

1 **Pharmacokinetics and Safety of Long-Acting Testosterone Undecanoate Injections**  
2 **in Hypogonadal Men: An 84 Week Phase III Clinical Trial**

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12 **Running Title:** Treatment with Testosterone Undecanoate

13 **Key words:** Male hypogonadism, Testosterone Replacement, Sex Hormone levels, Long  
14 acting testosterone injections

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16 **Precis:** Testosterone undecanoate injections given at 10 week intervals to hypogonadal  
17 men result in serum testosterone, dihydrotestosterone and estradiol levels within the adult  
18 male range in most men, and demonstrated good tolerability and safety.

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24 **ABSTRACT**

25 Currently available testosterone (T) injections in the United States are administered at 2  
26 to 3 weekly intervals. Less frequent injections with favorable serum T pharmacokinetics  
27 would benefit hypogonadal men. The objective of this study is to assess the  
28 pharmacokinetics of long-acting testosterone undecanoate (TU) IM injection in  
29 hypogonadal men. An unblinded, multicenter, phase 3 clinical trial was conducted in 31  
30 academic centers and contract research organizations. 130 males over 18 years of age  
31 with serum total T < 300 ng/dL were enrolled and received TU 750 mg injections at week  
32 0, 4, and every 10 weeks thereafter for 9 injections over 84 weeks. The main outcome  
33 variables were serum total T, free T, dihydrotestosterone (DHT), estradiol (E<sub>2</sub>) levels and  
34 safety parameters. After the first injection patients maintained average trough T  
35 concentrations in the adult male range (300-1000 ng/dL or 10.4-34.7 nmol/L) before each  
36 injection and at multiple time points measured after the third and fourth injections. Serum  
37 free T, DHT and E<sub>2</sub> levels and their ratios to serum T remained relatively consistent once  
38 steady-state was attained. TU injections were generally well tolerated with safety profiles  
39 similar to other T replacement. We conclude that hypogonadal patients treated for 84  
40 weeks with TU 750 mg IM injection every 10 wk demonstrated average concentrations of  
41 T, its metabolites (DHT and E<sub>2</sub>), as well as ratios DHT:T and E<sub>2</sub>:T, within the adult male  
42 reference range at all time points measured. TU injections would be an acceptable  
43 alternative to the currently available 2-3 weekly injectables.

44

45 ***Introduction***

46 The currently available replacement for men with testosterone (T) deficiency in the  
47 United States includes: two bi-weekly injection options (T enanthate and cypionate); the  
48 daily transdermal testosterone patches and gels; and a buccal delivery system (Behre et  
49 al, 2004; Nieschlag, 2006; Qoubaitary et al, 2005). The buccal delivery system requires  
50 twice a day application; some men cannot tolerate the gel tablet applied on their gums.  
51 The transdermal patches are associated with significant local skin irritation. The gels are  
52 an open system where the skin irritation is minimal but there is a potential for transfer of  
53 the T applied on the skin to women and children; this has resulted in labeling that  
54 requires showering or wearing protective clothing before close skin to skin contact. Many  
55 men currently are relying on bi-weekly injectables for T replacement. These preparations  
56 have less favorable pharmacokinetics with high peaks and low troughs and in some men  
57 may produce variations in mood and energy levels and crops of acne after injections  
58 (Snyder et al, 1980; Sokol et al, 1982). However, these injectables are less costly and  
59 have long term safety records. Some patients have been trained to self administer these  
60 injectables, although many patients rely on their health providers to administer the oil-  
61 based injections.

62 Outside the United States, oral T undecanoate capsules have been available for many  
63 years. The twice daily administration of oral TU produced peaks of serum T about five  
64 hours after dosing and serum levels fall to pre-treatment levels in about 8 to 12 hours  
65 (Nieschlag et al, 1975; Skakkebaek et al, 1981). Despite the pharmacokinetics profile,  
66 hypogonadal men report improvement in symptoms and oral TU has long term safety  
67 data (Gooren, 1994). Injectable TU in tea seed oil was first reported to be used as a

68 relatively long acting injectable for hypogonadal men in China where 500 mg of TU was  
69 administered every 4 weeks with serum T levels within the adult range for most  
70 hypogonadal men (Zhang et al, 1998). TU was then reformulated in castor oil and  
71 administered as 1000 mg per IM injection. The injections were generally well tolerated  
72 and multi-dose pharmacokinetics showed that the most hypogonadal men would receive  
73 adequate replacement with physiological ranges of serum T when TU in castor oil was  
74 administered at 6 weeks after the first injection and then followed by every 12 week  
75 injections thereafter (Behre et al, 1999; Nieschlag et al, 1999; Schubert et al, 2004; von  
76 Eckardstein S. et al, 2002). If more frequent injections are administered the trough serum  
77 T levels rose progressively. A 30 week study compared T enanthate with TU injections  
78 and showed that both injectables improved sexual function and mood in hypogonadal  
79 men (Jockenhovel et al, 2009). Longer term study (over 2 years) showed that TU 1000  
80 mg administered IM increased grip strength, decreased waist to hip ratio, serum total and  
81 LDL cholesterol. HDL cholesterol decreased initially but later increased. Hemoglobin  
82 and hematocrit increased in the first 30 weeks and then showed no further increases.  
83 Prostate volume and serum Prostate Specific Antigen (PSA) levels increased in the first  
84 12 months of treatment and then remained stable. The results from these studies indicate  
85 that TU 1000mg administered at week 0, 6 and then every 12 weeks provides  
86 pharmacokinetic profiles of serum T concentrations that would rendered most  
87 hypogonadal men eugonadal (Harle et al, 2005; Jockenhovel et al, 2009; Minnemann et  
88 al, 2007; Minnemann et al, 2008).

