Efficacy of Nasal Testosterone Gel (Natesto®) Stratified by Baseline Endogenous Testosterone Levels

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Objective: Pharmacokinetic and efficacy data from a phase 3 testosterone nasal gel (TNG) study were stratified by baseline endogenous testosterone level in patients with testosterone deficiency. Total testosterone (TT), LH, and FSH levels, as well as erectile function, mood, and lean body mass for each group were compared. In a subset of patients with very low baseline endogenous testosterone levels (<100 ng/dL), we investigated whether TNG is a suitable treatment option.

Materials and Methods: Patients with testosterone deficiency (serum TT <300 ng/dL) were treated with TNG for 3 months, followed by safety extension periods of 90 and/or 180 days. Pharmacokinetic parameters were calculated from serum hormone levels on days 30 and 90, along with efficacy measurements, which were analyzed by comparison with baseline values. Baseline and/or predose TT values were used for patient stratification.

Results: Prestudy and predose endogenous testosterone concentrations correlated. The maximal concentration of TT was nearly identical across all cohorts at days 30 and 90, whereas the average concentration over 24 hours had a slight positive dependence relative to predose levels. LH levels remained in the normal range but were decreased more in patients with higher starting baseline levels. These findings indicate that TNG works with an active hypothalamic-pituitary-gonadal axis that responds to each dose of TNG throughout the treatment period. Patients with the lowest endogenous testosterone levels received maximum exposure impact from each TNG dose. Patients with severe testosterone deficiency had similar efficacy improvements as the remainder of the study population.

Conclusion: All testosterone-deficient cohorts were successfully treated with TNG.

Freeform/Key Words: testosterone, testosterone deficiency syndrome, testosterone nasal gel, maximal concentration, predose, luteinizing hormone

Testosterone deficiency syndrome (TDS), also known as late-onset hypogonadism, is a clinical and biochemical syndrome that can occur in men as they age. The condition is characterized by deficient testicular production of testosterone. It may affect multiple organ systems and can result in substantial health consequences [1, 2].

Abbreviations: AE, adverse event; C_{avg}, average concentration; C_{max}, peak serum total testosterone concentration; HPG, hypothalamic-pituitary-gonadal; IIEF, International Index of Erectile Function; PANAS, Positive and Negative Affect Schedule; PK, pharmacokinetic; TDS, testosterone deficiency syndrome; TNG, testosterone nasal gel; TT, total testosterone; TTh, testosterone therapy.

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The clinical diagnosis of TDS is made on the basis of recognized symptoms and persistent morning total testosterone (TT) levels <300 ng/dL (10.4 nmol/L). Symptoms of TDS include, but are not limited to, decreased energy, decreased libido, impaired erectile function, depressed mood, decreased muscle mass, and increased body fat [3].

In North America, TDS can be treated with exogenous testosterone using one of a variety of therapeutic options [4, 5], including topical transdermal gels, oral and buccal agents, IM injections, subcutaneous injections, subcutaneous pellets, and nasal products. Patients and physicians weigh advantages and disadvantages of each option to select a treatment that best fits the therapeutic needs, preferences, safety, tolerances, and lifestyle of the patient. Factors may include convenience, cost, potential adverse local (*e.g.*, irritation) or systemic (*e.g.*, cardiovascular, hematocrit) reactions, transference, smell or odor, and physician recommendations [6–12].

TNG 4.5% testosterone nasal gel (Natesto®; Acerus Pharmaceuticals Corporation, Mississauga, Ontario, Canada) is a thixotropic gel that is applied in the nasal cavity [13]. Testosterone levels or symptoms are used to guide titration decisions [13] between either twice- or thrice-daily doses used to restore testosterone levels to the normal range. Surprisingly, patients report higher convenience with TNG than with once-daily topical gels [14].

The pharmacokinetic (PK) profile of TNG of different concentrations has been studied in a series of single and multidose PK studies, including in women, healthy volunteers with allergic rhinitis, and men with TDS [15]. The 24-hour PK profile of testosterone for patients receiving TNG treatment has two or three discrete peaks ("pulses") of testosterone provoked by LH secretions that occur, on average, every 2 hours. A maximal peak of testosterone appears at about 1 hour, followed by a return to endogenous, predose levels 4 to 6 hours later (half-life ~1 hour) [4]. The nadir (trough) between doses correlates well with pretreatment endogenous levels at diagnosis.

