CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205488Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 205488	Submission Dates: 4/29/2013, 6/19/2013, 7/30/2013, 8/16/2013, 9/4/2013, 10/4/2013, 10/9/2013, 11/4/2013, 1/13/2014, 2/6/2014, and 3/11/2014
Proposed Brand Name:	NATESTO
Generic Name:	Testosterone (T)
Clinical Pharmacology Primary Reviewer:	Chongwoo Yu, PhD
Clinical Pharmacology Secondary Reviewer:	Myong-Jin Kim, PharmD
Pharmacometrics Primary Reviewer:	Jiang Liu, PhD
Pharmacometrics Secondary Reviewer:	Yaning Wang, PhD
OCP Divisions:	Division of Clinical Pharmacology 3 (DCP3) and Division of Pharmacometrics
OND Division:	Division of Bone, Reproductive, and Urologic Products (DBRUP)
Sponsor:	Trimel Biopharma SRL
Submission Type:	Original / 505(b)(2)
Relevant IND	IND 70512
Formulation, Strength, and Dosing Regimen	Nasal gel (4.5% T), 33 mg/day (11 mg TID) fixed dose
Indication:	Treatment of male hypogonadism

An Optional Inter-Division Clinical Pharmacology Briefing was held on Wednesday, April 23, 2014. The attendees were as follows: C. Yu, M-J Kim, L. Lee, H. Kim, L. Li, S. Al Habet, P. Balimane, M. Hirsch, R. Wiederhorn, L. Reid, J. Shon, and N. Zhang. Concurrence on the recommendations in this review was obtained from DCP3 Division Director, Dr. E. D. Bashaw on April 23, 2014.

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1 EXECUTIVE SUMMARY

The Sponsor submitted a 505(b)(2) New Drug Application (NDA) for NATESTO (i.e., TBS-1 formulation) on April 29, 2013. NATESTO is a testosterone (T) nasal gel (4.5% w/w) available in a dispenser with a metered dose pump for the treatment of male hypogonadism associated with a deficiency or absence of endogenous T.

The Sponsor originally proposed to initiate NATESTO therapy with 11 mg T two times daily (BID) dosing, (b) (4) However, the Division's analysis o (b) (4) dosing regimen. This concern was conveyed to the Sponsor on October 9, 2013. Subsequently, the Sponsor submitted a major amendment on January 13, 2014 with a new proposal to administer NATESTO as an 11 mg T TID regimen (b) (4). The review clock was extended for 3 months due to this major amendment and the new Prescription Drug User Fee Act (PDUFA) goal date is May 28, 2014. The primary efficacy and safety analyses for this NDA are based on the TBM 11 mg T TID regimen. Therefore, the Question Based Review (QBR) portion of this review is mainly focused on the 11 mg TID regimen whereas the Appendix (i.e., Individual Study Reviews and Pharmacometric review) also discusses about data and analyses of other dosing regimens that were considered earlier.

The proposed dosing regimen of NATESTO is 11 mg of T (i.e., an (b) (4) actuation of 5.5 mg of T per nostril) administered TID intranasally, once in the morning, once in the afternoon, and once in the evening (i.e., about 6-8 hours apart), preferably, at the same time each day (i.e., daily dose of 33 mg T). Serum total T concentrations should be monitored after initiation of therapy to ensure that the desired concentrations (i.e., 300-1050 ng/dL) are achieved.

The Sponsor submitted 9 Clinical Pharmacology/Biopharmaceutics and Clinical studies including the pivotal Phase 3 study (Study TBS-1-2011-03), a Phase 2 dose-finding study conducted in hypogonadal males (Study TBS-1-2010-01), a Phase 1 relative bioavailability (BA) study comparing NATESTO administration using a prefilled syringe and a multiple-dose dispenser (Study TBS-1-2011-01), and a Phase 1 drug-drug interaction (DDI) study (Study TBS-1-2011-04) to assess the relative BA, safety, and tolerance of NATESTO when administered to patients with seasonal allergic rhinitis in the symptomatic/untreated, symptomatic/treated, and asymptomatic states. Of the 9 clinical studies submitted, 4 studies were conducted using the to-be-marketed formulation. The other 5 studies were conducted using earlier investigational formulations that are not relevant to the TBM formulation and therefore, they were not reviewed.

A formal consult to the Office of Scientific Investigations (OSI) was made for clinical and bioanalytical study site inspections and there are no unresolved inspection findings related to the approvability of NATESTO.

1.1 Recommendation

The Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology 3 (DCP-3) has reviewed NDA 205488 submitted on April 29, 2013, June 19, 2013, July 30, 2013, August 16, 2013, September 4, 2013, October 4, 2013, October 9, 2013, November 4, 2013, January 13, 2014, February 6, 2014, and March 11, 2014. The overall Clinical Pharmacology information submitted to support this NDA is acceptable and NATESTO is recommended for approval from the Clinical Pharmacology standpoint.

1.2 Post-marketing Requirements or Commitments

None

1.3 Summary of Important Clinical Pharmacology Findings

The Sponsor originally proposed to initiate NATESTO therapy with 11 mg T BID dosing, (b) (4) The following comment was conveyed to the Sponsor via an information request (IR) letter on October 9, 2013:

We have conducted an analysis of the primary efficacy data from TBS-1-2011-03 and (b) (4) *the to-be-marketed dosing regimen. In the intent-to-treat (ITT) population, using last observation carried forward (LOCF) methodology for missing data, the point estimates and 95% confidence intervals that we determined for the various treatment groups (including BID, BID to TID, BID plus BID to TID, and TID) indicate that the agreed-upon level of success was achieved* (b) (4) *in the TID group (n=73).*

Subsequently, the Sponsor submitted a major amendment on January 13, 2014 with a new proposal to administer NATESTO as an 11 mg T TID regimen (b) (4). This review will focus on the evaluation of the 11 mg T TID regimen unless specified otherwise as the Sponsor is no longer pursuing other dosing regimens.

Formulation:
NATESTO is a slightly yellow nasal gel that is a viscous bioadhesive oil-based formulation containing solubilized T. The active pharmacologic ingredient in NATESTO is T. Early development of NATESTO formulation involved varying the volume of the gel applied to the nasal cavity, the concentration of T (i.e., % w/w), the dose, and the daily dosing regimen. The TBM formulation of NATESTO is supplied in a labeled clear, non-aerosol, multiple dose pump container. The multiple-dose dispenser uses a finger-actuated dispensing system designed to dispense NATESTO from a non-pressurized container. Each actuation (i.e., (b) (4)) contains 5.5 mg of T (4.5% w/w) in 122.5 mg NATESTO gel. Each dose consists of two actuations, one actuation per nostril (i.e., total of 11 mg T/dose). The commercial dispenser containing 11.0 g of NATESTO gel is designed to deliver 30 doses (i.e., 60 actuations). Of the 9 clinical studies submitted, 4 studies (i.e., Studies TBS-1-2011-03, TBS-1-2010-01, TBS-1-2011-04, and TBS-1-2011-01) were conducted using the TBM formulation.

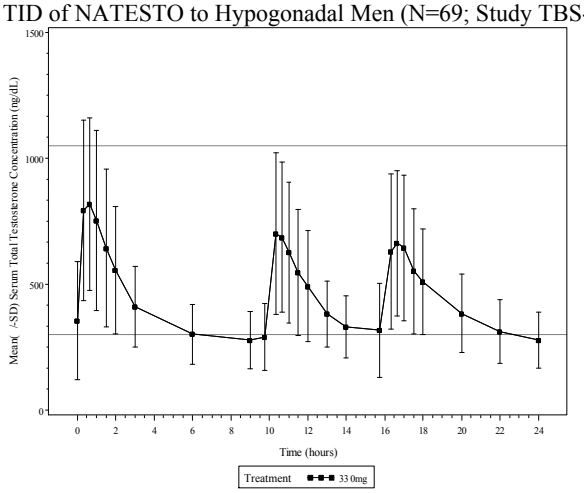
Absorption
Table 1 summarizes the arithmetic mean (SD) PK parameters of serum total T on Days 30 and 90 and Figure 1 shows the 24-hour serum total T concentration-time curve on Day 90.

Table 1: Arithmetic Mean (SD) PK Parameters of Serum Total T on Days 30 and 90 Following Administration of 11 mg T TID of NATESTO to Hypogonadal Men (Study TBS-1-2011-03)

	Day 30 (N=73[b])	Day 90 (N=69[b])
AUC(0-24) (ng·hr/dL)	9956.0 (2727.0)	10101.2 (2782.4)
C_{max} (ng/dL)	912.7 (342.9)	1043.9 (378.1)
C_{min} (ng/dL)	211.0 (73.2)	214.7 (73.8)
C_{avg} (ng/dL)	414.8 (113.6)	420.9 (115.9)
T_{max} (hr)[a]	0.70 (0.3, 8.0)	0.65 (0.3, 6.1)

[a] Median (min, max)
[b] Number of subjects who had a valid C_{max} at that visit. Sixty nine (69) subjects completed the 90-day treatment.

Figure 1: Plot of Mean (SD) Serum Total T Concentrations on Day 90 Following Administration of 11 mg T TID of NATESTO to Hypogonadal Men (N=69; Study TBS-1-2011-03)



Distribution, Metabolism, and Excretion

Distribution: Circulating T is primarily bound in the serum to sex hormone-binding globulin (SHBG) and albumin. Approximately 40% of T in plasma is bound to SHBG, 2% remains unbound (free) and the rest is bound to albumin and other proteins.

Metabolism: There is considerable variation in the half-life of T as reported in the literature, ranging from 10 to 100 min. T is metabolized to various 17-keto steroids through two different pathways. The major active metabolites of T are 17β-estradiol (E2) and dihydrotestosterone (DHT). T is metabolized to DHT by steroid 5α-reductase located in the skin, liver, and urogenital tract of the male. DHT concentration increased in parallel with T concentration during NATESTO treatment. The serum DHT/T C_{avg} ratio for NATESTO on Day 90 ranged between 0.05 and 0.22 with a mean value of 0.09.

Excretion: About 90% of a dose of T given intramuscularly is excreted in the urine as glucuronic and sulfuric acid conjugates of T and its metabolites; about 6% of a dose is excreted in the feces, mostly in the unconjugated form. Inactivation of T occurs primarily in the liver.

Overall Efficacy and Safety Conclusion: The efficacy and safety of NATESTO was demonstrated successfully in hypogonadal males with the TBM dosing regimen (i.e., 11 mg T TID).

Primary Efficacy Endpoint Analysis

The Sponsor submitted one Phase 3 study to support the clinical efficacy and safety of NATESTO. Study TBS-1-2011-03 was an open-label, multicenter (i.e., 34 U.S. sites) study consisting of a 90-day treatment period and 2 safety extension periods (i.e., 90 days and an additional 180 days) conducted in hypogondal men (i.e., 18-80 yrs. of age; body mass index [BMI] of 18.5-35 kg/m^2). Three hundred six (306) subjects were randomly assigned across the 2 treatment groups in a 3:1 ratio, to either 11 mg T BID (i.e., administered at 9 pm and 7 am on the following morning; 22 mg/day) or 11 mg T TID (i.e., administered at 9 pm and 7 am and 1 pm on the following day; 33 mg/day).

The primary efficacy analysis was conducted based on the total T C_{avg} data collected from the 11 mg T TID treatment group on Day 90 LOCF with the following endpoints.

- 75% or more of patients having a total T C_{avg} in the normal range of 300-1,050 ng/dL

- Lower limit of the 95% confidence interval (CI) being 65% or higher

The pre-specified efficacy criteria were achieved on Day 90 LOCF (Table 2).

Table 2: The Number and Percentage of the Subjects in the ITT Population by Serum Total T C_{avg} Categories on Day 90 LOCF Following Administration of 11 mg T TID of NATESTO to Hypogonadal Men (N=73[a]; Study TBS-1-2011-03)

C_{avg} in normal range ($300 \leq C_{avg} \leq 1050$ ng/dL)	
Yes (N)	66
%	90
95% CI for frequency[b]	(84, 97)
C_{avg} below normal range ($C_{avg} < 300$ ng/dL)	
Yes (N)	7
%	10
C_{avg} above normal range ($C_{avg} > 1050$ ng/dL)	
Yes (N)	0
%	0

[a] Subjects in the ITT population on Day 90 LOCF
[b] The CI for the frequency was approximated by a binomial distribution within each treatment.

Critical Secondary Safety Endpoint Analysis
The critical secondary safety endpoint, total T C_{max}, had the following criteria that were expected to be met on Day 90:

- Having < 5% of subjects with a serum total T C_{max} in the range of 1,800-2,500 ng/dL
- No subjects with a serum total T C_{max} of > 2,500 ng/dL
- Having a serum total T $C_{max} \leq 1,500$ ng/dL in at least 85% of subjects

The following criteria of the critical secondary safety endpoint, total T C_{max}, were met:

- Having < 5% of subjects with a serum total T C_{max} in the range of 1,800-2,500 ng/dL
- No subjects with a serum total T C_{max} of > 2,500 ng/dL

However, 0.9% less subjects (i.e., 84.1%) had a serum total T $C_{max} \leq 1,500$ ng/dL on Day 90 compared to the pre-specified criteria. Table 3 presents the number and percentage of subjects in the ITT population on Day 90.

Table 3: Number (Percentage) of Subjects in the ITT Population by Selected Ranges of Serum Total T C_{max} on Day 90 Following Administration of 11 mg T TID of NATESTO to Hypogonadal Men (Study TBS-1-2011-03)

Number of subjects[a]	69
$C_{max} \leq 1,500$ ng/dL	58 (84.1)
1800 ng/dL $\leq C_{max} \leq 2,500$ ng/dL	1 (1.4)
$C_{max} > 2,500$ ng/dL	0 (0)

[a] The number of subjects who had a C_{max} value at Day 90

OSI consult: A formal consult to the OSI was made for clinical study site inspections and there are no unresolved inspection findings related to the approvability of NATESTO. Reference is made to Dr. Gopa Biswas's OSI Memorandum dated December 20, 2014 under NDA 205488 in DARRTS.

Drug-Drug Interaction
***DDI in males with seasonal allergic rhinitis treated with nasal decongestant, oxymetazoline*:**
A Phase 1, open label, randomized 3-way crossover, 3-treatment, 3-period DDI study (Study TBS-1-2011-04) in male subjects with seasonal allergic rhinitis (aged 18-45 years) in symptomatic/untreated, symptomatic/treated, or asymptomatic states to assess the relative BA,

safety, and tolerance of NATESTO was conducted. The baseline-uncorrected serum T PK parameters are summarized in Table 4.

Table 4: Baseline-Uncorrected Serum T PK Parameters
in Healthy Men With Seasonal Allergic Rhinitis by Treatment State
Following 11 mg T TID Administration of NATESTO for 1 Day (N=14; Study TBS-1-2011-04)

	Treatments	Mean	SD	% Change from Asymptomatic
AUC(0-24) (ng·hr/dL)	Pre-treatment	10949.8	2215.0	NA
	Asymptomatic	16746.9	3894.3	-
	Symptomatic	13217.4	3589.1	21.1% ↓
	Sympt. treated	12778.2	3379.6	23.7% ↓
C_{max} (ng/dL)	Pre-treatment	631.4	149.7	NA
	Asymptomatic	1063.2	223.0	-
	Symptomatic	909.9	241.8	14.4% ↓
	Sympt. treated	872.0	267.7	18.0% ↓
C_{avg} (ng/dL)	Pre-treatment	456.6	92.1	NA
	Asymptomatic	695.6	163.7	-
	Symptomatic	549.3	149.6	21.0% ↓
	Sympt. treated	532.2	141.0	23.5% ↓

NA: Not applicable

Total T exposure (i.e., AUC[0-24], C_{max}, and C_{avg}) was higher under asymptomatic state compared to symptomatic states regardless of treatment with oxymetazoline. The difference between the 2 symptomatic states were relatively small compared to the difference of those with the asymptomatic state, indicating that administration of oxymetazoline might not hugely impact the absorption of T following the administration of NATESTO.

Other available information on T DDI:
The following information is available in the labeling of topical drugs in the same drug class (i.e., Testim®, AndroGel®, or Axiron®): Changes in insulin sensitivity or glycemic control may occur in patients treated with androgens. In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, may necessitate a decrease in the dose of anti-diabetic medication. Changes in anticoagulant activity may be seen with androgens. Therefore, more frequent monitoring of International Normalized Ratio (INR) and prothrombin time is recommended in patients taking warfarin, especially at the initiation and termination of androgen therapy. The concurrent use of T with corticosteroids may result in increased fluid retention and requires monitoring particularly in patients with cardiac, renal, or hepatic disease.

Use in Specific Populations and Pediatric Study Waiver Request
Geriatric Use: There have not been sufficient numbers of geriatric patients involved in controlled clinical studies utilizing NATESTO to determine whether efficacy in those over 65 years of age differs from younger subjects. Of the 306 subjects enrolled in the Phase 3 study utilizing NATESTO (Study TBS-1-2011-03), 78 subjects were randomized to the 11 mg T TID treatment group. Among those 78 subjects, 17 subjects were 65 years of age or older. No subgroup analysis for efficacy and safety was conducted by the Sponsor. Additionally, there were insufficient long-term safety data in geriatric patients utilizing NATESTO to assess a potential increased risk of cardiovascular disease and prostate cancer.

Renal / Hepatic Impaired Patients: No studies were conducted in patients with renal or hepatic impairments.

Pediatric Use and Pediatric Study Waiver Request: No pediatric studies with NATESTO were conducted and the Sponsor submitted a full pediatric study waiver request for all pediatric age

groups (i.e., children from birth to age of 18 years). Safety and efficacy of NATESTO has not been established in males < 18 years of age.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because NATESTO is administrated intranasally (i.e., new route of administration), PREA is triggered. The Agency's pediatric review committee (PeRC) discussed the Sponsor's request on November 20, 2013 and agreed with the requested full waiver because pediatric studies are impossible or highly impractical because the disease/condition does not occur in children.

Bioanalytical Methods
Serum samples were analyzed for total T, DHT, and E2 using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods. A formal consult to the OSI was made for the bioanalytical study site inspection and there are no unresolved inspection findings related to the approvability of NATESTO. Reference is made to Dr. Gopa Biswas's OSI Memorandums dated December 20, 2014 and March 14, 2014 under NDA 205488 in DARRTS.

The acceptance criteria and performance of the total T, DHT, and E2 bioanalytical methods are in compliance with the Agency's *Bioanalytical Method Validation Guidance*. The method validation and performance of the bioanalytical methods in clinical studies are acceptable.

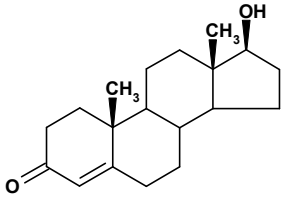
2 QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What is NATESTO and what is its active pharmacological ingredient?

NATESTO is a slightly yellow nasal gel that is a viscous bioadhesive oil-based formulation containing solubilized T. The active pharmacologic ingredient in NATESTO is T. The empirical formula of T is $C_{19}H_{28}O_2$ and its molecular weight is 288.4. T USP is a white to practically white crystalline powder chemically described as 17-beta hydroxyandrost-4-en-3-one.

Figure 2: Structural Formula of T



$C_{19}H_{28}O_2$ MW = 288.4

The inactive ingredients are castor oil, oleoyl polyoxylglycerides, and colloidal silicon dioxide.

2.1.2 What clinical data and related information was submitted to support the approval of NATESTO?

The Sponsor submitted 9 Clinical Pharmacology/Biopharmaceutical and Clinical studies including a Phase 3 study (Study TBS-1-2011-03), a Phase 2 dose-finding study conducted in hypogonadal males (Study TBS-1-2010-01), a Phase 1 relative BA study comparing NATESTO administration using a prefilled syringe and a multiple-dose dispenser (Study TBS-1-2011-01), and a Phase 1 DDI study (Study TBS-1-2011-04) to assess the relative BA, safety, and tolerance of NATESTO when administered to patients with seasonal allergic rhinitis in the symptomatic/untreated, symptomatic/treated, and asymptomatic states.

In addition, the Sponsor submitted the following information:

- Draft labeling in physician labeling rule (PLR) format
- Bioanalytical study reports and method validation reports
- Request of waiver for pediatric studies

2.2 General Clinical Pharmacology

2.2.1 What is the proposed mechanism of action?

Endogenous androgens, including T and DHT, are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include the growth and maturation of prostate, seminal vesicles, penis, and scrotum; the development of male hair distribution, such as facial, pubic, chest, and axillary hair; laryngeal enlargement, vocal cord thickening, alterations in body musculature and fat distribution. T and DHT are necessary for the normal development of secondary sex characteristics. Male hypogonadism results from insufficient secretion of T and is characterized by low serum T concentrations. Signs/symptoms associated with male hypogonadism include erectile dysfunction and decreased sexual desire, fatigue and loss of energy, mood depression, regression of secondary sexual characteristics and osteoporosis.

Male hypogonadism has two main etiologies. Primary hypogonadism is caused by defects of the gonads, such as Klinefelter's Syndrome or Leydig cell aplasia, whereas secondary hypogonadism is the failure of the hypothalamus (or pituitary) to produce sufficient gonadotropins (i.e., follicle-stimulating hormone [FSH], luteinizing hormone [LH]).

NATESTO was developed with an aim to ensure that the desired serum total T concentrations (i.e., 300-1,050 ng/dL) are achieved in hypogonadal men following intranasal treatment with NATESTO.

2.2.2 What are the proposed dosing regimen and administration instructions?

The Sponsor originally proposed to initiate NATESTO therapy with 11 mg T BID dosing, (b) (4) [redacted]. The following comment was conveyed to the Sponsor via an IR letter on October 9, 2013:

We have conducted an analysis of the primary efficacy data from TBS-1-2011-03 and (b) (4) [redacted] *the to-be-marketed dose regimen. In the ITT population, using LOCF methodology for missing data, the point estimates and 95% confidence intervals that we determined for the various treatment groups (including BID, BID to TID, BID plus BID to TID, and TID) indicate that the agreed-upon level of success was achieved* (b) (4) *in the TID group (n=73).*

Subsequently, the Sponsor submitted a major amendment on January 13, 2014 with a new proposal to administer NATESTO as an 11 mg T TID regimen (b) (4).

The proposed dosing regimen of NATESTO is 11 mg of T (i.e., an (b) (4) actuation of 5.5 mg of T per nostril) administered intranasally three times daily, once in the morning, once in the afternoon, and once in the evening (i.e., about 6-8 hours apart), preferably, at the same time each day. Serum total T concentrations should be measured after initiation of therapy to ensure that the desired concentrations (i.e., 300-1,050 ng/dL) are achieved. NATESTO should not be administered to other parts of the body.

In the *Dosage and Administration* Section of the proposed NATESTO product label, the Sponsor proposes the following:

- NATESTO should be administered intranasally three times daily (i.e., 11 mg T TID) once in the morning, once in the afternoon, and once in the evening (i.e., about 6-8 hours apart), preferably at the same time each day.
- The user should refrain from blowing his nose or sniffing for (b) (4) minutes after administration.

In the Phase 3 efficacy and safety study (Study TBS-1-2011-03), NATESTO was given as 11 mg T, once in the late evening (i.e., 9 pm), once in the early morning (i.e., 7 am), and in the early afternoon (i.e., 1 pm) of the following day. Considering that NATESTO will be given chronically three times a day, the Sponsor's proposal of starting the dose in the morning appears to be reasonable. It should be also noted that subjects who participated in this study were instructed not to blow their nose or sniff for 1 hour after intranasal administration of NATESTO and this should be reflected (i.e., 1 hour instead (b) (4) minutes) of in the *Dosage and Administration* Section of the product label.

When using NATESTO for the first time, patients should be instructed to prime the pump by depressing the pump 10 times, discard any small amount of product dispensed directly onto a tissue. This priming should be done only prior to the first use of each dispenser. After priming, patients should completely depress the pump 1 time per nostril to dispense 5.5 mg T for each nostril (i.e., a total of 11 mg T per dose).

Keeping the dispenser upright, in front of a mirror, patients should advance the tip of the actuator into one nostril until the thumb or index finger on the pump reaches the base of the nose. The opening on the tip of the actuator should face the mucosa that lines the outer nasal wall. The pump should be depressed until it stops and the actuator should be slowly removed from the nose. The process should be repeated for the other nostril. Once the gel is administered into the nose, the nostrils may be pressed lightly together and massaged. Users should replace the cap on the dispenser for storage.

2.2.3 What are the multiple dose PK parameters of total T following administration of NATESTO?

Complete PK profiles of serum total T on Days 30 and 90 were characterized in a Phase 3, 2-group, multicenter (i.e., 34 centers in the U.S.) study consisting of 90-day treatment period and 2 safety extension periods (i.e., 90 days and an additional 180 days) conducted in hypogondal men (i.e., 18-80 yrs. of age). Three hundred six (306) subjects were randomly assigned across the 2 treatment groups in a 3:1 ratio to either 11 mg T BID or 11 mg T TID dosing regimen. NATESTO was administered nasally using a multiple-dose dispenser. On Day 1, the first dose was administered at 9 pm at the study site.

- 11 mg T BID treatment group: 5.5 mg T per nostril from NATESTO at 9 pm and 7 am for a total daily dose of 22 mg/day.
- 11 mg T TID treatment group: 5.5 mg T per nostril from NATESTO at 9 pm, 7 am, and 1 pm for a total daily dose of 33 mg/day.

Administration of study drug occurred at ± 5 min from the indicated time. On Days 30 and 90, subjects brought their NATESTO medication to the site for administration and performance of the 24-hour post-dose complete PK characterization of serum total T, DHT, and E2.

