Study Number: IP157-001 (Parts C & D)

Title of Study: A Two-Arm, Open-Label, Randomized, Multi-Center Pharmacokinetic and Long-Term Safety Study of Intramuscular Injections of 750 mg and 1000 mg Testosterone Undecanoate in Hypogonadal Men (This report represents Part C [single-arm study] and a subset of patients from Part C who crossed over into Part D.)

Principal Investigator: One Principal Investigator per investigative center

Study Center(s): Multicenter study of 31 investigative centers in the United States

Publications (Reference): Wang C, Harnett M, Dobs AS, Swerdloff RS. Pharmacokinetics and safety of long-acting testosterone undecanoate injections in hypogonadal men: an 84-week phase III clinical trial. *J Androl*. 2010;31(5):457-465.

Studied Period (Years):	**Phase of Development:** Phase 3
Date first patient enrolled (Part C): 19-Mar-2007	
Date last patient completed (Part C): 12-Jan-2009	

Objectives:

The study was conducted in 5 parts (Parts A, B, C, C2, and D). Enrollment into each part was independent, except for Part D, where subsets of Part A and Part C patients crossed over into Part D. Results for Parts A, B, and C2 are reported separately. The Part D safety data are presented in the Part A and Part C reports, respectively. In addition, data for the initial period for Part A and Part C (referred to as Stage 1) have been summarized in interim CSRs and have been previously submitted. This CSR describes the objectives of Parts C and D and presents results for data collected through all visits in Part C and data collected from Part C patients who crossed over into Part D of the study.

Part C (Intramuscular Injections):

Primary Objective (Part C):

- The primary objective for Part C of the study was to evaluate the pharmacokinetics of testosterone from Testosterone Undecanoate (TU) 750 mg given intramuscularly at baseline, at 4 weeks, and then every 10 weeks thereafter, over the 10-week interval following the 3rd injection, via multiple measurements of serum total testosterone, in up to approximately 130 hypogonadal men.

Secondary Objective (Part C):

- To evaluate the pharmacokinetics of testosterone from TU 750 mg given intramuscularly at baseline, at 4 weeks, and then every 10 weeks thereafter, over the 10-week interval following the 4th injection, via multiple measurements of serum total testosterone.
- To compare serum levels of dihydrotestosterone (DHT), estradiol, and sex hormone binding globulin (SHBG) to simultaneous levels of serum total testosterone over the 3rd injection interval.
- To evaluate safety in patients treated with TU 750 mg given intramuscularly at baseline, at 4 weeks, and then every 10 weeks thereafter, through up to 9 injections in hypogonadal men.

Part D (Subcutaneous Injections):

Part D was exploratory and was intended to compare the pharmacokinetics of testosterone from subcutaneous administration of TU in subsets of patients from Parts A and C of the study. Only the objectives, assessments, and data pertaining to the subset of patients from Part C who crossed over into Part D are included in this CSR. The subset of patients from Part A is described in the Part A abbreviated CSR.

Primary Objective (Part D):

- The primary objective of Part D was to evaluate the pharmacokinetics of testosterone from

TU 750 mg given subcutaneously at the next consecutive dosing interval injection (ie, when patients crossed over into Part D to receive subcutaneous injection at the next consecutive dosing interval), via multiple measurements of serum total testosterone, in approximately 20 patients from Part C. (For the subset of Part C patients who crossed into Part D, serum total testosterone levels were measured, but the pharmacokinetics of testosterone from TU 750 mg given subcutaneously were not evaluated.)

Secondary Objective (Part D):

- The secondary objective of Part D was to evaluate the safety and tolerability of subcutaneous TU injections given in 2 divided doses of 1.5 mL each for 750 mg total in each remaining dosing interval period (ie, remaining dosing interval in the study).

Methodology:

Part C (Intramuscular Injections):

Part C was designed as a multicenter, single-arm, open-label study with a planned enrollment of up to 130 patients. The total exposure for individual patients was up to 9 injections (approximately 20 months/84 weeks). The treatment arm was:

- TU 750 mg in 3 mL (250 mg/mL) oily solution, injected intramuscularly at baseline, at 4 weeks and then every 10 weeks thereafter.

All patients underwent intensive pharmacokinetic (IPK) assessments during the 3rd and 4th injection intervals. Patients also underwent a trough (immediately prior to injection) pharmacokinetic (PK) assessment at each 10-week dosing interval visit through Injection 8 (changes were made to the PK sample collection per Protocol Amendment 10). Safety was assessed throughout the study (ie, up to 9 injections [up to approximately 20 months/84 weeks]).