The unique, pulsatile PK profile is believed to have limited impact on the hypothalamic-pituitary-gonadal (HPG) axis, with substantial trough time preserving LH, FSH, and endogenous testosterone production, and sperm counts [16, 17], while also limiting excess red blood cell production, estradiol, DHT, and prostate-specific antigen levels in clinical trials [4]. However, it was unclear whether TNG was sufficient to produce strong efficacy outcomes when baseline endogenous production was very low. This was the impetus to perform a *post hoc* analysis of phase 3 data with particular attention to prestudy baseline values and their effects on PKs and symptomatic efficacy. Of particular interest was the subset of patients who had very low baseline endogenous testosterone [<100 ng/dL (3.5 nmol/L)] to determine if TNG is a suitable treatment option for this population.

1. Materials and Methods

A. Study Design

The current investigation was structured as a *post hoc* analysis of a previously reported phase 3 study [16]. The phase 3 study was approved by institutional review boards and the participants all signed an informed consent form. To summarize, this was a 39-site, open-label study that enrolled 306 adult men with TDS who had received testosterone therapy (TTh) or not. The men were 29 to 80 years old (mean age, 54.4 years): 28 men were <40 years old, 77 were 40 to 49 years old, 97 were 50 to 59 years old, 78 were 60 to 69 years old, and 26 were age ≥70 years.

After a 3- to 7-week screening period that included a 2- or 4-week washout period for patients who had previously been receiving topical TTh and injectable TTh, respectively, patients were randomly assigned to either twice- or thrice-daily treatment groups. The twice-daily group could be uptitrated to three times daily on day 45, on the basis of achieving certain morning serum TT levels. Each dose consisted of 5.5 mg/nostril for a total of 11 mg of TNG per

dose. In general, patients were followed for 90 days. Body mass index assessments extended to 180 days of follow-up.

On days 30 and 90, patients had blood samples collected for PK studies at 15 minutes prior and 0.33, 0.67, 1.00, 1.50, 2.00, 3.00, 6.00, and 9.00 hours after dosing at the time of both the morning and the evening dose. Serum TT levels were evaluated using a validated liquid chromatography—tandem mass spectrometry method using an API 4000 liquid chromatography—tandem mass spectrometry system (Analytical Biochemical Laboratory, Assen, Netherlands) [16]. The analytical range for the assay was 0.500 to 50.0 ng/mL. LH and FSH levels and lean body mass were assessed on days 1 and 90, and change from baseline was calculated using day 1 levels as the baseline.

B. PK Analyses

Values below the lower level of detection were treated as missing in the calculation of PK parameters. The average concentration (C_{avg}) was calculated over 24 hours.

C. Clinical Efficacy Measurements

On days 0, 30, 60, and 90, the International Index of Erectile Function (IIEF) [18] and Positive and Negative Affect Schedule (PANAS) [19] questionnaires were administered to the participants. IIEF score change from baseline was calculated using day 0 as the baseline.

Lean body mass was measured on days 0 and 180. Change in lean body mass was calculated by subtracting baseline measurement from the day 180 measurement.

D. Adverse Events

Adverse events (AEs) for the study have been described [16]. In summary, most AEs were mild in severity. The most common AEs (≥5%) included nasopharyngitis (8.2%), rhinorrhea (7.8%), epistaxis (6.5%), nasal discomfort (5.9%), scab (5.2%), and parosmia (5.2%). At least one severe AE was experienced by 4.6% of patients, and one patient (0.3%) had a severe drug-related AE (myalgia, which did not require study drug discontinuation or dose adjustment and remitted after concomitant medication was initiated). Although eight patients had serious AEs in the study, none was considered related to study medication.

E. Statistical Analyses

All analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC). P values were calculated using the ANOVA PROC GLM models in SAS. Baseline or predose strata were used as a fixed effect. Linear regression was used to test the relationship between two parameters for nonstratified data. Statistical significance was set at α of 0.05.

2. Results

In this *post hoc* analysis, qualifying patients (n = 180) who completed days 30 and 90 evaluations were stratified on the basis of predose endogenous trough TT between 0 and 300 ng/dL [10.4 nmol/L; increments of 50 or 100 ng/dL (1.7 or 3.5 nmol/L) TT]. The chosen strata provided five groups having similar numbers of patients in each group. Demographic parameters of stratified subgroups are listed in Table 1 as mean testosterone levels and IIEF and PANAS values at baseline for the five groups.