89 In our study we recruited 130 hypogonadal men to assess the pharmacokinetics of long-  
90 acting TU administered as 750 mg IM injection at baseline, week 4, and every 10 weeks

91 thereafter for 84 weeks (through 9 injection intervals). The dose of TU 750 mg was  
92 selected based on pharmacokinetics simulation based on prior studies suggesting that  
93 most men would attain serum T concentrations within the adult healthy men reference  
94 range while maintaining Cmax values within the normal range. Serum T data through 24  
95 weeks (first three injections) were previously reported (Morgentaler et al, 2008). The  
96 current study reports safety data (through 9 injection intervals), and testosterone and sex  
97 hormone data through 84 weeks of treatment.

98

## 99 ***Subjects and Methods***

### 100 Study Design

101 This was a multicenter, open-label, US-based study of the efficacy and safety of  
102 treatment with TU 750 mg in 3 mL castor oil (250 mg/mL), with deep IM injections  
103 administered to the gluteus muscle at week 0 (baseline), week 4, and every 10 weeks  
104 thereafter through 9 injections. The TU was manufactured by Bayer Schering (Berlin,  
105 Germany). One hundred thirty subjects from 31 study sites were enrolled to ensure that  
106 least 100 subjects completed the initial 4 injection intervals. A washout period of 28 days  
107 for injectable preparations and 7 days for gels and patches was required for men who had  
108 previously received T preparations. Blood samples for hormone concentrations were  
109 obtained immediately prior to each injection through the 8<sup>th</sup> injection, i.e., 64 week time  
110 point, with more frequent serum samples drawn for hormones at days 4, 7, 11, 14, 21, 28,  
111 42, 56, and 70 after the third injection, and for serum T at days 4, 7, 11, 14, 21 42, and 70  
112 after the fourth injection. Safety outcomes were followed for an additional 20 weeks (2  
113 more injection intervals, through a total of 84 weeks).

114 Blood samples were obtained at baseline and on-treatment time points for PSA,  
115 hematology [including hemoglobin (HGB) and hematocrit (HCT)], serum chemistry, and  
116 sex hormones. Safety outcomes, including digital rectal examinations and vital signs,  
117 were assessed pre-treatment and at on-treatment time points. Adverse events (AEs) were  
118 collected and classified using the MedDRA coding dictionary Version 9.1 (Chantilly,  
119 VA).

### 120 ***Subjects***

121 Eligible subjects were males with primary or secondary hypogonadism who were at least  
122 18 years of age and had a morning (7:00 to 10:00 AM) screening T concentration <300  
123 ng/dL (<10.4 nmol/L, conversion to SI unit X 0.347) . Subjects were excluded if they  
124 had an American Urological Association Prostate Symptom score  $\geq 15$  or significant  
125 prostatic symptoms; a history or suspicion of carcinoma, tumors, or induration of the  
126 prostate or the male mammary gland; screening serum PSA level >4 ng/mL or  
127 hyperplasia of the prostate (size >75 mL as measured by transrectal ultrasonography);  
128 serious psychiatric disease or uncontrolled medical illness ; or use of any sex hormones  
129 or steroidal anabolic drug supplements within 28 days before screening for enrollment or  
130 at any time throughout the study.

### 131 ***Hormone Measurements***

132 Covance Bioanalytical Services (Indianapolis, IN) performed the analyses for serum T  
133 and dihydrotestosterone (DHT). Serum with added deuterium labeled internal standards  
134 (T-d3 and DHT-d4) was extracted from serum by liquid-liquid extraction, and after  
135 evaporation under nitrogen, the residue was reconstituted and analyzed using liquid  
136 chromatography with tandem mass spectrometry. The standard curve range was 20 to

137 5000 ng/dL and 5 to 1250 ng/dL for T and DHT respectively using a serum sample  
138 volume of 0.5 mL. The lower limit of quantification (LLOQ) for T and DHT was 20.0  
139 and 5 ng/dL respectively. Concentrations for calibration standards were within the range  
140 of 85.0% to 115.0% of theoretical values (80.0% to 120.0% at the LLOQ) for both T and  
141 DHT. Serum samples were batched in groups of 50 to 100 per run. The within and  
142 between precision had coefficients of variation of less than 10 % for both T and DHT.  
143 All other hormones were also measured at Covance using validated methods. Estradiol  
144 (E<sub>2</sub>) was assayed using a double-antibody radioimmunoassay using kits from Diagnostic  
145 Products Corporation (Los Angeles, CA). SHBG was assessed via a solid-phase, two-site  
146 chemiluminescent immunometric assay (Immulite 2000, Siemens Healthcare  
147 Diagnostics, Deerfield, IL). Free testosterone concentrations were calculated based on  
148 the results of total testosterone and SHBG using the formula of Vermeulen et al  
149 (Vermeulen et al, 1999).