Subjects were instructed not to blow their nose or sniff for 1 hour after intranasal administration of NATESTO. Subjects were confined to the study site after the 9 pm NATESTO administration and were provided standardized meals during characterization of the 24-hour PK profiles on Days 30 and 90. For the 11 mg T TID treatment group, PK blood samples were collected at the following time points: at 0.25 hour pre-dose and 0.33, 0.66, 1.0, 1.5, 2.0, 3.0, 6.0, 9.0, 9.75, 10.33, 10.66, 11.0, 11.5, 12.0, 13.0, 14.0, 15.75, 16.33, 16.66, 17.0, 17.5, 18.0, 20.0, 22.0, and 24.0 hours post-dose (total 26 blood draws). Blood draws were took within ± 5 min from the indicated times when blood draw intervals were ≤ 30 min and within ± 15 min when blood draws were > 30 min.

Table 5 summarizes the arithmetic mean (SD) PK parameters of serum total T on Days 30 and 90 and Figure 3 is a plot of the 24-hour serum total T concentration-time curve obtained with a dose of 11 mg T TID (33 mg/day) of NATESTO that was administered intranasally using a multiple-dose dispenser to hypogonadal men for 90 days.

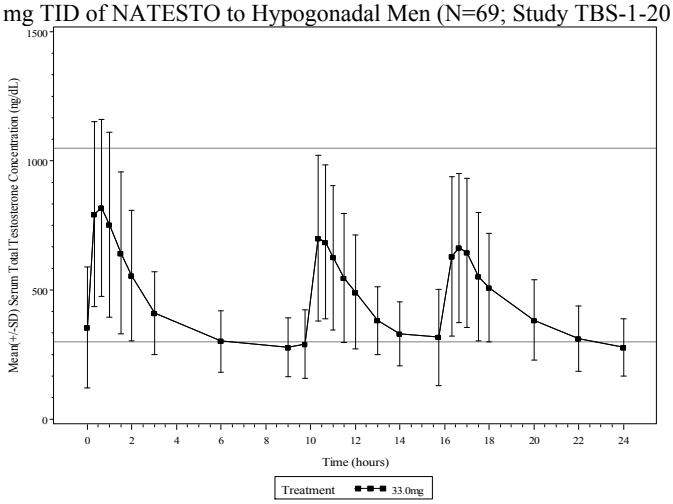
Table 5: Arithmetic Mean (SD) PK Parameters of Serum Total T on Days 30 and 90 Following Administration of 11 mg T TID of NATESTO to Hypogonadal Men (Study TBS-1-2011-03)

	Day 30 (N=73[b])	Day 90 (N=69[b])
AUC(0-24) (ng·hr/dL)	9956.0 (2727.0)	10101.2 (2782.4)
C_{max} (ng/dL)	912.7 (342.9)	1043.9 (378.1)
C_{min} (ng/dL)	211.0 (73.2)	214.7 (73.8)
C_{avg} (ng/dL)	414.8 (113.6)	420.9 (115.9)
T_{max} (hr)[a]	0.70 (0.3, 8.0)	0.65 (0.3, 6.1)

[a] Median (min, max)

[b] Number of subjects who had a valid C_{max} at that visit. Sixty nine (69) subjects completed the 90-day treatment.

Figure 3: Plot of Mean (SD) Serum Total T Concentrations at Day 90 Following Administration of 11 mg TID of NATESTO to Hypogonadal Men (N=69; Study TBS-1-2011-03)



As shown in Table 5 and Figure 3, mean T_{max} was at approximately 40 minutes post-dose regardless of the treatment length (i.e., 30 days vs. 90 days). The mean AUC(0-24), C_{max}, and C_{avg} values on Day 90 were slightly higher than those on Day 30.

2.2.4 How were the dose and the dosing regimen of NATESTO for the Phase 3 study and TBM product determined?

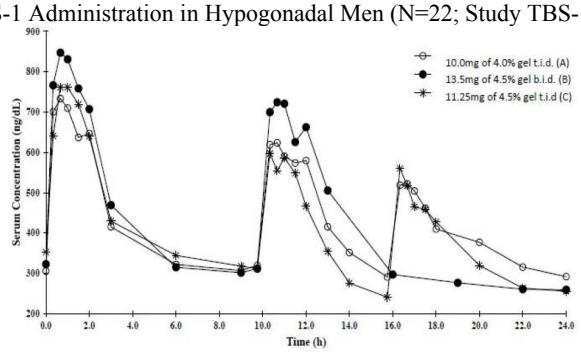
Reference is made to the minutes of the End of Phase 2 (EOP2) meeting held between the Division and the Sponsor on March 14, 2011 (dated May 4, 2011 under IND 70512 in DARRTS). A Phase 2 study, Nasobol-01-2009, examined the efficacy and tolerability of the 3.2% TBS-1 nasal gel formulation. In this study, the results for the 11 mg T BID dose did not meet the Agency's principle acceptance criterion for standard T therapies (i.e., at least 75% of subjects should achieve an average total T concentration within the normal range of 300-1,050 ng/dL). In addition, a linear increase in T concentrations with escalating doses was not achieved. The Sponsor believed that the lack of a linear increase suggested that T absorption was limited by inability of the nasal cavity to hold the tested volumes of the 3.2% TBS-1 formulation.

The dosing regimen selected for the Phase 3 efficacy and safety study (Study TBS-1-2011-03) was based on results from Studies TBS-1-2010-01 and TBS-1-2011-01. Based on the results of Study Nasabol-01-2009, the Sponsor conducted a Phase 2, dose-finding study, TBS-1-2010-01, evaluating higher concentrations of TBS-1 (i.e., 4.0% and 4.5% T w/w) formulations in reduced volumes. Study TBS-1-2010-01 was an open label, randomized, balanced, 3-treatments (4.0% TID, 4.5% BID, and 4.5% TID), parallel design, dose-finding, PK study of TBS-1 administered intranasally in 22 hypogonadal males (age of 35-73 years). Subjects were randomized to one of the following 3 treatment groups:

- Treatment A (N=8): TBS-1 syringes pre-filled with 125 µL 4.0% gel to deliver 5.0 mg of T per nostril (intranasal) given TID at 9 pm, 7 am, and 1 pm (total dose: 30 mg/day).
- Treatment B (N=7): TBS-1 syringes pre-filled with 150 µL 4.5% gel to deliver 6.75 mg of T per nostril (intranasal) given BID at 9 pm and 7 am (total dose: 27.0 mg/day).
- Treatment C (N=7): TBS-1 syringes pre-filled with 125 µL 4.5% gel to deliver 5.625 mg of T per nostril (intranasal) given TID at 9 pm, 7 am, and 1 pm (total dose 33.75 mg/day).

TBS-1 was administered for 7 days as per treatment group assignment. On Day 7, subjects for all treatment groups returned to their study centers and underwent a 24-hour PK sample collection after the 9 pm dosing. Total T PK profiles and parameters are presented in Figure 4 and Table 6.

Figure 4: Mean Serum T Concentration Over a 24-hour Dosing Period
on Day 7 of TBS-1 Administration in Hypogonadal Men (N=22; Study TBS-1-2010-01)



Source: Study TBS-1-2010-01 CSR, Figure 11.4.2.3-1.
N=8 for 10.0 mg TID and N=7 for both 13.5 mg BID and 11.25 mg TID.
0 hours corresponds to the time of administration of the dose (2100 hours).
BID=twice daily, h=hours, TID=three times per day.

Table 6: Mean Serum T PK Parameters Following 7 Days of TBS-1 Administration in Hypogonadal Men (N=22; Study TBS-1-2010-01)

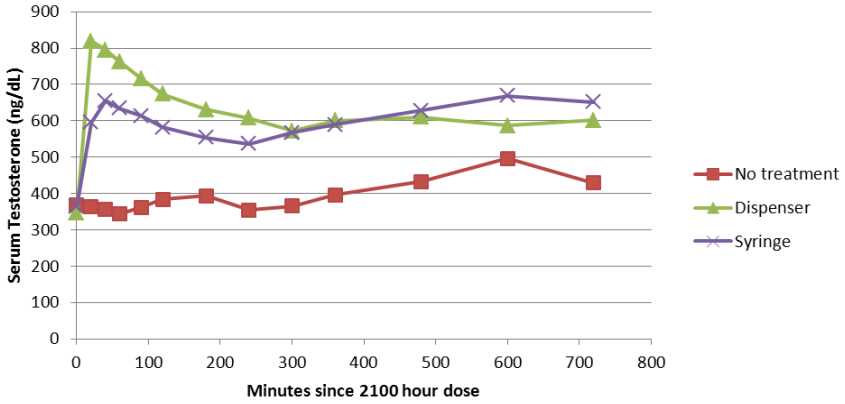
PK Parameter	Statistic	TBS-1 dose		
		10.0 mg TID (n=8)	13.5 mg BID (n=7)	11.25 mg TID (n=7)
AUC_{0-24} (h*ng/dL)	Mean (SD)	9920.07 (3300.65)	9781.39 (3532.43)	9505.03 (2650.59)
C_{avg} (ng/dL)	Mean (SD)	413 (138)	408 (147)	396 (110)
C_{max} (ng/dL)	Mean (SD)	830 (188)	1050 (463)	883 (346)
C_{min} (ng/dL)	Mean (SD)	239 (77.6)	224 (98.6)	222 (57.1)
Patients with C_{avg} below the normal range	%	12.50%	14.29%	14.29%
Patients with C_{avg} within the normal range	%	87.50%	85.71%	85.71%
Patients with C_{avg} above the normal range	%	0	0	0

Source: Study TBS-1-2010-01 CSR, Table 11.4.2.3-1.
AUC_{0-24}=area under the serum concentration-time curve from 0 to 24 hours postdose; BID=twice daily; C_{avg}=average observed concentration; C_{max}=maximum observed concentration; C_{min}=minimum observed concentration; n=number of patients included in the PK Population; PK=pharmacokinetic; SD=standard deviation; TID=three times per day.

Concentrating TBS-1 from 3.2% to 4.5% T (w/w) allowed for administration of a smaller amount of gel, resulting in improved and consistent absorption of T, and a higher response rate (i.e., achieving serum T average concentration [C_{avg}] values within the normal range) of subjects using 4.0% T and 4.5% T (w/w) versus 3.2% T (w/w) TBS-1 formulation. Regardless of the concentration of formulation and the dose, approximately 86-88% of the subjects had a total T C_{avg} within the normal range of 300-1,050 ng/dL. Two (2) out of 7 subjects (i.e., Subject 01-005 C_{max} = 1,670 ng/dL; Subject 02-006 C_{max} = 1,570 ng/dL) who were in the 13.5 mg BID (4.5% w/w) treatment group had a T C_{max} > 1,500 ng/dL. While both the BID and TID doses administered in this study had similar C_{avg} (approximately 400 ng/mL) within the normal range, the 13.5 mg BID (4.5% T w/w) regimen had a C_{max} value above the normal range, while the 11.25 mg TID (4.5% T w/w) regimen did not. All 3 treatments also demonstrated expected increases in mean serum DHT and E2 concentrations following TBS-1 administration (data not shown). The major limitation of this study was that it was a parallel study design instead of being a crossover design (that would allow a direct and accurate comparison between treatment groups). Modeling and simulation of profiles for 200 subjects based on data from the 22 subjects from Study TBS-1-2010-01 supported a reduction from 11.25 mg to 11 mg T per dose without compromising efficacy. Reference is made to Dr. LaiMing Lee's Clinical Pharmacology review dated September 21, 2011 under IND 70512 in DARRTS.

Study TBS-1-2011-01 was a Phase 1, randomized, crossover study conducted in 12 healthy men (age of 18-28 years), to compare the BA following a single dose of 11 mg T of TBS-1 from a multiple-dose dispenser (i.e., the proposed commercial method of administration) to that following a single dose of 11 mg T of TBS-1 from a prefilled syringe (i.e., the method of administration used in several studies earlier in the TBS-1 development program). A 12 hour baseline T profile was characterized for each subject to determine their endogenous T concentrations. The TBS-1 treatment was administered at 9 pm. A total of 13 blood samples were collected for each subject over a 12 hour post-dose period. Each treatment period was separated by a washout period of at least 6 days.

Figure 5: Mean Baseline-Corrected Serum Total T Concentration-Time Curves Following a Single Dose of 11 mg T of TBS-1 Using a Multiple-Dose Dispenser or a Prefilled Syringe in Healthy Men (N=12; Study TBS-1-2011-01)



As shown in Figure 5, the multiple-dose dispenser had higher AUC(0-12) values compared to those with the prefilled syringe, while also having a higher C_{max}. Based on this finding, the Sponsor decided to select the multiple-dose dispenser as the proposed commercial method of administration.

Based on the findings from Studies TBS-1-2010-01 and TBS-1-2011-01, an 11.0 mg T dose of TBS-1 administered as a 22.0 mg T daily dose (i.e., BID dosing) or 33.0 mg T daily dose (i.e., TID dosing) using the multiple-dose dispenser was selected for the Phase 3 efficacy and safety study (Study TBS-1-2011-03).

Based on the results of the Phase 3 study, TBS-1-2011-03, the final proposed dosing regimen for NATESTO was determined to be 11 mg T TID (i.e., 33 mg/day).

2.2.5 How were the efficacy and safety of NATESTO assessed and what were the results?

The Sponsor has originally proposed to initiate NATESTO therapy with 11 mg T BID dosing, (b) (4). However, the Sponsor submitted a major amendment on January 13, 2014 with a new proposal to administer NATESTO as an 11 mg T TID regimen (b) (4). Therefore, the primary efficacy and safety analyses were based on the TBM 11 mg T TID group.

The efficacy and safety of NATESTO was assessed in a Phase 3, multicenter study (TBS-1-2011-03) consisting of 90-day treatment period and 2 safety extension periods (i.e., 90 days and an additional 180 days) conducted in hypogondal men. Among the 306 subjects enrolled, 228 subjects were randomized to the 11 mg T BID group and 78 subjects were randomized to the 11 mg T TID group. Out of the 78 subjects randomized to the 11 mg T TID treatment group, there were 9 (11.5%) subjects who discontinued the study during the treatment period. A total of 69 (88.5%) subjects completed the 90-day treatment period. NATESTO was administered intranasally using a multiple-dose dispenser. On Days 30 and 90, the 24-hour post-dose PK of serum total T, DHT, and E2 were characterized as described in Section 2.2.3.

Primary Efficacy Endpoint: The number and percentage of subjects with a serum total T C_{avg} within the normal range of ≥ 300 ng/dL and ≤ 1,050 ng/dL on Day 90. The primary efficacy endpoint, C_{avg}, was calculated from the AUC using the following formula and actual collection times were used in the calculation:

$$C_{avg} = AUC(0\text{-}24) / 24$$

Critical Secondary Safety Endpoint, C_{max}: The critical secondary safety endpoint, C_{max}, had the following criteria that were expected to be met on Day 90:

- Having < 5% of subjects with a serum total T C_{max} in the range of 1,800-2,500 ng/dL
- No subjects with a serum total T C_{max} of > 2,500 ng/dL
- Having a serum total T $C_{max} \leq$ 1,500 ng/dL in at least 85% of subjects

Other Secondary Efficacy/Safety Endpoints:

- The number and percentage of subjects with a serum total T C_{avg} in the normal range of ≥ 300 ng/dL and ≤ 1,050 ng/dL on Day 30;
- The complete serum total T PK profiles on Days 30 and 90;
- The time within the normal range for serum total T based on the PK profiles on Days 30 and 90;
- The PK profiles of serum DHT and E2 on Days 30 and 90;
- The ratio of DHT C_{avg} to total T C_{avg} on Days 30 and 90;

Despite the Division's recommendations to include a placebo control group and blinding in the Phase 3 study, the study was conducted unblinded and without a concurrent control. As a result, several clinical (pharmacodynamics) endpoints such as erectile function, libido, body composition, and mood were considered exploratory and were not reviewed.

Primary Efficacy Endpoint Analysis Results: The primary endpoint of the study was assessed based on the total T C_{avg} data of the ITT population collected on Day 90 LOCF. On Day 90 LOCF, there were 73 subjects in ITT population of the 11 mg T TID treatment group with valid serum total T C_{avg}.

Efficacy was to be deemed established if 75% or more of patients had a total T C_{avg} in the normal range of 300-1,050 ng/dL on Day 90. According to the Division's recommendation, the value of the lower limit of the 95% CI also had to be not less than 65% in order to establish definitive evidence of efficacy in the study. Reference is made to the Advice/Information Request letter sent to the Sponsor on October 31, 2011.

Table 9 presents the number and percentage of subjects in the ITT population by serum total T C_{avg} category on Day 90 LOCF.

Table 9: The Number and Percentage of the Subjects in the ITT Population by Serum Total T C_{avg} Category on Day 90 LOCF Following Administration of 11 mg T TID of NATESTO to Hypogonadal Men (N=73[a]; Study TBS-1-2011-03)

C_{avg} in normal range (300 ≤ C_{avg} ≤ 1050 ng/dL)	
Yes (N)	66
%	90
95% CI for frequency[b]	(84, 97)
C_{avg} below normal range (C_{avg} < 300 ng/dL)	
Yes (N)	7
%	10
C_{avg} above normal range (C_{avg} >1050 ng/dL)	
Yes (N)	0
%	0

[a] Subjects in the ITT population on Day 90 LOCF
[b] The CI for the frequency was approximated by a binomial distribution within each treatment.

As shown in Table 9, the analysis of the primary efficacy data indicates that the pre-specified efficacy criteria were achieved in the population that was administered with the TBM treatment (i.e., 11 mg T TID).

Critical Secondary Safety Endpoint (total T C_{max}) Analysis Results: The following criteria of the critical secondary safety endpoint, total T C_{max}, were met on Day 90:

- Having < 5% of subjects with a serum total T C_{max} in the range of 1,800-2,500 ng/dL
- No subjects with a serum total T C_{max} of > 2,500 ng/dL

However, 0.9% less subjects (i.e., 84.1%) had a serum total T $C_{max} \leq$ 1,500 ng/dL at Day 90 compared to the pre-specified criteria. Table 10 presents the number and percentage of subjects in the ITT population on Day 90.

Table 10: Number (Percentage) of Subjects in the ITT Population by Selected Ranges of Serum Total T C_{max} on Day 90 Following Administration of 11 mg T TID of NATESTO to Hypogonadal Men (Study TBS-1-2011-03)

Number of subjects[a]	69
$C_{max} \leq$ 1,500 ng/dL	58 (84.1)
1800 ng/dL $\leq C_{max} \leq$ 2,500 ng/dL	1 (1.4)
C_{max} > 2,500 ng/dL	0 (0)

[a] The number of subjects who had a C_{max} value at Day 90

Daily time of serum total T in normal range: The mean daily time during which serum total T concentrations were within the normal range of 300-1,050 ng/dL on Day 90 LOCF is summarized in Table 11.

Table 11: Summary of Time (hours) Within Normal Range for Serum Total T on Day 90 LOCF of the ITT Population Following Administration of 11 mg T TID of NATESTO to Hypogonadal Men (Study TBS-1-2011-03)

N	73
Mean	15.8
SD	5.9
Median	16.0
Minimum	1.5
Maximum	24.1

Serum DHT and E2 PK: Observed increases in serum DHT and E2 concentrations were consistent with the dosing with T (see Section 4.1.1 of this review).

Ratio of serum DHT C_{avg} to total T C_{avg}: Table 12 displays a summary of the ratio of serum DHT C_{avg}/total T C_{avg} on Day 90 for the ITT population during the treatment period.

Table 12: Summary of the Ratio of Serum DHT C_{avg} /total T C_{avg} by Treatment on Day 90 LOCF for the ITT Population Following Administration of 11 mg T TID of NATESTO to Hypogonadal Men (Study TBS-1-2011-03)

N	73
Mean	0.094
SD	0.029
Minimum	0.05
Maximum	0.22

The serum DHT C_{avg}/total T C_{avg} ratio for NATESTO (i.e., 11 mg T TID) on Day 90 ranged between 0.05 and 0.22 with a mean value of 0.09 and did not exceed the normal limit reported in literature (i.e., 0.05-0.33 reported by Diver *et al*., 2003). The mean serum DHT C_{avg}/total T C_{avg}

ratio of 0.09 is comparable with the reported values of 0.05-0.11 from most of the other FDA approved T replacement products.

Safety Analysis: Overall, intranasal NATESTO was well tolerated. The adverse event (AE) profile was consistent with other T replacement products, with the majority of AEs mild in intensity. The incidence of the events associated with the intranasal route of administration was relatively low and did not increase with treatment duration. The occurrence of AEs associated with laboratory abnormalities caused by T replacement therapy (i.e., prostate-specific antigen [PSA], hematocrit, and lipid profile abnormalities) was comparable to other marketed T therapies and did not increase with treatment duration.

Overall Efficacy and Safety Conclusion: The efficacy and safety of NATESTO was demonstrated successfully in hypogonadal males with the TBM dosing regimen (i.e., 11 mg T TID).

2.3 Intrinsic Factors

2.3.1 Was there any age effect observed in the efficacy and safety of NATESTO?

There have not been sufficient numbers of geriatric patients involved in controlled clinical studies utilizing NATESTO to determine whether efficacy in those over 65 years of age differs from younger subjects. Of the 306 subjects enrolled in the Phase 3 study utilizing NATESTO (Study TBS-1-2011-03), 78 subjects were randomized to the 11 mg T TID treatment group. Among those 78 subjects, 17 subjects were 65 years of age or older. No subgroup analysis for efficacy and safety was conducted by the Sponsor. Additionally, there were insufficient long-term safety data in geriatric patients utilizing NATESTO to assess a potential increased risk of cardiovascular disease and prostate cancer.

2.3.2 What is the Sponsor's justification of the pediatric waiver request and is it acceptable?

No pediatric studies with NATESTO were conducted and the Sponsor submitted a full pediatric study waiver request for all pediatric age groups (i.e., children from birth to age of 18 years) for the reasons listed below. Safety and efficacy of NATESTO has not been established in males < 18 years of age.

- Studies would be highly impractical to conduct,
- The disease/condition does not exist in children and,
- The product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients.

T production is dormant until the time of puberty, at which time endogenous T levels increase, leading to secondary male sex characteristics. Therefore, there is likely to be no therapeutic use for T in the neonate, infant, or child. The Sponsor's request is acceptable from the Clinical Pharmacology standpoint.

Under the PREA (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because NATESTO is administrated intranasally (i.e., new route of administration), PREA is triggered.

The Agency's PeRC discussed the Sponsor's request on November 20, 2013 and agreed with the requested full waiver because pediatric studies are impossible or highly impractical because the disease/condition does not occur in children.

2.3.3 Did the Sponsor conduct PK studies in population with renal or hepatic impairment?

No. The Sponsor did not conduct any studies in patients with renal or hepatic impairments. As NATESTO is given intranasally, significant PK profile changes in renal or hepatic impaired patients are not expected.

2.4 Extrinsic Factors

2.4.1 Did the Sponsor conduct any DDI studies?

Yes. A Phase 1, open label, randomized 3-way crossover, 3-treatment, 3-period DDI study (Study TBS-1-2011-04) in male subjects, aged 18-45 years, with seasonal allergic rhinitis in symptomatic/untreated, symptomatic/treated, or asymptomatic states to assess the relative BA, safety, and tolerance of NATESTO was conducted.

Oxymetazoline (i.e., Afrin nasal spray) was selected to be used in this study per the Division's recommendation. Reference is made to the minutes of the EOP2 meeting held on March 14, 2011 (dated May 4, 2011 under IND 70512 in DARRTS). The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) has provided the following comment: Oxymetazoline is sold over-the-counter (OTC) and is used (short term - not recommended for use more than 3 days) for nasal congestion. It does not have an effect on the other symptoms of allergic rhinitis and it is not the most commonly used medication for allergic rhinitis (these are usually antihistamines or nasal steroid sprays). However, the potential for reducing systemic absorption of T is probably greatest with the use of oxymetazoline because of its vasoconstrictor effect. Therefore, given the objective of the study, oxymetazoline was probably the best choice to use in this situation.

Subjects were randomized to 1 of the 3 sequence groups and the following treatments were given according to the pre-defined order for each sequence group:

- Treatment 1 (symptomatic state): Subjects entered the environmental challenge chamber (ECC) and were exposed (i.e., inhaled) to dactylis glomerata pollen prior to each administration of NATESTO. Once subjects met the symptomatic state criteria, they were dosed with 11 mg T TID (total daily dose of 33 mg). NATESTO was given at 7 am, 1 pm, and 9 pm (± 30 minutes).
- Treatment 2 (symptomatic state but treated): Subjects were induced by exposure (i.e., inhalation) to dactylis glomerata pollen in the ECC prior to each NATESTO administration. Once subjects met the symptomatic state criteria, they were immediately dosed with a decongestant (oxymetazoline) and 30 minutes thereafter with 11 mg NATESTO. Each of the oxymetazoline dose consisted of 4 puffs (2 per nostril) of 0.05% oxymetazoline hydrochloride using a multi-dose dispenser administrated intranasally. NATESTO was administered 11 mg T TID (total daily dose of 33 mg). NATESTO was given at 7 am, 1 pm, and 9 pm (± 30 minutes). Oxymetazoline was administered 30 minutes prior to the 7 am NATESTO dose and 12 hours after the first dose of oxymetazoline.
- Treatment 3 (asymptomatic state): Subjects were verified by filling out a symptom diary card. Those who were verified as asymptomatic received NATESTO as 11 mg T TID

(total daily dose of 33 mg). NATESTO was given at 7 am, 1 pm, and 9 pm (± 30 minutes).

Blood samples were drawn at the following time points for 24-hour baseline characterization (i.e., control without any treatment) or for 24 hours following each of the 3 treatments of NATESTO. There was a washout period of at least 4 days between dosing of each period.