Mean PK parameters, such as peak serum TT concentration (C_{max}), area under the plasma concentration-time curve during a dosage interval, and C_{avg}, were determined for TT for each stratum at days 30 and 90. Notably, C_{max} did not significantly differ across strata at day 30 despite the predose endogenous TT levels differing by nearly 250 ng/dL (8.7 nmol/L) between the highest and lowest groups (Fig. 1). This observation was consistent across strata regardless of whether the PK analysis was from day 30 morning (P = 0.08; Fig. 2a) or evening

Table 1. Demographics, Baseline Testosterone, and Questionnaire Scores of Patient Cohorts Grouped by Baseline TT as Measured Before the First Study Dose

Baseline TT, ng/dL	No. of Patients	Age (y)	Weight (kg)	Height (cm)	BMI (kg/m^2)	Average TT Concentration (ng/dL)	PANAS Score, Positive	PANAS Score, Negative	IIEF Score
<100	26	55.6 (13.3)	91.3 (14.4)	177.7 (5.9)	28.8 (3.6)	61.8 (31.5)	30.7 (7.9)	16.7 (6.6)	28.7 (20.0)
<150	30	55.6 (9.7)	91.5 (11.9)	177.7 (5.9)	28.8 (3.3)	128.5 (14.7)	32.0 (8.6)	17.6 (7.3)	32.7 (18.2)
<200	47	52.9 (10.8)	97.6 (14.5)	179.0 (6.2)	30.4 (3.6)	172.9 (15.0)	29.3 (10.8)	16.7 (7.7)	35.2 (20.3)
<250	56	56.3 (10.6)	93.2 (12.4)	176.4 (6.4)	29.9 (3.2)	223.8 (14.4)	27.3 (11.7)	15.1 (7.4)	32.3 (21.4)
<300	75	53.7 (11.1)	94.6 (13.9)	176.5 (7.7)	30.3 (3.5)	272.4 (15.0)	30.6 (7.8)	16.4 (5.6)	38 (19.3)

Data are reported as mean (SD).
Abbreviation: BMI, body mass index.

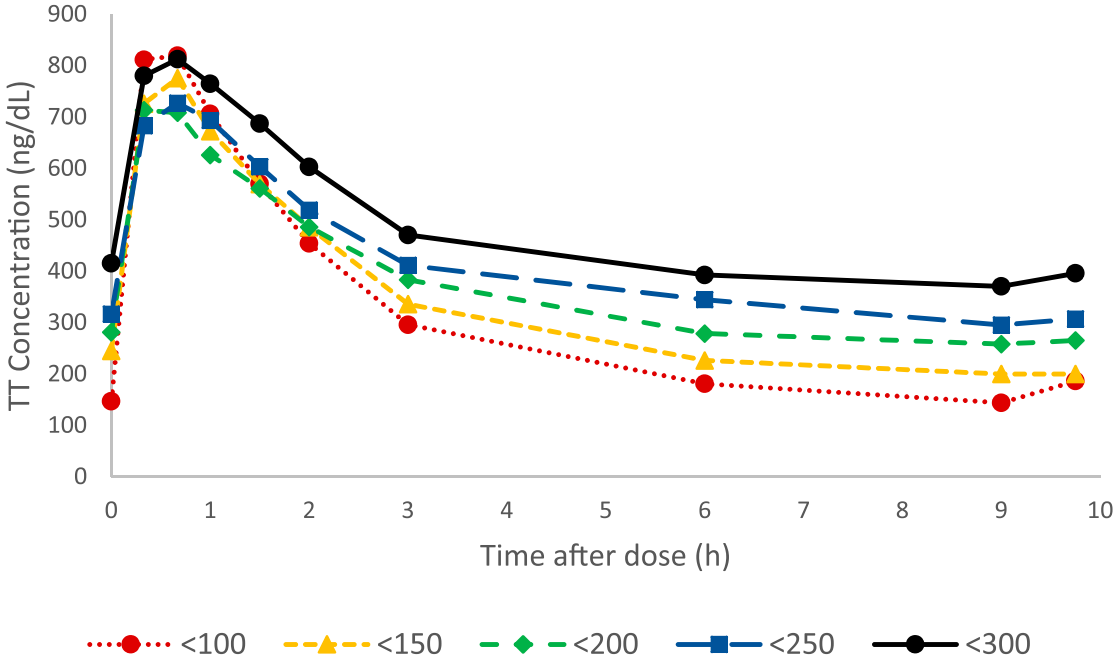

Figure 1. Average TT concentrations from dosing to 10 h after dosing. Patients were stratified by their predose concentration.

