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Journal of the Endocrine Society
Endocrine Society

Submitted: May 15, 2019
Accepted: June 20, 2019
First Online: June 26, 2019

Journal of the Endocrine Society; Copyright 2019 DOI: 10.1210/js.2019-00183

Nasal Testosterone in Low Testosterone Patients

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

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Received 15 May 2019. Accepted 20 June 2019.

Objective: Pharmacokinetic and efficacy data from a Phase 3 Testosterone Nasal Gel (TNG) study were stratified based on testosterone deficient patients' baseline endogenous testosterone. Total testosterone (TT), gonadal hormones (LH and FSH), erectile function, mood and lean body mass for each group were compared. Of particular interest was the subset of patients who presented with very low baseline endogenous testosterone (<100 ng/dL), to determine if TNG is a suitable treatment option for severely testosterone deficient patients.

Materials and Methods: The phase 3 study has previously been described. [1] Testosterone deficient patients (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 measured by LC-MS/MS on Days 30 and 90 along with efficacy measurements such as lean body mass, erectile function as measured using the International Index of Erectile Function (IIEF) and mood as measured using Positive and Negative Affect Schedule (PANAS). Efficacy was analyzed by comparing against baseline values. Baseline and/or pre-dose TT values were used for patient stratification. Linear regression was used to test the relationship between two parameters for non-stratified data.

Results: Pre-study endogenous testosterone readily correlated to pre-dose concentrations. Interestingly, TT C_{max} (maximal concentration) was nearly identical across all cohorts at both Day 30 and 90, while C_{avg} (average concentration over a 24-hour time period) showed a slight positive dependence relative to pre-dose levels. LH levels remained in the normal range, but showed a stronger decrease for subjects with higher starting baseline than those with lower baseline testosterone. These observations affirm that TNG works with an active hypothalamic–pituitary–gonadal axis (HPG) that responds to each dose of TNG throughout the treatment period. Interestingly, patients with the lowest endogenous testosterone receive maximum exposure impact from each dose TNG. These severely testosterone deficient patients show similar efficacy improvements when compared to the remainder of the study population. Conclusions: All testosterone deficient cohorts, including those with severe testosterone deficiency, were successfully treated with TNG.

Keywords: Testosterone, testosterone deficiency syndrome, Testosterone Nasal Gel, C_{max}, pre-dose, Luteinizing Hormone

Introduction:

Testosterone deficiency syndrome (TDS), also known as late-onset hypogonadism, is a clinical and biochemical syndrome that can occur in men in association with advancing age. The condition is characterized by deficient testicular production of testosterone. It may affect multiple organ systems and can result in substantial health consequences.[2,3]

The Clinical diagnosis of TDS is made on the basis of recognized symptoms and persistent morning total testosterone levels below 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.[4]

In North America, TDS can be treated with exogenous testosterone using one of a variety of therapeutic options[5,6] including topical transdermal gels, oral and buccal agents, intra-muscular 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. Factors may include convenience, cost, potential adverse local (irritation) or systemic (cardiovascular, hematocrit) reactions, transference, smell/odor and physician recommendations.[7–13]

TNG 4.5% testosterone nasal gel (Natesto®) is a thixotropic gel that is applied into the nasal cavity.[14] Testosterone levels or symptoms are used to guide titration decisions[14] between either twice daily or three times a day doses used to restore testosterone levels to the normal range. Surprisingly, patients report higher convenience with TNG than once-daily topical gels.[15]

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 TDS men.[16] The 24-hour pharmacokinetic profile of testosterone for patients on 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 1h (T_{max}) followed by a return to endogenous, pre-dose levels, 4-6 hours later ($t_{1/2}$ ~1h).[5] The nadir (trough) between doses correlates well with pre-treatment endogenous levels at diagnosis.