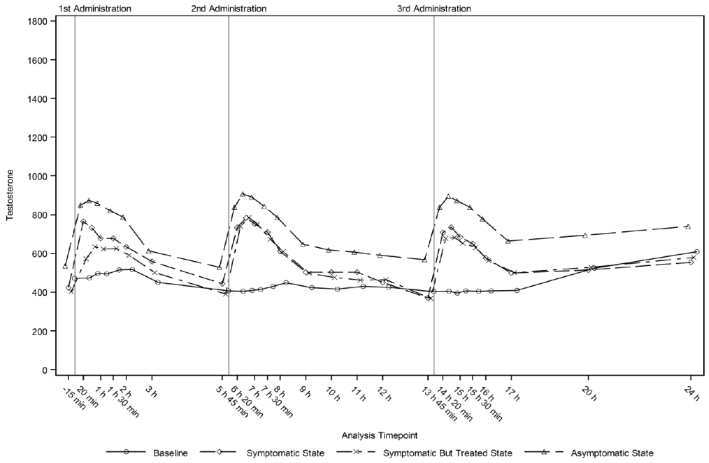
A total of 18 subjects were enrolled in the study with 6 subjects in each sequence group and 14 subjects completed all 3 treatments during the study. The disposition of the subjects is summarized in Table 13.

Table 13: Disposition of Subjects by Treatments (Total N=18; Study TBS-1-2011-04)

	Completed Subjects	Incomplete Subjects	Incomplete subjects ID	Incomplete reason (early termination)
Symptomatic (Treatment 1)	15	3	Subjects 14, 15, 17	Not qualified for treatment TNSS < 6 in one of the treatment periods
Symptomatic but treated (Treatment 2)	17	1	Subject 18	Not qualified for treatment TNSS < 6 in one of the treatment periods
Asymptomatic (Treatment 3)	18	0	-	-

Fourteen out of 18 subjects had evaluable PK profiles and were included in the PK analysis.

Figure 6: Arithmetic Mean Serum T Concentration vs. Time Curves in Healthy Men with Seasonal Allergic Rhinitis, by Treatment State Following Administration of 11 mg T TID of NATESTO for 1 Day (N=14; Study TBS-1-2011-04)



Although the same dose of NATESTO was administered under all treatment conditions, the curve of asymptomatic state was generally higher (i.e., higher AUC) than the curves of both symptomatic/untreated and symptomatic/treated states. It should be noted that asymptomatic state had a higher mean pre-dose T concentration compared to the other 2 treatment conditions.

Since the baseline was not characterized for each specific treatment period (i.e., just subtracting the same baseline for all 3 treatment periods), it should be noted that this review focused on the difference of the baseline-uncorrected mean AUC(0-24), C_{max}, and C_{avg} values between each treatment group. The baseline-uncorrected serum T PK parameters are summarized in Table 14.

Table 14: Baseline-Uncorrected Serum T PK Parameters
in Healthy Men With Seasonal Allergic Rhinitis, by Treatment State (N=14; Study TBS-1-2011-04)

	Treatments	Mean	SD	% Change from Asymptomatic
AUC(0-24) (ng·hr/dL)	Pre-treatment	10949.8	2215.0	NA
	Asymptomatic	16746.9	3894.3	-
	Symptomatic	13217.4	3589.1	21.1% ↓
	Sympt. treated	12778.2	3379.6	23.7% ↓
C_{max} (ng/dL)	Pre-treatment	631.4	149.7	NA
	Asymptomatic	1063.2	223.0	-
	Symptomatic	909.9	241.8	14.4% ↓
	Sympt. treated	872.0	267.7	18.0% ↓
C_{avg} (ng/dL)	Pre-treatment	456.6	92.1	NA
	Asymptomatic	695.6	163.7	-
	Symptomatic	549.3	149.6	21.0% ↓
	Sympt. treated	532.2	141.0	23.5% ↓

NA: Not applicable

Total T exposure (i.e., AUC[0-24], C_{max}, and C_{avg}) was higher under asymptomatic state compared to symptomatic states regardless of treatment with oxymetazoline. The difference between the 2 symptomatic states were relatively small compared to the difference of those with the asymptomatic state, indicating that administration of oxymetazoline might not hugely impact the absorption of T following the administration of NATESTO.

The baseline-uncorrected mean AUC(0-24), C_{max}, and C_{avg} values for DHT in the symptomatic/untreated and symptomatic/treated states decreased when compared to the asymptomatic state (see Section 4.1.2 of this review).

2.4.2 Is there any additional drug interaction information available?

Yes. The following information is available in the labeling of topical drugs in the same drug class (i.e., Testim®, AndroGel®, or Axiron®): Changes in insulin sensitivity or glycemic control may occur in patients treated with androgens. In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, may necessitate a decrease in the dose of anti-diabetic medication. Changes in anticoagulant activity may be seen with androgens. Therefore, more frequent monitoring of INR and prothrombin time is recommended in patients taking warfarin, especially at the initiation and termination of androgen therapy. The concurrent use of T with corticosteroids may result in increased fluid retention and requires monitoring particularly in patients with cardiac, renal, or hepatic disease.

2.5 General Biopharmaceutics

2.5.1 What is the quantitative composition of the drug products used in the clinical trials of this application?

NATESTO is a slightly yellow nasal gel that is a viscous bioadhesive oil-based formulation containing solubilized T. The active pharmacologic ingredient in NATESTO is T. Early development of NATESTO formulation involved varying the volume of the gel applied to the nasal cavity, the concentration of T, the dose, and the daily dosing regimen. An investigational formulation, TBS-1A containing 4.0 or 8.0% T (10 mg dose), was used in early clinical studies and contained different excipients from the final formulation TBS-1. TBS-1 formulations containing 3.2, 4.0, or 4.5% T (w/w) were used in clinical studies. These TBS-1 formulations (with T concentrations) differed only in their T and castor oil compositions; an increase in T was

always accompanied by a reduction in castor oil. Doses of 11 mg T QD, BID, or TID (multiple-dose dispenser) or 11 mg T QD, 11.25 mg T TID, or 13.5 mg T BID (syringe) of the 4.5% formulation (TBM) were evaluated in clinical studies (Table 16).

NATESTO is supplied in a labeled clear, non-aerosol, multiple dose pump container. The multiple-dose dispenser uses a finger-actuated dispensing system designed to dispense NATESTO from a non-pressurized container. Each actuation (i.e., (b) (4)) contains 5.5 mg of T (4.5% w/w) in 122.5 mg NATESTO gel. Each dose consists of two actuations, one actuation per nostril (i.e., total of 11.0 mg T/dose). The commercial dispenser is designed to deliver 30 doses (i.e., 60 actuations). Of the 9 clinical studies submitted, 4 studies (i.e., Studies TBS-1-2011-03, TBS-1-2010-01, TBS-1-2011-04, and TBS-1-2011-01) were conducted using the TBM formulation.

Table 15: Composition of the TBM Formulation of NATESTO (TBS-1)

Component	Amount (% w/w)	Amount Delivered per Actuation (mg)	Amount Delivered per Dose (mg)	Quantity per Unit[a] (mg)	Function	Quality Standard
Testosterone	4.5%	5.5	11.0	(b) (4)	Active ingredient	USP
Castor oil	(b) (4)					USP
Oleoyl polyoxylglycerides						Ph. Eur./NF
Colloidal silicon dioxide						NF
Total						N/A

[a] Unit is the multiple dose dispenser

Table 16: Summary of Clinical Studies using the TBM Formulation of NATESTO (TBS-1)

Study	Study Description	% T (w/w)	Administration Method	T Dose (Regimen)
TBS-1-2010-01	Phase 2, Dose-finding	4.0	syringe	10.0 mg (TID)
		4.5	syringe	11.25 mg (TID)
		4.5	syringe	13.5 mg (BID)
TBS-1-2011-01	Phase 1, BA Comparison between syringe and multiple-dose dispenser	4.5	Multiple-dose dispenser	11.0 mg (QD)
		4.5	syringe	11.0 mg (QD)
TBS-1-2011-03	Phase 3, Efficacy and safety	4.5	Multiple-dose dispenser	11.0 mg (BID or TID)
TBS-1-2011-04	Phase 1, DDI study in men with seasonal allergic rhinitis	4.5	Multiple-dose dispenser	11.0 mg (TID)

2.6 Bioanalytical Methods

2.6.1 Did the Sponsor use validated bioanalytical methods to generate the study data?

Yes. Serum samples were analyzed for total T, DHT, and E2 using validated LC-MS/MS methods. Same methods for each analyte were used for the 4 clinical studies reviewed (i.e., Studies TBS-1-2010-01, TBS-1-2011-01, TBS-1-2011-03, and TBS-1-2011-04). The dynamic ranges for total T, DHT, and E2 were 0.5-50 ng/mL, 0.1-10 ng/mL, and 5-100 pg/mL, respectively.

A formal consult to the OSI was made for the bioanalytical study site inspection and there are no unresolved issues related to the approvability of NATESTO. Reference is made to Dr. Gopa Biswas's OSI Memorandums dated December 20, 2014 and March 14, 2014 under NDA 205488 in DARRTS.

The acceptance criteria and performance of the total T, DHT, and E2 bioanalytical methods are in compliance with the Agency's *Bioanalytical Method Validation Guidance*. In summary, the method validation and performance of the bioanalytical methods in clinical studies are acceptable and there are no unresolved issues related to the approvability of NATESTO.

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4 APPENDICES

4.1 Individual Study Reviews

Reviewer Comment: *Initially, the Sponsor has proposed to initiate NATESTO therapy with 11 mg T BID dosing,* (b) (4) *However, the Sponsor has submitted a major amendment on January 13, 2014 with a new proposal to administer NATESTO as an 11 mg T TID regimen* (b) (4) *. While* ***the primary efficacy and safety analysis was based on the 11 mg T TID regimen****, evaluations on various aspects of other dosing regimens are also included in the individual study reviews.*

4.1.1 Phase 3 Study (Study TBS-1-2011-03): Efficacy and Safety Study

Title: A 90-Day, Randomized, Dose-Ranging Study, Including Potential Dose Titration, Evaluating the Efficacy and Safety of NATESTO (4.5 % TBS-1 nasal gel) in the Treatment of Male Hypogonadism with Sequential Safety Extension Periods of 90 and 180 Days

Primary Objectives: To determine the efficacy of NATESTO, administered as 2 or 3 daily intranasal doses of 5.5 mg per nostril, as demonstrated by an increase in the 24-hour average concentration (C_{avg}) of serum total T to the normal range (≥ 300 ng/dL and ≤ 1050 ng/dL) in ≥ 75% of male subjects treated for hypogonadism; and to determine the safety and tolerability of NATESTO after 90, 180, and 360 days of treatment.

Clinical Study Center: Multiple Centers (34 U.S. sites). Of the planned 39 sites, Sites 006, 019, 027, 049, and 054 did not enroll any subjects.

Clinical Study Period: September 23, 2011 - March 11, 2013 (including the safety extension period)

Bioanalytical Study Center: (b) (4)

Bioanalysis Period: November 30, 2011 - October 30, 2012 (for treatment period bioanalysis)

Study Design, Treatments, and Drug Administration:
This was a Phase 3, multicenter (34 centers in the U.S.) study consisting of 4 study periods including 2 safety extension periods as follows:

- A 3- to 7-week screening period that included medication washout for subjects who were currently receiving T treatment;
- A 90-day treatment period during which subjects received 11 mg T (5.5 mg T per nostril) BID or 11 mg T TID from NATESTO with potential daily dose adjustment on Day 45 for subjects in the BID treatment group as determined by the serum total T PK profile;
- A 90-day, open-label safety extension period (safety extension period 1); and
- An additional 180-day, open-label safety extension period (safety extension period 2)

The population for this study was adult men 18-80 yrs. of age, inclusive with two fasting morning (9 am ± 30 min) serum total T concentrations < 300 ng/dL, a week apart (i.e., Week -3 and Week -2). If 1 out of the 2 measurements was < 300 ng/dL, a third measurement was done and if 2 out of 3 measurements were < 300 ng/dL, they were enrolled into the study. Three hundred six (306) subjects were randomly assigned across the 2 treatment groups in a 3:1 ratio to 11 mg T BID or 11 mg T TID. Two hundred twenty eight (228) subjects were assigned to the BID treatment group, and 78 subjects were to be assigned to the TID treatment group. Subjects who were being

treated with T at the time of enrollment must have undergone 2-4 weeks of washout depending on the type of T therapy and the date of their last dose (i.e., at least 4 weeks between the last T injection and the first morning T measurement; and at least 2 weeks between the last oral, topical, or buccal T administration and the first morning T measurement). There was no active comparator control and there was only dosing regimen comparison (i.e., 11 mg T BID vs. 11 mg T TID).

The study drug, NATESTO, was provided in a multiple-dose dispenser. Each finger-actuation deposited 5.5 mg of T into each nostril. The T (i.e., drug substance) used for production of NATESTO was obtained from (b) (4)

Blood sampling for total T, DHT, and E2 PK characterization took place according to the pre-defined sampling schedule (see the *PK Sampling and Characterization* section below for details).

Reviewer's Comment: *Originally, the Sponsor has proposed to initiate NATESTO therapy with 11 mg T BID dosing,* (b) (4) *. The study started out with 2 different treatment groups (i.e., 11 mg T BID treatment group and 11 mg T TID treatment group). Subjects randomized to the 11 mg BID group with an estimated serum total T* C_{avg} *< 300 ng/dL on Day 30 were instructed to increase the daily dose of NATESTO to 11 mg TID on Day 45 (i.e., BID/TID treatment group). Refer to the Dose Titration Section for detail information on the dose titration scheme.*

On January 13, 2014, the Sponsor submitted a major amendment with a new proposal to administer NATESTO as a 11 mg T TID fixed regimen (b) (4) *. Therefore, the primary evaluation will be based on the TID treatment group.*

Inclusion Criteria:

- Male between 18-80 years. of age;
- Had two fasting morning (i.e., 9 am ± 30 min) serum total T concentrations < 300 ng/dL, a week apart (i.e., Week -3 and Week -2);
- BMI between 18.5-35 kg/m^2;
- Hemoglobin level ≥ 13.0 g/dL; and
- Normal prostate for age based on digital rectal examination (DRE) and a serum PSA < 4.0 ng/mL

Exclusion Criteria:

- In the opinion of the Investigator, significant inter-current disease of any type, in particular liver, kidney, heart disease, or psychiatric illness;
- Hyperparathyroidism, uncontrolled diabetes mellitus, hypothyroidism, or hyperthyroidism (thyroid stimulating hormone [TSH] should be ≤ 1.5-times the upper limit of normal [ULN]);
- Alanine transaminase (ALT) or aspartate transaminase (AST) > 2-times ULN; unexplained creatine kinase > 3-times ULN; HbA1c > 7.0% (9.5 mmol/L), or any other laboratory abnormalities deemed clinically significant based on the Investigator's judgment and discussion with the medical monitor;
- Hematocrit > 54% at screening;
- History of pituitary or hypothalamic tumors or history of malignancy within the past 5 years, excluding basal cell or squamous cell carcinoma of the skin curatively treated by surgery;

- History of nasal surgery, specifically turbinoplasty, septoplasty, rhinoplasty, "nose job," or sinus surgery;
- History of nasal fractures within the past 6 months and/or prior nasal fractures that caused a severely deviated anterior nasal septum;
- Active allergies, such as rhinitis, rhinorrhea, and nasal congestion;
- Mucosal inflammatory disorders, specifically pemphigus or Sjogren's syndrome;
- Sinus disease, specifically acute sinusitis, chronic sinusitis, or allergic fungal sinusitis;
- History of nasal disorders (e.g., polyposis, recurrent epistaxis [> 1 nose bleed per month], abuse of nasal decongestants);
- History of sleep apnea;
- Use of any form of intranasal medication delivery, specifically nasal corticosteroids and oxymetazoline-containing nasal sprays (e.g., Dristan® 12-hour nasal spray);
- History of severe adverse drug reaction or leukopenia;
- A known hypersensitivity to lidocaine or any materials that may have been used during the study;
- History of abnormal bleeding tendencies or thrombophlebitis unrelated to venipuncture or intravenous cannulation;
- History of hepatitis B, a positive test for hepatitis B surface antigen, a history of hepatitis C, or a positive test for hepatitis C antibody;
- Presence of human immunodeficiency virus infection or antibodies;
- History of asthma and ongoing asthma treatment;
- History of significant sleeping problems or a shift worker;
- Smoker of > 10 cigarettes (or equivalent) per day;
- Regular consumption of more than 4 units of alcohol daily (1 unit was defined as 300 mL of beer, 1 glass of wine, or 1 measure of spirit) or difficulty abstaining from alcohol during the 48 hours prior to the 24-hour blood sampling visits;
- History or current evidence of abuse of alcohol or any drug substance;
- Treatment with androgen therapy within at least 2 weeks prior to baseline evaluations (subjects on androgen therapy required a washout period of 4 weeks for depot products administered intramuscularly [e.g., T enanthate 200 mg/mL] and 2 weeks for products administered orally or topically [oral, patch, gel, or buccal]);
- Current treatment with other androgens (e.g., dehydroepiandrosterone [DHEA]), anabolic steroids, or other sex hormones;
- Treatment with estrogens, gonadotropin-releasing hormone (GnRH) agonists, or growth hormone within the previous 12 months;
- Treatment with drugs that interfere with the metabolism of T, such as anastrozole, clomiphene, dutasteride, finasteride, flutamide, ketoconazole, spironolactone, or testolactone;
- Treatment with any antihypertensive, antidepressant, tranquilizer, or histamine 2 (H2) receptor blocker that was not part of a stable regimen (stable dose for at least 3 months prior to baseline);
- Poor compliance history or low likelihood of maintaining attendance;
- Participation in any other research study during the conduct of this study or 30 days prior to the initiation of this study; or
- Blood donation at any time during this study and within the 12-week period prior to screening

Reviewer's Comment: *Sponsor did not provide their rationale/justification for excluding smokers of consuming > 10 cigarettes per day. It should be noted that smokers that consume >*

25 cigarettes per day were excluded from the bioequivalence study for T gel (NDA 202763; approved on February 14, 2012).

Removal of Subjects from the Study:
Subjects could be discontinued from the study at any time, at the discretion of the Investigator. The Sponsor or their representative was to be notified if a subject was discontinued because of an AE or laboratory abnormality. Subjects were followed until the AE or laboratory abnormality was resolved. A subject could be withdrawn for any of the following reasons:

- Subject withdrew consent or requested discontinuation from the study for any reason;
- Sponsor discontinued the study;
- Occurrence of a clinical or laboratory AE, either serious or non-serious, at the discretion of the Investigator;
- Need to initiate therapy with an excluded concomitant medication;
- Increase in serum PSA concentration > 1.4 ng/mL above baseline;
- Increase in hematocrit to > 54%; or
- Any medical condition or personal circumstance that, in the opinion of the Investigator, exposed the subject to risk by continuing in the study or precluded adherence to the protocol

Drug Administration:
At Visit 3 (Day 1), subjects who met the entry criteria were randomly assigned in a 3:1 ratio to 11 mg T BID or 11 mg T TID. The first dose was administered at 9 pm at the study site.

- 11 mg BID treatment group: 5.5 mg T per nostril from NATESTO at 9 pm (± 5 minutes) and 7 am (± 5 minutes) for a total daily dose of 22 mg T.
- 11 mg TID treatment group: 5.5 mg T per nostril from NATESTO at 9 pm (± 5 minutes), 7 am (± 5 minutes), and 1 pm (± 5 minutes) for a total daily dose of 33 mg T.

Subjects were instructed not to blow their nose or sniff for 1 hour after intranasal administration of NATESTO.

At Visit 4 (Day 30) and Visit 6 (Day 90), subjects brought their NATESTO medication to the site for administration and characterization of the 24-hour post-dose PK profiles of serum total T, DHT, and E2.

Prior and Concomitant Medications:
Any medications administered during the study were documented on the Concomitant Medication electronic case report form (eCRF). Subjects were prohibited to take any investigational medication within 30 days prior to screening. Subjects could not participate in any other clinical study involving an investigational agent while participating in this study. T medications that were part of the subject's regimen at screening were discontinued for the duration of the study. Subjects on T therapy required a washout period of 4 weeks for injection formulations and 2 weeks for oral, buccal, or topical formulations in order to participate in the study.

Subjects undergoing current treatment with other androgens (i.e., DHEA), anabolic steroids, other sex hormones, or drugs that interfere with the metabolism of T (i.e., anastrozole, clomiphene, dutasteride, finasteride, flutamide, ketoconazole, spironolactone, and testolactone) were excluded from the study. Subjects treated within the past 12 months with estrogens, GnRH agonists, or growth hormones were also excluded.

Administration of any other intranasal medication, specifically nasal corticosteroids and oxymetazoline-containing nasal sprays (e.g., Dristan® 12-hour nasal spray), was prohibited during the study. Treatments with antihypertensives, antidepressants, tranquilizers, and H2 antagonists that were not part of a stable regimen (i.e., stable dose for at least 3 months prior to baseline) were also prohibited.

Treatment Compliance:
Study drug was dispensed in amounts exceeding the amount required for the period of time until the next visit. Subjects received 3 study drug dispensers (i.e., enough for 135 doses of NATESTO) and were instructed that 1 of 3 dispensers provided was reserved for emergency or back-up use during the study. Subjects were instructed to return all unused study drug at the next visit. Compliance to the study drug regimen was evaluated by weighing the study drug dispensers and reviewing the daily diary at each visit. If compliance was not between 80-120%, subjects were counseled about the importance of compliance to the regimen.

PK Sampling and Characterization:
Subjects were required to remain at the site for 24 hours after the 9 pm NATESTO administration at Visit 4 (Days 30) and Visit 6 (Day 90), and complete post-dose PK profiles for serum total T, DHT, and E2 were obtained:

- 11 mg BID group: PK blood samples were collected at 0.25 hour pre-dose and 0.33, 0.66, 1.0, 1.5, 2.0, 3.0, 6.0, 9.0, 9.75, 10.33, 10.66, 11.0, 11.5, 12.0, 13.0, 16.0, 19.0, 22.0, and 24.0 hour post-dose (total 20 blood draws)
- 11 mg TID group: PK blood samples were collected at 0.25 hour pre-dose and 0.33, 0.66, 1.0, 1.5, 2.0, 3.0, 6.0, 9.0, 9.75, 10.33, 10.66, 11.0, 11.5, 12.0, 13.0, 14.0, 15.75, 16.33, 16.66, 17.0, 17.5, 18.0, 20.0, 22.0, and 24.0 hours post-dose (total 26 blood draws)

Blood draws were conducted within ± 5 min from the indicated times when blood draw intervals were ≤ 30 min and within ± 15 min when blood draws were > 30 min. Administration of NATESTO occurred at ± 5 min from the indicated time (9 pm and 7 am for BID dosing and 9 pm, 7 am, and 1 pm for TID dosing). Subjects were confined to the study site and were provided standardized meals during performance of the 24-hour PK profiles on Days 30 and 90. If a subject with a history of allergic rhinitis developed an exacerbation of rhinitis during the study, continued application of study drug was permitted, provided the symptoms were mild according to the Investigator's assessment. Mild symptoms required sporadic treatment for control and were generally characterized by normal sleep, no impairment of activities of daily living, and no troublesome symptoms. Subjects with moderate and severe allergic rhinitis symptoms that caused an impairment of sleep and/or activities of daily living and that required daily treatment were instructed to temporarily discontinue study drug application until symptoms improved. The 24-hour PK assessment was not to be conducted in subjects with allergic rhinitis symptoms of any severity. This assessment was to be postponed until the symptoms improved, but no longer than 72 hours from the initially planned date. If these symptoms lasted longer than 72 hours, or if longer treatment was required, subjects were evaluated for discontinuation from the study.

PK analyses included AUC(0-24), C_{avg}, C_{max}, and C_{min} values for serum total T, DHT, and E2 with descriptive statistics, including the arithmetic mean, standard deviation (SD), coefficient of variation (% CV), geometric mean, median, minimum, and maximum by treatment at Days 30 and 90. The time within the normal range for serum total T was determined.

Concentrations below the lower limit of quantitation (LLOQ) prior to the first measurable concentration were treated as zero in the summary statistics and for the calculation of PK profile

parameters. Concentrations below LLOQ after the time point of the first measurable concentration were set to missing and not included in the calculation of AUC.

Dose Titration:
On Day 30, C_{avg} of serum total T for subjects in the 11mg BID group was estimated based on the sum of serum total T concentrations collected at 2 sampling points: the sample collected at 9 hours (at 1 hour before the 7 am dose; Sample A) and the sample collected at 10.33 hours (20 min after the 7 am dose; Sample B). The following titration criteria were used:

- If the sum of the serum total T concentration values for PK samples collected at the 2 sampling points was < 755 ng/dL, then the estimated C_{avg} was < 300 ng/dL, and
- If the sum of the serum total T concentration values for PK samples collected at the 2 sampling points was ≥ 755 ng/dL, then the estimated C_{avg} was ≥ 300 ng/dL

Subjects randomized to the 11 mg BID group with an estimated serum total T C_{avg} < 300 ng/dL were instructed to increase the daily dose of NATESTO to 11 mg TID on Day 45. This daily dose was continued throughout the remainder of the treatment period and, as applicable, both safety extension periods.

Reviewer's Comment: *The Sponsor's titration scheme only had an option to titrate up from 11 mg T BID to 11 mg T TID based on each individual's response to NATESTO but was not designed to predict if the serum total T C_{avg} would exceed 1,050 ng/dL.*

Sample Size Determination:
A planned sample size of approximately 280 subjects (210 subjects randomized to the BID treatment group and 70 subjects randomized to the TID treatment group) was selected to provide a sufficient number of subjects to determine the efficacy, safety, and tolerability of NATESTO. No formal sample size calculation was performed.

Efficacy Variables and Assessments
The primary efficacy endpoint: The number and percentage of subjects with a serum total T C_{avg} within the normal range of ≥ 300 ng/dL and ≤ 1050 ng/dL on Day 90.

The primary efficacy endpoint, C_{avg}, was calculated from the AUC using the following formula:

$$C_{avg} = AUC(0\text{-}24) / 24$$

The AUC curve for both the BID and TID dosing regimens was determined for the 0-24 hour time interval by using linear trapezoidal and linear interpolation methods. Actual collection times were used in the calculation.

