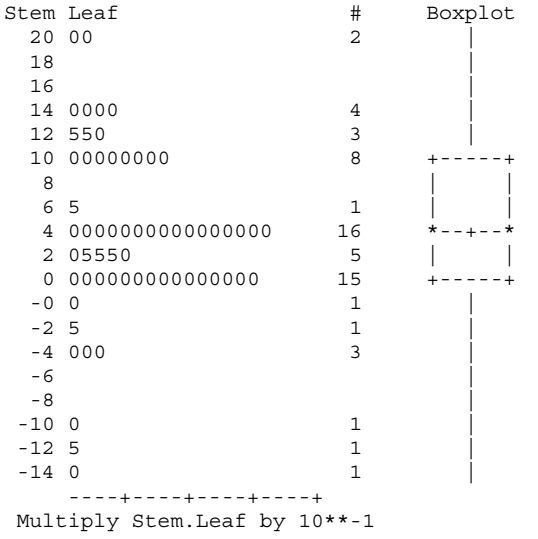



Figure 6

Bone Maturation Age Advancement

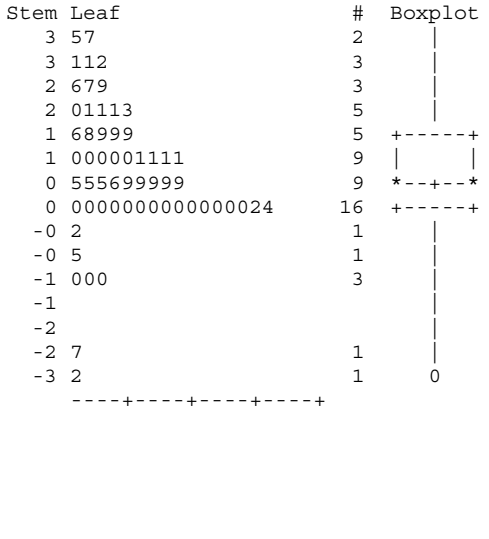
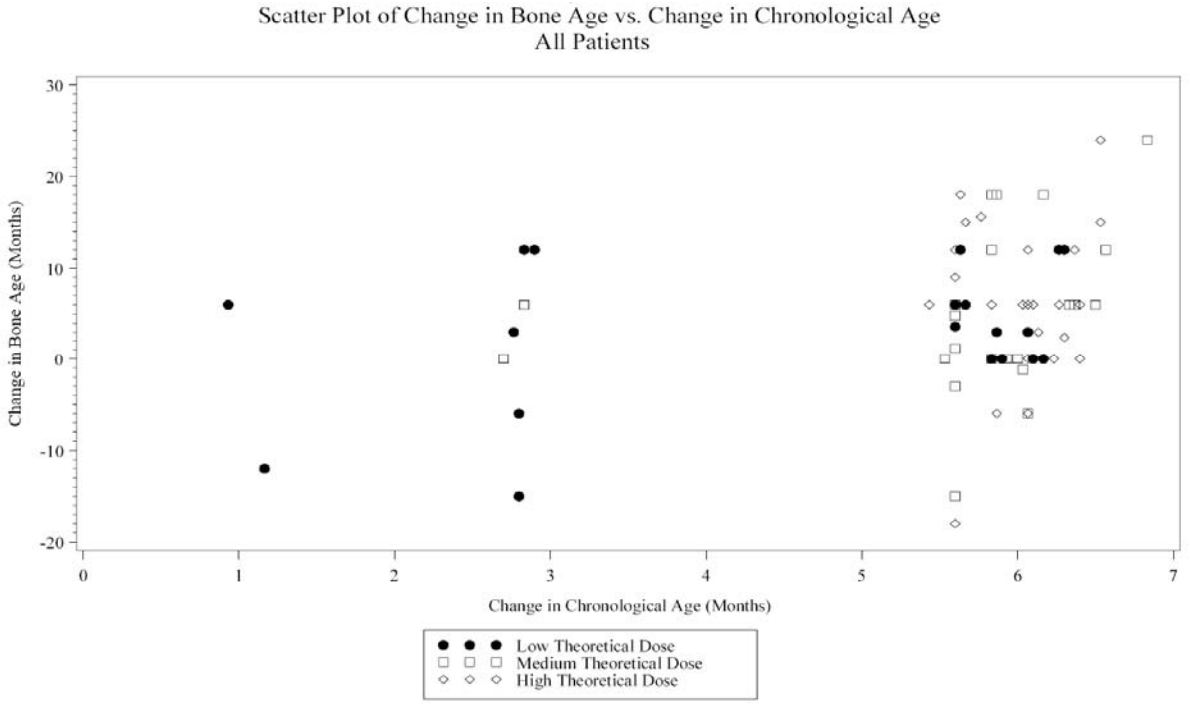