#### 150 *Statistical Methods*

151 Serum T pharmacokinetics (PK) were considered the primary outcome in this study.  
152 There were several PK analyses performed. For the single-injection interval assessment,  
153 subjects who had a minimum of four testosterone concentration values taken during the  
154 third injection interval (weeks 14 to 24) were included. PK parameters by patient for  
155 testosterone including maximum concentration (C<sub>max</sub>) and average concentration  
156 (C<sub>avg</sub>), time to maximum concentration (T<sub>max</sub>), and area under the curve (AUC) for the  
157 10-week dosing interval were determined using noncompartmental methods, with  
158 nominal (protocol-scheduled) timeunpick44\* from dosing used to estimate these PK  
159 parameters. These patients were also included in an assessment of their PK during the

160 fourth injection interval to assess how consistent the T replacement was from interval to  
161 interval. For the long-term PK assessment, in order to provide a reliable assessment of the  
162 effects within the same group of patients from time point to time point, analysis of the  
163 trough PK concentrations (including other sex hormone assessments) beyond the fourth  
164 injection were performed using those patients with a PK blood sample collected through  
165 the 64-week time point.

166 Safety outcomes were assessed in all patients treated with at least one injection. Change  
167 from pre-treatment to study endpoint (or the early termination endpoint, for those patients  
168 not completing the study) were derived for laboratory (biochemical) parameters,  
169 including hematology, serum chemistry, and lipid profiles. Adverse events (AE) are  
170 reported as overall incidence (number and percent of patients) by body system and by  
171 preferred term (each patient contributed once to incidence counts for each type of AE).

172 WinNonLin<sup>®</sup> Professional (Pharsight Corp., Mountain View, CA) Version 5 was used to  
173 derive pharmacokinetic parameters. SAS<sup>®</sup> (SAS Institute, Inc., Cary, NC) Version 9.1  
174 was used to perform statistical analysis.

## 175 ***Results***

### 176 *Study Subjects Characteristics*

177 Between March 26 and November 8, 2007, 130 subjects were enrolled from 31  
178 investigational centers in the United States; 93 (71.5%) patients completed the 84 week  
179 study, with a total of 1001 injections of TU 750 mg given. Patients entered the study  
180 with mean ( $\pm$ SE) screening serum T of  $214.7 \pm 6.0$  ng/dL ( $7.45 \pm 0.2$  nmol/L). Their  
181 mean age was  $54.2 \pm 0.90$  years, weight  $101.2 \pm 1.58$  Kg, height  $177.9 \pm 0.66$  cm and BMI  
182 of  $32.0 \pm 0.48$  kg/m<sup>2</sup>. The patients were from a mixed racial background: 74.6 % were

183 white, 12.3% African American, 10.8% Hispanic, 2.3% others and none were Asians.  
184 117 (90%) subjects were included in the pharmacokinetic analysis for the third and fourth  
185 injection intervals, while 98 (75.4%) subjects were included in the long-term PK analysis  
186 through the 8<sup>th</sup> injection. Approximately 70% of the patients enrolled in the study were  
187 diagnosed with primary hypogonadism, with the remainder diagnosed with secondary  
188 hypogonadism. Most patients had been diagnosed (with hypogonadism) within the last 5  
189 years prior to their enrollment into the study. Forty-nine patients never received T therapy  
190 before participating in the study (of these patients naïve to testosterone treatment, 60%  
191 had primary and 40% had secondary hypogonadism). For those patients having taken  
192 prior T therapy, 27.7% of patients having taken AndroGel® at least once prior to study  
193 entry. Other T medications used before study entry included Depo-Testosterone® IM  
194 injections (16.2% of patients), Testim® (16.9% of patients) and the rest (< 15 % for each  
195 preparations) included other IM injections, oral androgens or compounded creams or  
196 gels. All prior T medications were washed out prior to initiation of study treatment.

#### 197 *Serum T pharmacokinetics*

198 Figure 1 provides the mean concentrations of serum T in 117 men over the 10 week  
199 interval after the third and fourth injection of TU 750mg. The serum T levels peaked at  
200 about 7 days after each injection. Then serum T levels gradually decreased to reach a  
201 mean serum T level just above 300 ng/dL (10.4 nmol/L) 10 weeks after the injection. The  
202 serum T profiles were identical after the third and fourth injections. The summary of the  
203 key PK parameters after the third TU injection is shown in Table 1. The C<sub>avg</sub>, C<sub>max</sub>,  
204 and C<sub>min</sub> (trough) serum T concentrations were each within the adult male range, while  
205 median T<sub>max</sub> was 7 days after injection (range, 4 to 42 days). The variability of the PK

206 parameters was relatively low, with coefficients of variation for all key PK parameters  $\leq$   
207 40% (Table 1).

#### 208 *Serum Levels of Free T, DHT, E<sub>2</sub> and SHBG*

209 Serum Free T, DHT, E<sub>2</sub> and SHBG concentrations for 10 weeks after the third TU  
210 injection are provided in Figure 2. Serum free T, DHT and E<sub>2</sub> concentration after the  
211 third TU 750mg injection followed the same pattern as serum T with peaks at about 7  
212 days and troughs before the next injection. Serum SHBG showed steady levels which was  
213 not changed throughout the 10 weeks after the TU injection.