Reviewer's Comment: *The Sponsor submitted the final protocol for this study with the primary efficacy endpoint mentioned above on September 2, 2011 and it was reviewed by the Clinical Pharmacology and Clinical review teams. There were no comments or alternative recommendations on the proposed normal range of serum total T C_{avg} (i.e., ≥ 300 ng/dL and ≤ 1,050 ng/dL) on Day 90. The following recommendation was made in Dr. Harry Handelsman's Clinical review dated October 25, 2011 under IND 70512 in DARRTS: "In order to achieve success for the primary endpoint, at least 75% of patients should achieve a C_{avg} within the eugonadal range on Day 90, with a lower bound of the 95% confidence interval not less than 65%." This recommendation was conveyed to the Sponsor via an Advice/Information Request Letter dated October 31, 2011. Upon completion of her review on the proposed Phase 3 study protocol, Dr. LaiMing Lee concluded that overall, the protocol appears to be reasonable to proceed and did not have any comments or alternative recommendations on the proposed*

primary efficacy endpoint in her Clinical Pharmacology review dated September 21, 2011 under IND 70512 in DARRTS.

Critical Secondary Safety Endpoint:
The critical secondary safety endpoint, total T C_{max}, had the following criteria that were expected to be met on Day 90:

- Having < 5% of subjects with a serum total T C_{max} in the range of 1,800-2,500 ng/dL
- No subjects with a serum total T C_{max} of > 2,500 ng/dL
- Having a serum total T $C_{max} \leq$ 1,500 ng/dL in at least 85% of subjects

Other Secondary efficacy/safety variables:

- The number and percentage of subjects with a serum total T C_{avg} in the normal range of ≥ 300 ng/dL and ≤ 1050 ng/dL on Day 30;
- The complete serum total T PK profile (including C_{avg}, C_{min}, C_{max}, and T_{max}) on Days 30 and 90;
- The time within the normal range for serum total T based on the PK profiles on Days 30 and 90;
- The PK profile of serum DHT and E2 on Days 30 and 90;
- The ratio of DHT C_{avg} to total T C_{avg} on Days 30 and 90;
- The International Index of Erectile Dysfunction (IIEF) scores at baseline, Day 30, Day 60, and Day 90;
- The positive and negative affect schedule (PANAS) scores at baseline, Day 30, Day 60, and Day 90;
- The change in bone mineral density (BMD) from baseline to Day 180 and from baseline to Day 360; and
- The change in body composition (total body mass, lean body mass, fat mass, and percent fat) from baseline to Day 180 and from baseline to Day 360

Reviewer's Comment: *Despite the Division's recommendations to include a placebo control group and blinding in the Phase 3 study, the study was conducted unblinded and without a concurrent control. As a result, several clinical (pharmacodynamics) endpoints such as erectile function, libido, body composition, and mood were considered exploratory and were not reviewed.*

Non-PK Safety Assessment Schedule:

- Visit 4 (Day 30): a basic ear, nose, and throat (ENT) examination (non-endoscopic otolaryngology), vital sign measurements, IIEF and PANAS questionnaires, and clinical laboratory evaluations
- Visit 5 (Day 60): safety assessments, including a basic ENT examination, AEs, and vital sign measurements, were performed. The IIEF and PANAS questionnaires were also administered
- Visit 6 (Day 90): 12-lead ECG, physical examination, vital sign measurements, digital rectal examination (DRE) of the prostate, basic ENT examination, IIEF, and PANAS questionnaires, and clinical laboratory evaluations.
- Safety Extension Period 1 (Days 90-180): All subjects continued into the 90-day Safety Extension Period 1 and were instructed to continue their current daily dose of NATESTO. Subjects returned to the site for monthly visits. Monthly assessments included a basic ENT examination, vital signs, and AEs. On Day 180 (or early termination), subjects also underwent a physical examination, 12-lead ECG, DRE of the prostate, dual-energy X-ray absorptiometry (DEXA) scan, and laboratory assessments.

- Safety Extension Period 2 (Days 180-360): The subset of subjects who continued into safety extension period 2 consisted of the first subjects to complete safety extension period 1. For the duration of this period, subjects remained on the same daily dose of NATESTO administered on Day 90 of the treatment period and throughout safety extension period 1. Subjects returned to the site for monthly visits. Monthly assessments included a basic ENT examination, vital signs, and AEs. On Day 270 and Day 360 (or early termination), subjects also underwent a physical examination, 12-lead electrocardiogram (ECG), DRE of the prostate, DEXA scan (Day 360 only), and laboratory assessments.

It should be noted that no 24-hour PK measurements for T were made during Safety Extension Periods 1 and 2.

The schedule of procedures of this study is presented in Table A-1-1 below.

Table A-1-1: Schedule of Procedures (Study TBS-1-2011-03)

Study Phase	Screening					Treatment Period				Safety Extension Period 1		Safety Extension Period 2[d]				Early Termination
	Prior Testosterone Treatment			Testosterone Treatment Naïve		Randomization	Efficacy Analysis			Safety Analysis		Subset Safety Analysis				
Study Timing	Week -7 or -5[a]	Week -3	Week -2	Week -3	Week -2	Day 1	Day 30-Day 31[b]	Day 60	Day 90-Day 91[c]	Day 120 and Day 150	Day 180	Day 210 and Day 240	Day 270	Day 300 and Day 330	Day 360	
Visit Number	1	1.1[b]	2	1	2	3	4[c]	5	6	7-8[e]	9	10-11[e]	12	13-14	15	
Study Procedures																
Inclusion/exclusion criteria	x	x	x	x	x											
Informed consent	x			x												
Medical interview	x			x												
Physical examination	x			x					x		x		x		x	x
Height and weight	x			x												
Vital signs (HR, BP, RR, and temperature)	x			x		x[f]	x[f]	x	x[g]	x	x	x	x	x	x	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
DRE of the prostate	x			x					x		x		x		x	x
Chemistry profile and hematology[f]	x	x		x			x		x		x		x		x	x
Fasting lipid profile[g]	x	x		x			x		x		x		x		x	x
Liver function tests[h]	x	x		x			x		x		x		x		x	x
HbA_{1c} and endocrine profile[i]		x		x					x							x
Urinalysis[j]	x	x		x					x		x		x		x	x
Urine drug and alcohol screen	x			x												
PSA		x		x					x		x		x		x	x
Estradiol and DHT[k]		x		x		x			x		x		x		x	x
Free testosterone		x		x					x							x
12-lead ECG			x		x				x		x		x		x	x
Fasting serum total testosterone[k]		x	x	x	x	x					x		x		x	x
ENT exam with nasal endoscopy[l]			x		x											
DEXA[m]			x		x						x				x	
IIEF and PANAS questionnaires						x	x	x	x							x[n]
Administered study drug at the site						x	x		x							
24-h PK profile for serum total testosterone, DHT, and estradiol							x		x							
Basic ENT examination (non-endoscopic)						x	x	x	x	x	x	x	x	x	x	x
Potential study drug daily dose titration							x									
Distributed and/or reviewed daily diary[o]						x	x	x	x	x	x[s]	x	x	x	x	
Weighed study drug dispensers						x	x	x	x	x	x	x	x	x	x	x
Primed study drug dispensers and distributed to subjects						x	x	x	x	x	x[s]	x	x	x	x	
Assessed AEs		x	x		x	x	x	x	x	x	x	x	x	x	x	x

[a]Visit 1 for subjects receiving intramuscular testosterone injections at the time of screening was to occur at up to Week -7. Visit 1 for subjects receiving buccal, oral, or topical testosterone was to occur at up to Week -5.
[b]Visit 1.1 was only required for subjects who underwent washout of testosterone therapy and was to take place 4 weeks after the last administration of testosterone for subjects who were taking testosterone injections and 2 weeks after the last testosterone administration for subjects who were taking buccal, oral, or topical testosterone.
[c]Based on the PK profile for serum total testosterone performed at Visit 4, some subjects in the BID treatment group had their daily dose increased to TID. Subjects that required a daily dose increase were contacted by phone and instructed to increase their daily dose on Day 45.
[d]A subset of approximately 75 subjects was enrolled in Safety Extension Period 2.
[e]During Safety Extension Period 1 and Safety Extension Period 2, study visits were conducted once per month.
[f]Chemistry profile included: creatine kinase, sodium, potassium, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, and uric acid. Hematology included: hemoglobin, hematocrit, red blood cell count, white blood cell count and differential, platelets, reticulocyte count, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration.
[g]Fasting lipid profile included: total cholesterol, low-density lipoprotein-cholesterol (direct), high-density lipoprotein cholesterol, and triglycerides.
[h]Liver function tests included: total bilirubin, albumin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and gamma glutamyl transferase.
[i]Endocrine profile included: thyroid-stimulating hormone, morning cortisol, sex hormone-binding globulin, luteinizing hormone, follicle-stimulating hormone, and prolactin.
[j]Urinalysis included: specific gravity, glucose, protein, ketones, pH, blood, bilirubin, urobilinogen, nitrite, and leukocyte esterase.
[k]Fasting serum total testosterone, DHT, and estradiol were to be collected at 0900 h ± 30 min at Visits 1, 1.1, 2, 9, 12, 15, and Early Termination and at 2045 h at Visit 3. In subjects with a known history of male hypogonadism, if 1 of the 2 serum total testosterone levels collected at screening was ≥300 ng/dL, the serum total testosterone level could be retested once. After retesting, if 2 of the 3 levels were <300 ng/dL, then the subject was eligible to participate in the study.
[l]ENT examination with nasal endoscopy performed by an ENT specialist was scheduled for the interval between Visit 2 and Visit 3 (Day 1 [randomization]) on qualified subjects.
[m]DEXA scans to evaluate body composition (total body mass, lean body mass, fat mass, and percent fat) and bone density (lumbar spine and hip) were performed in the interval between Visit 2 and Visit 3 on qualified subjects. Follow-up DEXA scans were obtained at Visit 9 (Day 180) and Visit 15 (Day 360), if scheduling was available, or within ±2 weeks of Visit 9 and Visit 15.
[n]Daily diary was distributed to subjects to record date and time of study drug administration.
[o]IIEF and PANAS questionnaires were administered to subjects at Early Termination if subjects terminated on or before Visit 6 (Day 90).
[p]On Day 31 of Visit 4, the following procedures were performed: vital sign measurements, basic ENT examination, administered questionnaires (may have been performed on Day 30 or Day 31), and dispensed daily diary.
[q]On Day 91 of Visit 6, the following procedures were performed: vital sign measurements, basic ENT examination, dispensed daily diary, administered questionnaires (may have been performed on Day 90 or Day 91), performed DRE (may have been performed on Day 90 or Day 91), and performed physical examination (may have been performed on Day 90 or Day 91).
[r]At Visit 3 (Day 1), vital sign measurements were obtained prior to first dose of study drug and at approximately 1 hour after the first dose of study drug (at 2200 h). On Day 30 of Visit 4 and Day 90 of Visit 6, vital sign measurements were obtained once prior to administration of study drug. On Day 31 of Visit 4 and Day 91 of Visit 6, vital sign measurements were obtained at the following approximate times after administration of study drug: 6 hours (at 0300 h), 12 hours (at 0900 h), 18 hours (at 1500 h), and 24 hours (at 2100 h).
[s]At Visit 9, study drug dispensers and daily diaries were only distributed to subjects entering Safety Extension Period 2.
AE = adverse event; BID = twice daily; BP = blood pressure; DEXA = dual-energy X-ray absorptiometry; DHT = dihydrotestosterone; DRE = digital rectal examination; ECG = electrocardiogram; ENT = otorhinolaryngological; HbA_{1c} = glycosylated hemoglobin; HR = heart rate; IIEF = International Index of Erectile Function; PANAS = Positive and Negative Affect Schedule; PK = pharmacokinetic; PSA = prostate specific antigen; RR = respiratory rate; TID = three times daily.
Source: Study Protocol (Appendix 16.1.1)

Bioanalytical Methods:
Bioanalysis for total T, DHT, and E2 was conducted at [redacted] (b) (4) In this study, Aliquot 1 samples were collected for the determination of total T and DHT and aliquot 2 samples were collected for the determination of E2 in human serum. Human serum samples were analyzed using LC-MS/MS methods for the determination of total T, DHT, and E2 concentrations. Serum samples were stored in the freezer at or lower than -18°C until sample analysis.

T and DHT were extracted from serum by a liquid-liquid extraction (LLE) with a mixture of pentane and diethyl ether. The extracted samples were dried under a stream of nitrogen and thereafter, subjected to derivatization with picolinic acid. After derivatization a sample clean-up was performed with C-18 solid phase extraction (SPE) followed by a LLE with tertiary butyl methyl ether (TBME).

E2 was extracted from serum by SPE using C-18 SPE cartridge. Thereafter, E2 was derivatized with dansyl chloride under alkali conditions. Finally, derivatized E2 was extracted by LLE with a mixture of TBME and pentane. After extraction, the organic layer was evaporated to dryness under a gentle stream of nitrogen.

Reconstituted sample extracts (200 µL) were analyzed using a Shimadzu SIL-20AC high performance liquid chromatography (HPLC) System equipped with an Applied Biosystems SCIEX API 4000 triple quadrupole mass spectrometer. Chromatographic separation was performed on a Phenomenex Luna C18(2) column for T and DHT; and on a Phenomenex Hypersil C18 BDS column for E2 using gradient elution. Positive ions generated from the Turbo Ion Spray ion source were detected using the multiple reaction monitoring (MRM) mode. Quantitation was performed using a weighted linear regression (1/concentration) of the determined peak area ratios for T, DHT, and T-d_3 (internal standard [IS]) as well as for E2 and E2-d_5 (IS). The LC-MS/MS method was developed and validated with the dynamic range of 0.5-50 ng/mL, 0.1-10 ng/mL, and 5-100 pg/mL for total T, DHT, and E2, respectively. Serum concentration values below the LLOQ were reported as < LLOQ in the report.

Calibration standards for T, DHT, and E2 were prepared in a 4% solution of BSA in 0.9% saline. Quality control (QC) samples for T and DHT were prepared in a pool of female serum and QC samples for E2 were prepared in a pool of postmenopausal female serum. In order to establish the target values of the QC samples, total T and DHT concentrations in pooled blank female serum was determined and E2 concentrations in pooled postmenopausal female serum was determined. Six pooled samples were analyzed in three different analytical runs. Since the endogenous concentrations of total T and DHT in the pool of blank female serum were below the LLOQ for this method, 0.500-0.650 ng/mL T or 0.100-0.140 ng/mL DHT was spiked into the pooled blank female serum, respectively, in order to obtain a detectable concentration level. Additional spiking for E2 was not necessary. Then, the mean concentrations for T and DHT of the 18 pooled blank female serum samples for each batch were determined. The mean concentrations for E2 in blank postmenopausal female serum samples were determined in the same way. Subsequently, each batch of pooled blank female serum was spiked with 0.75, 10.0, and 40.0 ng/mL of T for Low QC, Medium QC, and High QC samples, respectively; and with 0.15, 2.0, and 8.0 ng/mL of DHT for Low QC, Medium QC, and High QC samples, respectively, to obtain detectable T and DHT concentrations. For E2, each batch of pooled blank postmenopausal female serum was spiked with 5.0, 35.0, and 75.0 pg/mL for Low QC, Medium QC, and High QC samples, respectively. The target concentrations for each of the Low QC, Medium QC, and High QC samples were calculated as the mean concentration of the pooled

blank female or postmenopausal serum (determined in this study) plus the additional spiked T, DHT, or E2 concentrations. For example, the mean total T concentration in the blank pooled female serum batch Q-4077 was 0.743 ng/mL. The target concentration for the T Low QC sample using blank pooled female serum batch Q-4077 was determined to be 1.493 ng/mL (i.e., 0.743 ng/mL + 0.75 ng/mL).

Accuracy of the calibration standards and QC samples during sample analysis was expressed as percent difference from theoretical concentration (i.e., % RE). For serum total T, the %RE ranged from -1.1% to 1.1% for the 8 calibration standards in the range of 0.5-50 ng/mL and -5.0% to 4.1% for low, medium, and high QCs. For serum DHT, the % RE ranged from -0.6% to 1.0% for the 8 calibration standards in the range of 0.1-10 ng/mL and -8.6% to 3.7% for low, medium, and high QCs. For serum E2, the % RE ranged from -1.1% to 0.9% for the 7 calibration standards in the range of 5.0-100 pg/mL and -1.1% to 3.4% for low, medium, and high QCs.

Precision of the calibration standards and QC samples during sample analysis was expressed as the percent coefficient of variation (% CV). For serum total T, the % CV ranged from 1.0% to 4.9% for the 8 calibration standards in the range of 0.5-50 ng/mL and 2.8% to 6.2% for low, medium, and high QCs. For serum DHT, the % CV ranged from 1.0% to 5.8% for the 8 calibration standards in the range of 0.1-10 ng/mL and 3.7% to 9.1% for low, medium, and high QCs. For serum E2, the % CV ranged from 2.2% to 4.9% for the 7 calibration standards in the range of 5.0-100 pg/mL and 5.2% to 10.8% for low, medium, and high QCs.

Linearity during sample analysis was described as the correlation coefficient, r of the standard curves. The mean r values were 0.9998, 0.9997, and 0.999 for serum total T, DHT, and E2, respectively.

Long-term storage stability for T, DHT, and E2 in human serum at ≤ -18°C were established for 957 days, 750 days, and 940 days, respectively.

After one, two, and three freeze/thaw cycles, the % REs of the replicate analyses of T, DHT, and E2 Low, Medium, and High QC samples were always ≤ 15%.

After 24 hours of storage in a refrigerator at a temperature of 2-8°C, the % REs of the replicate analyses of T, DHT, and E2 Low, Medium, and High QC samples were always ≤ 15%.

After 24 hours of storage on the bench-top at room temperature, the % REs of the replicate analyses of T, DHT, and E2 Low, Medium, and High QC samples were always ≤ 15%.

After regular sample preparation and 102 hours (for T and DHT) or 134 hours (for E2) of waiting for analysis under regular conditions in the auto-sampler set at 10°C, the % REs of the replicate analyses of T, DHT, and E2 Low, Medium, and High QC samples were always ≤ 15%.

Incurred sample reanalysis (ISR) was not conducted on samples from this study. Instead, ISR was conducted in two Phase 1 studies (i.e., Studies TBS-1-2011-01 and TBS-1A-2011-01) that were conducted in healthy male subjects and in one Phase 2 study (i.e., Study TBS-1-2010-01) that was conducted in hypogonadal men.

In Study TBS-1-2010-01, ISR was conducted on 66 samples (11.5%) for total T and E2 (i.e., 3 samples each from 22 subjects) and 62 samples (10.8%) for DHT out of a total of 572 study samples. For all 66 ISR samples, total T concentrations were within ± 20% of the original results.

For DHT, 59 out of 62 ISR samples (95.2%) were within ± 20% of the original results. For E2, 63 out of 66 ISR samples (95.5%) were within ± 20% of the original results.

ISR results from the other 2 studies (i.e., TBS-1-2011-01 and TBS-1A-2011-01) were comparable to ISR results from Study TBS-1-2010-01. These ISR results confirmed the reproducibility of the bioanalytical method.

Reviewer's Comment: *While the Sponsor did not perform ISR on study samples from this study, they have performed ISR in other studies that used the same bioanalytical method as this study and the ISR results were found to be acceptable.*

OSI Inspection of the bioanalytical study site: The Clinical Pharmacology review team requested a bioanalytical site inspection on June 17, 2013. The bioanalytical study site (i.e., (b) (4) (b) (4)) was inspected during (b) (4) and the inspection report was issued on December 20, 2013. A copy of the inspection report can be found in DARRTS under NDA 205488.

After evaluation of inspectional observations and the responses from the bioanalytical laboratory, the OSI inspector recommended that the bioanalytical data should not be accepted until the following data are provided:

(a) Data that performance of calibrators prepared in artificial matrix is comparable to calibrators prepared in human serum, after adjustment for endogenous hormone concentrations; and

(b) Data for extraction recovery and matrix effects in human serum and the impact of lipemia on the accuracy of determinations of T, DHT, and E2 concentrations.

Reviewer's Comment: *Responses to the OSI observations noted in the December 20, 2013 OSI inspection report were received from the bioanalytical laboratory (i.e., (b) (4) (b) (4)) on January 15, 2014, February 7, 2014, and February 10, 2014 and were reviewed by the OSI reviewer, Dr. Gopa Biswas. The responses submitted were found to be acceptable by Dr. Biswas. Reference is made to Dr. Gopa Biswas' OSI memorandum dated March 14, 2014. A copy of this memorandum can be found in DARRTS under NDA 205488. This reviewer concurs with Dr. Biswas' recommendation.*

The acceptance criteria and performance of the total T, DHT, and E2 bioanalytical methods are in compliance with the Agency's Bioanalytical Method Validation Guidance. In summary, the method validation and performance of the bioanalytical methods in clinical studies are acceptable and there are no unresolved bioanalytical issues related to the approvability of NATESTO.

Statistical Analysis:
The Sponsor summarized the results by the following NATESTO treatment groups: 11 mg T BID, 11 mg T BID/TID (for subjects who up-titrated at Day 45), and 11 mg T TID. The Randomized population consisted of all subjects who signed the informed consent form and were assigned a randomization number at Visit 3 (Day 1).

Disposition of Subjects:
In total, 306 subjects were randomized: 228 subjects to the 11 mg T BID group and 78 subjects to the 11 mg T TID group.

Of the 306 subjects randomized, 32 (10.5%) subjects discontinued the study during the treatment period. A total of [redacted] %) subjects completed the 90 day treatment period. Table A-1-2 summarizes subject disposition for the randomized population for the 90-day treatment period of the study.

Table A-1-2: Subject Disposition of Treatment Period (Days 1-90) for Randomized Population

	Randomized to TBS-1 BID n (%)	Randomized to TBS-1 TID n (%)	Total n (%)
Randomized Population [1]	228 (100.0)	78 (100.0)	306 (100.0)
Completed the 90-day Treatment Period	[redacted]	69 (88.5)	[redacted]
Discontinued During the Treatment Period		9 (11.5)	
Withdrew consent		4 (5.1)	
Sponsor discontinued the study		0 (0.0)	
Adverse event		4 (5.1)	
Therapy with an excluded concomitant medication		0 (0.0)	
Serum PSA concentration >1.4 ng/mL above baseline		0 (0.0)	
Increase in hematocrit >54%		0 (0.0)	
Investigator opinion		0 (0.0)	
Lost to follow-up		0 (0.0)	
Other		1 (1.3)	

1. The Randomized Population consisted of all subjects who signed the informed consent form and were assigned a randomization number at Visit 3 (Day 1).
BID = twice daily; PSA = prostate specific antigen; TID = three times daily.
Source: Post-text Table 1.1

Reviewer's Comment: *According to Listing 11.1 (i.e., individual PK Profiles of serum total T in randomized population) provided in the study report, the PK profiles of 204 subjects randomized to the 11 mg T BID group (i.e., [redacted] subjects in the 11 mg T BID group and [redacted] subjects in the 11 mg T BID/TID group) and [redacted] subjects in total were reported. In the Sponsor's March 11, 2014 submission, the Sponsor clarified that 274 subjects completed the 90-day treatment period but [redacted] subjects had valid 24-hour serum total T Day 90 PK profile because Subject 047-022 did not come for the Day 90 visit as required per protocol. However, the investigator allowed this subject to continue into Safety Extension Period 1. This subject was lost to follow-up after that and didn't come back for future visits.*

In total, 274 subjects entered the safety extension period 1. Of those, 29 (10.6%) subjects discontinued the study during the safety extension period 1.

A subset of 75 subjects entered the safety extension period 2. Of those, 8 (10.7%) subjects discontinued during the safety extension period 2. A total of 55 (73.3%) subjects have completed safety extension period 2. There were 12 (16.0%) subjects still enrolled in safety extension period 2 as of the database lock of February 15, 2013. Table A-1-3 summarizes subject disposition of the randomized population for the safety extension periods.

Table A-1-3: Subject Disposition of the Randomized Population for Safety Extension Periods

	TBS-1 BID n (%)	TBS-1 TID n (%)	Total n (%)
Entered Safety Extension Period 1	122 (100.0)	152 (100.0)	274 (100.0)
Completed Safety Extension Period 1	107 (87.7)	138 (90.8)	245 (89.4)
Discontinued During Safety Extension Period 1	15 (12.3)	14 (9.2)	29 (10.6)
Withdrew consent	6 (4.9)	5 (3.3)	11 (4.0)
Sponsor discontinued the study	0 (0.0)	0 (0.0)	0 (0.0)
Adverse event	2 (1.6)	1 (0.7)	3 (1.1)
Therapy with an excluded concomitant medication	0 (0.0)	0 (0.0)	0 (0.0)
Serum PSA concentration >1.4 ng/mL above baseline	1 (0.8)	0 (0.0)	1 (0.4)
Increase in hematocrit >54%	0 (0.0)	0 (0.0)	0 (0.0)
Investigator opinion	0 (0.0)	1 (0.7)	1 (0.4)
Lost to follow-up	4 (3.3)	3 (2.0)	7 (2.6)
Other	2 (1.6)	4 (2.6)	6 (2.2)
Entered Safety Extension Period 2	35 (100.0)	40 (100.0)	75 (100.0)
Completed Safety Extension Period 2	25 (71.4)	30 (75.0)	55 (73.3)
Still Enrolled in Safety Extension Period 2	5 (14.3)	7 (17.5)	12 (16.0)
Discontinued During Safety Extension Period 2	5 (14.3)	3 (7.5)	8 (10.7)
Withdrew consent	4 (11.4)	2 (5.0)	6 (8.0)
Sponsor discontinued the study	0 (0.0)	0 (0.0)	0 (0.0)
Adverse event	0 (0.0)	1 (2.5)	1 (1.3)
Therapy with an excluded concomitant medication	0 (0.0)	0 (0.0)	0 (0.0)
Serum PSA concentration >1.4 ng/mL above baseline	0 (0.0)	0 (0.0)	0 (0.0)
Increase in hematocrit >54%	0 (0.0)	0 (0.0)	0 (0.0)
Investigator opinion	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	1 (2.9)	0 (0.0)	1 (1.3)
Other	0 (0.0)	0 (0.0)	0 (0.0)

Note: The denominator used in the percentage calculation of each period was the number of subjects who entered the period.
BID = twice daily; PSA = prostate specific antigen; TID = three times daily.
Source: Post-text Table 1.2

Data Sets Analyzed:

- The ITT population was defined as all subjects who received randomized study drug and had at least 1 valid post-baseline efficacy measurement in the period. The ITT population included 303 subjects during the treatment period.
- The Per-Protocol Population consisted of all ITT subjects who completed the 90-day treatment period without any major protocol deviations. Subjects could be excluded from the Per-Protocol Population for major violations of eligibility criteria for randomization, withdrawal prior to Day 90 or missing the Day 90 PK profile, taking restricted concomitant medication during the treatment period, or for any other major protocol deviation that could interfere with the assessment of drug efficacy. The Per-Protocol Population included (b) (4) subjects.
- The Safety Population for each period consisted of all subjects who received randomized study drug and had safety measurements in the respective period. The Safety Population included 306 subjects during the treatment period, 274 subjects during safety extension period 1, and 75 subjects during safety extension period 2.