The unique, pulsatile, pharmacokinetic profile is believed to have limited impact on the HPG axis with significant trough time preserving luteinizing hormone (LH), follicle stimulating hormone (FSH), endogenous testosterone production and sperm counts[1,17], while also limiting excess RBC production, estradiol, DHT and PSA in clinical trials.[5] However, it was previously

unclear whether TNG was sufficient to produce strong efficacy outcomes when baseline endogenous production was very low, thus the impetus to perform a post-hoc analysis of Phase 3 data with particular attention to pre-study baseline and its effects on pharmacokinetics and symptomatic efficacy. Of particular interest was the subset of patients who presented with very low baseline endogenous testosterone (<100 ng/dL (3.5 nmol/L)) to determine if TNG is a suitable treatment option for this population.

Materials and Methods:

Study design

The current investigation was structured as a post-hoc analysis of a previously reported phase 3 study. [1] To summarize, this was a 39 site, open-label study that enrolled both testosterone therapy (TTh) naïve and TTh experienced TDS adult males (N=306) from 29 up to 80 years of age (mean age 54.4, 28 subjects <40 years old, 77 subjects 40-49 years old, 97 subjects 50-59 years old, 78 subjects 60-69 years old, 26 subjects ≥70 years old). After a 3 to 7-week screening period that included a 2 or 4-week washout period for patients that had previously been receiving topical TTh and injectable TTh, respectively, subjects were randomized into either twice daily or three times a day treatment groups. The twice daily group could be uptitrated to three times a day on Day 45 based on achieving certain morning serum total testosterone levels. Each dose consisted of two 5.5 mg/nostril for a total of 11 mg of TNG per dose. In general, subjects were followed for 90- days. Body mass index (BMI) assessments extended to 180 days of follow up. On Days 30 and 90, subjects had PK blood draws taken 15 minutes prior and at 0.33, 0.67, 1.0, 1.5, 2.0, 3.0, 6.0, 9.0 hours after dosing at the time of both the morning and the evening dose. Serum total testosterone (TT) levels were evaluated using a validated LC-MS/MS method using an API 4000 LC-MS/MS system by Analytical Biochemical Laboratory (ABL, Assen, Netherlands). [1] The analytical range for the assay was 0.500 – 50.0 ng/mL. LH, FSH and lean body mass were assessed on Day 1 and day 90 and change from baseline was calculated using Day 1 levels as baseline.

The phase 3 study was approved by institutional review boards and the subjects all signed an informed consent form.

Pharmacokinetic Analyses

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

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 subjects. IIEF 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 from the day 180 measurement.

Adverse Events

Adverse Events (AEs) for the study have previously been described. [1] 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%). 4.6% of subjects had at least one severe AE and one subject (0.3%) had a severe drug-related AE (myalgia, which did not require study drug discontinuation or dose adjustment and

remitted after initiating concomitant medication). Although 8 subjects had serious AEs in the study, none were considered related to study medication.

Statistical analyses

All analyses were performed using SAS (version 9.4; Cary, NC). P values were calculated using ANOVA PROC GLM. Baseline or pre-dose strata were used as a fixed effect. Linear regression was used to test the relationship between two parameters for non-stratified data. A significance level (α) of 0.05 was used.

Results:

In this post-hoc analysis, qualifying patients (N=180) who completed day 30 and 90 evaluations were stratified based on pre-dose 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 5 groups having similar numbers of subjects in each group.

Demographic parameters of stratified subgroups are found in Table 1. Table 1 also provides mean testosterone levels, as well as IIEF and PANAS values at baseline for the 5 groups.

Mean PK parameters, such as peak serum total testosterone concentration (C_{max}), area under the plasma concentration-time curve during a dosage interval (τ) (AUCτ) and average plasma drug concentration over a 24-hour period (C_{avg}), were determined for TT for each stratum at day 30 and day 90. Notably, peak total testosterone (C_{max}) did not significantly differ across strata at day 30 despite the pre-dose endogenous TT levels differing nearly 250 ng/dL (8.7 nmol/L) between the highest and lowest groups (Figure 1). This observation was consistent across strata regardless of whether the PK analysis was from day 30 morning (p=0.08) (Figure 2a) or evening (p=0.72) dosing (Figure 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 testosterone to the circulating endogenous TT concentration (p=0.06) (Figure 2c). A similarly limited increase in the C_{avg} was seen for subjects on both twice daily and three times a day doses (data not shown). Mean AUCτ also showed a very modest increase as a function of the pre-dose TT (baseline) concentration (data not shown).