Part C had 4 defined periods: Screening, Baseline, Stage 1, and Stage 2:

- Screening: Approximately 1- to 5-week screening period (washout from select prior testosterone replacement therapies could extend this period for some patients).
- Baseline: Final prestudy measurements were captured and patients were enrolled.
- Stage 1 (The first 3 injections): This included the first injection at the baseline visit. The end of Stage 1 was the 4th injection visit. The Stage 1 analysis included only data through the 4th injection visit and the analysis results were presented separately in a Part C Stage 1 CSR.
- Stage 2 (Long-term safety extension): The study continued following the 4th injection visit, with up to 5 additional injections (at 10-week intervals) during an extended treatment phase. The Stage 2 analysis included all patients and all safety data.

Part D (Subcutaneous Injections):

Approximately 20 patients from Part C were to cross over into Part D and were to receive subcutaneous injections (3 mL in divided doses [1.5 mL, each]) of TU 750 mg, as tolerated, for the remainder of their study participation. Patients received their first subcutaneous injection with their 8th injection in Part D.

Number of Patients (Planned and Analyzed):

Part C: Planned: 130; Enrolled: 130; Total Patient Sample: 130; PK Population: 117; Steady-State PK Population: 104; Long-Term PK Population: 98

Part D: Planned enrollment from Part C: 20; Enrolled from Part C: 21

Diagnosis and Main Criteria for Inclusion: Male with primary or secondary hypogonadism at least 18 years of age with morning screening serum testosterone concentration <300 ng/dL. If receiving endocrine replacement hormones (eg, thyroid), antihypertensives, lipid lowering agents, antidepressants, or anxiolytic medications, the dose must be stable for at least 28 days prior to the first administration of the study drug.

Test Product, Dose and Mode of Administration, Batch Number:

Part C: Intramuscular injections of TU 750 mg administered slowly into the buttock (deep gluteal muscle) at baseline, at 4 weeks, and then every 10 weeks thereafter for up to 9 injections. Each dose comprised 3 mL of TU in oily solution.

Part D: Each subcutaneous dose comprised of 3 mL of TU 750 mg in oily solution and was administered into the left and right side of the abdomen in 2 equally divided doses of 1.5 mL each (375 mg/individual injection for a total of 750 mg). Patients received their first subcutaneous injection (in place of the intramuscular injection) with their 8th injection of TU 750 mg; but if not tolerated well, could return back to the intramuscular injection route with their 9th injection.

Lot Numbers: N00501, N01001

Duration of Treatment: Up to 9 injections (intramuscular or subcutaneous) of TU 750 mg (up to 20 months/84 weeks).

Reference Therapy, Dose and Mode of Administration, Batch Number: None

Criteria for Evaluation:

Part C (Intramuscular Injections):

Pharmacokinetics (Part C):

PK parameters $AUC_{0\text{-}70days}$, C_{avg}, C_{max}, C_{trough}, T_{max}, T_{last} were derived for each IPK interval following the 3rd and 4th injection.

Trough-level (immediately prior to injection) PK assessments were performed at every injection visit through injection 8 or at early discontinuation from Part C.

Efficacy (Part C):

The primary hypothesis in Part C of the study was:

- H_o: TU 750 mg given intramuscularly at baseline, at 4 weeks, and then every 10 weeks thereafter during the 3rd injection interval does not provide adequate testosterone replacement in hypogonadal men.
- H_a: TU 750 mg given intramuscularly at baseline, at 4 weeks, and then every 10 weeks thereafter during the 3rd injection interval does provide adequate testosterone replacement in hypogonadal men.

A patient was considered a responder if his serum total testosterone average concentration (C_{avg}) was in the normal range (300 to 1000 ng/dL), where C_{avg} was derived as the area under the concentration-time curve (AUC) of the dose interval divided by the duration of the dosing interval, ie, $C_{avg} = AUC_{0\text{-}70\ days}/70$ days.

A patient was considered NOT a responder if his C_{avg} was either <300 ng/dL or >1000 ng/dL.

In order to reject the primary PK null hypothesis in favor of the alternative hypothesis, the lower bound of the 2-sided 95% confidence interval (CI) about the primary efficacy variable must be no lower than 65%, and the point estimate for the primary efficacy variable must be at least 75%.

In other words, where ρ=observed proportion, the following 2 criteria must be met in order to reject the null hypothesis H_o in favor of the alternative hypothesis H_a

- $\rho * 100 \geq 75\%$, and;
- $\left(\rho - 1.96 * \sqrt{\frac{\rho(1-\rho)}{n}}\right) * 100 \geq 65\%$

The time period for assessment of the primary efficacy outcome was the post 3rd injection interval: $C_{avg} = AUC_{0\text{-}70\ days}/70$ days.