Figure 7




This reviewer also evaluated a subset of patients (n = 29) who used the 0.5 g/day dose at all times during the trial, as identified by the medical reviewer. Among the 29 patients, 24 were completers, but only 15 of them had bone age advancement data at Month 6. The mean and median ratios for those 15 patients were 1.0 and 0.6, respectively, with a range from 0 to 3.5. The findings were somewhat consistent with what were observed previously.

To facilitate the medical officer's review, Table 10 below presents the bone maturation age advancement data using the differences between changes from baseline in bone age at Month 6 and changes from baseline in chronological age at Month 6. As the findings based on the ratios shown above, there were more subjects with greater bone age advancement observed in the higher dose groups than in the low dose group. For example, while only 1 patient in the low cumulative dose group, 5 patients in the medium and 6 patients in the high cumulative dose groups had their bone ages advanced at least 6 months more than their chronological ages at the end of the trial.

Table 10 – Number of Subjects in Each Bone Maturation Age Advancement Categories at Month 6

| Difference [1] | Ratio [2] | Low Dose | Medium Dose | High Dose |
|---|---|---|---|---|
| < -6 months [3] | (< 0) | 2 (0) | 4 (4) | 7 (3) |
| ≥ -6 months, < -3 months [3] | (0 – 0.5) | 3 (5) | 6 (6) | 3 (7) |
| ≥ -3 months, < 0 months | (0.5 – 1) | 2 (2) | 4 (4) | 5 (5) |
| ≥ 0 month, < 3 months | (1 – 1.5) | 2 (2) | 1 (1) | 2 (2) |
| ≥ 3 months, < 6 months | (1.5 – 2) | 2 (2) | 1 (1) | 3 (3) |
| ≥ 6 months, < 12 months | (2 – 3) | 1 (1) | 2 (2) | 4 (4) |
| ≥ 12 months, < 18 months | (3 – 4) | 0 (0) | 3 (3) | 2 (2) |
| | | | | |
| Mean ± SD (n) | | -1.1 ± 4.8 (12) | -0.9 ± 9.1 (21) | -0.3 ± 8.7 (26) |
| 95% C.I. | | (-3.9, 1.6) | (-4.8, 3.0) | (-3.6, 3.1) |
| Median | | Median = -2.4 | Median = -0.8 | Median = -0.1 |
| Min - Max | | -6.2 – 6.4 | -20.6 – 17.2 | -23.6 – 17.5 |

1. Difference = Change from baseline in bone age – change from baseline in chronological age

2. Ratio = Change from baseline in bone age / change from baseline in chronological age

3. There were 6 subjects whose bone ages after slightly more than 6 months of treatment were still the same as their baselines. Therefore, their differences for bone maturation age advancement were < -6 months, but the ratios were 0.

### 3.2 Evaluation of Safety

In consultation with the reviewing medical officer, except for bone maturation age advancement parameter, there were no other aspects of safety that required review by a statistician. See Dr. Dragos Roman's report for the complete safety evaluation.

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Race, and Age

No subgroup analyses for gender, race, and age were performed since the study subjects were all adolescent boys aged between 12 and 18 years and the majority (86%) of them were White.