#### 214 *Trough concentration of T and other hormones before each of the eight TU injections*

215 Average trough T concentrations remained in the adult male reference range at every  
216 trough time point during treatment measured throughout the 64 weeks of monitoring,  
217 with on-treatment average troughs ranging from 309.6 to 389.8 ng/dL (10.8 to 13.5  
218 nmol/L). Trough values of free T, SHBG, DHT, and E<sub>2</sub> remained relatively consistent  
219 once steady-state was attained after the third injection at week 14 (Figure 3). Similarly,  
220 ratios of the DHT to T and E<sub>2</sub> to T (Figure 4) at each trough time point remained  
221 consistent from baseline and throughout the treatment period. As anticipated, mean serum  
222 LH and FSH levels were significantly suppressed by  $3.3 \pm 0.3$  ( $p < 0.01$ ) and  $5.7 \pm 0.6$   
223 IU/L ( $p < 0.01$ ), respectively at the end of treatment.

#### 224 *Adverse Events*

225 A total of 37.7% of patients experienced at least one possibly treatment-related AE  
226 during the study. The most commonly reported AEs were acne (6.2%), injection site pain  
227 (5.4%), increase in serum PSA to above 4 ng/mL (5.4%) and increased hemoglobin and  
228 hematocrit (2.3%). Two patients died (one of myocardial infarction, the other of cardiac

229 arrest; neither event was judged by the investigator to be at least possibly related to study  
230 medication. These two patients were morbidly obese with other co-morbidities including  
231 hypertension, hypercholesterolemia, diabetes, baseline electrocardiographic abnormalities  
232 and were taking numerous medications for these conditions (Table 2). Seven (5.4%)  
233 patients discontinued to at least possibly related AEs, including one patient each for  
234 increased hematocrit, increased estradiol (serum estradiol rose from a baseline of 8 to 71  
235 pg/mL after the third injection without adverse events but was judged by the site  
236 investigator to be significant requiring discontinuation), acne, mood swings, and two  
237 patients due to diagnosis of prostate cancer (on Days 196 and 369 of treatment).

238 There was one patient who experienced a potential injection-based pulmonary reaction  
239 event in this study. During his third injection he experienced a mild coughing episode  
240 lasting for about 10 minutes following the injection. The event resolved and the patient  
241 continued in the study and received all six additional study injections with no further  
242 incident.

243 Mean hemoglobin and hematocrit increased from pre-treatment to end of study at week  
244 84 by  $1.2 \pm 0.1$  g/dL ( $p < 0.001$ ) and  $4.2 \pm 0.4$  % ( $p < 0.001$ ), respectively. Mean serum  
245 HDL cholesterol decreased significantly by  $3.6 \pm 0.8$  mg/dL ( $p < 0.01$ ) without significant  
246 changes in serum total and LDL cholesterol levels. While other clinical chemistry  
247 parameters shifted either upwards or downwards during the study, most changes were  
248 very small and not clinically relevant.

249 Average PSA increased from 1.0 ng/mL at pre-treatment to 1.4 ng/mL at endpoint,  
250 reflecting an average PSA velocity of 0.25 ng/mL/year over the 84-week observational  
251 period. Patients with a confirmed PSA level that was over 4 ng/mL were required to have

252 a negative prostate biopsy to remain in the trial. There were 6 (4.6%) patients with at  
253 least one PSA value over 4 ng/mL during the 21-month treatment period. Two patients  
254 were diagnosed with cancer, neither participant had received any testosterone treatment  
255 prior to the study. One prostate cancer was found in a 63 year old subject with a pre-study  
256 history of elevated PSA level (4.16 ng/mL) and two previous negative prostate biopsies  
257 (before study entry), while the other prostate cancer was detected in a 60 year old men  
258 with a baseline PSA level of 2.5 ng/mL within 5 months after the start of treatment (PSA  
259 rose to 5 ng/mL).

## 260 *Discussion*

261 We presented data of long term administration of a long-acting T injection, TU, at a dose  
262 of 750 mg at week 0, 4 and then every 10 weeks for nine injections over an observation  
263 period of 84 weeks. The pharmacokinetics of serum T reached steady state after the third  
264 injection administered at 14 week. In our prior publication we presented data showing  
265 that in the 10 weeks interval following the third injection, 94% of all hypogonadal men  
266 achieved a  $C_{avg}$  of serum T within the young healthy adult male range (300-1000 ng/dL)  
267 (Morgentaler et al, 2008). Here we substantiated our prior data showing that serum T  
268 levels achieved were similar between the third and the subsequent injections. Serum T  
269 levels remained at levels within the reference adult male range at all measured time  
270 points, including all trough time points. Serum free T, DHT and  $E_2$  mimicked the  
271 pharmacokinetics profile of serum T, while serum SHBG did not show significant  
272 changes, indicating that that the T administered most likely was adequate and probably  
273 within the physiological range. The trough levels of all serum hormones after the third  
274 injection remained steady throughout the study period after the third injection. Ratios of