The secondary hypothesis in Part C of the study was:

- H_o: TU 750 mg given intramuscularly at baseline, at 4 weeks, and then every 10 weeks thereafter during the 3rd injection interval does result in excessively high serum total testosterone values in hypogonadal men.
- H_a: TU 750 mg given intramuscularly at baseline, at 4 weeks, and then every 10 weeks thereafter during the 3rd injection interval does not result in excessively high serum total testosterone values in hypogonadal men.

The time period for assessment of this secondary outcome was the post 3rd injection interval (Weeks 14 to 24).

The secondary hypothesis was tested as summarized below:

Serum Total Testosterone Maximum Concentration (C_{max}) Observed During the 3rd Injection Interval	**Criteria for Success**	**Not Meeting the Criteria for Success**
≤1500 g/dL	≥85% of Patients	<85% of Patients
1800-2500 ng/dL	≤5% of Patients	>5% of Patients
>2500 ng/dL	No Patients	At least 1 patient

All 3 criteria must be met in order to reject the null hypothesis in favor of the alternative hypothesis. If any of the 3 criteria does not meet its Criteria for Success, the null hypothesis cannot be rejected.

Similar hypothesis testing was applied to data collected during the 4th injection interval (Weeks 24 to 34).

Additional Secondary Efficacy Outcomes in Part C of the Study:

Based on Pharmacokinetic Data:

- The proportion of patients with serum total testosterone concentration values falling below 300 ng/dL at any time during the 3rd injection interval.
- The time to first observation of serum total testosterone value below 300 ng/dL during the 3rd injection interval.
- "Clinical Success": This was defined based on C_{avg} and the Day 70 concentration (C_{trough}) of serum total testosterone during the 3rd injection interval. Patients were classified as "Clinical Success" if both their C_{avg} and C_{trough} values fell within the normal range of 300 to 1000 ng/dL.
- Steady-state assessment of serum total testosterone concentrations during the 4th injection interval.
- Serum total testosterone maximum concentration (C_{max}).

Based on Clinical Symptomatology:

- Male-Patient Global Assessment (M-PGA):
  - Proportion of patients for each M-PGA category
  - Correlation (Pearson coefficients) of each M-PGA category with serum total testosterone C_{max}, C_{avg}, and C_{trough} on Day 0 and Day 21 of the 3rd injection interval
- Body Weight and Body Mass Index (BMI)
  - Changes in body weight and BMI from pretreatment to 4th injection visit
  - Correlation (Pearson coefficients) of changes in body weight and BMI from pretreatment to 4th injection visit with serum total testosterone C_{max}, C_{avg}, and C_{trough}

Part D (Subcutaneous Injections):

Pharmacokinetics (Part D):

IPK assessments were to be performed at the first subcutaneous injection dosing interval; a trough-level PK assessment was performed at the initiation of the Part D single subcutaneous injection dosing interval.

Efficacy (Part D):

A Patient Satisfaction Questionnaire (PSQ) was completed to assess patient tolerability and preference of injection route (intramuscular or subcutaneous).

Part C and Part D:

Safety (Part C and Part D):

Safety evaluation was based on adverse events (AEs) (including serious adverse events [SAEs] and AEs of special interest [injection site reactions and immediate post-injection reactions]); clinical laboratory tests (hematology, chemistry, urinalysis); sex hormones (DHT, estradiol, free testosterone [measured and calculated], and SHBG); vital signs, body weight and BMI; electrocardiogram (ECG); prostate specific antigen (PSA) levels; digital rectal examinations (DREs); and local tolerability of the injection site.

Statistical Methods:

Pharmacokinetics:

Pharmacokinetics was assessed for the following PK populations:

- PK population: patients who had a minimum of 4 serum total testosterone concentration values within the 3rd injection dosing interval.
- Steady State PK Population: patients in the PK population with non-missing 4th and 5th injection serum total testosterone concentrations.
- Long-term PK Population: patients in the Steady State PK population with a non-missing 8th injection serum total testosterone concentration.

PK parameters were estimated from the serum concentration data using noncompartmental methods within each patient. PK parameters were summarized using descriptive statistics (including number of patients (N), arithmetic mean, standard deviation (SD), coefficient of variation (CV%), median, minimum, maximum, and geometric mean).

Subgroup analyses of serum total testosterone PK parameters during the 3rd injection interval were performed by age (<45, 45-65, >65 years), race (white, black, other), baseline weight (<100 kg, ≥100 kg), baseline BMI (<26 kg/m^2, 26-30 kg/m^2, >30 kg/m^2), prior testosterone replacement therapy (TRT) use (prior TRT, no prior TRT), and preinjection 3 (ie, immediately prior to 3rd injection) serum total testosterone level (<300 ng/dL, 300-450 ng/dL, >450 ng/dL).