### 4.2 Other Special/Subgroup Populations

Special subgroup analyses were discussed in Section 3.1.5 above.

## 5. SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

In this reviewer's opinion, the issues that impact the overall conclusions of the study are more related to the study design aspects such as free dose titration scheme, no concurrent

control group, possible incomplete washout from previous testosterone treatment (as acknowledged by the sponsor), and many inclusion/exclusion criterion violators. The patient population was very heterogeneous in terms of baseline characteristics (e.g., serum total testosterone concentration, Tanner pubic hair stage, testicular volume, disease diagnosis, and use of prior AndroGel treatment at baseline). The serum total testosterone concentration data were highly variable within and across patients. The pump-head type delivering the study drug was different for some patients during some parts of the study. In addition, there were some clinically implausible decreased on-treatment bone ages when compared to baselines. All of the mentioned facts confound the data and make the interpretation of the results much more difficult.

In general, this reviewer's findings based on the observed data were similar to the sponsor's results based on the observed and LOCF data. The findings for the hypogonadal population were similar to the ones for the CDGP population. The following collective evidence was based on the whole study population.

***Efficacy.*** For subjects using the starting dose, 0.5 g, during the first week of AndroGel treatment (n = 74), the median change in serum total testosterone concentration was 75 ng/dL from baseline to Week 1 and the 95% confidence interval of the mean change was (76.6, 124.4). In addition, for the subgroups defined by prior AndroGel use (naïve, non-naïve), Tanner Pubic Hair Stage (I, > I), disease diagnosis (hypogonadism, CDGP), and pump-head type (b) (4) the mean and median changes from baseline in serum total testosterone concentration at Week 1 and the associated upper bounds of 95% confidence intervals were all well below 200 ng/dL, a threshold that was liberally defined by the reviewing medical officer.

After 6 months of treatment with AndroGel, the patients' serum total testosterone concentrations were still generally increased (mean change = 177.7 ng/dL, median change = 158.3 ng/dL, minimum change = -210 ng/dL, and maximum change = 885 ng/dL). Also, around 60% of the evaluable subjects (= 42/71) had their Tanner pubic hair stages shifted at least 1 stage higher toward puberty and the majority of them were the subjects with early Tanner pubic hair stages (I/II) at baseline. Specifically, for the 39 subjects who had a Tanner Pubic Hair Stage = I or II at baseline, 87% (= 34/39) of them had a progressed stage at Month 6 (see Table 6 above).

The median changes from baseline in serum total testosterone concentration at Month 6 across the 3 cumulative dose groups were all slightly higher in subjects with at least 1 progressed stage than in subjects with no change (see Table 8 above), and also in the naïve subjects than in the non-naïve subjects (see Table 4 above). The subjects in the low

cumulative dose group (< 100 g) generally had a smaller change in serum total testosterone concentration at Month 6 when compared to the subjects in the medium (100 – 240 g) and high (> 240 g) cumulative dose groups, regardless of Tanner pubic hair stages and prior testosterone treatment use.

***Safety.*** After 6 months of treatment with AndroGel, the mean change from baseline in bone age was 0.4 years and the median change was 0.5 years. In other words, the patients' bone ages were generally advanced about 6 months or so at the end of this 6-month trial (both mean and median ratios of change in bone age to change in chronological age = 0.9). According to the 95% confidence interval of the mean ratio or difference (bone maturation age advancement), the bone age could be advanced more or less than the chronological age by 3 months at the end of the trial. There was a positive dose-response in bone maturation age advancement at 6 months, i.e., patients with higher cumulative doses normally had greater advances in bone age relative to chronological age after 6 months of testosterone treatment. Specifically, while none in the low cumulative dose group, 3 subjects in the medium and 2 subjects in the high cumulative dose groups had their bone ages advanced at least 12 months more than their chronological ages at Month 6. Note that there were 8 out of 62 evaluable subjects with a biologically implausible decreased bone age at Month 6 when compared to baseline and they were all from the medium and high cumulative dose groups. When those negative changes were excluded from the data or replaced with a zero, similar findings to the ones based on the whole evaluable population were also observed (see Table 9 above).