Figure 3 illustrates changes in erectile function (IIEF) and Figure 4 highlights mood changes (PANAS) 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 pre-doses <100 ng/dL (3.5 nmol/L) had similar (≈40%) improvements in erectile function on days 30, 60 and 90 as patients with TT pre-doses >100 ng/dL (3.5 nmol/L) (p=0.89). Similar findings were noted in PANAS scores. Specifically, patients with TT pre-doses <100 ng/dL (3.5 nmol/L) had similar increases in positive mood states (p=0.92) and similar decreases in negative mood states (p=0.37) at day 90 as patients with pre-doses >100 ng/dL (3.5 nmol/L) (Figure 4).

Mean LH and FSH levels when measured at 2 hours, and 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 pre-dose levels of TT (Figure 5a). Patients with low levels of endogenous testosterone also had significant improvements in lean body mass (Figure 5b).

Discussion:

TNG is a product that maintains the endogenous HPG axis. This is clearly visible in single dose PK profiles in healthy and TDS men where the pre-dose value (t=0) which corresponds to the patients endogenous TT level, is found again at the bottom of the trough between peaks and is maintained through 90 days of treatment (both on twice daily and three times a day doses). Further evidence of active HPG when on TNG treatment is found in a recent trial showing unchanged sperm counts after 6 months TNG treatment (three times a day dose only).[17] In larger trials, LH and FSH measurements were made proximal to a peak of TNG and were somewhat depressed, but remained in the normal range.[1] Our interpretation of these observations is that the HPG axis is active and that there is temporal suppression when TNG doses are administered. This suppression appears to recover completely based on consistent trough values over time.

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 based on pre-dose TT levels. The stratification produced groups that were similar in number and characteristics, to the exception of their hormone levels.

TNG restored mean C_{avg} TT levels in all of the groups, to the exception of the most androgen deficient patients for whom a mean value of 295 ng/dL (10.2 nmol/L) was obtained and only 35% were above 300 ng/dL (10.4 nmol/L). A significant portion of these patients were on the bid dose. Regardless, all groups showed statistically significant improvement in 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} is the same across all stratified groups, regardless of the starting pre-treatment/pre-dose (baseline) TT levels (Figure 1 and Figure 2); (ii) LH and FSH suppression occurs at 2 hours post dose in all instances with the largest suppression occurring for patients with higher initial LH and FSH levels (Figure 5a); (iii) there is a trend of increasing C_{avg} with increasing baseline TT but it appears to be well below what would be expected (Figure 2c). All of 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 are not independently quantifiable in this study. When exogenous testosterone is administered, there is a suppression of LH and testosterone production. Endogenous testosterone levels decrease as a result of ongoing elimination and reduced or halted production. Later (more than 1 hour after administration), as the exogenous testosterone absorption rate is reduced and elimination predominates resulting in a drop in exogenous testosterone, the HPG recovers re-initiating endogenous testosterone production (Figure 6a). The degree of HPG suppression appears to be proportional to the initial baseline TT. For less severe HG patients with a supposedly more active HPG and higher baseline TT level, there is more endogenous testosterone suppression during each dose than for a more severe HG patient with less HPG axis potential (Figure 6b). This model is supported by the larger decreases in LH in patients with higher baseline TT seen in this study. It should be noted that administration of TNG to healthy males with a pre-dose baseline of 534 ng/dL (18.4 nmol/L) also showed C_{max} peak levels in the same range as seen here and again a return to pre-dose baseline nearly 6 hours after a dose.[16]

Thus, TNG's ultradian profile is the means to maintain an active HPG. In spite of 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 subjects with very low endogenous TT levels were smallest. 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 pre-dose and pre-study baseline levels were not absolutely identical over all timepoints in the study and 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 subjects had a C_{max} of 1800–2500 ng/dL (63.0-87.0 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 side effects of testosterone treatment, such as hematocrit overproduction (no subjects 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. And, lastly, as shown here, the combination of peaks and troughs are sufficient to achieve symptom efficacy even for the most severe TDS patients in this study. Overall, there are positive benefits to a treatment approach that is compatible with HPG physiology.