Efficacy:

Efficacy was assessed for the PK population. The PK population was defined as: all patients who had a minimum of 4 serum total testosterone concentration values within the 3rd injection dosing interval.

Descriptive statistics or frequency distributions were calculated for the primary and secondary efficacy data. M-PGA responses were tabulated by original responses and by a collapsed set of categories. For the first 4 questions, the proportion of patients with improvement (eg, very much improved, much improved, or minimally improved) were collapsed into a single category, while proportion of the corresponding group with worsening (very much worse, much worse, or minimally worse) were collapsed into a second category. 'No change' responses comprised the third category. Similar categories were to be derived for the PSQ (the responses to the PSQ were listed by patient). Two-sided 95% CIs were constructed for the PK primary and secondary efficacy outcomes.

Safety:

Safety was assessed for the Total Patient Sample. The Total Patient sample was defined as: all patients who were enrolled and dosed with at least 1 injection of study medication.

Safety data from Parts C and D (collected through 9 injections during approximately a 20 month/ 84 week period) were combined and analyzed, regardless of route of administration, with the exception of local injection site tolerability, which was analyzed separately for each part of the study.

Treatment-emergent adverse events (TEAEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 9.1. The occurrence of TEAEs was summarized by system organ class (SOC) and preferred term for all TEAEs, TEAEs by severity, and treatment-related TEAEs. Treatment-emergent SAEs (including deaths) and TEAEs leading to discontinuation of study drug were listed separately and described in patient narratives. Sex hormone data were summarized by descriptive statistics; concentration-time-plots were also produced. Clinical laboratory data, vital signs, and ECG data were summarized by descriptive statistics or frequency distributions. Potentially clinically significant (PCS) values are presented for clinical laboratory test results, vital signs, ECG, and PSA.

Subgroup analyses of the incidence of TEAEs were performed by age, race, baseline weight, baseline BMI, and 3rd injection interval C_{max} (<1500 ng/dL, ≥1500 ng/dL).

SUMMARY:

A total of 130 hypogonadal men were enrolled in Part C and 93 patients (71.5%) completed the study. Reasons for early discontinuation were: AEs (15 patients [11.5%]), withdrew consent (10 patients [7.7%]), non-compliance (5 patients [3.8%]), lost to follow-up (3 patients [2.3%]), and other reasons (4 patients [3.1%]).

The mean age of patients was 54.2 years (range: 24 to 75 years), and the majority (74.6%) were white. Baseline mean weight was 101.2 kg (range: 59.0 to 158.0 kg), mean height was 177.9 cm (range: 152.0 to 193.0 cm), and mean BMI was 32.0 kg/m^2 (range: 17 to 51.0 kg/m^2). The mean serum total testosterone concentration at screening was 214.7 ng/dL (range: 24.0 to 299.0 ng/dL). Use of at least 1 prior TRT medication was reported by 81 patients (62.3%); the most common were AndroGel (36 patients [27.7%]), Testim (22 patients [16.9%]), and Depo-Testosterone (21 patients [16.2%]).

Efficacy Results:

The evaluation of the efficacy of intramuscular injection of TU 750 mg was based primarily on PK and clinical symptomatology assessments during the 3rd injection interval. The primary analysis was based on the PK Population consisting of 117 patients (90.0%) who received intramuscular injections of TU.

TU 750 mg given intramuscularly at baseline, at 4 weeks, then at 10-week intervals thereafter provided adequate TRT as measured by C_{avg}.