**To evaluate whether the 0.5 g/day dose is a safe starting dose for adolescent boys with delayed puberty**, the data of subjects with 0.5 g/day dose at any visits during the trial and the data from the low cumulative dose group (< 100 g) were reviewed. It was noted that there were 9 out of 74 evaluable subjects (12%) with a ≥ 200 ng/dL change from baseline in serum total testosterone concentration at Week 1, which was considered excessive by the reviewing medical officer. For the subjects who received the 0.5 g/day dose at a particular visit during Months 1-6, although the mean and median changes in serum total testosterone concentration were all around 100 – 200 ng/dL, there were quite a few subjects showing large changes from baseline which may also be a concern from a safety standpoint. For example, 8/23 subjects with the 0.5 g/day dose at Month 6 had a change ≥ 200 ng/dL from baseline.

In addition, there was an unplanned pump-head type used to deliver drug for some patients during the study, as acknowledged by the sponsor. The unplanned type, (b) (4) pump-head, was designed to deliver (b) (4) testosterone gel 1% per actuation (b) (4) It was found that the median

change from baseline in serum total testosterone at Week 1 in patients receiving the (b) (4) dose via the (b) (4) pump-head (114 ng/dL for n = 23) was significantly larger than those in patients receiving the (b) (4) dose via the (b) (4) pump-head (63 ng/dL for n = 39, p = 0.0186 from the Wilcoxon-Mann-Whitney test performed by this reviewer). (b) (4)

Table 11 below shows that for subjects receiving the (b) (4) dose from the (b) (4) pump-head at Week 1, most of them had a progressed Tanner pubic hair stage at Month 6, particularly the ones with a baseline Tanner stage at I, II, or III. Table 12 (copied from the sponsor's clinical study report) further shows that for subjects receiving the (b) (4) dose from the (b) (4) pump-head at a particular visit, their serum total testosterone concentrations were generally increased over that at baseline.

Table 11 – Tanner Pubic Hair Staging
**for subjects receiving (b) (4) from (b) (4) pump-head at Week 1**

| | Stage at Month 6 | | | | | |
|---|---|---|---|---|---|---|
| Stage at Baseline | I | II | III | IV | V | Total |
| I | 0 | 5 | 2 | 1 | 0 | 8 |
| II | - | 1 | 3 | 7 | 0 | 11 |
| III | - | - | 1 | 4 | 1 | 6 |
| IV | - | - | - | 6 | 2 | 8 |
| V | - | - | - | | 4 | 4 |
| Total | 0 | 6 | 6 | 18 | 7 | 37 |

Table 12 – Serum Total Testosterone Concentration (ng/dL)
**for subjects receiving (b) (4) from (b) (4) pump-head**

| Observed | Mean ± SD (n) | Median | Min – Max |
|---|---|---|---|
| Baseline | 93.0 ± 112.0 (42) | 44.5 | 3 – 470 |
| Week 1 | 193.9 ± 147.9 (39) | 143.0 | 28 – 674 |
| Month 1 | 225.1 ± 179.2 (12) | 221.0 | 16 – 610 |
| Month 2 | 215.0 ± 161.1 (13) | 223.0 | 36 – 599 |
| Month 3 | 232.5 ± 162.3 (10) | 208.5 | 55 – 511 |
| Month 4 | 155.3 ± 119.7 (4) | 157.5 | 34 – 272 |
| Month 6 | 318.2 ± 195.9 (6) | 281.5 | 120 – 626 |

There were 27 subjects grouped into the low cumulative dose group (< 100 g) in the study and 21 of them completed the trial. However, only 12 of the completers (57%) had bone maturation age and advancement data at Month 6. Among the 12 evaluable subjects in the low cumulative dose group, 3 subjects had a 12-month advancement in bone age. Their bone maturation age advancement ratios were 2.1, 1.9, and 1.9, respectively, meaning that their

bone ages were advanced approximately 6 months more than their chronological ages at the end of the trial.