Table A-1-4 displays the Sponsor's analysis populations during the treatment period and safety extension periods for the randomized population.

Table A-1-4: Sponsor's Analysis Populations for Treatment Period and Safety Extension Periods

	TBS-1 BID n (%)	TBS-1 BID/TID n (%) [4]	Combined TBS-1 BID n (%)	TBS-1 TID n (%)	Combined TBS-1 TID n (%)	Total n (%)
Treatment Period						
Entered Treatment Period	(b) (4)			78 (100.0)		(b) (4)
ITT Population [1]				77 (98.7)		
Per-Protocol Population [2]				67 (85.9)		
Safety Population [3]				78 (100.0)		
Safety Extension Period 1						
Entered Safety Extension Period 1	122 (100.0)	--	--	152 (100.0)	--	274 (100.0)
Safety Population [3]	120 (98.4)	--	--	152 (100.0)	--	272 (99.3)
Safety Extension Period 2						
Entered Safety Extension Period 2	35 (100.0)	--	--	40 (100.0)	--	75 (100.0)
Safety Population [3]	34 (97.1)	--	--	40 (100.0)	--	74 (98.7)

Note: The denominator used in the percentage calculation of each period is the number of subjects who entered the period.
1. The ITT Population consisted of all subjects who received randomized study drug and had at least 1 valid post-baseline efficacy measurement.
2. The Per-Protocol Population consisted of all ITT subjects who completed the 90-day Treatment Period without any major protocol deviations.
3. The Safety Population consisted of all subjects who received randomized study drug and had safety measurements in the treatment period.
4. The TBS-1 BID/TID group consisted of subjects who were titrated up to TID on Day 45.
BID = twice daily; ITT = Intent-to-Treat; TID = three times daily.
Source: Post-text Tables 2.1 and 2.2

Reviewer's Comment: *According to Tables 9.4.1, 10.4.1, and 11.4.1 (i.e., Summary of PK parameters for total T, E2, and DHT of ITT population during treatment period) provided in the study report, the ITT population for the 11 mg T BID, 11 mg T BID/TID, 11 mg T TID groups, and total consist of* (b) (4) *, 77, and 303 subjects, respectively.*

Demographics of Subjects:
In total, there were 306 male subjects enrolled. The majority of subjects were White/Caucasian race (88.6%). The overall mean age of subjects at the time of informed consent was 54.4 years (range: 28-80 years). The mean weight, height, and BMI at screening were 93.34 kg, 177.1 cm, and 29.69 kg/m^2, respectively. In total, 71.6% of subjects had primary hypogonadism and 28.4% had secondary hypogonadism. The mean duration of hypogonadism prior to screening was 4.6 years. Overall, 27.1% of subjects required a wash-out from their previous T replacement therapy at screening. Subjects who did not require a wash-out were either naïve (73.2%) or discontinued their previous treatment with T prior to enrollment in the study.

The mean qualifying fasting serum total T concentration was 200.8 ng/dL,. Mean DHT at screening was 19.2 ng/dL and mean screening E2 was 18.2 pg/mL.

Table A-1-5: Demographic and Baseline Characteristics of the Randomized Population (N=306)

Randomized Treatment Assignment	Randomized to TBS-1 BID			Randomized to TBS-1 TID	
Treatment Group Characteristic Category/Statistic	TBS-1 BID (b) (4)	TBS-1 BID/TID[5]	Combined TBS-1 BID (b) (4)	TBS-1 TID (N=78)	Total (N=306)
Age (years)					
n				78	306
Mean (SD)	52.9 (10.36)	56.7 (11.41)	54.4 (10.90)	54.4 (11.49)	54.4 (11.03)
Age Group - n (%)					
<65 years	(b) (4) (85.2)	(b) (4) 74.4)	(b) (4) (81.1)	61 (78.2)	246 (80.4)
≥65 years	(14.8)	25.6)	(18.9)	17 (21.8)	60 (19.6)
Ethnicity - n (%)					
Hispanic or Latino	(16.9)	(9.3)	(14.0)	9 (11.5)	41 (13.4)
Not Hispanic or Latino	(83.1)	90.7)	(86.0)	69 (88.5)	265 (86.6)
Race - n (%)					
Asian	(b) (4) 4.9)	(b) (4) (7.0)	(b) (4) (5.7)	3 (3.8)	16 (5.2)
American Indian or Alaskan Native	0.0)	(0.0)	(0.0)	0 (0.0)	0 (0.0)
Black/African or African American	4.9)	(8.1)	(6.1)	4 (5.1)	18 (5.9)
Native Hawaiian or Other Pacific Islander	0.0)	(0.0)	(0.0)	0 (0.0)	0 (0.0)
White/Caucasian	0.1)	84.9)	88.2)	70 (89.7)	271 (88.6)
Other	0.0)	(0.0)	(0.0)	1 (1.3)	1 (0.3)
Weight at Screening (kg)					
n			(b) (4)	78	306
Mean (SD)	92.22 (14.730)	94.82 (14.284)	93.20 (14.586)	93.73 (13.417)	93.34 (14.277)
Height at Screening (cm)					
n			(b) (4)	78	306
Mean (SD)	177.1 (7.62)	177.1 (5.91)	177.1 (7.01)	176.9 (6.64)	177.1 (6.91)
BMI at Screening (kg/m^2)					
n			(b) (4)	78	306
Mean (SD)	29.30 (3.633)	30.13 (3.775)	29.62 (3.701)	29.89 (3.237)	29.69 (3.585)
BMI Category - n (%)					
BMI <30 kg/m^2	(b) (4) (54.9)	(b) (4) 51.2)	(b) (4) (53.5)	43 (55.1)	165 (53.9)
BMI ≥30 kg/m^2	(45.1)	48.8)	(46.5)	35 (44.9)	141 (46.1)
Hypogonadism Etiology - n (%)					
Primary	(b) (4) (77.5)	(b) (4) (66.3)	(b) (4) (73.2)	52 (66.7)	219 (71.6)
Secondary	(22.5)	(33.7)	(26.8)	26 (33.3)	87 (28.4)

1. More than 1 option could be selected.
2. Duration of Hypogonadism was calculated by the year of informed consent – the year of diagnosis + 1.
3. The average of the qualifying values during Screening period was used.
4. Not currently being treated with a testosterone product at the time of screening.
5. The TBS-1 BID/TID group consisted of subjects who were titrated up to TID on Day 45.

BID = twice daily; BMI = body mass index; SD = standard deviation; TID = three times daily.
Source: Post-text Table 3

Randomized Treatment Assignment	Randomized to TBS-1 BID			Randomized to TBS-1 TID	
Treatment Group Characteristic Category/Statistic	TBS-1 BID	TBS-1 BID/TID[5]	Combined TBS-1 BID	TBS-1 TID (N=78)	Total (N=306)
Testosterone Therapy at Visit 1 - n (%) [1]					
Naïve [4]	(b) (4) 73.2)	(b) (4) 74.4)	(b) (4) 73.7)	56 (71.8)	224 (73.2)
Injection	14.8)	(9.3)	12.7)	10 (12.8)	39 (12.7)
Oral	(0.7)	(0.0)	(0.4)	2 (2.6)	3 (1.0)
Topical	12.0)	16.3)	13.6)	10 (12.8)	41 (13.4)
Buccal	(0.0)	(0.0)	(0.0)	0 (0.0)	0 (0.0)
Previous Treatment for Naïve Subjects - n (%) [1, 4]					
None	(b) (4) 45.1)	(b) (4) 39.5)	(b) (4) 43.0)	32 (41.0)	130 (42.5)
Injection	10.6)	7.4)	13.2)	11 (14.1)	41 (13.4)
Oral	(0.7)	4.7)	(2.2)	1 (1.3)	6 (2.0)
Topical	17.6)	5.1)	16.7)	13 (16.7)	51 (16.7)
Buccal	(0.7)	3.5)	(1.8)	1 (1.3)	5 (1.6)
Duration of Hypogonadism (years) [2]					
n			(b) (4)	78	306
Mean (SD)	4.2 (3.53)	5.0 (4.69)	4.5 (4.02)	5.0 (5.67)	4.6 (4.49)
Qualifying Fasting Serum Total Testosterone during Screening (ng/dL) [3]					
n			(b) (4)	78	306
Mean (SD)	200.44 (67.648)	192.79 (68.364)	197.55 (67.870)	210.35 (51.510)	200.82 (64.260)
Estradiol (pg/mL) at Screening					
n			(b) (4)	76	302
Mean (SD)	17.65 (7.234)	18.03 (6.395)	17.79 (6.915)	19.58 (7.460)	18.24 (7.086)
DHT (ng/dL) at Screening					
n			(b) (4)	76	302
Mean (SD)	19.50 (9.457)	17.60 (7.956)	18.78 (8.945)	20.54 (8.980)	19.22 (8.971)

1. More than 1 option could be selected.
2. Duration of Hypogonadism was calculated by the year of informed consent – the year of diagnosis + 1.
3. The average of the qualifying values during Screening period was used.
4. Not currently being treated with a testosterone product at the time of screening.
5. The TBS-1 BID/TID group consisted of subjects who were titrated up to TID on Day 45.

BID = twice daily; BMI = body mass index; SD = standard deviation; TID = three times daily.
Source: Post-text Table 3

In general, the treatment groups were comparable with respect to demographic and baseline characteristics.

Protocol Deviations:
Observed protocol deviations included the following:

- The BMI of subjects enrolled were not between 18.5 and35.0 kg/m^2.
- Subjects missing the dose(s) of the investigational product (IP)
- Deviation from the titration scheme
- Subjects not administering the IP within the indicated time (e.g., ± 5 minutes) of the dosing schedule
- Deviation from the PK sample collection schedule
- Investigational product accountability was < 80% and > 120% when checked at each visit
- PE and DRE not performed at Visit 1
- DEXA scan not performed at Visit 9

Reviewer's Comment: *None of these were considered to be significant enough to be withdrawn from the study by the Investigator. However, since the deviation from the titration scheme could affect the outcome of the efficacy results, this reviewer conducted further analysis on the deviation from the titration scheme below. Refer to the Dose Titration Scheme Evaluation Section below.*

Treatment Compliance Results:
Compliance to the study drug regimen was evaluated by weighing the study drug dispensers and reviewing the daily diary at each visit. If compliance was not between 80-120% during the

Treatment Period, subjects were counseled about the importance of compliance to the regimen. Table A-1-6 summarizes the treatment compliance results based on the ITT population at Day 90.

Table A-1-6: Treatment Compliance Results Based on the ITT Population at Day 90

(b) (4)

Concomitant Medication Results:
The types of concomitant medications were typical for hypogonadal men. The most common types of concomitant medications were HMG CoA reductase inhibitors (31.0% for treatment period, 33.1% for safety extension period 1, and 25.7% for safety extension period 2), platelet aggregation inhibitors excluding heparin (24.2% for treatment period, 25.7% for safety extension period 1, and 21.6% for safety extension period 2), and drugs used in erectile dysfunction (18.0% for treatment period, 19.1% for safety extension period 1, and 23.0% for safety extension period 2). Overall usage of concomitant medications was generally similar for the treatment groups as shown in Table A-1-7.

Table A-1-7: Summary of Concomitant Medications for the Randomized Population (N=306) During the Treatment Period (Days 1-90)

	BID (N=143)	BID/TID (N=85)	TID (N=78)	Overall (N=306)
With any concomitant medications	(b) (4)		68 (87.2%)	264 (86.3%)
HMG CoA reductase inhibitors			25 (32.1%)	95 (31.0%)
Platelet aggregation inhibitors excluding heparin			22 (28.2%)	74 (24.2%)
Erectile dysfunction			14 (17.9%)	55 (18.0%)

OSI inspection of the clinical study sites:
The Clinical Pharmacology review team has requested inspections on clinical study sites on July 26, 2013. As a result, 3 clinical study sites (i.e., Sites 025, 051, and 052) were inspected during August 19, 2013 - November 14, 2013 and the inspection report was issued on December 20, 2013. A copy of the inspection report can be found in DARRTS under NDA 205488.

After evaluation of inspectional observations and the responses from the clinical study sites, the OSI inspector recommended that:

(a) The OCP reviewer should assess the impact of early dose adjustments from BID to TID for subject #051-036 (clinical site #2) on the safety and efficacy of the treatment.

(b) Abnormal results for subject #051-014 ((b) (6)) during Visit #6 should be reviewed for safety evaluations.

Reviewer's Comment: *Regarding recommendation (a), Subject 051-036's titration prediction sample concentration (i.e., sum of total T concentration of Samples A and B) was 560 ng/dL*

indicating a need to titrate up to the 11 mg TID regimen. This subject was titrated up to 11 mg T TID on Day 38 instead of Day 45.

Table A-1-8: Summary of Subject 051-036's PK Parameters

Day 30 total T C_{avg}		(b) (4) ng/dL
Day 90 total T C_{avg}		ng/dL
Day 30 total T C_{max}		ng/dL
Day 90 total T C_{max}		ng/dL

As shown, in Table A-1-8, Subject 051-036's PK parameters were carefully evaluated and no significant impact regarding efficacy and safety was identified. Given the fact that titration on Day 45 is based on the measurements on Day 30, the impact of titrating up on Day 38 instead of Day 45 appears to be negligible.

Regarding recommendation (b), Subject 051-014 had abnormal laboratory findings of increased ALT/SGPT, AST/SGOT, GGT, and creatine kinase on Days 30 and 90 after being randomized into the study. These were not reported as AEs as illustrated in Table A-1-9 below:

Table A-1-9: Abnormal Clinical Laboratory Findings from Subject 051-014

Visit	ALT/SGPT (6-41 U/L)	AST/SGOT (9-34 U/L)	GGT (11-52 U/L)	Creatine Kinase (25-210 U/L)
Visit #1(Screen) (21 Apr 12J	50 U/L	37 U/L	169 U/L	385 U/L
Visit #3 (Randomization/Day!) (OS May 12)	57 U/L	37 U/L	207 U/L	199 U/L
Visit #4 /Day #30 (23 Jun 12)	77 U/L	50 U/L	**301 U/L**	**549 U/L**
Visit #6 /Day 90 (25 Aug 12)	**93 U/L**	**189 U/L**	**185 U/L**	**7070 U/L**

The clinical investigator reviewed the abnormal laboratory results and decided that they were not clinically significant. The clinical investigator did not consider the elevated creatine kinase result during Visit 6 (Day 90) as an AE because the subject was involved in strenuous physical exercise before the visit. The clinical relevance is unknown and this reviewer defers this evaluation to the clinical review team.

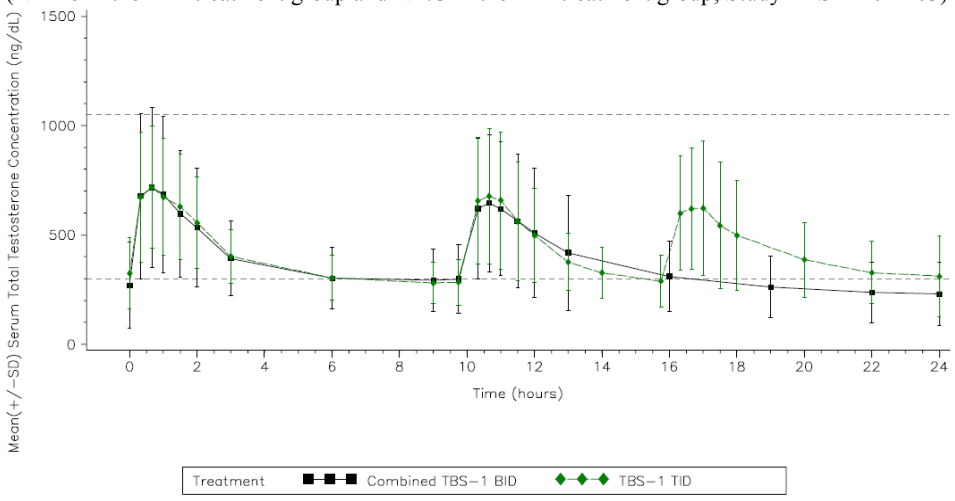
Serum total T PK

Complete PK profiles of serum total T were characterized on Days 30 and 90. Two hundred eighty nine (289) and (b) (4) subjects were included in the PK analysis on Days 30 and 90, respectively. This study started out with 2 treatment groups (i.e., 11 mg T BID and 11 mg T TID). On Day 30, the 24-hour C_{avg} of serum total T for subjects in the BID group was estimated based on the sum of serum total T concentrations collected at 2 sampling points (i.e., 9 and 10.33 hours post-dose of the 9 pm dose). Subjects with an estimated serum total T C_{avg} < 300 ng/dL were instructed to increase the daily dose of NATESTO to 11 mg T TID on Day 45 (i.e., 11 mg T BID/TID treatment group). This daily dose was continued throughout the remainder of the treatment period and, as applicable, both safety extension periods. It should be noted that the 11 mg TID treatment group was consisted of the subjects that were randomized to and maintained the 11 mg TID regimen throughout the study. While the proposed dosing regimen for NATESTO is 11 mg T TID, PK analysis was conducted for all 3 treatment groups (i.e., 11 mg T BID, 11 mg T BID/TID, and 11 mg T TID).

Figures A-1-1 is a plot of the 24-hour serum total T concentration-time curve by the 2 treatment groups (that the study started out with) at Day 30 for the ITT population with complete PK

profiles. The Day 30 24-hour serum total T PK profiles for the 11 mg T BID group and the 11 mg T BID/TID group (based on their titration on Day 45) are plotted separately in Figure A-1-2. Figure A-1-3 is a plot of the 24-hour serum total T concentration-time curve by treatment groups at Day 90 for the ITT population with complete PK profiles.

Figure A-1-1: Plot of Serum Total T Concentrations by Treatment (based on randomization) and Time Points at Day 30 for the ITT Population with Complete PK Profiles
(N=216 in the BID treatment group and N=73 in the TID treatment group; Study TBS-1-2011-03)



BID = twice daily; SD = standard deviation; TID = three times daily.

Figure A-1-2: Plot of Serum Total T Concentrations by Treatment (based on their titration on Day 45) and Time Points at Day 30 for the ITT Population with Complete PK Profiles (N (b) (4) in the BID treatment group, N (b) (4) in the BID/TID treatment group, and N=73 in the TID treatment group; Study TBS-1-2011-03)

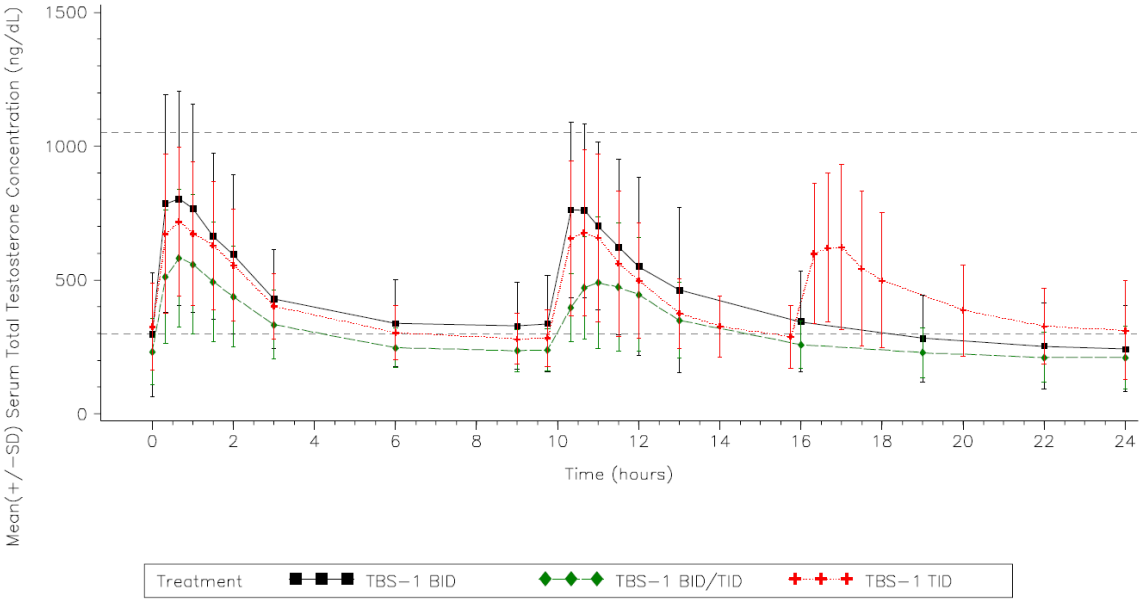


Figure A-1-3: Plot of Serum Total T Concentrations by Treatment (based on their titration on Day 45) and Time Points at Day 90 for the ITT Population with Complete PK Profiles (N[(b) (4)] in the BID treatment group, N[(b) (4)] in the BID/TID treatment group, and N=69 in the TID treatment group; Study TBS-1-2011-03)

Tables A-1-10 and A-1-12 summarize these PK parameters for serum total T by treatment groups at Days 30 and 90 for the ITT population. The Day 30 serum total T PK parameters for the BID group and the BID/TID group (based on their titration on Day 45) are summarized separately in Table A-1-11.

Table A-1-10: Summary of Arithmetic Mean (SD) PK Parameters of Serum Total T by Treatment (based on randomization) at Day 30 for ITT Population with Complete PK Profiles (N=289; Study TBS-1-2011-03)

	BID (N=216)	TID (N=73)
AUC(0-24) (ng·hr/dL)	[(b) (4)]	9956.0 (2727.0)
C_{max} (ng/dL)		912.7 (342.9)
C_{min} (ng/dL)		211.0 (73.2)
C_{avg} (ng/dL)		414.8 (113.6)
T_{max} (hr)[a]		0.70 (0.3, 8.0)

[a] Median (min, max)

Table A-1-11: Summary of Arithmetic Mean (SD) PK Parameters of Serum Total T by Treatment (based on their titration on Day 45) at Day 30 for ITT Population with Complete PK Profiles (N=289; Study TBS-1-2011-03)

	BID (N[(b) (4)]	BID/TID (N[(b) (4)]	TID (N=73)
AUC(0-24) (ng·hr/dL)	[(b) (4)]	[(b) (4)]	9956.0 (2727.0)
C_{max} (ng/dL)			912.7 (342.9)
C_{min} (ng/dL)			211.0 (73.2)
C_{avg} (ng/dL)			414.8 (113.6)
T_{max} (hr)[a]			0.70 (0.3, 8.0)

[a] Median (min, max)
[b] N=132; Subject 015-009 in the BID treatment group did not have an AUC(0-24) and C_{max} value reported.

Table A-1-12: Summary of Arithmetic Mean (SD) PK Parameters of Serum Total T by Treatment (Based on Their Titration on Day 45) at Day 90 for ITT Population with Complete PK Profiles (N= (b) (4): Study TBS-1-2011-03)

	BID (N (b) (4))	BID/TID (N (b) (4))	TID (N=69[b])
AUC(0-24) (ng·hr/dL)	(b) (4)		10101.2 (2782.4)
C_{max} (ng/dL)			1043.9 (378.1)
C_{min} (ng/dL)			214.7 (73.8)
C_{avg} (ng/dL)			420.9 (115.9)
T_{max} (hr)[a]			0.65 (0.3, 6.1)

[a] Median (min, max)
[b] Number of subjects who had a C_{max} at the Day 90 visit.

As shown in Figures A-1-2 and A-1-3, mean T_{max} was at approximately 40 minutes post-dose regardless of the treatment group and treatment length (i.e., 30 days vs. 90 days). The mean C_{avg} and AUC(0-24) of total T following daily administration with 22 mg T (i.e., 11 mg T BID) and 33 mg T (i.e., 11 mg T TID) for 30 and 90 days were not dose-proportional but exposure increased with increasing the dose and the 11 mg T TID group had higher values compared to the 11 mg T BID and 11 mg T BID/TID groups. The mean C_{max} values at Days 30 and 90 were slightly higher for the BID treatment group compared to the TID treatment group. It should be noted that the BID/TID group had lower AUC(0-24), C_{max}, and C_{avg} values compared to the BID or TID treatment groups.

Daily time of serum total T in normal range: The time within the normal range for serum total T concentrations was calculated based on the 24-hour PK profiles obtained on Days 30 and 90. The mean daily time period during which serum total T concentrations was within the normal range of 300-1,050 ng/dL at Day 90 LOCF is summarized in Table A-1-13.

Table A-1-13: Summary of Time (hours) Within Normal Range for Serum Total T at Day 90 LOCF of the ITT Population (Study TBS-1-2011-03)

Treatment	BID	BID/TID	TID	Total
N	(b) (4)		73	289
Mean			15.8	13.3
SD			5.9	6.4
Median			16.0	13.0
Minimum			1.5	0
Maximum			24.1	24.1

Reviewer Comment: *It should be noted that Day 90 LOCF of the ITT population would have the same number of subjects in each treatment group as the Day 30 ITT population since it is carrying forward the last observation of Day 30 if Day 90 value was missing.*

The TID treatment group had a longer mean time of which the serum total T concentrations were within the normal range compared to the BID or BID/TID treatment group at Day 90.