Conclusions

Testosterone nasal gel treatment restores TT levels while preserving significant aspects of HPG function, including continued release of gonadotropins and production of endogenous testosterone, which allows maintenance of baseline levels. Both modest TDS (TT 250-300 ng/dL; (8.7 – 10.4 nmol/L)) and more severe TDS patients (TT 0-100 ng/dL (0 – 3.5 nmol/L), when treated with TNG, achieve max TT levels around 800 ng/dL (27.7 nmol/L). Efficacy, as measured by erectile function and mood were 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 testosterone deficient patients can effectively be treated with it.

Acknowledgments:
The authors would like to thank Ricky Tang for his statistical contributions.

Clinical Trials Identifier: NCT01446042

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Disclosure:
MAG, RWO and NB are employed by and own shares and options in Acerus Pharmaceuticals Corporation.

DATA AVAILABILITY

The datasets 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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Figure 1: Average total testosterone concentrations from dosing to 10 hours post-dose. Patients are stratified by their pre-dose concentration.

Figure 2: Effect of pre-dose 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 pre-doses below 100, "150" contains patients from 100 to <150, etc. c) Effect of pre-dose concentration on C_{avg} over 24 hours on day 90.

Figure 3: IIEF change from baseline to day 90. Subjects are stratified by their pre-dose concentration. The numbers indicate strata that contain patients with pre-dose values less than the indicated number down to the number to its left.

Figure 4: a) Positive and b) Negative PANAS scores in patients with baseline testosterone concentrations below 100 or above 100. PANAS was measured at baseline and then every 30 days.

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 pre-dose concentrations. Line of best fit is indicated.

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 more severe TDS patient, and ii) a less severe TDS patient.