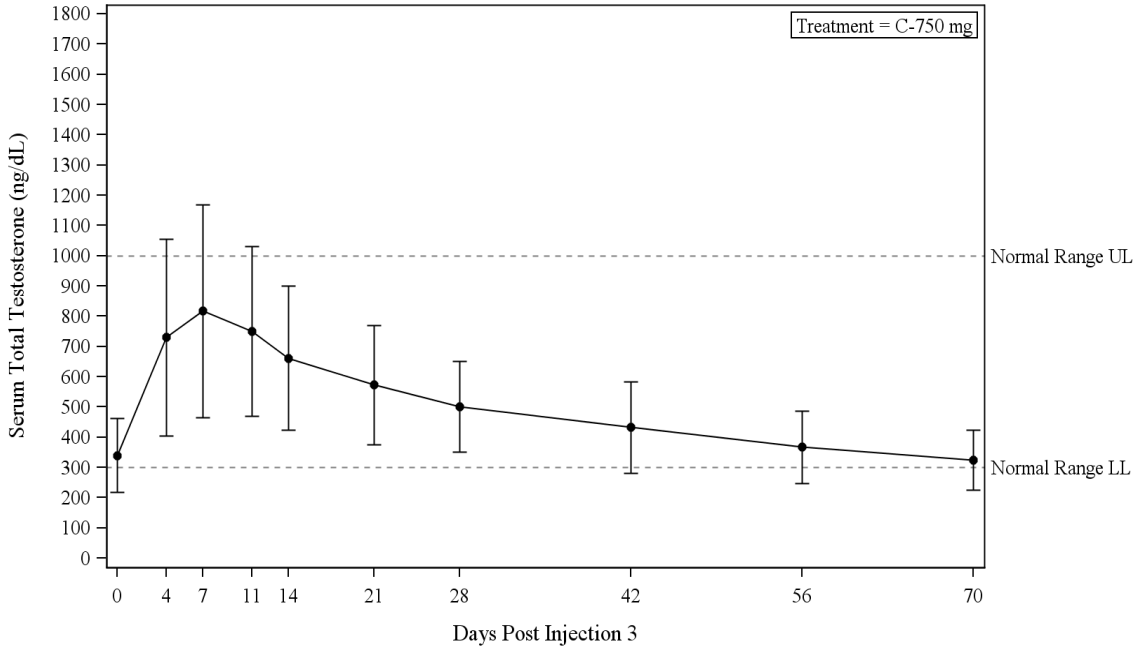
Number (%) of Patients (and 2-Sided 95% CI) Meeting Serum Total Testosterone C_{avg} Criteria for a Responder During the 3rd Injection Interval, Pharmacokinetic Population

	C-750 mg (N=117)	
Serum Total Testosterone C_{avg} Criteria	**N (%)**	**95% CI**
Responder		
C_{avg} within 300-1000 ng/dL	110 (94.0%)	89.7%-98.3%
Not a Responder		
C_{avg} <300 ng/dL	6 (5.1%)	1.1%-9.1%
C_{avg} >1000 ng/dL	1 (0.9%)	0.0%-2.5%

Note: Percentages based on non-missing data. C-750 mg refers to TU 750 mg.

At all time points measured during the 3rd injection interval, the mean serum total testosterone concentrations remained within the normal range (300 to 1000 ng/dL).

Mean (SD) Serum Total Testosterone Concentrations (ng/dL) Resulting from the 3rd Intramuscular Injection of Testosterone Undecanoate, Pharmacokinetic Population



Note: C-750 mg refers to TU 750 mg.

Serum total testosterone PK parameters during the 3rd injection interval are shown in the table below.

Descriptive Statistics for the 3rd Injection Serum Total Testosterone (ng/dL) Pharmacokinetic Parameters, Pharmacokinetic Population

	C-750 mg (N=117)							
	N	**Mean**	**Std. Dev**	**Min**	**Median**	**Max**	**%CV**	**Geometric Mean**
$AUC_{0\text{-}70days}$ (days·ng/dL)	117	34645.6	9902.45	13755.1	33342.2	70016.9	28.6	33263.6
C_{trough} (ng/dL)	117	323.5	99.11	138.2	316.9	611.1	30.6	309.0
C_{max} (ng/dL)	117	890.6	345.11	311.0	813.6	1758.5	38.8	826.8
T_{max} (days)	117	10.0	7.11	4.0	7.0	42.0	71.1	8.4
C_{avg} (ng/dL)	117	494.9	141.46	196.5	476.3	1000.2	28.6	475.2

$AUC_{0\text{-}70days}$=Area under curve from Day 0 through Day 70; C_{avg}=Average concentration; C_{max}=Maximum concentration; C_{trough}=Day 70 concentration; CV=Coefficient of variation; T_{max}=Time of maximum concentration

Note: C-750 mg refers to TU 750 mg.

The C_{max} criteria for success were met, demonstrating that TU 750 mg given intramuscularly at baseline, at 4 weeks, then at 10-week intervals thereafter does not result in excessively high serum total testosterone values in hypogonadal men.

Number (%) of Patients (and 2-Sided 95% CI) Meeting Serum Total Testosterone C_{max} Criteria for Success During the 3rd Injection Interval, Pharmacokinetic Population

Serum Total Testosterone C_{max} Observed During 3rd Injection Interval	Criteria for Success[a]	C-750 mg (N=117)	
		N (%)	95% CI
≤1500 ng/dL	≥85% of Patients	108 (92.3%)	87.5%-97.1%
1800-2500 ng/dL	≤5% of patients	0	
>2500 ng/dL	No Patients	0	

[a] All 3 criteria must be met in order to reject the null hypothesis in favor of the alternate hypothesis. If any of the 3 criteria does not meet its Criteria for Success, the null hypothesis cannot be rejected.