Primary Efficacy Evaluation Results:
Initially, the Sponsor has proposed to initiate NATESTO therapy with 11 mg T BID (b) (4) However, the Sponsor has submitted a major amendment on January 13, 2014 with a new proposal to administer NATESTO as a 11 mg T TID regimen (b) (4). Therefore, the primary efficacy analysis was based on the TID group.

The primary efficacy analysis was conducted based on the ITT population (i.e., that is defined as all subjects who received randomized study drug and had at least 1 valid post-baseline efficacy measurement in the treatment period) at Day 90 LOCF. At Day 90 LOCF, there were 289 subjects in the ITT population with valid serum total T C_{avg} (i.e., subjects with a serum total T concentration at Day 90 or LOCF of Day 30 if Day 90 value was missing). Among these 289 subjects, 216 subjects started out with 22 mg/day (11 mg T BID) and 73 subjects started out on 33 mg/day (11 mg T TID). Of these 216 subjects that started out with 11 mg T BID, (b) (4) subjects (including Subject 010-005 [titrated up on Day 90 instead of Day 45]) were titrated up to the 11 mg TID regimen (33 mg/day; the 11 mg BID/TID group) on Day 45 and (b) (4) subjects continued with their BID regimen.

Table A-1-14 presents the number and percentage of subjects in the ITT population by serum total T C_{avg} category at Day 90 LOCF per the analysis. At Day 90 LOCF, there were 289 subjects in the ITT population with valid 24-hour serum total T C_{avg}.

Table A-1-14: The Number and Percentage of the Subjects in the ITT Population by Serum Total T C_{avg} Category at Day 90 LOCF (Study TBS-1-2011-03)

Treatment	BID	BID/TID	BID + BID/TID Combined	TID	Total
Total number of subjects	(b) (4)			73	(b) (4)
C in normal range (300 < C < 1050 ng/dL)					
Yes	(b) (4)			66	(b) (4)
%				90	
95% CI for frequency*				(84, 97)	
C_{avg} below normal range (C_{avg} < 300 ng/dL)					
Yes	(b) (4)			7	(b) (4)
%				10	
C_{avg} above normal range (C_{avg} >1050 ng/dL)					
Yes	(b) (4)			0	(b) (4)
%				0	

* The CI for the frequency was approximated by a binomial distribution within each treatment.
Source: Extracted from Tables 1 and 4 of Dr. Jiang Liu's Pharmacometric Review (See Section 4.2 of this review)

Reviewer's Comment: *The pre-defined, primary efficacy endpoint in the Study TBS-1-2011-03 was the proportion of subjects with C_{avg} total T concentrations within the normal range of 300-1,050 ng/dL on Day 90. The Sponsor was advised that ≥ 75% of subjects would achieve the primary endpoint, with the lower bound of the 95% confidence interval > 65%. Reference is made to the Advice/Information Request letter sent to the Sponsor on October 31, 2011.*

As shown in Table A-1-14, in the ITT population using LOCF methodology for missing data, the point estimate and 95% CI for the 11 mg T TID group (N=73) indicates that the agreed-upon level of success was achieved (b) (4)

Dose Titration Scheme Evaluation

While the final proposed dosing regimen is 11 mg T TID, it should be noted that the Sponsor has developed and evaluated a dose titration scheme for the dosing regimen that was initially proposed to be 11 mg T BID (b) (4)

Day 30 Total T C_{avg} and Day 45 Titration Outcome: On Day 30 of the treatment, the sum of the serum total T concentration values for PK samples collected at the 2 sampling points (i.e.,

Samples A and B) for titration was < 755 ng/dL (i.e., indicating a need to titrate up from 11 mg BID to 11 mg TID [33 mg/day]) for (b) (4) subjects of the 216 subjects in the ITT population who were randomized to 11 mg BID. (b) (4) subjects were titrated up to the 11 mg TID dosing regimen on Day 45.

Titration predictions were completed for 216 patients in the ITT Population who were randomized to 11 mg BID. On Day (b) (4)

(b) (4)

Table A-1-16: Subjects that Deviated from the Titration Scheme (Study TBS-1-2011-03)

	Subject #	Sample A (1 hr pre-dose) (ng/dL)	Sample B (20 min post-dose) (ng/dL)	Samples A + B (ng/dL)	Day 30 C_{avg} (ng/dL)	Day 90 C_{avg} (ng/dL)
Subjects not titrated up to 11 mg TID on Day 45 despite Samples A + B < 755 ng/dL on Day 30 (N [(b) (4)])	[redacted]					
Subjects titrated up to 11 mg TID on Day 45 despite Samples A + B ≥ 755 ng/dL on Day 30 (N [(b) (4)])						

Neither serum total T C_{max} nor C_{avg} on Day 90 exceeded the upper limit of normal (i.e., 2,500 ng/dL for C_{max} and 1,050 ng/dL for C_{avg}) for total T in any of the patients who were incorrectly titrated from 11 mg BID to the 11 mg TID regimen.

Prediction accuracy of the titration scheme: The prediction accuracy of the titration scheme (i.e., based on the sum of total T concentrations of Samples A and B) is summarized in Table A-1-17.

Table A-1-17: Summary of Prediction Accuracy of the Titration Scheme in ITT population originally randomized to the 11 mg BID Group (N = 216 subjects; Study TBS-1-2011-03)

	Number of subjects (%)
Over-estimated	[(b) (4)]
Under-estimated	

The over-estimated group consists of subjects that were predicted to have [(b) (4)]

[redacted]

Reviewer's Comment: *It should be noted that the Sponsor reported the titration prediction success rate to be* [(b) (4)] *% which is different from this reviewer's own analysis. The overall titration success rate should be calculated by accounting for all of the over-estimated and under-estimated subjects as described above.*

Cut-off point and sampling time for titration prediction: The cut-off point for titration prediction was determined by comparing various points as summarized in Table A-1-18.

Table A-1-18: Summary of Titration Success Rates at Various Cut-off Points (N=216; Study TBS-1-2011-03)

Samples A + B Total T Concentration (ng/dL)	Titration Prediction Accuracy (%)	Over-estimated subjects (%)	Under-estimated subjects (%)
(b) (4)			

The success or failure of each titration prediction was determined by comparing the titration prediction (i.e., sum of total T concentrations of Samples A and B) with the actual C_{avg} at Day 30.

Figure A-1-4: NATESTO Titration Development: Percentage of Correct Titration Predictions vs. Cut-off Point (Sample A + Sample B Total T Concentration) (N=216; Study TBS-1-2011-03)

(b) (4)

Under titrated: over-estimated
Over titrated: under-estimated

Same type of analysis was conducted for the timing of collecting Sample B as shown in Table A-1-19.

(b) (4)

Reviewer's Comment: (b) (4) [redacted]

[redacted]

(b) (4) [redacted] *The mean total T C_{avg} at Day 90 were* (b) (4) *and 420.9 ng/dL for the BID, BID/TID, and TID groups, respectively (Table A-1-12). In addition, none of the subjects in the 11 mg T TID group had a total T C_{avg} value > 1,050 ng/dL at Day 90.*

Considering these facts, one would be more concerned about the efficacy of NATESTO than safety and therefore, it is important to (b) (4) [redacted] *However, the Sponsor has reported that safety and PK data from Study TBS-1-2010-01 indicates that subjects that were on the 11.25 mg TID regimen did not show any supra-therapeutic concentrations of total T and therefore, would be no safety concerns with subjects who were titrated to the 11 mg TID regimen when they achieved normal total T concentrations on the 11 mg BID regimen. Reference is made to Dr. LaiMing Lee's Clinical Pharmacology review dated September 21, 2011 in DARRTS (IND 70,512, SDN: 039).*

Considering the advantage of having a shorter wait time for sampling in clinical practice and the fact that 20 minutes post-dose sampling showed a lower under-estimation rate compared to other sampling points, the Sponsor's approach appears to be reasonable.

Secondary Efficacy and Safety Evaluation Results:
Critical Secondary Safety Endpoint (Serum total T C_{max} at Day 90): The critical secondary safety endpoint, total T C_{max}, had the following criteria that were expected to be met on Day 90:

- Having < 5% of subjects with a serum total T C_{max} in the range of 1,800-2,500 ng/dL
- No subjects with a serum total T C_{max} of > 2,500 ng/dL
- Having a serum total T $C_{max} \leq$ 1,500 ng/dL in at least 85% of subjects

Table A-1-20 presents the number and percentage of subjects in the ITT population with a serum total T C_{max} in each range on Day 90.

Table A-1-20: Number (Percentage) of Subjects by Serum Total T C_{max} in Selected Ranges at Day 90 by Treatment of ITT Population

Treatment	BID	BID/TID	BID + BID/TID Combined	TID	Total
Number of subjects	122	82	204	69	273
$C_{max} \leq 1,500$ ng/dL	107 (87.7)	77 (93.9)	184 (90.2)	58 (84.1)	242 (88.6)
1800 ng/dL $\leq$ $C_{max} \leq 2,500$ ng/dL	6 (4.9)	2 (2.4)	8 (3.9)	1 (1.4)	9 (3.3)
$C_{max} > 2,500$ ng/dL	1 (0.8)	0 (0)	1 (0.5)	0 (0)	1 (0.4)

The number of subjects in each group is the number of subjects who had a C_{max} at the Day 90 visit.

There were no subjects with a serum total T $C_{max} > 2,500$ ng/dL in the TID treatment group. The values of C_{max} and C_{avg} from subjects that had $C_{max} > 1,500$ ng/dL at Day 90 are summarized in Table A-1-21.

Table A-1-21: C_{max} and C_{avg} of Subjects that had $C_{max} > 1,500$ ng/dL at Day 90

Subject #	Day 30 C_{max} (ng/dL)	Day 90 C_{max} (ng/dL)	Day 30 C_{avg} (ng/dL)	Day 90 C_{avg} (ng/dL)	Day 90 DHT/T C_{avg}
001-045	683	1660	374.9	603.2	0.065
003-001	1410	1690	228.2	434.2	0.081
011-020	796	1600	421.8	432.3	0.132
013-002	1730	1770	657.5	716.0	0.089
013-008	2520	2260	889.0	764.1	0.103
013-009	847	1550	379.2	458.7	0.092
022-001	1670	1540	580.6	409.5	0.147
022-028	1100	1640	250.7	324.6	0.087
025-030	998	1550	518.0	693.7	0.222
028-005	1230	1630	623.8	613.7	0.090
030-008	994	1780	414.6	465.2	0.107

Overall, 1 (0.4%) subject (Subject 052-024 in the 11 mg BID group) had serum total T C_{max} of 3,570 ng/dL at Day 90. This subjects' serum total T C_{max} at Day 30 was 1,690 ng/dL.

Reviewer's Comment: *The serum total T C_{avg} and the DHT/T C_{avg} ratio at Day 90 for Subject 013-008, the only subject in the TID treatment group that had a $C_{max} \geq 1,800$ ng/dL at Day 90, were 764.1 ng/dL and 0.103, respectively. These values are in the normal total T range (i.e., 300-1,050 ng/dL) and the normal DHT/T ratio range of 0.05-0.33 reported by Diver et al., 2003.*

Sponsor suggests that Subject 052-024's high serum total T C_{max} value of 3,570 ng/dL could be attributed to a possible continuing post-treatment effect of finasteride (i.e., a 5α-reductase inhibitor) on hormone metabolism and states that Subject 052-024's normal DHT/T ratio of 0.06 supports this possibility. No other safety concerns were identified for these subjects during the study per the Investigator.

In summary, the following criteria of the critical secondary safety endpoint, total T C_{max}, were met:

- Having < 5% of subjects with a serum total T C_{max} in the range of 1,800-2,500 ng/dL
- No subjects with a serum total T C_{max} of > 2,500 ng/dL

However, 0.9% less subjects (i.e., 84.1%) had a serum total T $C_{max} \leq 1,500$ ng/dL on Day 90 compared to the pre-specified criteria. Table 3 presents the number and percentage of subjects in the ITT population on Day 90.

Serum total T C_{avg} in normal range at Day 30: Table A-1-22 presents the number and percentage of subjects in the ITT population by serum total T C_{avg} category at Day 30 per Sponsor's analysis.

Table A-1-22: Number and Percentage of Subjects by Serum Total T C_{avg} Category at Day 30 for the ITT Population

	TBS-1 BID (N=141) n (%)	TBS-1 BID/TID (N=85) n (%)	Combined TBS-1 BID (N=226) n (%)	TBS-1 TID (N=77) n (%)	Total (N=303) n (%)
C_{avg} in Normal Range (300≤C_{avg}≤1050 ng/dL)					
N'	131	85	216	73	289
Yes - n	104	36	140	61	201
%	79	42	65	84	70
95% CI for Frequency [1]	(72.46, 86.32)	(31.85, 52.86)	(58.45, 71.18)	(75.06, 92.06)	(64.24, 74.86)
C_{avg} Below Normal Range (C_{avg}<300 ng/dL)					
N'	131	85	216	73	289
Yes - n	25	49	74	12	86
%	19	58	34	16	30
C_{avg} Above Normal Range (C_{avg}>1050 ng/dL)					
N'	131	85	216	73	289
Yes - n	2	0	2	0	2
%	2	0	1	0	1

1. The CI for the frequency was approximated by a binomial distribution within each treatment.
BID = twice daily; C_{avg} = average concentration; CI = confidence interval; TID = three times daily.
Source: Post-text Table 7.1

In the ITT Population, 30% of subjects had C_{avg} below the target range on Day 30. There were 2 (1%) subjects in the 11 mg T BID group who had C_{avg} above the target range:

- Subject 047-003 had serum total T C_{avg} of 1,221 ng/dL
- Subject 014-010 had serum total T C_{avg} of 1,570 ng/dL. He was taking Avodart® (dutasteride), a prohibited medication that can interfere with T metabolism.

Reviewer's Comment: *Both of Subjects 047-003 and 014-010 were on the 11 mg T BID regimen throughout the 90-day treatment period. Their PK and titration prediction parameters are listed in Table A-1-23 below.*

Table A-1-23: PK and Titration Prediction Parameters of Subjects that had C_{avg} above the target range at Day 30

Subject #	Sample A (1 hr pre-dose) (ng/dL)	Sample B (20 min post-dose) (ng/dL)	Samples A + B (ng/dL)	Day 30 C_{avg} (ng/dL)	Day 90 C_{avg} (ng/dL)	Day 30 C_{max} (ng/dL)	Day 90 C_{max} (ng/dL)
047-003	743	1880	2623	1220.9	1097.7	3070	2320
014-010	1510	1590	3100	1570.0	524.9	2660	1400

There were no removal criteria based on abnormal C_{avg} values and these subjects stayed in the study throughout the 90-day treatment period. While their Day 30 C_{avg} and C_{max} values were of concern, their Day 90 C_{max} values were < 2,500 ng/dL and the Day 90 C_{avg} value for Subject 047-003 were slightly above the target value of ≤ 1,050 ng/dL.

Serum total T C_{max} at Day 30: Table A-1-24 presents the number and percentage of subjects in the ITT population with a serum total T C_{max} in each range at Day 30 per Sponsor's analysis.

Table A-1-24: Number and Percentage of Subjects by Serum Total T C_{max} at Day 30 for the ITT Population

	TBS-1 BID (N=141) n (%)	TBS-1 BID/TID (N=85) n (%)	Combined TBS-1 BID (N=226) n (%)	TBS-1 TID (N=77) n (%)	Total (N=303) n (%)
Day 30	N'=132	N'=85	N'=217	N'=73	N'=290
C_{max} ≤1500 ng/dL	116 (87.9)	83 (97.6)	199 (91.7)	69 (94.5)	268 (92.4)
1800 ng/dL ≤ C_{max} ≤2500 ng/dL	4 (3.0)	0 (0.0)	4 (1.8)	0 (0.0)	4 (1.4)
C_{max} >2500 ng/dL	2 (1.5)	0 (0.0)	2 (0.9)	1 (1.4)	3 (1.0)

Note: N' is the number of subjects who had a C_{max} at the specified visit. %=n/N'.
BID = twice daily; C_{max} = maximum concentration; TID = three times daily.
Source: Post-text Table 8.1

Three (1.0%) subjects had serum total T C_{max} > 2,500 ng/dL at Day 30: 2 (1.5%) subjects in the BID group (Subjects 014-010 and 047-003), and 1 (1.4%) subject in the TID group (Subject 013-008).

Reviewer's Comment: *Per Sponsor, Subject 014-010's high C_{max} value of 2,660 ng/dL could possibly be explained by concomitant use of the prohibited medication Avodart (i.e., a 5α-reductase inhibitor). His low DHT/T ratio of 0.004 also supports this possibility. For the 2 other subjects, the increase in C_{max} values (2,520 ng/dL for Subject 013-008, and 3,070 ng/dL for Subject 047-003) was accompanied by an elevation of DHT concentrations (DHT C_{max} of 160 ng/dL and 191 ng/dL, respectively) and the cause is unknown.*

All 3 subjects completed the Treatment Period with Day 90 C_{max} values < 2,500 ng/dL (i.e., 2,260 ng/dL for Subject 013-008, 1,400 ng/dL for Subject 014-010, and 2,320 ng/dL for Subject 047-003), and without any safety concerns identified by the investigator.

Fasting serum total T concentrations during Safety Extension Periods: Fasting serum total T concentrations were measured as a part of the safety laboratory assessment during Safety Extension Periods 1 and 2 on Days 180, 270, and 360. The Sponsor states that there were no specific requirements with regards to the timing of the sample collection vs. the time of study drug dosing were provided in the study protocol and therefore, high variability of data is not unexpected. The descriptive statistics are provided in Table A-1-25 below.

Table A-1-25: Summary of Fasting Serum Total T Concentrations Measured during the Safety Extension Periods Following 11 mg T TID Administration of NATESTO (Study TBS-1-2011-03)

	Day 180	Day 270	Day 360
N	57	15	15
Arithmetic Mean (ng/dL)	562.3	633.7	670.8
SD	307.6	410.8	426.1
% CV	54.7	64.8	63.5
Geometric Mean (ng/dL)	483.8	511.2	529.3
Median (ng/dL)	480.0	443.0	682.0
Minimum (ng/dL)	157.0	154.0	68.6
Maximum (ng/dL)	1590.0	1470.0	1590.0

Reviewer Comment: *It should be noted that one subject (047-003) that was in 11 mg T BID group showed a fasting serum T concentration of 2870 ng/dL on Day 180. The Sponsor states that this subject started to take a prohibited medication (i.e., anastrozole) on Day 178 (i.e., 2 days before his 180-day visit). There were no subjects with a fasted serum total T concentration higher than 1590 ng/dL with the maximum daily dose of 33 mg T/day (i.e., 11 mg T TID).*

Serum DHT PK: Complete PK profiles of serum DHT on Days 30 and 90 were characterized. Tables A-1-26 and A-1-27 summarize these PK parameters for serum DHT by treatment for the ITT population during the treatment period. Observed increases in serum DHT concentrations were consistent with dosing with T.

Table A-1-26: Summary of Arithmetic Mean (SD) PK Parameters
of Serum DHT at Day 30 for ITT Population with Complete PK Profiles (N=289; Study TBS-1-2011-03)

	BID (N=131)	BID/TID (N=85)	TID (N=73)
AUC(0-24) (ng·hr/dL)	831.8 (376.7)	675.4 (239.0)	934.1 (333.4)
C_{max} (ng/dL)	56.0 (25.1)[b]	45.5 (15.9)	61.6 (22.1)
C_{min} (ng/dL)	22.8 (11.3)[b]	19.2 (7.6)	26.1 (10.2)
C_{avg} (ng/dL)	34.7 (15.7)	28.1 (10.0)	38.9 (13.9)
T_{max} (hr)[a]	1.40 (0.4, 14.1)[b]	1.50 (0.3, 14.1)	1.55 (0.3, 9.0)

[a] Median (min, max)
[b] N=132; Subject 015-009 in the BID treatment group did not have an AUC(0-24) and C_{max} value reported.

Table A-1-27: Summary of Arithmetic Mean (SD) PK Parameters
of Serum DHT at Day 90 for ITT Population with Complete PK Profiles (N=273; Study TBS-1-2011-03)

	BID (N=122)	BID/TID (N=82)	TID (N=69)
AUC(0-24) (ng·hr/dL)	803.5 (391.7)	797.7 (361.8)	961.5 (490.4)
C_{max} (ng/dL)	59.0 (28.4)	53.4 (25.8)	64.6 (42.6)
C_{min} (ng/dL)	21.1 (10.7)	22.1 (10.9)	26.5 (13.6)
C_{avg} (ng/dL)	33.5 (16.3)	33.2 (15.1)	40.1 (20.4)
T_{max} (hr)[a]	1.42 (0.3, 14.0)	1.50 (0.3, 9.8)	1.45 (0.3, 9.7)

[a] Median (min, max)

Serum E2 PK: Complete PK profiles of serum E2 on Days 30 and 90 were characterized. Tables A-1-28 and A-1-29 summarize these PK parameters for serum E2 by treatment for the ITT population during the treatment period. Observed increases in serum E2 concentrations were consistent with dosing with T.

Table A-1-28: Summary of Arithmetic Mean (SD) PK Parameters
of Serum E2 at Day 30 for ITT Population with Complete PK Profiles (N=289; Study TBS-1-2011-03)

	BID (N=131)	BID/TID (N=85)	TID (N=73)
AUC(0-24) (pg·hr/dL)	566.3 (249.3)	518.1 (177.8)	647.6 (237.4)
C_{max} (pg/dL)	37.5 (15.5)[b]	34.8 (14.6)	43.3 (15.7)
C_{min} (pg/dL)	16.2 (8.2)[b]	14.7 (5.2)	17.8 (7.3)
C_{avg} (pg/dL)	23.6 (10.4)	21.6 (7.4)	27.0 (9.9)
T_{max} (hr)[a]	1.50 (0.3, 12.1)[b]	1.50 (0.3, 9.7)	1.58 (0.3, 9.7)

[a] Median (min, max)
[b] N=132; Subject 015-009 in the BID treatment group did not have an AUC(0-24) and C_{max} value reported.

Table A-1-29: Summary of Arithmetic Mean (SD) PK Parameters
of Serum E2 at Day 90 for ITT Population with Complete PK Profiles (N=273; Study TBS-1-2011-03)

	BID (N=122)	BID/TID (N=82)	TID (N=69)
AUC(0-24) (pg·hr/dL)	565.5 (203.6)	600.7 (210.4)	672.2 (238.0)
C_{max} (pg/dL)	38.6 (14.6)	38.3 (14.4)	45.2 (19.0)
C_{min} (pg/dL)	16.0 (5.7)	16.7 (6.2)	18.8 (7.4)
C_{avg} (pg/dL)	23.6 (8.49)	25.0 (8.8)	28.0 (9.9)
T_{max} (hr)[a]	1.50 (0.3, 14.0)	1.70 (0.3, 9.0)	1.57 (0.3, 9.0)

[a] Median (min, max)

Ratio of serum DHT C_{avg} to total T C_{avg}: Table A-1-30 displays a summary of the ratio of serum DHT/T C_{avg} at Day 90 by treatment for the ITT population during the treatment period.

Table A-1-30: Summary of the Ratio of Serum DHT/T C_{avg} by Treatment at Day 90 LOCF
for the ITT Population (Study TBS-1-2011-03)

Treatment	BID Fixed	BID/TID	TID Fixed	Total
N	131	85	73	289
Mean	0.089	0.092	0.094	0.091
SD	0.029	0.027	0.029	0.028
Minimum	0.02	0.03	0.05	0.02
Maximum	0.18	0.16	0.22	0.22

Reviewer Comment: *It should be noted that DHT/T ratios at 8 different time points during the 24 hr period were reported for Axiron® (NDA 022504), while the serum DHT/T C_{avg} ratio was reported for Fortesta® (NDA 021463).*

The serum DHT/T C_{avg} ratio for NATESTO TID treatment group ranged between 0.05 and 0.22 and did not exceed the normal limit reported in literature (i.e., 0.05-0.33 reported by Diver et al., 2003). The mean serum DHT/T C_{avg} ratio of 0.09 is comparable with the reported values of 0.05-0.11 from most of the other approved T replacement products.

Safety Results:
Overall, NATESTO was well tolerated. The AE profile was consistent with other T replacement products, with the majority of AEs mild in intensity. The incidence of the events associated with the intranasal route of administration was relatively low and did not increase with treatment duration. The occurrence of AEs associated with laboratory abnormalities caused by T replacement therapy (i.e., PSA, hematocrit, and lipid profile abnormalities) was comparable to other marketed T therapies and did not increase with treatment duration. The majority of the subjects (88.6%) had their total T C_{max} concentrations of ≤ 1,500 ng/dL.

There was no significant increase from baseline in treatment-emergent ENT symptoms or examination findings noted for any of the treatment groups during the study. The vast majority of subjects had no abnormal changes in physical examination, DRE, ECG, and vital signs findings that would suggest an association with the study medication. There were instances of chemistry, hematology, lipid, liver, and urinalysis parameters outside the normal range during the study; however, none occurred at a frequency or magnitude of effect to suggest a safety concern.

Conclusion:
The primary efficacy endpoint was met in the TBM treatment (i.e., 11 mg T TID) group. In addition, the following criteria of the critical secondary safety endpoint, total T C_{max}, were met:

- Having < 5% of subjects with a serum total T C_{max} in the range of 1,800-2,500 ng/dL
- No subjects with a serum total T C_{max} of > 2,500 ng/dL

However, 0.9% less subjects (i.e., 84.1%) had a serum total T C_{max} ≤ 1,500 ng/dL on Day 90 compared to the pre-specified criteria. Table 3 presents the number and percentage of subjects in the ITT population on Day 90.