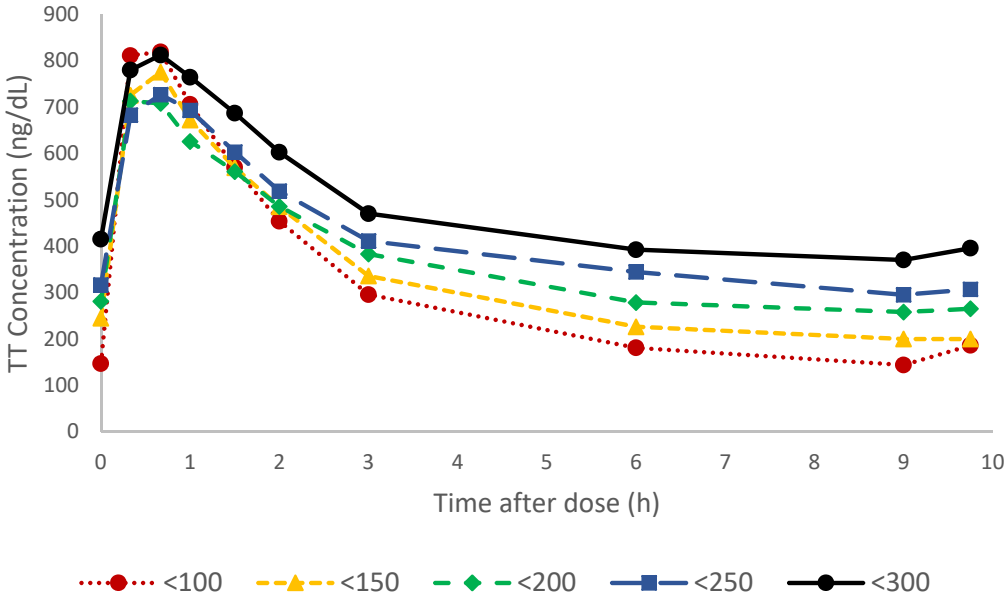


Figure 1

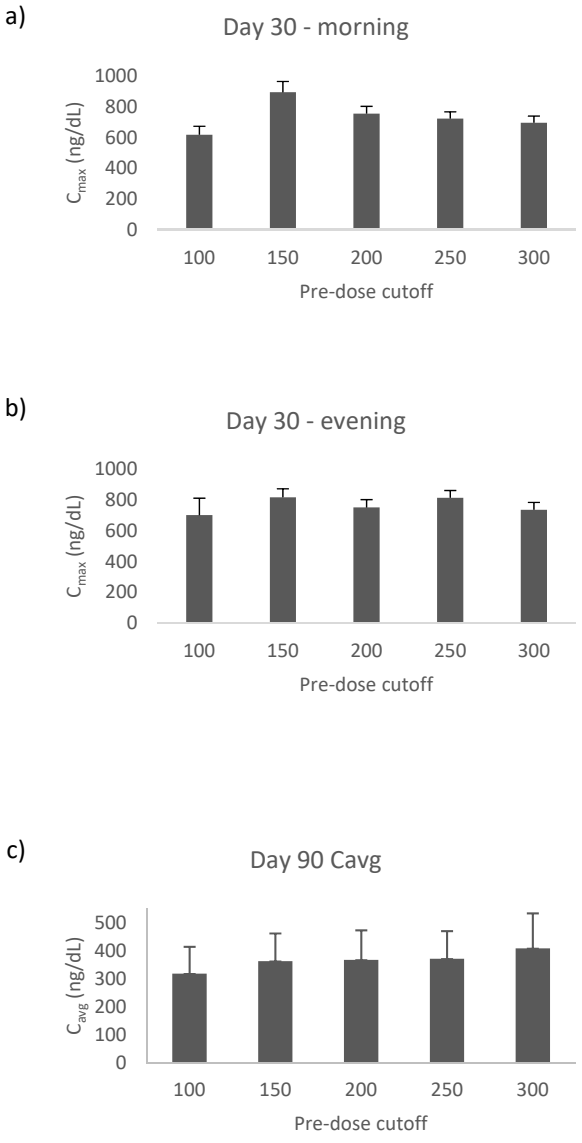


Figure 2

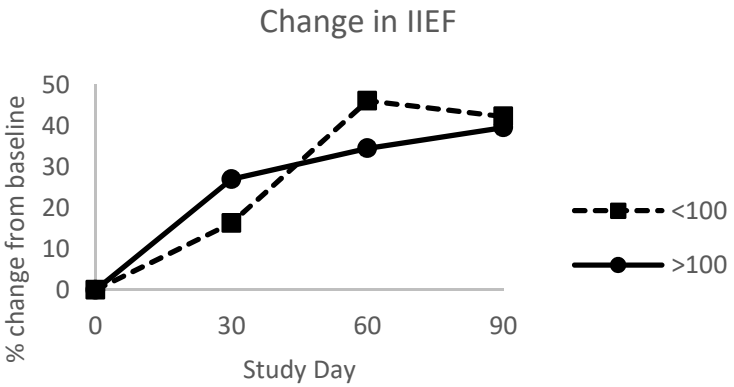
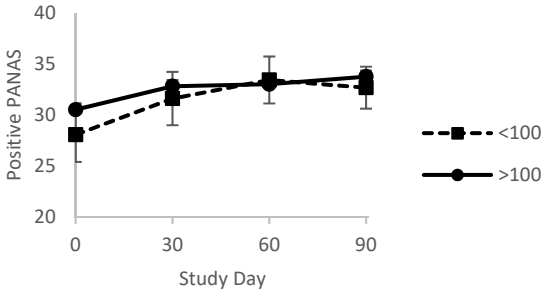


Figure 3

a)



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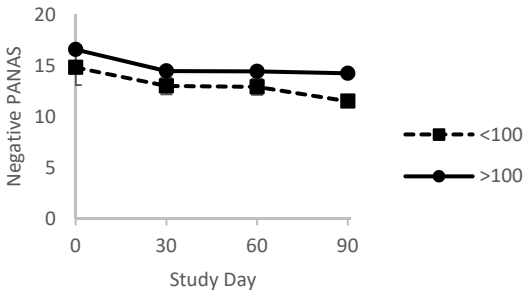
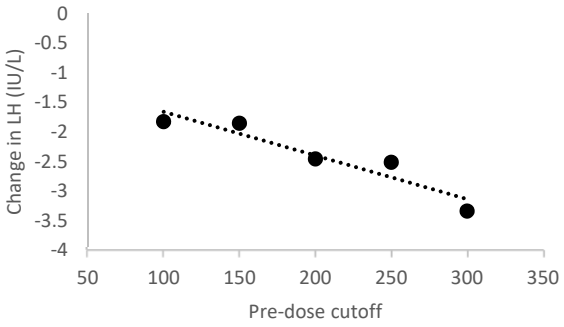