(P = 0.72) dosing (Fig. 2b) or day 90 morning (P = 0.47) or evening (P = 0.84) dosing (data not shown).

Mean C_{avg} determinations showed that combined testosterone exposure from all sources, exogenous and endogenous, increased with the application of TNG. However, the extent of the hormonal increase in the mean 24-hour C_{avg} was much smaller than would be expected based on the simple addition of a single dose of 11 mg of testosterone to the circulating endogenous TT concentration (P = 0.06; Fig. 2c). A similarly limited increase in the C_{avg} was seen in patients receiving twice daily doses and those receiving thrice-daily doses (data not shown). The mean plasma concentration-time curve during a dosage interval also showed a very modest increase as a function of the predose TT (baseline) concentration (data not shown).

Figure 3 illustrates changes in erectile function (according to IIEF data) and Fig. 4 highlights mood changes (according to PANAS data) resulting from treatment with TNG on each of the strata. In general, PANAS and IIEF [18] improvements correlated with changes in TTh. Interestingly, patients with TT predoses <100 ng/dL (3.5 nmol/L) had similar (approximately 40%) improvements in erectile function on days 30, 60, and 90 to those of patients with TT predoses >100 ng/dL (3.5 nmol/L; P = 0.89). Similar findings were noted in PANAS scores. Specifically, patients with TT predoses <100 ng/dL (3.5 nmol/L) had increases in positive mood states (P = 0.92) and similar decreases in negative mood states (P = 0.37) at day 90 similar to those of patients with predoses >100 ng/dL (3.5 nmol/L; Fig. 4).

Mean LH and FSH levels when measured at 2 hours (thus proximal to a dose of TNG) decreased relative to baseline in all cohorts. There were larger decreases observed for patients in strata with higher predose levels of TT (Fig. 5a). Patients with low levels of endogenous testosterone also had significant improvements in lean body mass (Fig. 5b).

3. Discussion

TNG maintains the endogenous HPG axis. This is clearly evident in single-dose PK profiles in healthy men and those with TDS for whom the predose value (t = 0), which corresponds to the patient's endogenous TT level, was found again at the bottom of the trough between peaks