275 serum DHT to T and E<sub>2</sub> to T also did not change from baseline and remained constant  
276 throughout the treatment period. This is in contrast to the serum DHT to T ratios which  
277 have been reported to be increased after oral TU administration (Schnabel et al, 2007)  
278 and after application of T scrotal patches (Cunningham et al, 1989) and T gels (Steidle et  
279 al, 2003; Swerdloff et al, 2000). Because DHT is the main androgen in the prostate, high  
280 serum DHT to T serum levels may affect the androgen concentrations within the prostate  
281 and thus promote prostate growth. However long term study after oral TU (Gooren,  
282 1994) or T scrotal patches (Snyder et al, 1999) did not report increased prostate disease.  
283 A recent report where prostate biopsies were obtained after administration of T enanthate  
284 injections showed no significant changes in serum T and DHT after T enanthate  
285 administration (Marks et al, 2006).

286         The pharmacokinetic profile of serum T at steady state was achieved following a  
287 TU 750 mg IM dosing regimen of 2 injections 4 weeks apart followed by subsequent  
288 injections every 10 weeks provides an advantage over the T ester injections that are  
289 currently available in the United States. Serum T levels after IM injections of T  
290 enanthate peaked between 1 to 3 days and then gradually decreased to levels below the  
291 adult male range between 2 to 3 weeks (Snyder and Lawrence, D. A., 1980; Sokol et al,  
292 1982). Thus in most patients 26 injections of T enanthate or cypionate per year are  
293 required, compared to the 5 to 6 injections of TU 750mg per year using the injection  
294 schedule of 0, 4 weeks and then 10 weekly thereafter. Although this treatment would  
295 require fewer injections than the currently available injectable androgen preparations,  
296 prior published studies suggest that this preparation is associated with improvement in  
297 outcomes and anticipated adverse side effects similar to the currently available treatment.

298 TU injections have been available since 2004 in Europe, Asia and Australia and are  
299 administered with a flexible and adjustable regimen (generally a 1000 mg dose given at  
300 weeks 0, 6 and then every 12 weeks thereafter). Such a regimen has been shown to be  
301 well tolerated, acceptable to hypogonadal men, and to improve sexual function, decrease  
302 waist to hip ratio and increase grip strength in hypogonadal men comparable to the  
303 effects of T enanthate {Jockenhovel et al 2009;Minnemann et al, 2007;Minnemann et al,  
304 2008;Schubert et al, 2004).

305 In this current long-term study, following administration of TU with a 750 mg dose every  
306 10 weeks, the  $C_{max}$  of serum T was  $890.6 \pm 345.1$  ng/dL ( $30.9 \pm 11.9$  nmol/L) and 92% of  
307 subjects with a  $C_{max}$  below 1500 ng/dL, thus avoiding supraphysiological levels in the  
308 majority of patients. Over 94% of subjects had a  $C_{avg}$  within the young healthy adult  
309 male range (300-1000 ng/dL). Average trough levels were between 309.6 to 389.8 ng/dL  
310 (10.8 to 13.5 nmol/L) after TU 750 mg. With serum T levels showing fewer excessive  
311 peaks and troughs and a decreased frequency of injections, TU injections may be more  
312 acceptable to hypogonadal men.

313 The volume of injection of TU in 750 mg is 3 mL which can be given as a single deep IM  
314 injection into the gluteal region. Pain at the injection site was reported in 5.4% of  
315 patients, while acne was reported in 6.2 % of subjects and led to the discontinuation of  
316 one subject. As anticipated with androgen treatment of hypogonadal men, hematocrit and  
317 hemoglobin levels increased after TU 750 mg IM treatment, but only one subject  
318 discontinued because treatment-related high red cell indices. Serum PSA increased with  
319 TU treatment and in two subjects prostate cancer was diagnosed during treatment. These  
320 androgen related adverse events are anticipated with androgen replacement over a period

321 of more than a year and the incidence is not higher than that of other androgens. Notably,  
322 gynecomastia was not reported in this study. Cough after the administration of TU was  
323 reported in one subject. Cough episodes had been described with 1.5% of patients after T  
324 enanthate injections in castor oil and has been ascribed to fat droplet micro-embolism but  
325 no evidence has been shown that such coughing episode was indeed due to fat embolism  
326 (Mackey et al, 1995). If this explanation is true, such episodes may be avoided if the deep  
327 IM injections are given in such a manner as to avoid any possibility of TU in oil reaching  
328 the blood vessels. In order to mitigate the risk of accidental intravascular injection, TU  
329 should not be self-administered but rather should be given by a health professional.

330

331 We conclude that hypogonadal patients treated for 21 months with TU 750 mg IM  
332 injection every 10 weeks showed consistent concentrations of T, its metabolites (DHT  
333 and E<sub>2</sub>), and other sex hormones. Ratios of DHT and E<sub>2</sub> to total T concentration curves  
334 over time were unchanged from baseline and consistent from one injection cycle trough  
335 to the next. SHBG remained unchanged from baseline throughout the study period. The  
336 oily depot of TU in the gluteal results in a concentration-time profile characterized by  
337 T<sub>max</sub> near Day 11; T concentrations then slowly decrease through the remainder of the  
338 dosing interval until the next injection is due. TU IM injections resulted in 10-week  
339 average serum testosterone levels within the adult male range in over 94 % of subjects  
340 following the third injection. A total of 1001 injections of TU were given, and  
341 tolerability was well-demonstrated, with over 70% of patients receiving all 9 of their  
342 scheduled injections and completing this 21-month study.