Figure 4

a)



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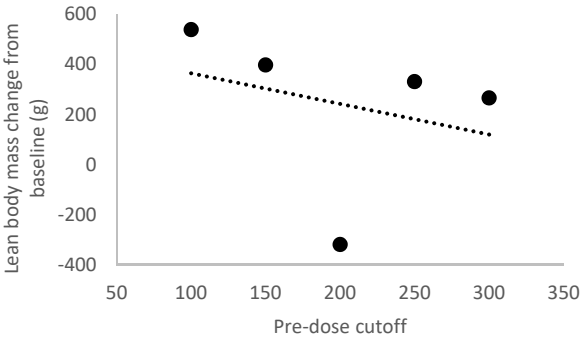

Figure 5

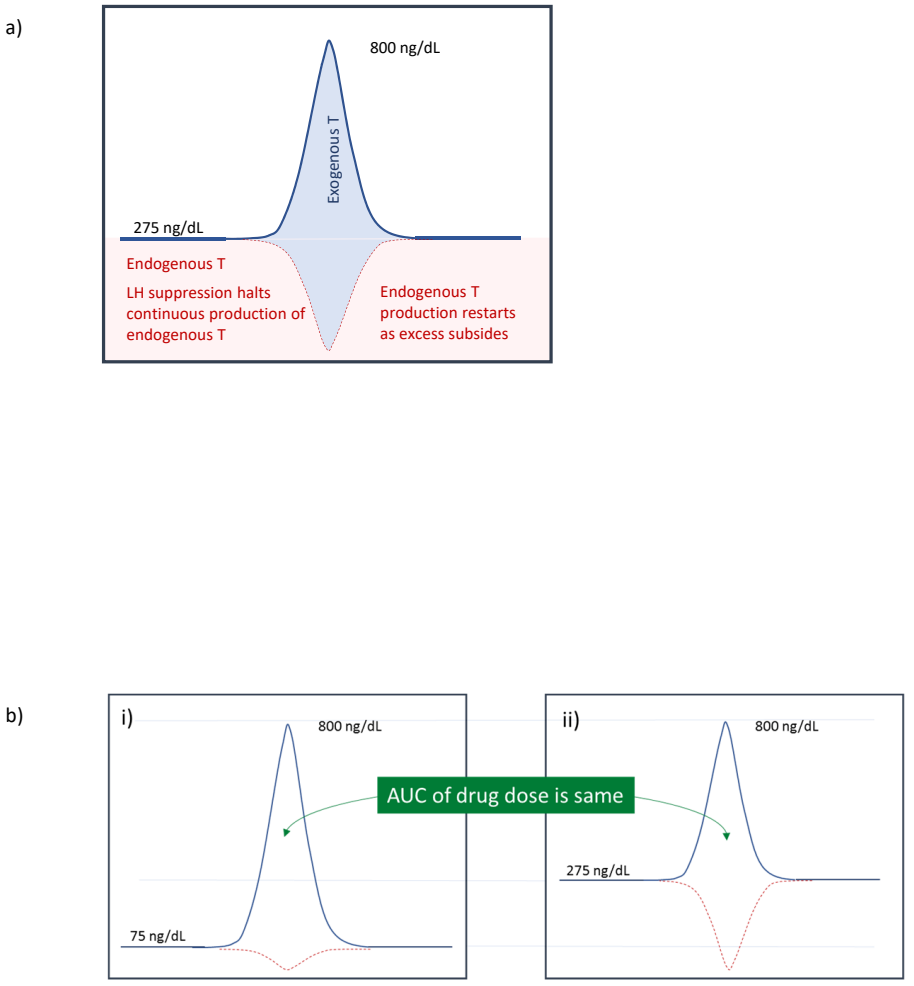

Figure 6