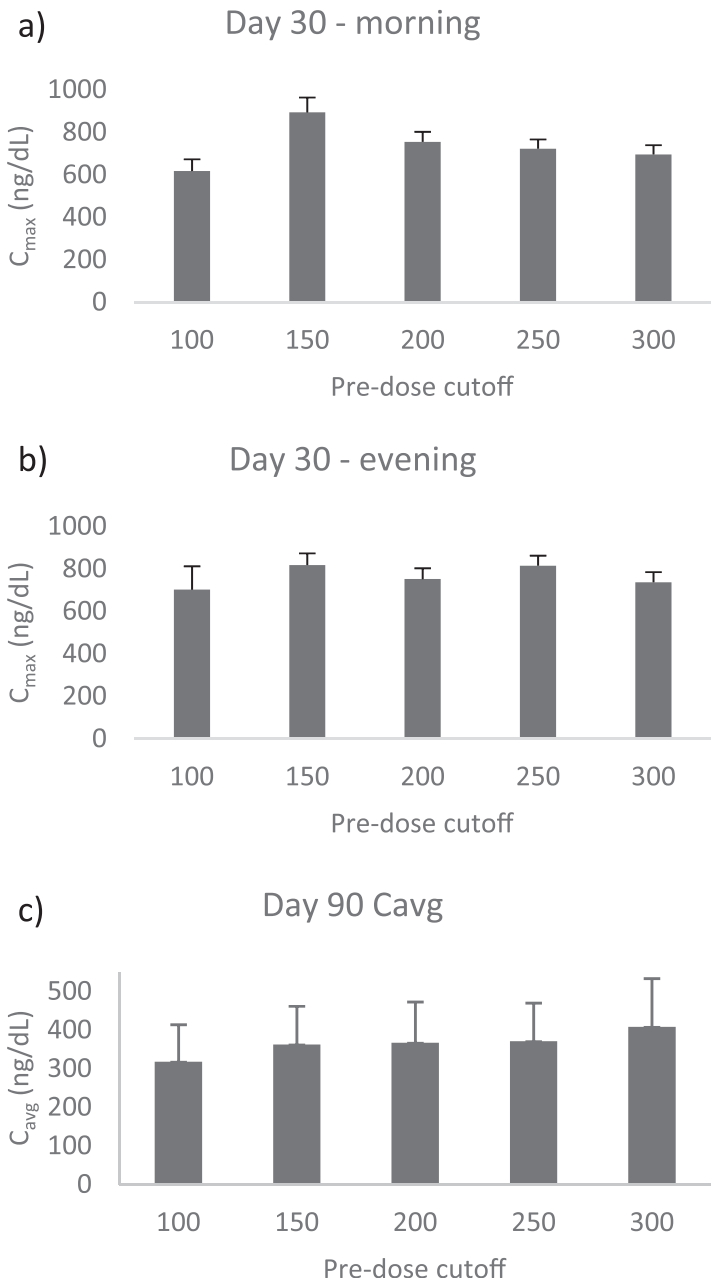

Figure 2. Effect of predose TT concentration on C_{max} after Natesto TNG given in the (a) morning or (b) evening on day 30 of the study. Patients were grouped such that "100" contains patients who had TT predoses <100 ng/dL, "150" contains patients with TT concentrations from 100 to <150 ng/dL, and so forth. (c) Effect of predose concentration on C_{avg} over 24 h on day 90.

and was maintained through 90 days of treatment (for twice- and thrice-daily doses). Additional evidence of active HPG when receiving TNG treatment is found in a recent trial showing unchanged sperm counts after 6 months of TNG treatment (thrice-daily dose only) [17]. In larger trials, LH and FSH measurements were made proximal to a peak of TNG and were somewhat depressed, but they remained in the normal range [16]. Our interpretation of these observations is that the HPG axis is active and there is temporal suppression when TNG doses are administered. This suppression appears to recover completely, on the basis of consistent trough values over time.

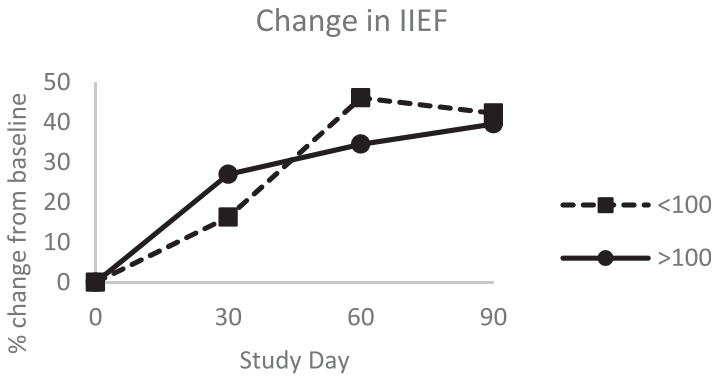

Figure 3. IIEF score change from baseline to day 90. Patients are stratified by their predose TT concentration. The numbers indicate strata that contain patients with predose TT values less than the indicated number down to the number to its left.

With this in mind, a *post hoc* analysis of the TNG phase 3 study was performed to look at PK parameters and efficacy of TNG in patients with differing endogenous testosterone levels. Patient outcomes were stratified on the basis of predose TT levels. The stratification produced groups that were similar in number and characteristics, with the exception of their hormone levels.

TNG restored mean C_{avg} TT levels in all groups, with the exception of the patients most deficient in androgen for whom a mean TT value of 295 ng/dL (10.2 nmol/L) was obtained and only 35% had TT levels >300 ng/dL (10.4 nmol/L). A substantial portion of these patients were on the twice-daily dose. Regardless, all groups showed statistically significant improvement in