343 The long acting injectable TU is a valuable addition to the currently available  
344 transdermal, buccal and injectable methods of T substitution for hypogonadal men.  
345 However, TU may be more acceptable to the patients due to the significantly longer  
346 dosing interval and the favorable pharmacokinetics of T and ratios to other sex hormones.

347 ***Study Sites***

348 Philip Aliotta, MD, Center for Urologic Research of WNY; Stephen Auerbach, MD,  
349 California Professional Research; Adrian Dobs, MD The Clinical Trials Unit, Johns  
350 Hopkins University; Robert Feldman, MD, Connecticut Clinical Research Center;  
351 Kenneth Goldberg, MD, Texas Urology; Evan Goldfischer, MD, Hudson Valley  
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353 University Urology Associates; Joel Kaufman, MD, Urology Research; L. Dean Knoll,  
354 MD, Medical Research Associates of Nashville; Edward Loizides, MD, Medical and  
355 Clinical Research Assoc, LLC; Kurt Meissner, MD, Urology San Antonio Research;  
356 David Mobley, MD, Mobley Research; Tommy Mook, MD, Regional Urology; Myron  
357 Murdock, MD; Howard Tay, MD, HOPE Research Institute; Anthony Ricottone, MD,  
358 WNY Urology Associate; Johnny Roy, MD; Barry Shepard, MD, Urological Surgeons of  
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370

371 ***Disclosures***

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373 and served as temporary consultants for Indevus and ENDO pharmaceuticals. Dr. Harnett  
374 is a past employee of Indevus and a current employee of ENDO pharmaceuticals. Dr.  
375 Wang received research support from Acrux, Clarus and Abbott, research materials from  
376 Besins Healthcare and served as a temporary consultant to Acrux. Dr. Dobs serves as  
377 temporary consultant to Auxillium. Dr. Swerdloff received research support from Clarus  
378 Therapeutics, received research material from Solvay (now Abbott) and served as  
379 temporary consultant to Clarus Therapeutics.

380

381 Figure Legends

382 Figure 1: Mean (+SD) serum T concentrations after the third and fourth injections of TU  
383 750 mg IM administered at week 14 and 24 respectively. Serum T concentration reached  
384 steady state after the third injection of TU when the first and second injections were  
385 administered at week 0 and 4.

386 Figure 2. Serum free T, DHT, E<sub>2</sub> and SHBG concentrations after the third injection of TU  
387 750 mg at week 14.

388 Figure 3. Trough serum Total and free T, DHT, E<sub>2</sub> and SHBG concentrations before TU  
389 750 mg IM injections at weeks 0, 4 and then every 10 weeks.

390 Figure 4. Ratios of trough serum E and DHT to serum T concentration before TU 750 mg  
391 IM injections at weeks 0, 4 and then every 10 weeks.

392

393

394

395 Table 1: Pharmacokinetic parameters of serum total T concentration (ng/dL) following  
 396 the third injection of TU 750 mg IM

<b>Pharmacokinetic Parameter</b>	<b>N</b>	<b>Mean</b>	<b>Standard Deviation</b>	<b>Minimum</b>	<b>Median</b>	<b>Maximum</b>	<b>CV (%)</b>	<b>Geometric Mean</b>
AUC <sub>(0-70)</sub> (days x ng/dL)	117	34645.6	9902.45	13755.1	33342.2	70016.9	28.6	33263.6
C <sub>Trough</sub> (Week 14)	117	339.5	122.69	122.7	303.0	754.1	36.1	319.8
C <sub>Trough</sub> (Week 24)	117	323.5	99.11	138.2	316.9	611.1	30.6	309.0
C <sub>max</sub> (ng/dL)	117	890.6	345.11	311.0	813.6	1758.5	38.8	826.8
T <sub>max</sub> (days)	117	10.0	7.11	4.0	7.0	42.0	71.1	8.4
C <sub>avg, 0-70</sub> (ng/dL)	117	494.9	141.46	196.5	476.3	1000.2	28.6	475.2

397

398 Table 2: Incidence of Adverse Events in All Enrolled Patients (>2.0% of Patients),  
 399 Judged by the Investigator to be At Least Possibly Related to Treatment,

<b>MedDRA Preferred Term</b>	<b>Number of patients (%)</b> <b>N=130</b>
Acne	8 (6.2)
Injection Site Pain	7 (5.4)
Prostate Specific Antigen Increased	7 (5.4)
Fatigue	6 (4.6)
Estradiol Increased	4 (3.1)
Hemoglobin Increased	3 (2.3)
Hematocrit Increased	3 (2.3)
Insomnia	3 (2.3)
Irritability	3 (2.3)
Mood Swings	3 (2.3)