Considering that there were no significant safety concerns identified for NATESTO in this study, it is concluded that the efficacy and safety was demonstrated successfully in hypogonadal males using the TBM dosing regimen.

4.1.2 Phase 1 Study (Study TBS-1-2011-04): Extrinsic Factor and DDI Study

Title: A randomized 3-way crossover study to assess the relative BA, safety, and tolerability of TBS-1 (4.5% w/w) when administered to male subjects with seasonal allergic rhinitis in symptomatic, symptomatic but treated (oxymetazoline), and asymptomatic states using an environmental challenge chamber (ECC) model

Primary Objective:
To determine and compare the PK profile of 11 mg T administered from NATESTO intranasally TID in subjects who suffered from seasonal allergic rhinitis, whilst they are in the symptomatic, symptomatic but treated (with the common OTC nasal decongestant spray, oxymetazoline [Nasivin®]) and asymptomatic states.

Secondary Objective:
To determine and compare the local and systemic safety and tolerability following 3 administrations of NATESTO in subjects with seasonal allergic rhinitis.

Clinical Study Center: Fraunhofer Institute for Toxicology and Experimental Medicine (Germany)
Clinical Study Period: March 5, 2012 - March 30, 2012

Bioanalytical Study Center: (b) (4)
Bioanalysis Period: April 12, 2011 - May 8, 2012

Study Design, Treatments, and Drug Administration:
This was an open label, randomized 3-way crossover, 3-treatment, 3-period study PK study conducted in 18 Caucasian male subjects, aged 18-45 years (BMI of ≤ 30 kg/m^2), with seasonal allergic rhinitis in an asymptomatic state. Subjects were randomized to 1 of 3 sequence groups (A, B, or C) below.

Table A-2-1: Summary of Sequence Groups and Treatments

	PERIOD I Visit 3	PERIOD II Visit 4	PERIOD III Visit 5
Sequence group A	Treatment 1*	Treatment 2*	Treatment 3**
Sequence group B	Treatment 2*	Treatment 3**	Treatment 1*
Sequence group C	Treatment 3**	Treatment 1*	Treatment 2*

* Subjects in the symptomatic state (Treatment 1) and symptomatic but treated state (Treatment 2) had to get up between 2.40 and 3.15 to enter the pollen chamber between 4.20 and 4.45.
** Subjects in the asymptomatic state (Treatment 3) had to get up at between 5.30 and 6.00, as no 'priming' in the ECC was required.

Subjects were randomized to 1 of the 3 sequence groups and the following treatments were given according to the pre-defined order for each sequence group:

- Treatment 1 (symptomatic state): Subjects entered the ECC and were exposed (i.e., inhaled) to dactylis glomerata pollen prior to each administration of NATESTO. The ECC was designed to mimic the situation for the subjects under quasi-natural conditions (i.e., the pollen exposure in the ECC did not present a greater risk than natural exposure during the grass pollen season in summer) and was continuously monitored for allergen concentration, temperature, and humidity. Subjects had to complete diary cards every 15 minutes for 4 hours. To continue in the study, subjects had to have at least 6/12 for total nasal symptom score (TNSS) and 2/3 for congestion score on at least one of the last 4 diary cards (between Hours 1 and 2) prior to the morning dose. Once subjects met the criteria, they were dosed with 11 mg T TID (total daily dose of 33 mg). NATESTO was given at 7 am, 1 pm, and 9 pm (± 30 minutes).

- Treatment 2 (symptomatic state but treated): Subjects were induced by exposure (i.e., inhalation) to dactylis glomerata pollen in the ECC prior to each NATESTO administration. Subjects had to complete diary cards every 15 minutes for 4 hours. Before the first treatment with oxymetazoline after 2 hours, subjects had to have at least 6/12 for TNSS and 2/3 for congestion score on at least one of the last 4 diary cards. Once subjects met the criteria, they were immediately dosed with a decongestant (oxymetazoline) and 30 minutes thereafter with 11 mg NATESTO. Each of the oxymetazoline dose consisted of 4 puffs (2 per nostril) of 0.05% oxymetazoline hydrochloride using a multi-dose dispenser administrated intranasally. Subjects then remained in the ECC for an additional 1.5 hours, resulting in a total duration of 4 hours. NATESTO was administered 11 mg T TID (total daily dose of 33 mg). NATESTO was given at 7 am, 1 pm, and 9 pm (± 30 minutes). Oxymetazoline was administered 30 minutes prior to the 7 am NATESTO dose and 12 hours after the first dose of oxymetazoline.
- Treatment 3 (asymptomatic state): Subjects were verified by filling out a symptom diary card. Those who were verified as asymptomatic by having a TNSS < 3 and congestion score < 2 received NATESTO as 11 mg T TID (total daily dose of 33 mg). NATESTO was given at 7 am, 1 pm, and 9 pm (± 30 minutes).

Reviewer's Comment: *Oxymetazoline (i.e., Afrin nasal spray) was selected to be used in this study per the Division's recommendation. Reference is made to the minutes of the EOP2 meeting held on March 14, 2011 (dated May 4, 2011 under IND 70512 in DARRTS). The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) has provided the following comment: Oxymetazoline is sold over-the-counter (OTC) and is used (short term - not recommended for use more than 3 days) for nasal congestion. It does not have an effect on the other symptoms of allergic rhinitis and it is not the most commonly used medication for allergic rhinitis (these are usually antihistamines or nasal steroid sprays). However, the potential for reducing systemic absorption of T is probably greatest with the use of oxymetazoline because of its vasoconstrictor effect. Therefore, given the objective of the study, oxymetazoline was probably the best choice to use in this situation.*

The TNSS scale is shown in Table below.

Table A-2-2: TNSS Scale

Nasal congestion	0	= none
	1	= mild (slight congestion, intermittent, easily tolerated)
	2	= moderate (continuous congestion that is bothersome but tolerable)
	3	= severe (nose completely blocked, hard to breathe through the nose)
Rhinorrhea	0	= none
	1	= mild (intermittent rhinorrhea, easily tolerated)
	2	= moderate (continuous rhinorrhea that is bothersome but tolerable)
	3	= severe (continuous rhinorrhea that is hard to tolerate)
Nasal itching	0	= none
	1	= mild (intermittent itching, easily tolerated)
	2	= moderate (continuous itch that is bothersome but tolerable)
	3	= severe (continuous itch requiring rubbing and that is hard to tolerate)
Sneezing	0	= none
	1	= mild (intermittent sneezing, easily tolerated)
	2	= moderate (occasional sneezing that is bothersome but tolerable)
	3	= severe (frequent sneezing that is hard to tolerate)

[1] Nasal symptoms were evaluated by the subject prior to and every 15 minutes during allergen challenge according to the 4 point severity scale for each symptom.

All subjects received doses of study medications (i.e., self-administered in the presence of a trained site staff member) for 1 day per treatment period (i.e., 11 mg TID) and were monitored by study personnel during the dosing procedures and for 1 hour post-dosing of NATESTO. Subjects were not allowed to blow his nose or sniff for the first hour after NATESTO administrations.

Inclusion Criteria:

- Males between 18-45 yrs. of age with seasonal allergic rhinitis in asymptomatic state , which was defined by a positive case history and a positive skin prick and/or intradermal test for Dactylis glomerata pollen allergen within 12 months of screening;
- TNSS of ≥ 6/12 and a congestion score of ≥ 2/3 on at least one card during the 2-hour screening challenge
- BMI of ≤ 30 kg/m^2
- Non-smokers or ex-smokers for at least 6 months
- Absence of significant disease or clinically significant abnormal laboratory values, medical history or physical examination during screening
- Otorhinolaryngological examination without clinically significant abnormal findings within 4 weeks of screening

Exclusion Criteria:

- Personal/family history of allergy or hypersensitivity to T or related drugs
- Any major illness in the past 3 months or any clinically significant ongoing chronic medical illness (e.g., congestive heart failure, hepatitis, pancreatitis, etc.)
- Presence of any clinically significant abnormal values during screening (e.g., significant abnormality of liver function test, renal function test, etc.)
- Hemoglobin < 13 g/dL or hematocrit > 52% during screening
- Any cardiac, renal or liver impairment, any other organ or system impairment
- Asthmatic subjects with a forced expiratory volume in 1 second predicted < 80 %
- History of seizure or clinically significant psychiatric disorders
- Presence of disease markers for human immunodeficiency virus (HIV) 1 and/or 2, Hepatitis B and/or C (HBsAg and/or HCV) virus.
- History of nasal surgery, specifically turbinoplasty, septoplasty, rhinoplasty, “nose job”, or sinus surgery
- Subjects with prior nasal fractures
- Subjects with mucosal inflammatory disorders, specifically pemphigus, or Sjogren’s syndrome, rhinitis sicca
- Subjects with a sinus disease, specifically acute sinusitis, chronic sinusitis, or allergic fungal sinusitis
- History of nasal disorders (e.g., polyposis, recurrent epistaxis [> 1 nose bleed per month]), abuse of nasal decongestants or sleep apnea
- Subjects using any form of intranasal medication delivery, specifically nasal corticosteroids and oxymetazoline at the time of screening/enrollment
- History of asthma and/or ongoing asthma treatment
- Regular drinkers of more than 3 units of alcohol daily, or consumption of alcohol within 48 hours prior to dosing and during the study
- Subjects demonstrating a positive test for alcohol consumption at the time of check-in during the admission periods
- History of, or current evidence of, abuse of alcohol or any drug substance
- Receipt of any prescription drug therapy within 4 weeks of the first admission period

- Use of prescription or OTC medication (except for occasional acetaminophen/aspirin) for the duration of the study
- Subjects demonstrating serum PSA $\geq$ 4 ng/mL
- Participation in any other research study involving investigational new drug or device or studies that required blood sampling, during the conduct of this study or 30 days prior to screening of this study (Visit 1)
- Blood donation at any time during this study, or within the 12 week period before the sum of this study

Prior and Concomitant Medications
Subjects receiving treatment with prescribed or OTC medication at the time of screening were excluded. Only occasional acetaminophen or aspirin were allowed. More details on prior and concomitant medications can be found in the *Exclusion Criteria Section* above.

Primary Endpoints:
The following PK parameters for total T and DHT were determined for all subjects in all treatments: AUC(0-24), C_{avg}, C_{max}, C_{min}, and T_{max}. Baseline corrected AUC(0-24) and C_{max} were used for BE evaluation. Baseline corrected AUC(0-24) and C_{max} were determined for each individual as following:

- Baseline corrected AUC(0-24) = AUC(0-24) – $AUC(0\text{-}24)_{baseline}$
  $AUC(0\text{-}24)_{baseline}$ was defined as the serum AUC up to 24 hours for the baseline characterization (i.e., without any treatment)
- Baseline corrected $C_{max} = C_{max} - C_{max\ baseline}$
  $C_{max\ baseline}$ was defined as the C_{max} for the baseline characterization (i.e., without any treatment)

Secondary Endpoints (Safety Assessments):
Safety and tolerability were assessed by monitoring:

- AEs,
- Otolaryngological examiniation,
- Vital signs, Complete blood count to evaluate changes in white blood cell (WBC) count, hemoglobin, and hematocrit
- Clinical chemistry profile, and
- Urinalysis (urine specific gravity, glucose, protein, ketone, pH, blood, bilirubin, urobilinogen, nitrite, leukocytes)

PK Evaluation and Blood Sampling
Serum concentrations of T and DHT were determined during 24 hours under baseline conditions and during treatment with NATESTO in symptomatic (i.e., Treatment 1), symptomatic but treated (i.e., Treatment 2), and asymptomatic state (i.e., Treatment 3), respectively. Blood samples were drawn at the following time points for 24-hour baseline characterization (i.e., control without any treatment) or for each of the 3 treatments: 0.25 hours pre-dose and 0.33, 0.66, 1.00, 1.50, 2.00, 3.00, 5.75, 6.33, 6.66, 7.00, 7.50, 8.00, 9.00, 10.00, 11.00, 12.00, 13.75, 14.33, 14.66, 15.00, 15.50, 16.00, 17.00, 20.00, and 24.00 hours post-dose of NATESTO.

Study Flow chart
The study flow chart is shown in Table A-2-3.

Table A-2-3: Study Flow Chart

	Requirement		Screening	Baseline	Period I		Period II		Period III	
					Check-in	Check-out	Check-in	Check-out	Check-in	Check-out
	VISIT		1	2	3		4		5	
	DAY		1, 2	1, 2	1	2	1	2	1	2
1.	Written informed consent		*							
2.	Randomization			*						
3.	Electrocardiography (ECG)		*							
4.	Skin prick test		*							
5.	Height and weight		*							
6.	Spirometry (full spirometry at Visit 1, otherwise with the AM1 device)		*		*	*	*	*	*	*
7.	Demographics		*							
8.	Medical history		*							
9.	Medical examination	General	*							*
		Vital signs (Blood Pressure, Pulse, Body Temperature, Respiration Rate)	*	*	*	*	*	*	*	*
		Otorhinolaryngological examination[†]	*	*	*	*	*	*	*	*
10.	Clinical laboratory tests	Hematology	*							*
		Liver Function Tests	*							*
		GGT	*							*
		Blood cholesterol	*							*
		Serum: Sodium, potassium, chloride, calcium and blood glucose (random)	*							*
		Serum PSA	*							
		RFT (serum creatinine and BUN)	*							*
		Urine (Routine)	*							*
		Urinalysis for drugs of abuse (benzodiazepine, opiates, amphetamine, THC, cocaine)	*	*	*		*		*	
		Infectious disease screen (HIV 1 and 2, HBsAg, HCV)	*							
		Breath Alcohol Test	*	*	*		*		*	
11.	ECC with TNSS		*		*		*		*	
12.	AEs			*	*		*		*	
13.	TBS-1 administration				*		*		*	
14.	Oxymetazoline administration				*		*		*	
15.	PK Blood sampling			*	*		*		*	

[†] At screening, an endoscopic nasal examination was performed. At all other visits the physician conducted a physical nasal examination only

Bioanalytical Methods:

Bioanalysis for total T and DHT was conducted at [redacted] (b) (4) Human serum samples were analyzed using the same LC-MS/MS methods for the determination of total T and DHT concentrations in the Phase 3 study, TBS-1-2011-03. Refer to *Bioanalytical Methods* in Section 4.1.1 of this review for detail information on the methods and their validations.

Accuracy of the calibration standards and QC samples during sample analysis was expressed as percent difference from theoretical concentration (i.e., % RE). For serum total T, the %RE ranged from -1.3% to 1.4% for the 8 calibration standards in the range of 0.5-50 ng/mL and 3.7% to 6.4% for low, medium, and high QCs. For serum DHT, the % RE ranged from -0.6% to 1.0% for the 8 calibration standards in the range of 0.1-10 ng/mL and -9.0% to -6.1% for low, medium, and high QCs.

Precision of the calibration standards and QC samples during sample analysis was expressed as the percent coefficient of variation (% CV). For serum total T, the % CV ranged from 1.0% to 5.3% for the 8 calibration standards in the range of 0.5-50 ng/mL and 3.6% to 4.4% for low, medium, and high QCs. For serum DHT, the % CV ranged from 1.0% to 5.8% for the 8 calibration standards in the range of 0.1-10 ng/mL and 5.2% to 6.9% for low, medium, and high QCs.

Refer to the stability assessments (i.e., long term storage, freeze-thaw, refrigerator, bench-top, auto-sampler stability) that were conducted as a part of the method validation described under *Bioanalytical Methods* in Section 4.1.1 of this review.

ISR was not conducted on samples from this study. Instead, ISR was conducted in two Phase 1 studies (i.e., Studies TBS-1-2011-01 and TBS-1A-2011-01) that were conducted in healthy male subjects and in one Phase 2 study (i.e., Study TBS-1-2010-01; Refer to Section 4.1.3 of this review) that was conducted in hypogonadal men. These ISR results confirmed the reproducibility of the bioanalytical method.

Reviewer's Comment: *While the Sponsor did not perform ISR on study samples from this study, the studies they have performed ISR used the same bioanalytical method as this study and the ISR results were found to be acceptable.*

The acceptance criteria and performance of the total T and DHT bioanalytical methods are in compliance with the Agency's Bioanalytical Method Validation Guidance. In summary, the method validation and performance of the bioanalytical methods in this study are acceptable.

Statistical Methods
Continuous measurements were summarized by means of descriptive statistics (i.e., number of observations, arithmetic mean, SD, minimum, median, and maximum). Categorical variables were summarized by means of frequency tables (i.e., count and percentages). All baseline corrected PK parameters (i.e., using the control, 24-hour profile without any treatment as baseline) were tested regarding BE using ANOVA.

Sample Size Determination:
A formal sample size calculation was not performed. A total of 18 subjects (i.e., 6 subjects per treatment sequence group) were enrolled into the study.

Disposition of Subjects:
A total of 18 subjects were enrolled in the study with 6 subjects in each sequence group and 14 subjects completed all 3 treatments during the study. The disposition of the subjects is summarized in Table A-2-4.

Table A-2-4: Disposition of Subjects by Treatments (Total N=18)

	Completed Subjects	Incomplete Subjects	Incomplete subjects ID	Incomplete reason (early termination)
Symptomatic (Treatment 1)	15	3	Subjects 14, 15, 17	Not qualified for treatment TNSS < 6 in one of the treatment periods
Symptomatic but treated (Treatment 2)	17	1	Subject 18	Not qualified for treatment TNSS < 6 in one of the treatment periods
Asymptomatic (Treatment 3)	18	0	-	-

Subject Demographics:
All subjects in the study were Caucasian males. All subjects had a medical history of allergic conjunctivitis, and/or allergic rhinitis and/or seasonal allergy in accordance with the inclusion criteria. Subjects in each sequence group were comparable regarding their age, height, weight, and BMI as shown in Table A-2-5.

Table A-2-5: Demographics of Subjects

Parameter	Sequence group A N=6	Sequence group B N=6	Sequence group C N=6
Age [years]			
Mean (SD)	38.5 (3.9)	36.0 (5.7)	33.7 (7.3)
Range	32 - 43	29 - 43	27 - 44
Height [cm]			
Mean (SD)	180.0 (3.3)	181.2 (5.0)	186.5 (9.1)
Range	176 - 184	175 - 188	171 - 198
Weight [kg]			
Mean (SD)	82.5 (7.0)	85.0 (9.7)	87.2 (12.8)
Range	75 - 93	69 - 93	65 - 103
BMI [kg/m^2]			
Mean (SD)	25.5 (2.3)	25.9 (2.7)	25.0 (2.8)
Range	22.2 - 29.0	22.5 - 29.7	22.2 - 29.8

Protocol Deviations:

Based on the study protocol, one or more deviations from the pre-defined samples collection schedule were observed in 16 subjects (i.e., Subjects 01, 02, 03, 04, 05, 06, 07, 08, 09, 11, 12, 13, 14, 15, 16, and 17). However, the actual sampling times were used in the calculation of the PK parameters and the reported deviations were deemed no to have affected the outcome of the study.

PK Results:
All 18 randomized subjects were included in the safety analysis. Fourteen (14) out of 18 subjects had evaluable PK profiles and were included in the PK and BE analysis. The ANOVA revealed that neither sequence nor period of treatment had an effect on serum T or DHT concentrations; therefore, data were pooled from different sequence groups for each treatment state.

Total T PK: Mean values of the measured T concentrations during the 24-hour baseline characterization (i.e., without any treatment) ranged between 402.8-608.0 ng/dL and reached the peak at 7 am. Mean pre-dose (i.e., 15 min pre-dose) T concentrations were similar in the symptomatic/untreated (422.9 ng/dL) and symptomatic/treated state (401.5 ng/dL) but higher in the asymptomatic state (535.9 ng/dL). After each administration of NATESTO at t=0, t=6, and t=14 hours, serum T concentrations increased for subjects in all treatment states, so that 3 peaks occurred within the observation time of 24 hours (Figure A-2-1).

Reviewer's Comment: *Although the same dose of NATESTO was administered under all treatment conditions, the baseline uncorrected and baseline-corrected curves of asymptomatic state was generally higher (i.e., higher AUC) than the curves of both symptomatic/untreated and symptomatic/treated states. It should be noted that asymptomatic state had a higher mean pre-dose T concentration compared to the other 2 treatment conditions.*

Figure A-2-1: Arithmetic Mean Serum T Concentration vs. Time Curves in Healthy Men with Seasonal Allergic Rhinitis, by Treatment State Following Administration of 11 mg T TID of NATESTO for 1 Day (N=14; Study TBS-1-2011-04)

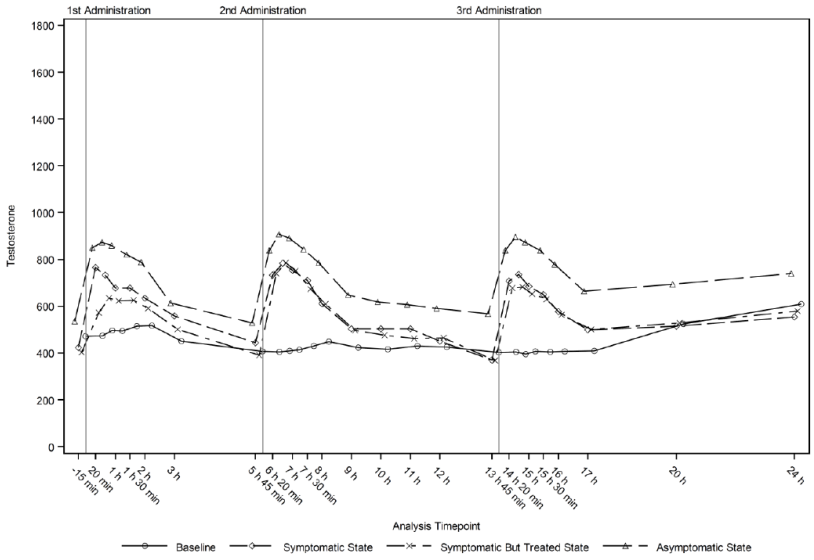


Table A-2-6: Baseline-Uncorrected Serum T PK Parameters
in Healthy Men With Seasonal Allergic Rhinitis, by Treatment State (N=14; Study TBS-1-2011-04)

	Treatments	Mean	SD	Minimum	Maximum	% CV
AUC(0-24) (ng·hr/dL)	Pre-treatment	10949.8	2215.0	7315.6	14702.3	20.2
	Asymptomatic	16746.9	3894.3	10959.0	24585.7	23.3
	Symptomatic	13217.4	3589.1	8821.6	21441.0	27.2
	Sympt. treated	12778.2	3379.6	8037.5	21189.5	26.5
C_{max} (ng/dL)	Pre-treatment	631.4	149.7	393.0	848.0	23.7
	Asymptomatic	1063.2	223.0	653.0	1440.0	21.0
	Symptomatic	909.9	241.8	496.0	1340.0	26.6
	Sympt. treated	872.0	267.7	585.0	1610.0	30.7
C_{avg} (ng/dL)	Pre-treatment	456.6	92.1	305.3	611.0	20.2
	Asymptomatic	695.6	163.7	454.9	1025.1	23.5
	Symptomatic	549.3	149.6	365.1	890.3	27.2
	Sympt. treated	532.2	141.0	335.3	882.7	26.5

The baseline-uncorrected mean AUC(0-24) values for T in the symptomatic/untreated and symptomatic/treated states demonstrated a decrease of 21.1% and 23.7%, respectively, when compared to the asymptomatic state. The baseline-uncorrected mean C_{max} values for T in the symptomatic/untreated and symptomatic/treated states demonstrated a decrease of 14.4% and 18.0%, respectively, when compared to the asymptomatic state. The baseline-uncorrected mean C_{avg} values for T in the symptomatic/untreated and symptomatic/treated states demonstrated a decrease of 21.0% and 23.5%, respectively, when compared to the asymptomatic state.

Reviewer Comment: *The T exposure as estimated by the baseline-corrected mean AUC(0-24) was higher for subjects in the asymptomatic state than for the symptomatic/untreated and the symptomatic/treated states (Table A-2-6). It should be noted that the baseline correction was made by using the PK parameter values for each individual obtained in the 24-hour baseline characterization (i.e., control without any treatment [pre-treatment]). Since the baseline was not characterized for each specific treatment period, this review focused on the difference of the baseline-uncorrected mean AUC(0-24), C_{max}, and C_{avg} values between each treatment group.*

In summary, total T exposure (i.e., AUC[0-24], C_{max}, and C_{avg}) was higher under asymptomatic state compared to symptomatic states regardless of treatment with oxymetazoline. The difference between the 2 symptomatic states were relatively small compared to the difference of those with the asymptomatic state, indicating that administration of oxymetazoline might not hugely impact the absorption of T following the administration of NATESTO.

DHT PK: After each administration of NATESTO at t=0, t=6, and t=14 hours, serum DHT concentrations increased for subjects in all treatment states as they did for T. As a result, 3 peaks occurred within the observation time of 24 hours (Figure A-2-2).