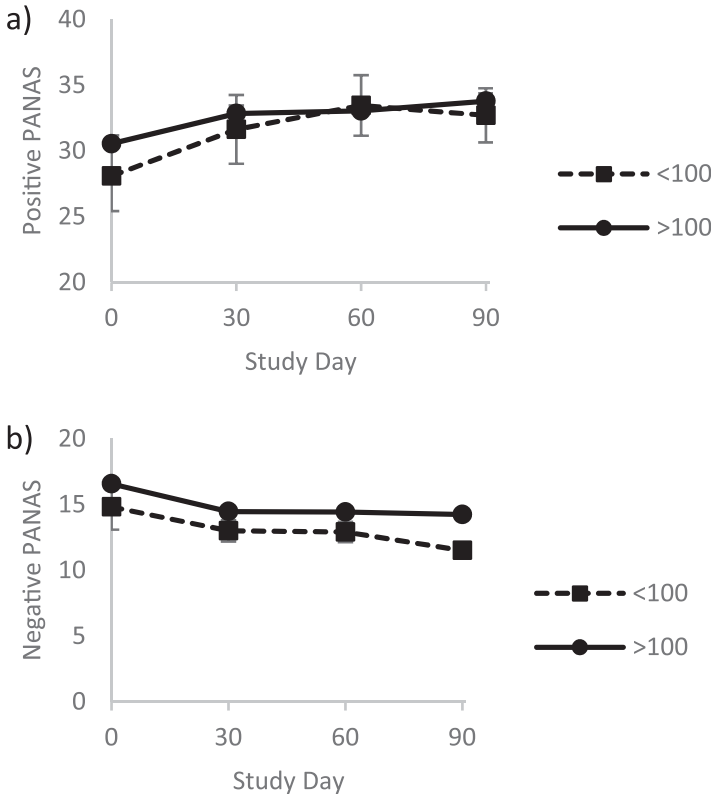

Figure 4. (a) Positive and (b) negative PANAS scores of patients with baseline TT concentrations <100 or >100 ng/dL. PANAS score was measured at baseline and then every 30 d.

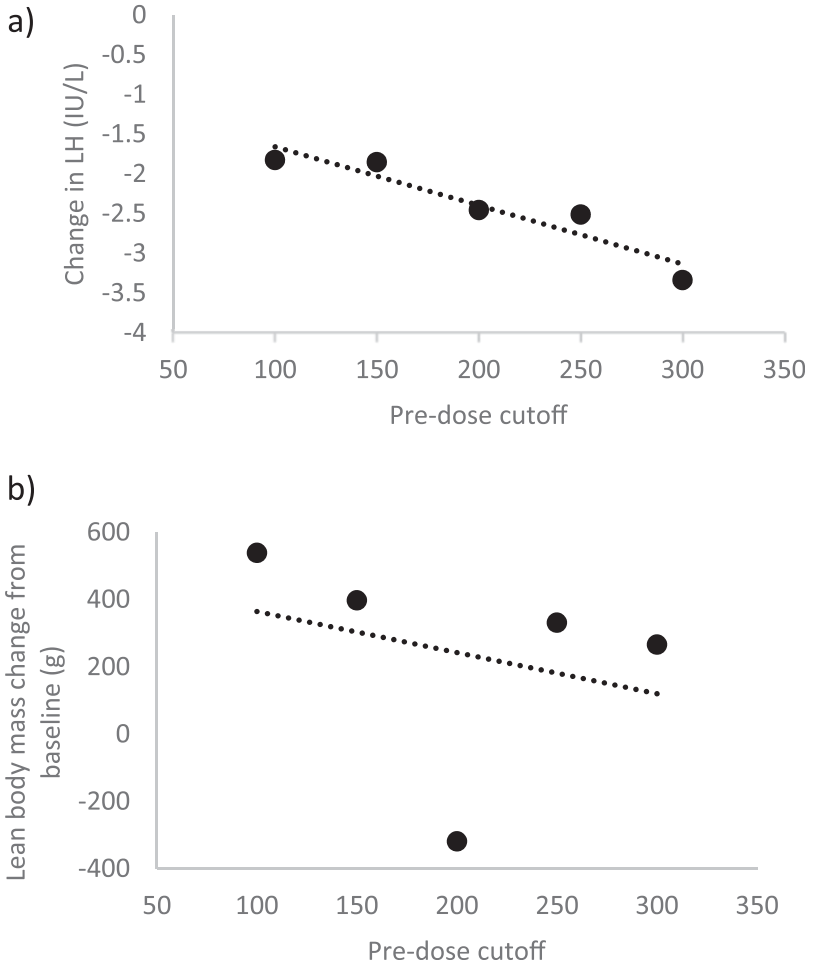

Figure 5. Change in (a) LH from baseline to day 90 and (b) lean body mass from baseline to day 180 in patients stratified by predose TT concentrations. Line of best fit is indicated.

symptoms. Erectile function and mood (both positive and negative) were significantly improved even in patients with the lowest baseline TT levels.