400

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Fig. 1

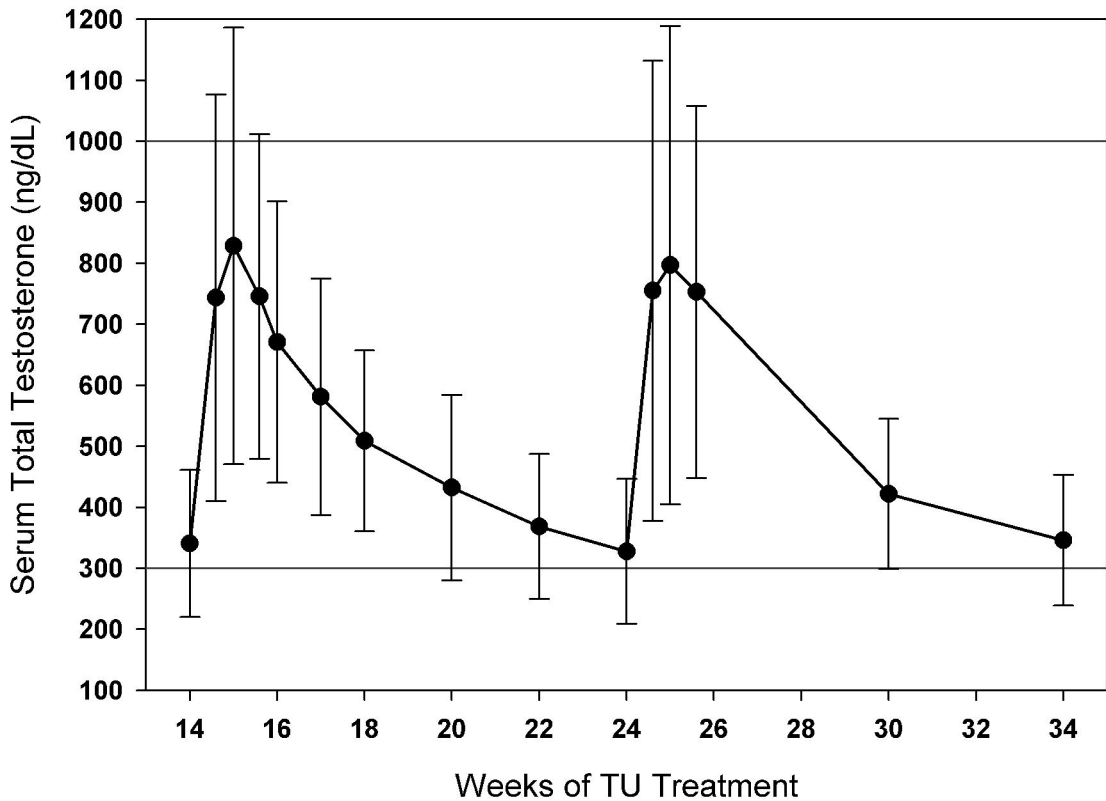


Fig. 2A

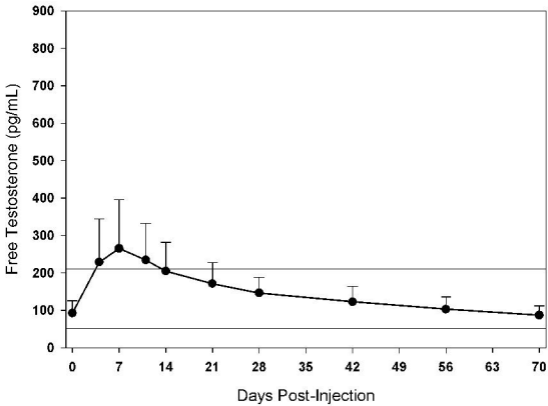


Fig. 2B

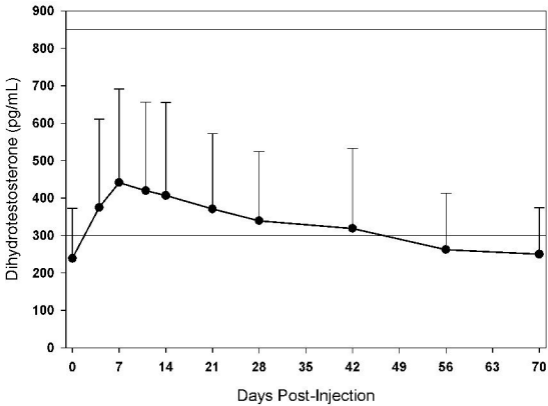


Fig. 2C

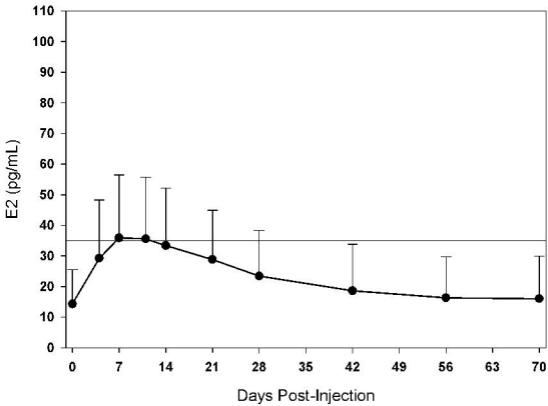


Fig. 2D

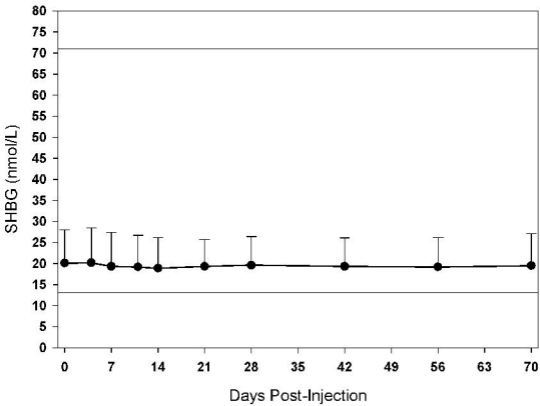


Fig. 3A

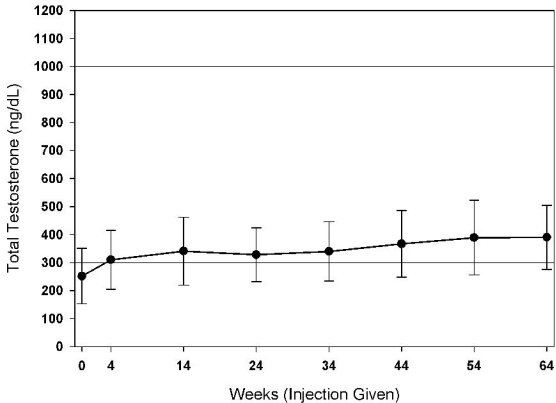