Similarly, for the 29 subjects who used the 0.5 g/day dose at all times during the trial, as identified by the medical reviewer, 24 of them completed the trial. However, only 15 of the completers (63%) had bone maturation age and advancement data at Month 6. Among the 15 evaluable subjects, 4 subjects had a 12-month advancement in bone age and 1 had a 24-month. Their bone maturation age advancement ratios were 2.1, 1.9, 1.9, 1.8, and 3.5, respectively, meaning that their bone ages were advanced approximately 6-18 months more than their chronological ages at the end of the trial.

**5.2 Conclusions and Recommendations**

Based on the summary statistics (e.g., mean, median, and 95% confidence interval) from the available data, (b) (4) there was no sign of bone age acceleration when compared to chronological age after 6 months.

However, the data were confounded by a number of factors such as free dose titration scheme, no concurrent control group, possible incomplete washout from previous testosterone treatment, very heterogeneous patient population, wide range of serum total testosterone concentration, other than the intended pump-head type for delivering drug, and possible measurement errors for some bone age data. In addition, for the low dose evaluation, only about 50% of the data were available and the number of subjects with excessive changes from baseline in serum total testosterone concentration and bone age concerns the medical reviewer. Moreover, the data from subjects receiving the (b) (4) dose from the (b) (4) pump-head (b) (4) show a mean/median increase from baseline in serum total testosterone concentration at Week 1. The data further suggest that there were improved serum total testosterone concentrations at Months 1-6 and Tanner pubic hair stages at Month 6 in subjects who used the (b) (4) dose from the (b) (4) pump-head.

(b) (4)

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## 6. Appendix I

Subjects with a change from baseline > 200 ng/dL in serum total testosterone concentration at Week 1

| Pt. No. | Disease | Naive | Testo. Volume | Finished Study | Final Dose | Dose Tertile | Testo. Baseline | Testo. Week 1 | Change Week 1 |
|---|---|---|---|---|---|---|---|---|---|
| 1161 | Hypo | Yes | 2 | No | 2.5 | Mid | 3.0 | 280 | 277.0 |
| 1243 | Hypo | Yes | . | No | 0.5 | Low | 9.9 | 297 | 287.1 |
| 1234 | Hypo | No | 0 | Yes | 0.5 | Low | 26.0 | 279 | 253.2 |
| 1022 | Hypo | No | 5 | Yes | 1.5 | High | 60.0 | 290 | 230.0 |
| 1025 | Hypo | No | 3 | Yes | 0.5 | Low | 354.0 | 674 | 320.0 |
| 1122 | Hypo | No | 4 | Yes | 1.0 | Mid | 225.0 | 555 | 330.0 |
| 1221 | Hypo | No | 1 | Yes | 1.5 | Mid | 6.8 | 540 | 533.2 |
| 1103 | CDGP | Yes | 8 | Yes | 0.5 | Low | 29.0 | 335 | 306.0 |
| 1027 | CDGP | No | 12 | Yes | 0.5 | Low | 277.0 | 523 | 246.0 |

All subjects here were from the UMD-01-090 trial.

| Pt. No. | Tanner Baseline | Tanner Month 6 | Bone Age Baseline | Bone Age Month 6 | Bone Age Advancement in Ratio |
|---|---|---|---|---|---|
| 1161 | II | . | 15.0 | . | . |
| 1243 | II | . | 13.0 | . | . |
| 1234 | II | . | 13.5 | . | . |
| 1022 | IV | IV | 13.5 | 13.5 | 0 |
| 1025 | IV | IV | . | . | . |
| 1122 | IV | V | . | . | . |
| 1221 | IV | IV | . | . | . |
| 1103 | I | II | 13.0 | 13.5 | 1.1 |
| 1027 | V | V | 16.0 | 17.0 | 2.1 |

All subjects here were from the UMD-01-090 trial.

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/s/
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