Several other trends became apparent: (i) C_{max} was the same across all stratified groups, regardless of the starting pretreatment or predose (baseline) TT levels (Figs. 1 and 2); (ii) LH and FSH suppression occurred at 2 hours after dosing in all instances, with the largest suppression occurring for patients with higher initial LH and FSH levels (Fig. 5a); and (iii) there was a trend of increasing C_{avg} with increasing baseline TT, but C_{avg} appeared to be well below what would be expected (Fig. 2c). All these trends could be explained if there is some temporal suppression of HPG and of endogenous testosterone production during the time of absorption of the exogenous dose and the amount of suppression is proportional to the endogenous HPG activity (*i.e.*, higher baseline testosterone levels can be suppressed more than lower baseline testosterone levels).

In fact, the observed PK profile after a TNG dose is a sum of all sources of testosterone [20, 21]; exogenous and endogenous sources were not independently quantifiable in this study. When exogenous testosterone was administered, there was a suppression of LH and testosterone production. Endogenous testosterone levels decreased as a result of ongoing elimination and reduced or halted production. Later (>1 hour after administration), as the exogenous testosterone absorption rate was reduced and elimination predominated, resulting in a drop in exogenous testosterone, the HPG recovered, reinitiating endogenous testosterone production (Fig. 6a). The degree of HPG suppression appeared to be proportional to the initial baseline TT. For patients with less severe hypogonadism with a supposedly more