Note: Percentages are based on non-missing data. C-750 mg refers to TU 750 mg.

Patients were classified as "clinical success" if both their C_{avg} and C_{trough} values fell within the normal range of 300 to 1000 ng/dL. Based on these criteria, 63 patients (53.8%) achieved clinical success. The median time to first observation of serum total testosterone concentration <300 ng/dL was 56 days.

There were no clinically meaningful changes from baseline in body weight and BMI during the 3rd injection interval.

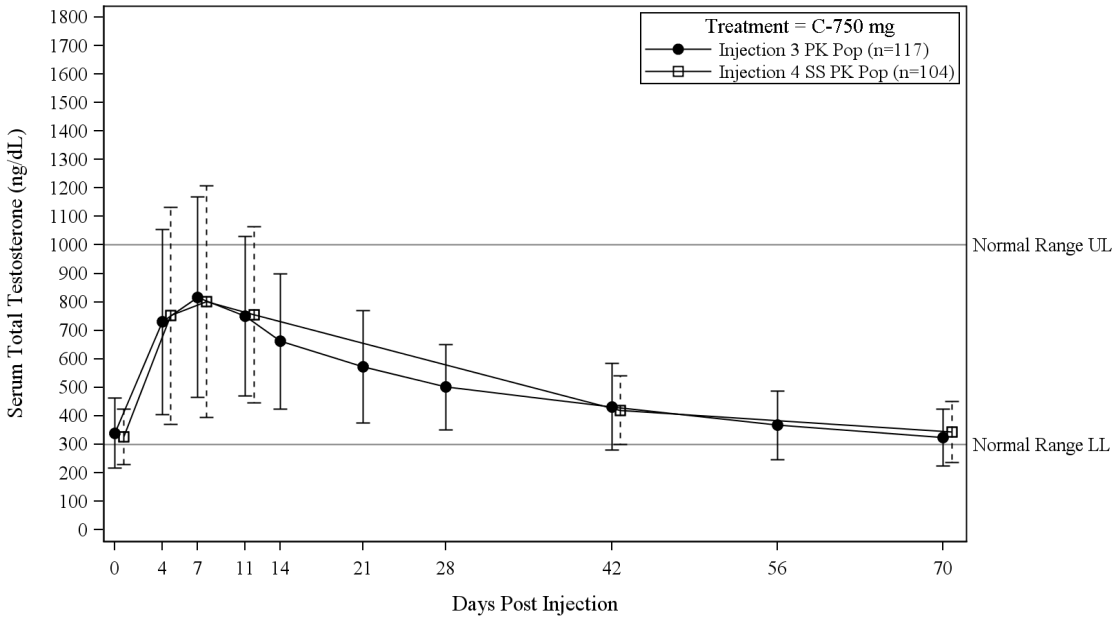
As early as Day 21 of the 3rd injection interval, at least 80% of patients reported improvements in symptoms associated with hypogonadism such as confidence/self-esteem, sexual performance, moods/behavior, and overall feeling of well-being; and 92.2% reported satisfaction with the study treatment.

The mean C_{avg} during the 4th injection interval was 514.3 ng/dL and was within the normal range (300 to 1000 ng/dL), with 100 patients (96.2% [2-sided 95% CI, 92.5%-99.8%]) achieving this range. The C_{max} criteria for success were met during the 4th injection interval; 96 patients (92.3% [2-sided 95% CI, 87.2%- 97.4%]) had a serum total testosterone C_{max} value ≤1500 ng/dL; 4 patients (3.8% [2-sided 95% CI, 0.2%-7.5%]) had a C_{max} value between 1800 and 2500 ng/dL; and no patient had a C_{max} value >2500 ng/dL during the 4th injection interval. The mean C_{max} was 837.6 ng/dL, mean C_{trough} was 342.8 ng/dL, mean $AUC_{0\text{-}70days}$ was 35999.5 days·ng/dL, and median T_{max} was 7 days following the 4th injection. Clinical success was achieved by 65 patients (62.5%) during the 4th injection interval. The median time to first observation of serum total testosterone concentration <300 ng/dL was 70 days.

Steady-state analysis was performed for patients with non-missing 4th and 5th injection serum total testosterone concentrations. A comparison of the group-mean serum total testosterone concentration-time profiles resulting from the 3rd and the 4th intramuscular injections of TU 750 mg demonstrate that the mean total testosterone concentrations at each of the time points measured were similar between the 2 injection intervals, suggesting that steady state was attained by the 3rd intramuscular injection.