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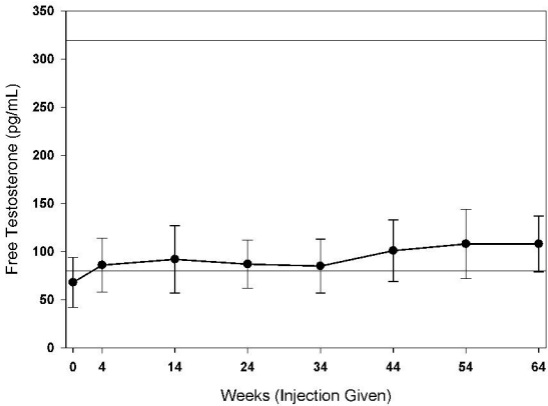


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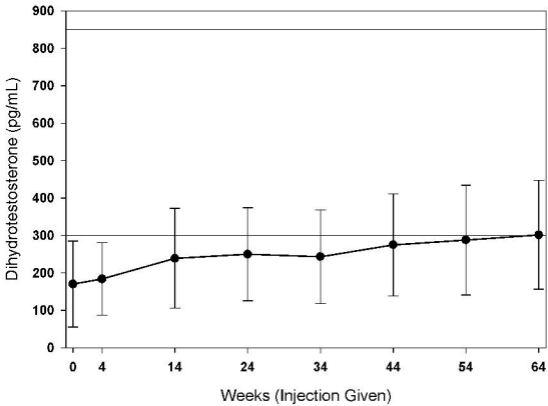


Fig. 3D

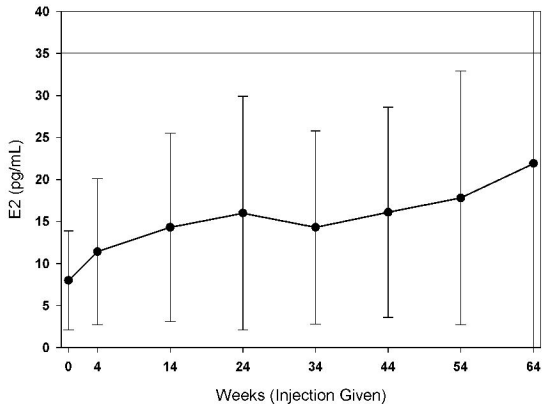


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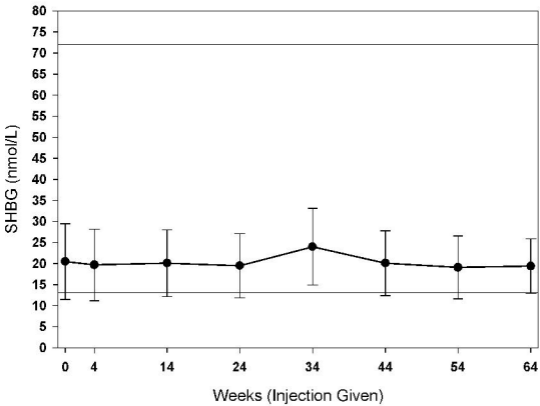


Fig. 4A

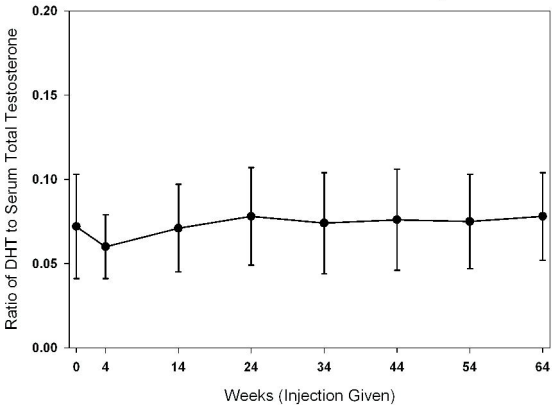


Fig. 4B