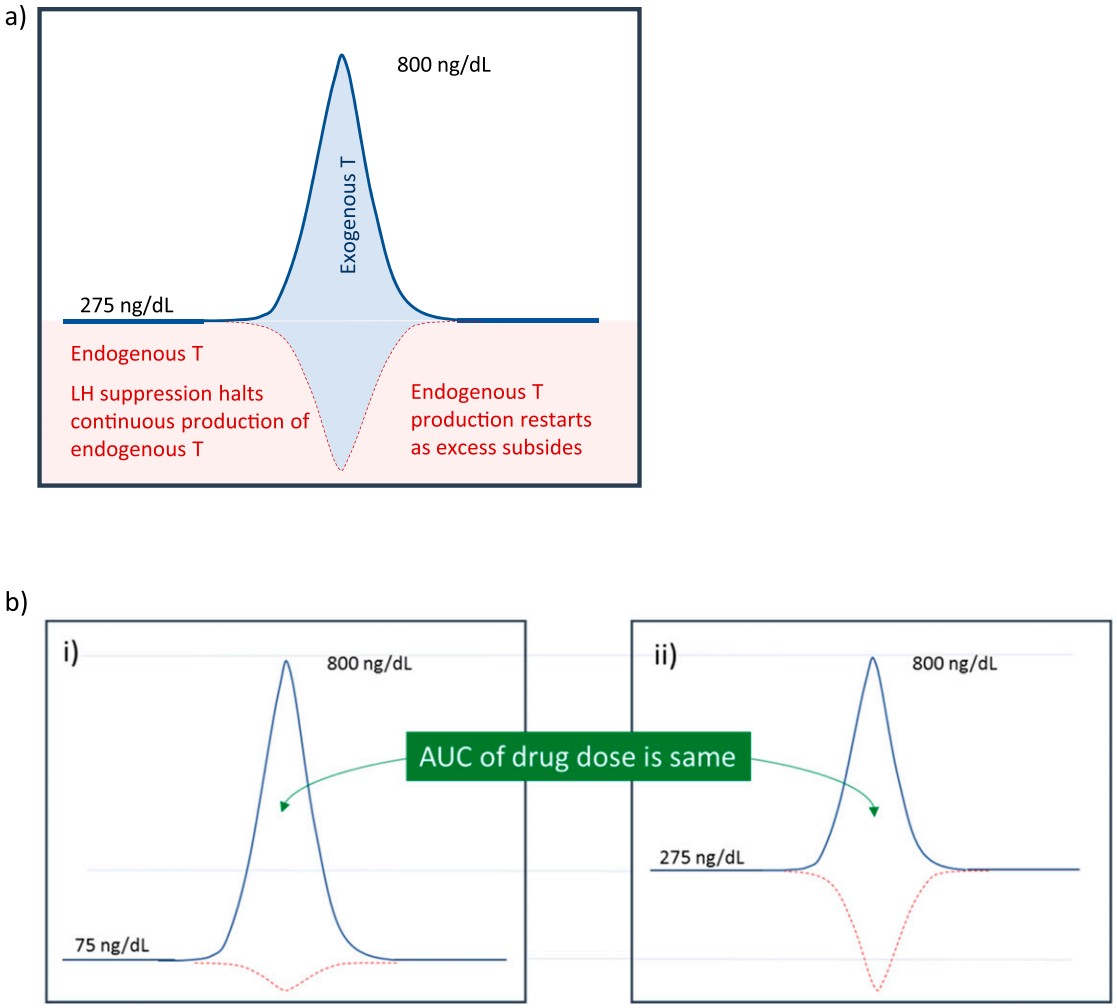

Figure 6. (a) Visual representation of the addition of testosterone into an active HPG system, which immediately attempts to correct for the excess of testosterone by reducing endogenous testosterone. (b) Visual representation of the suppression of endogenous testosterone production for (i) a patient with more severe TDS, and (ii) a patient with less severe TDS.

active HPG and higher baseline TT level, there was more endogenous testosterone suppression during each dose than for a patient with more severe hypogonadism with less HPG axis potential (Fig. 6b). This model is supported by the larger decreases in LH in patients with higher baseline TT concentration seen in this study. It should be noted that in the Rogol *et al.* study [15], administration of TNG to healthy men with a predose TT baseline of 534 ng/dL (18.4 nmol/L) also showed C_{max} peak levels in the same range as seen in this study and again a return to predose baseline nearly 6 hours after a dose.

Thus, TNG's ultradian profile is the means to maintain an active HPG. Despite modest C_{avg}, significant C_{max} values may be sufficient for positive symptom outcomes. TNG has up to 12 hours of trough time at or below patients' baseline (*i.e.*, below the normal range), which is likely a factor in limiting unwanted anabolic effects on hematocrit [22].

Limitations of the study are that the numbers of patients with very low endogenous TT levels were small. Nonetheless, the findings and trends were consistent across stratified groups. The LH levels were tested at one point proximal to a dose and, therefore, the description of the time course of suppression is inferred. Patients' predose and prestudy baseline levels were not absolutely identical over all time points in the study; therefore, depending on which value was used for stratification, the absolute results varied somewhat,

but the overall trends and conclusions remained unchanged irrespective of the baseline value selected for the analysis.

Thus, an ultradian, pulsatile PK profile allows maintenance of the endogenous feedback mechanism when treated with TNG, which serves multiple purposes. First, very high peaks of TT are only rarely observed [3.3% of patients had a C_{max} of 1800 to 2500 ng/dL (63.0 to 87.0 nmol/L) in the phase 3 study], because the active feedback mechanism provides a control mechanism keeping the TT levels in check. Second, troughs between peaks reduce overall exposure, helping to limit adverse effects of testosterone treatment, such as hematocrit overproduction (no patients had hematocrit values ≥54% in either the phase 3 or phase 4 studies) [22]. Third, troughs allow for secretion of gonadotropins that maintain active testicular testosterone production, as well as sperm. Last, as shown here, the combination of peaks and troughs is sufficient to achieve symptom efficacy even for patients with the most severe TDS in this study. Overall, there are positive benefits to a treatment approach that is compatible with HPG physiology.

Conclusions

TNG treatment restores TT levels while preserving important aspects of HPG function, including continued release of gonadotropins and production of endogenous testosterone, which allows maintenance of baseline levels. Patients with modest TDS [TT concentration, 250 to 300 ng/dL (8.7 to 10.4 nmol/L)] and those with more severe TDS [TT concentration, 0 to 100 ng/dL (0 to 3.5 nmol/L)], when treated with TNG, achieve maximum TT levels at ~800 ng/dL (27.7 nmol/L). Efficacy, as measured by erectile function and mood, was significantly improved to similar levels in both groups. The unique, ultradian, pulsatile nature of TNG, which does not depress endogenous testosterone production, means that a wide range of patients with testosterone deficiency can effectively be treated with TNG.

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Clinical Trial Information: ClinicalTrials.gov no. NCT01446042 (registered 4 October 2011).

Additional Information

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Disclosure Summary: M.A.G., R.W.O., and N.B. are employed by and own shares and options in Acerus Pharmaceuticals Corporation.

Data Availability: The data sets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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