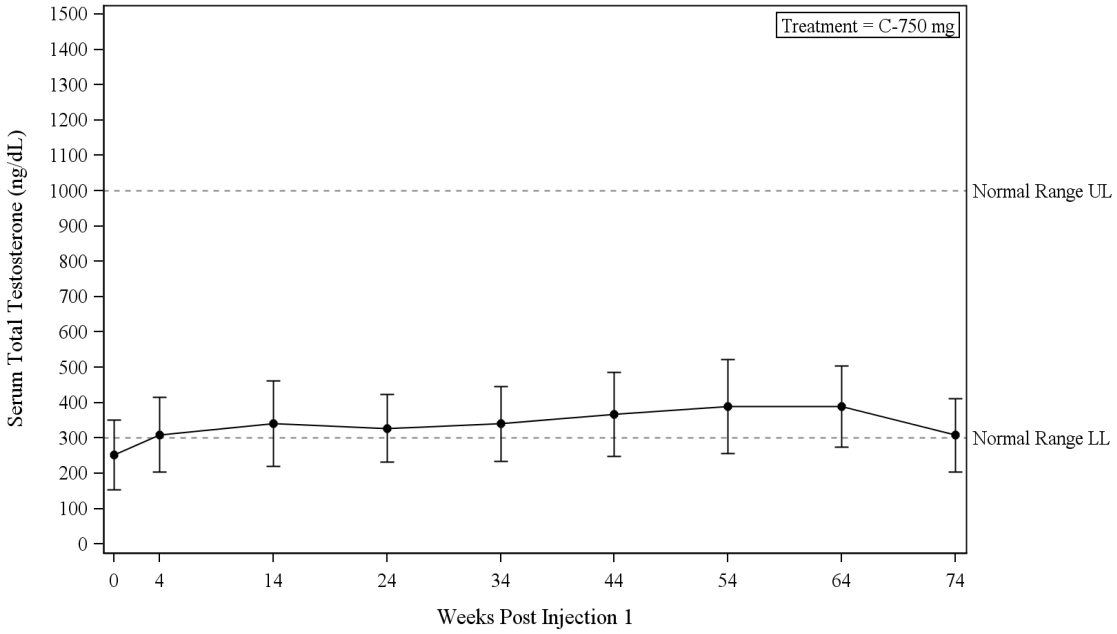
The trough concentrations of serum total testosterone were within the normal range at Week 4 post Injection 1 and remained within the normal range through Week 74.

Comparison of Serum Total Testosterone Concentrations (ng/dL) During the 3rd and 4th Injection Intervals, Pharmacokinetic and Steady-State Pharmacokinetic Populations



Note: C-750 mg refers to TU 750 mg.

Mean (SD) Serum Total Testosterone Concentrations (ng/dL) at Trough Time Points Through the 9th Injection Week (Week 74), Long-Term Pharmacokinetic Population



Note: C-750 mg refers to TU 750 mg

The mean trough concentrations of serum total testosterone after the first injection ranged from 307.8 to 389.8 ng/dL and were within the normal range (300 to 1000 ng/dL).

Adequate TRT was provided by intramuscular injections of TU 750 mg regardless of age, race, BMI, and prior TRT use.

The primary efficacy results based on the 3rd injection interval presented in this CSR are similar to those presented in the Part C (Stage 1) CSR.

Safety Results:

The mean duration of TU exposure was 498.9 days (range: 71 to 617 days), the mean number of injections received was 7.7 (range: 1 to 9) and the majority of patients (74.6%) received 9 injections.

There were no unexpected, safety-related concerns in this study. At least 1 TEAE was experienced by 94 patients (72.31%). The most common TEAEs were fatigue, increased prostatic specific antigen, and prostatitis (each reported by 10 patients [7.69%]). Most TEAEs were attributable to infections and infestations (40 patients [30.77%]), general disorders and administration site conditions (32 patients [24.62%]), and musculoskeletal and connective tissue disorders (28 patients [21.54%]). Treatment-related TEAEs were experienced by 49 patients (37.69%). The most common treatment-related events were acne (8 patients [6.15%]), injection site pain (7 patients [5.38%]), increased prostatic specific antigen (7 patients [5.38%]), and fatigue (6 patients [4.62%]).

A total of 21 patients (16.15%) experienced treatment-emergent SAEs during the study. Treatment-emergent SAEs experienced by 2 or more patients were spinal column stenosis (3 patients [2.31%]), prostate cancer (3 patients [2.31%]), and myocardial infarction (2 patients [1.54%]). Treatment-emergent SAEs that were possibly related to study drug were experienced by 3 patients (2.31%): prostate cancer (2 patients [1.54%]) and deep vein thrombosis (1 patient [0.77%]). Two (2) patients died from treatment-emergent SAEs of cardiac arrest and myocardial infarction, considered by the Investigator as remotely related or definitely not related to study drug.

TEAEs which led to discontinuation of study drug were experienced by 15 patients (11.54%). The most common events leading to discontinuation of study drug were prostate cancer (3 patients [2.31%]) and myocardial infarction, increased hematocrit, and mood swings, each reported by 2 patients (1.54%). Treatment-related TEAEs which led to discontinuation of study drug were experienced by 7 patients (5.38%); the most common treatment-related event leading to discontinuation of study drug was prostate cancer (2 patients [1.54%]). There were no TEAEs that led to temporary interruption of study drug.

One (1) patient experienced an immediate post-injection reaction of pulmonary oil microembolism (POME) (cough) following an intramuscular injection with TU. The patient experienced a mild and non-serious coughing fit lasting ~10 minutes immediately following his 3rd intramuscular injection. The Investigator reported the cough was nonproductive and that the patient experienced no wheezing or difficulty breathing; no intervention was given, and the patient recovered prior to leaving the office. The patient received a total of 9 intramuscular injections during the study. Other than the 3rd injection, there were no other cough events associated with any injection.

The most common possibly related injection site reaction was injection site pain, which occurred in 5.38% of patients.

The mean changes from baseline in clinical laboratory parameters, vital signs, and BMI were generally minor in magnitude and were not clinically meaningful. Shift from a no PCS value at baseline to a low or a high post-baseline PCS abnormal value occurred in few patients. The incidence for such shifts in the Total Patient Sample for hematology parameters (including erythropoiesis-related parameters such as hematocrit, hemoglobin, and RBCs) ranged from 0.8% to 4.8%; for serum chemistry, FSH, and LH parameters from 0.8% to 3.3%; for fasting lipids from 1.2% to 10.8%; for urinalysis parameters from 0.8% to 2.4%; for vital signs from 1.6% to 8.8%; and for ECG from 5% to 15.8%. The ECG results should be interpreted with caution as very few patients (n=21) had ECG assessments performed during the treatment period or at end of the study.

Changes in sex hormone parameters (DHT, estradiol, free testosterone [measured and calculated], and SHBG) were consistent with expected changes in hypogonadal men receiving TRT. The post-baseline mean serum concentrations of measured and calculated free testosterone, DHT, and estradiol closely paralleled those for total testosterone. The post-baseline mean ratios of each of these hormones to serum

total testosterone remained virtually constant at each post-baseline visit; the change in post-baseline mean ratios ranged from -0.0221 to 0.0128 for DHT:total testosterone, 0.0003 to 0.0028 for estradiol:total testosterone, 0.0005 to 0.0135 for measured free testosterone: total testosterone, and -0.0006 to 0.0061 for calculated free testosterone:total testosterone. The post-baseline mean serum concentrations of SHBG were virtually constant at each post-baseline visit. The post-baseline mean ratios of SHBG:total testosterone dropped slightly on Day 4 after the injection and then gradually increased after Day 7 towards the mean ratio for the Day 0 of the interval; the post-baseline mean SHBG:total testosterone ratios ranged from -2.9486 to -1.0779. Shift from a no PCS value at baseline to a high post-baseline PCS value was observed mostly for estradiol. The incidence for such shifts in the Total Patient Sample for total testosterone was 0.8% of patients, for estradiol was 20.9% of patients, and for estradiol:total testosterone ratio was 1.7% of patients.

Increased PSA has been observed in hypogonadal men receiving TRT. As expected, slight mean increases from baseline were seen at each post-baseline time point measured; however, the magnitude of the mean increase remained virtually constant over time. Shift from a no PCS value at baseline to a high (>4 ng/mL) post-baseline PCS value occurred in 14 patients (10.9%). Abnormal findings during prostate examination (via DRE) were seen in 22 patients (16.9%) at any time after the first injection, including enlargement (19 patients [86.4%]), hardening (3 patients [13.6%]), and other abnormalities such as softness, tenderness, firmness, or asymmetry in the prostate (7 patients [31.8%]).

Local tolerability at the intramuscular injection site was rated for pain, erythema/redness, swelling, and tenderness. Each symptom was rated as none or mild for at least 97% of patients at each injection visit and end of study. No intramuscular injection site symptom was rated as severe or life-threatening.

Age, race, BMI, and prior TRT use appeared to have minimal or no consistent effect on the nature and incidence of TEAEs. Analysis of the safety data by 3rd injection interval C_{max} subgroup did not show any consistent and clinically meaningful differences between the subgroups for TEAEs, serum chemistry, FSH, LH, and PSA; however, meaningful interpretation of the data was limited by the imbalance in the sample sizes between the 2 subgroups (n=9 for C_{max} ≥1500 ng/dL versus n=108 for C_{max} <1500 ng/dL).