Figure A-2-2: Arithmetic Mean Serum DHT Concentration vs. Time Curves in Healthy Men with Seasonal Allergic Rhinitis, by Treatment State Following Administration of 11 mg T TID of NATESTO for 1 Day (N=14; Study TBS-1-2011-04)

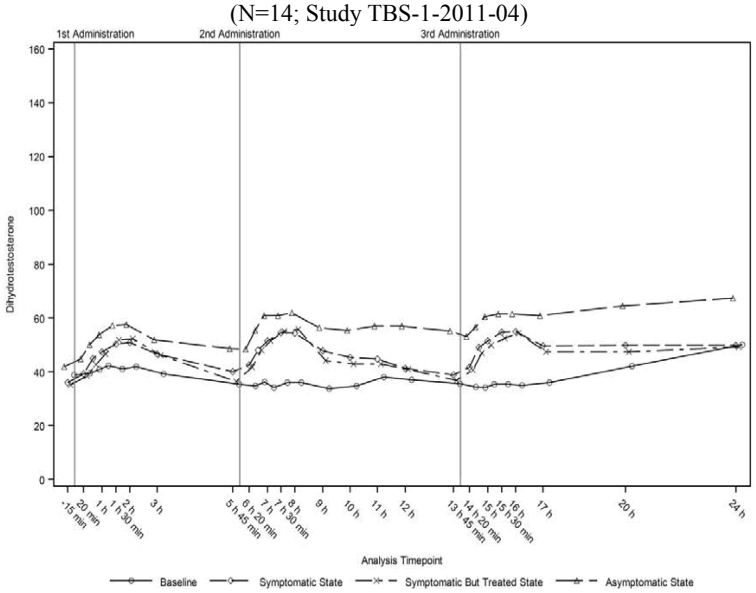


Table A-2-7: Baseline-Uncorrected and Baseline-Corrected Serum DHT PK Parameters in Healthy Men With Seasonal Allergic Rhinitis, by Treatment State (Total N=14)

PK parameter	Time frame	Treatment condition	Mean	SD	Min	Max	CV%
AUC (h*ng/dL)	0-24 h	Pre-treatment	923.5	268.9	536.0	1535.2	29.1
		Asymptomatic	1393.9	442.4	779.0	2411.5	31.7
		Symptomatic	1136.6	342.0	610.5	1707.6	30.1
		Sympt. Treated	1098.1	324.4	709.1	1702.6	29.5
	0-6 h, bc	Asymptomatic	70.9	40.6	2.9	150.3	57.2
		Symptomatic	34.9	31.4	-1.1	108.2	89.8
		Sympt. Treated	28.5	41.4	-49.1	122.3	145.3
	6-14 h, bc	Asymptomatic	165.5	101.9	64.6	412.4	61.6
		Symptomatic	78.3	44.7	10.0	144.3	57.0
		Sympt. Treated	68.2	48.9	-2.0	181.9	71.7
	14-24 h, bc	Asymptomatic	234.0	158.4	55.3	662.9	67.7
		Symptomatic	99.9	61.0	-13.6	228.1	61.1
		Sympt. Treated	78.0	64.5	-13.3	185.9	82.7
	0-24 h, bc	Asymptomatic	470.4	279.0	172.0	1198.9	59.3
		Symptomatic	213.1	125.3	3.5	471.0	58.8
		Sympt. Treated	174.6	128.4	-2.4	490.1	73.6
C_{avg} (ng/dL)	0-24 h	Pre-treatment	38.5	11.2	22.4	64.1	29.1
		Asymptomatic	57.9	18.5	32.5	100.5	32.0
		Symptomatic	47.2	14.2	25.3	71.3	30.1
		Sympt. Treated	45.7	13.5	29.5	70.9	29.6
	0-6 h, bc	Asymptomatic	12.3	6.9	0.8	25.8	56.0
		Symptomatic	6.0	5.5	-0.2	19.0	91.3
		Sympt. Treated	5.0	7.2	-8.3	21.3	145.1
	6-14 h, bc	Asymptomatic	20.8	12.9	8.2	52.0	62.0
		Symptomatic	9.9	5.6	1.2	18.3	56.2
		Sympt. Treated	8.5	6.1	-0.3	22.5	71.4
	14-24 h, bc	Asymptomatic	22.3	15.9	5.1	64.8	71.1
		Symptomatic	9.3	6.1	-2.0	21.9	65.4
		Sympt. Treated	7.5	6.2	-0.6	18.6	82.3
	0-24 h, bc	Asymptomatic	19.4	11.8	7.1	50.2	60.9
		Symptomatic	8.7	5.2	-0.1	19.5	60.1
		Sympt. Treated	7.2	5.4	-0.2	20.5	74.3
C_{max} (ng/dL)	0-24 h	Pre-treatment	50.6	13.3	28.4	79.8	26.3
		Asymptomatic	75.4	29.3	39.5	152.0	38.9
		Symptomatic	60.0	20.0	29.7	98.2	33.3
		Sympt. Treated	62.1	19.0	37.8	106.0	30.6
	0-24 h, bc	Asymptomatic	24.8	21.5	-0.4	86.4	86.6
		Symptomatic	9.4	9.0	-7.4	28.3	95.7
		Sympt. Treated	11.6	10.4	0.7	40.4	89.8
C_{min} (ng/dL)	0-24 h	Pre-treatment	29.7	9.6	16.5	50.2	32.4
		Asymptomatic	39.4	11.3	22.5	60.5	28.7
		Symptomatic	34.3	11.0	18.4	54.2	31.9
		Sympt. Treated	32.8	9.4	19.7	47.9	28.6

The baseline-uncorrected mean AUC(0-24) values for DHT in the symptomatic/untreated and symptomatic/treated states demonstrated a decrease of 18.5% and 21.2%, respectively, when

compared to the asymptomatic state. The baseline-uncorrected mean C_{max} values for DHT in the symptomatic/untreated and symptomatic/treated states demonstrated a decrease of 20.4% and 17.6%, respectively, when compared to the asymptomatic state. The baseline-uncorrected mean C_{avg} values for DHT in the symptomatic/untreated and symptomatic/treated states demonstrated a decrease of 18.5% and 21.1%, respectively, when compared to the asymptomatic state.

Safety Results:
All reported AEs were of mild or moderate intensity and all were transient. All reported AEs were judged to be not related to treatment with NATESTO. Physical examinations, vital signs, and clinical laboratory results did not reveal any clinically significant findings.

Conclusions:
Total T exposure (i.e., AUC[0-24], C_{max}, and C_{avg}) was higher under asymptomatic state compared to symptomatic states regardless of treatment with oxymetazoline. The difference between the 2 symptomatic states were relatively small compared to the difference of those with the asymptomatic state, indicating that administration of oxymetazoline might not hugely impact the absorption of T following the administration of NATESTO.

4.1.3 Phase 2 Study (Study TBS-1-2010-1): Dose-finding

Title: An open label, randomized, balanced, three treatments, parallel design, PK study of intra-nasal TBS-1 administration to hypogonadal men

Primary Objective:
To determine the systemic BA (AUC[0-24], C_{avg}, and C_{max}) of a 4.0% TBS-1 gel (applied TID) and 4.5% TBS-1 gel (applied BID and TID) in hypogonadal men.

Clinical Study Centers:
- Regional Urology, LLC, Shreveport, LA
- Pharmax Research Clinic, Inc,, Miami, FL
- Quality of Life Medical & Research Centre, Tucson, AZ

Clinical Study Period: August 27, 2010 - October 30, 2010

Bioanalytical Study Center: (b) (4)
Bioanalysis Period: December 14 - 24, 2010 (T and DHT); January 5-12, 2011 (E2)

Study Design, Treatments, and Drug Administration:
This was an open label, randomized, balanced, 3-treatments (4.0% TID, 4.5% BID, and 4.5% TID), parallel design, dose-finding, PK study of TBS-1 administered intranasally in 22 hypogonadal males (age of 35-73 years). Subjects were screened for eligibility (Visit 1) 2-4 weeks before receiving the first dose of TBS-1; subjects on T therapy required a washout period; four (4) weeks for depot products administered intra-muscularly (e.g. T enanthate 200 mg/mL), and 2 weeks for products administered orally, or topically (patch, gel, or buccal).

Subjects were randomized to one of the following 3 treatment groups:
- Treatment A (N=8): TBS-1 syringes pre-filled with 125 µL 4.0% gel to deliver 5.0 mg of T per nostril (intranasal) given TID at 9 pm, 7 am, and 1 pm (total dose: 30 mg/day).
- Treatment B (N=7): TBS-1 syringes pre-filled with 150 µL 4.5% gel to deliver 6.75 mg of T per nostril (intranasal) given BID at 9 pm and 7 am (total dose: 27.0 mg/day).
- Treatment C (N=7): TBS-1 syringes pre-filled with 125 µL 4.5% gel to deliver 5.625 mg of T per nostril (intranasal) given TID at 9 pm, 7 am, and 1 pm (total dose 33.75 mg/day).

TBS-1 was administered for 7 days as per treatment group assignment. On Day 7, subjects for all treatment groups returned to their study centers and underwent a 24-hour PK sample collection after the 9 pm dosing. Blood was drawn at 8:45 pm for baseline serum T, DHT, and E2 concentrations.

Inclusion Criteria:
- Males who were responders to T in the Nasobol-01-2009 trial (i.e., using an earlier 3.2% formulation)
- Males between 18 and 80 years of age
- Men with primary or secondary hypogonadism and a morning (0900 h ± 30 minutes) serum T concentrations > 150 ng/dL and ≤ 300 ng/dL, on blood drawn under fasting conditions
- BMI between 18.5 - 35 kg/m^2
- Normal otorhinolaryngological nasal endoscopy examination
- Prior, normal prostate examination (no palpable prostatic mass) from the Nasobol-01-2009 trial.

- A serum PSA ≤ 4.0 ng/mL

Exclusion Criteria:

- Significant inter-current disease of any type, in particular liver, kidney, or heart disease, any form of diabetes mellitus or psychiatric illness
- Limitations in mobility, defined as having difficulty walking two blocks on a level surface or climbing 10 steps
- Hematocrit > 54% at screening
- History of cancer, excluding skin cancer
- History of nasal surgery, specifically turbinoplasty, septoplasty, rhinoplasty, "nose job", or sinus surgery
- Patient with prior nasal fractures
- Patient with active allergies, such as rhinitis, rhinorrhea, and nasal congestion
- Patient with mucosal inflammatory disorders, specifically pemphigus, and Sjogren's syndrome
- Patient with sinus disease, specifically acute sinusitis, chronic sinusitis, or allergic fungal sinusitis
- History of nasal disorders (e.g. polyposis, recurrent epistaxis (> 1 nose bleed per month), abuse of nasal decongestants) or sleep apnea.
- Patient using any form of intra-nasal medication delivery, specifically nasal corticosteroids and oxymetazoline containing nasal sprays (e.g. Dristan 12-Hour Nasal Spray)
- History of severe adverse drug reaction or leucopenia
- History of abnormal bleeding tendencies or thrombophlebitis unrelated to venipuncture or intravenous cannulation
- Positive test for Hepatitis B, Hepatitis C, or HIV
- History of asthma and on-going asthma treatment
- History of sleeping problems
- Smokers (> 10 cigarettes per day)
- Regular drinkers of more than four (4) units of alcohol daily (1 unit = 300 mL beer, 1 glass wine, 1 measure spirit) or those that may have difficulty in abstaining from alcohol during the 48 hours prior to the 24-hour blood sampling visit
- History of, or current evidence of, abuse of alcohol or any drug substance, licit or illicit; or positive urine drug and alcohol screen for drugs of abuse and alcohol
- Current treatment with androgens (e.g. Dehydroepiandrostenedione, Androstenedione) or anabolic steroids (e.g., T, DHT)
- Treatment with Estrogens, GnRH antagonists, or Growth Hormone, within previous 12 months
- Treatment with drugs which interfere with the metabolism of T, such as; Anastrozole, Clomiphene, Dutasteride, Finasteride, Flutamide, Ketoconazole, Spironolactone and Testolactone
- Androgen treatment within the past four weeks (intramuscular, topical, buccal etc.)
- Subject with poor compliance history or unlikely to maintain attendance
- Participation in any other research study during the conduct of this study or 30 days prior to the initiation of this study, with the exception of Nasobol-01-2009
- Blood donation (usually 550 mL) at any time during this study, and within the 12 week period before the start of the study

Prior and Concomitant Medications:

The following medications were prohibited during the course of the study:

- Any form of intra-nasal medication delivery, specifically nasal corticosteroids and oxymetazoline containing nasal sprays (e.g., Dristan 12-Hour Nasal Spray)
- Androgens (e.g., Dehydroepiandrostenedione, Androstenedione) or anabolic steroids (e.g., T, DHT)
- Treatment with Estrogens, GnRH antagonists, or Growth Hormone, within previous 12 months
- Treatment with drugs which interfere with the metabolism of T, such as; Anastrozole, Clomiphene, Dutasteride, Finasteride, Flutamide, Ketoconazole, Spironolactone, and Testolactone.
- Androgen treatment within the past 4 weeks (intramuscular, topical, buccal, etc.).

PK Blood Sampling for Serum T, DHT, and E2 Measurements:

- ***Treatment A*:** Blood draws for TID dosing were done on Day 7 at the following times after the 9 pm drug administration; 0 (pre-dose), 0.33, 0.66, 1.0, 1.5, 2.0, 3.0, 6.0, 9.0, 9.75, 10.33, 10.66, 11.0, 11.5, 12.0, 13.0, 14.0, 15.75, 16.33, 16.66, 17.0, 17.5, 18.0, 20.0, 22.0 and 24.0 hours post-dose, (total blood draws; 25 + baseline).
- ***Treatment B*:** Blood draws for BID dosing were done on Day 7 at the following times after the 9 pm drug administration; 0 (pre-dose), 0.33, 0.66, 1.0, 1.5, 2.0, 3.0, 6.0, 9.0, 9.75, 10.33, 10.66, 11.0, 11.5, 12.0, 13.0, 16.0, 19.0, 22.0, and 24.0 hours post-dose, (total blood draws; 19 + baseline).
- ***Treatment C*:** Blood draws for TID dosing were done on Day 7 at the following times after the 9 pm drug administration; 0 (pre-dose), 0.33, 0.66, 1.0, 1.5, 2.0, 3.0, 6.0, 9.0, 9.75, 10.33, 10.66, 11.0, 11.5, 12.0, 13.0, 14.0, 15.75, 16.33, 16.66, 17.0, 17.5, 18.0, 20.0, 22.0 and 24.0 hours post-dose, (total blood draws; 25 + baseline).

PK Evaluation:

The serum concentrations of total T, DHT, and E2 were measured. The following PK parameters were determined for all subjects:

- For Treatments A and C (TID): AUC(0-τ), AUC(0-10), AUC(10-16), AUC(16-24), C_{max}, $C_{max\ 0\text{-}10}$, $C_{max\ 10\text{-}16}$, $C_{max\ 16\text{-}24}$, C_{min}, $C_{min\ 0\text{-}10}$, $C_{min\ 10\text{-}16}$, $C_{min\ 16\text{-}24}$, C_{avg}, $C_{avg\ 0\text{-}10}$, $C_{avg\ 10\text{-}16}$, $C_{avg\ 16\text{-}24}$, T_{max}, $T_{max\ 0\text{-}10}$, $T_{max\ 10\text{-}16}$, $T_{max\ 16\text{-}24}$, PTF, PTS.
- For Treatment B (BID): AUC(0-τ), AUC(0-10), AUC(10-24), C_{max}, $C_{max\ 0\text{-}10}$, $C_{max\ 10\text{-}24}$, C_{min}, $C_{min\ 0\text{-}10}$, $C_{min\ 10\text{-}24}$, C_{avg}, $C_{avg\ 0\text{-}10}$, $C_{avg\ 10\text{-}24}$, T_{max}, $T_{max\ 0\text{-}10}$, $T_{max\ 10\text{-}24}$, PTF, PTS.

The percent of subjects in each treatment group with a 24 hour C_{avg} less than, within and above the serum T reference range of 300-1050 ng/dL.

Bioanalytical Methods:

Bioanalysis for total T, DHT, and E2 was conducted at (b) (4). Human serum samples were analyzed using the same LC-MS/MS methods for the determination of total T, DHT, and E2 concentrations in the Phase 3 study, TBS-1-2011-03. Refer to *Bioanalytical Methods* in Section 4.1.1 of this review for detail information on the methods and their validations.

Accuracy of the calibration standards and QC samples during sample analysis was expressed as percent difference from theoretical concentration (i.e., % RE). For serum total T, the %RE ranged from -1.4% to 1.9% for the 8 calibration standards in the range of 0.5-50 ng/mL and 3.6% to 4.2% for low, medium, and high QCs. For serum DHT, the % RE ranged from -0.8% to 1.4% for the 8 calibration standards in the range of 0.1-10 ng/mL and -0.4% to 3.1% for low, medium,

and high QCs. For serum E2, the % RE ranged from -1.6% to 2.2% for the 7 calibration standards in the range of 5-100 ng/mL and -1.7% to 0.3% for low, medium, and high QCs.

Precision of the calibration standards and QC samples during sample analysis was expressed as the % CV. For serum total T, the % CV ranged from 0.6% to 2.1% for the 8 calibration standards in the range of 0.5-50 ng/mL and 2.2% to 2.6% for low, medium, and high QCs. For serum DHT, the % CV ranged from 0.8% to 3.5% for the 8 calibration standards in the range of 0.1-10 ng/mL and 4.6% to 5.7% for low, medium, and high QCs. For serum E2, the % CV ranged from 1.7% to 6.7% for the 7 calibration standards in the range of 5-100 ng/mL and 4.1% to 5.5% for low, medium, and high QCs.

Refer to the stability assessments (i.e., long term storage, freeze-thaw, refrigerator, bench-top, auto-sampler stability) that were conducted as a part of the method validation described under *Bioanalytical Methods* in Section 4.1.1 of this review.

ISR was performed on 66 samples (i.e., approximately 10% of the study samples). From each subject (where possible), 3 samples were selected so that the T concentration range of that subject would be covered (i.e., low, medium, and high concentration). ISR was considered acceptable, when at least two third of the re-analyzed samples (for each compound) showed a difference ≤ 20% compared to the first obtained result. For T all 66 ISR samples met the acceptance criteria and 59 out of 62 samples (95.2%) met the acceptance criteria for DHT. For E2, 63 out of 66 samples (95.5%) met the acceptance criteria. These ISR results confirmed the reproducibility of the bioanalytical method.

Reviewer's Comment: *The acceptance criteria and performance of the total T, DHT, and E2 bioanalytical methods are in compliance with the Agency's Bioanalytical Method Validation Guidance. In summary, the method validation and performance of the bioanalytical methods in this study are acceptable.*

Safety Evaluation:

- The Day 8 close-out findings were compared to the screening results, and clinically significant changes identified in the following:
    - Vital signs and AEs: blood pressure, body temperature, respiratory rate, heart rate
    - Otorhinolaryngological examination
    - Complete blood count to evaluate changes in white blood count, hemoglobin and hematocrit
    - Clinical chemistry profile; Na/K, glucose, urea, creatinine, calcium, phosphate, uric acid, total bilirubin, albumin, AST, ALT, ALP, GGT, CK, and PSA
    - Urinalysis

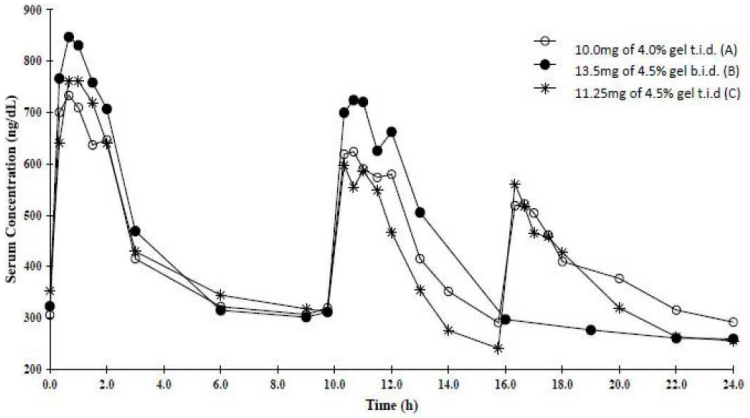
Disposition of Subjects:
Twenty one out of 22 subjects (95.5%) were Caucasians and there was 1 Black/African American. The mean age of patients was approximately 53 years (range: 35-73 years). A similar number of patients received each treatment: 8 patients received 10.0 mg TID (4.0%), 7 patients received 13.5 mg BID (4.5%), and 7 patients received 11.25 mg TID (4.5%).

Protocol Deviations:
There were no instances of subjects with protocol deviations leading to their exclusion from the study. There were no meaningful pharmacokinetic deviations.

PK Results:

Total T PK profiles and parameters are presented in Figure A-3-1 and Table A-3-1.

Figure A-3-1: Mean Serum T Concentration Over a 24-hour Dosing Period on Day 7 of TBS-1 Administration in Hypogonadal Men (N=22; Study TBS-1-2010-01)



Source: Study TBS-1-2010-01 CSR, Figure 11.4.2.3-1.
N=8 for 10.0 mg TID and N=7 for both 13.5 mg BID and 11.25 mg TID.
0 hours corresponds to the time of administration of the dose (2100 hours).
BID=twice daily, h=hours, TID=three times per day.

Table A-3-1: Mean Serum T PK Parameters Following 7 Days of TBS-1 Administration in Hypogonadal Men (N=22; Study TBS-1-2010-01)

PK Parameter	Statistic	TBS-1 dose		
		10.0 mg TID (n=8)	13.5 mg BID (n=7)	11.25 mg TID (n=7)
AUC_{0-24} (h*ng/dL)	Mean (SD)	9920.07 (3300.65)	9781.39 (3532.43)	9505.03 (2650.59)
C_{avg} (ng/dL)	Mean (SD)	413 (138)	408 (147)	396 (110)
C_{max} (ng/dL)	Mean (SD)	830 (188)	1050 (463)	883 (346)
C_{min} (ng/dL)	Mean (SD)	239 (77.6)	224 (98.6)	222 (57.1)
Patients with C_{avg} below the normal range	%	12.50%	14.29%	14.29%
Patients with C_{avg} within the normal range	%	87.50%	85.71%	85.71%
Patients with C_{avg} above the normal range	%	0	0	0

Source: Study TBS-1-2010-01 CSR, Table 11.4.2.3-1.
AUC_{0-24}=area under the serum concentration-time curve from 0 to 24 hours postdose; BID=twice daily; C_{avg}=average observed concentration; C_{max}=maximum observed concentration; C_{min}=minimum observed concentration; n=number of patients included in the PK Population; PK=pharmacokinetic; SD=standard deviation; TID=three times per day.

Regardless of the formulation, approximately 86-88% of the subjects had a total T C_{avg} within the reference range of 300-1,050 ng/dL. Two out of 7 subjects (i.e., Subject 01-005 C_{max} = 1670 ng/dL; Subject 02-006 C_{max} = 1570 ng/dL) who were in the 13.5 mg BID (4.5%) treatment group had a T C_{max} > 1,500 ng/dL.

All 3 treatments also demonstrated expected increases in mean serum DHT and E2 concentrations following TBS-1 administration (data not shown).

Reviewer's Comment: *Changing TBS-1 from 3.2% to 4.5% T (w/w) allowed for administration of a smaller amount of gel, resulting in improved and consistent absorption of T, and a higher response rate (i.e., achieving serum T average concentration [C_{avg}] values within the normal range) of subjects using 4.0% and 4.5% T (w/w) versus 3.2% T (w/w) TBS-1 formulation. The major limitation of this study was that it was a parallel study design (without any baseline*

correction) instead of being a crossover design that would allow a direct and accurate comparison between treatment groups. While both the BID and TID doses administered in this study had similar C_{avg} (approximately 400 ng/mL) within the normal range, the 13.5 mg BID (4.5%) dose had a C_{max} above the normal range, while the 11.25 mg TID (4.5%) dose did not.

Modeling and simulation of profiles for 200 subjects based on data from the 22 subjects from Study TBS-1-2010-01 suggested that the 11 mg TID (4.5% T w/w) dosing would adequately restore T to the normal concentration range without exceeding it (i.e., supporting a reduction of T from 11.25 mg to 11 mg per dose). Reference is made to Dr. LaiMing Lee's Clinical Pharmacology review under IND 70512 dated September 21, 2011 in DARRTS.

Safety Results:
TBS-1 treatment was well tolerated by subjects across the treatment groups. There were 8 AEs that occurred in 6 subjects. Six (6) of the events occurred during Treatment A and 2 occurred during Treatment B. There were no severe AEs, 1 moderate AE, and 7 mild AEs. The majority of the events were unrelated to study treatment. Two AEs of dizziness that were classified as possibly related to study treatment were mild and moderate and intensity respectively, resolved spontaneously and did not require any treatment. No application site related AEs were reported. Physical examination, vital signs and clinical laboratory evaluation results did not reveal any additional clinically significant findings. There were no discontinuations in this study.

Conclusions:
The major limitation of this study was that it was a parallel study design (without any baseline correction) instead of being a crossover design that would allow a direct and accurate comparison between treatment groups. Regardless of the formulation, approximately 86-88% of the subjects had a total T C_{avg} within the reference range of 300-1,050 ng/dL. Two out of 7 subjects who were in the 13.5 mg BID (4.5%) treatment group had a T C_{max} > 1,500 ng/dL. All 3 treatments also demonstrated expected increases in mean serum DHT and E2 concentrations following TBS-1 administration.

4.1.4 Phase 1 Study (Study TBS-1-2011-01): Comparison of BA Following TBS-1 Administration via a Multiple-dose Dispenser vs. a Prefilled Syringe

Study Title: A Phase 1, open label, randomized, crossover, two-groups, two-treatments, two-period, pilot study in healthy male subjects to determine the feasibility of a multiple dose dispenser for T nasal gel as measured by PK

Primary Objective: To compare the PK profile of T after administration of TBS-1 from two different dispensing devices in healthy male subjects

Clinical Study Center: Centre for Human Drug Research, The Netherlands
Clinical Study Period: March 2010 - April 2010

Bioanalytical Study Center: (b) (4)
Bioanalysis Period: May 2-11, 2011

Study Design:
This was a Phase 1, randomized, crossover study conducted in 12 healthy men, conducted to evaluate the comparability of administration of 11 mg TBS-1 from a multiple-dose dispenser (i.e., the proposed commercial method of administration) compared to 11 mg TBS-1 administration from prefilled syringes (i.e., the method of administration used in several studies earlier in the TBS-1 development program). A 12 hour baseline T profile was characterized on each subject to determine their endogenous T concentrations. Treatment was administered at 9 pm. All subjects were treated with TBS-1 using both the multiple-dose dispenser and prefilled syringes for administration. A total of 13 blood samples were collected for each subject over a 12 hour post-dose period as the following: 0 (pre-dose), 0.33, 0.66, 1.00, 1.50, 2.00, 3.00, 4.00, 5.00, 6.00, 8.00, 10.00, and 12.00 hour post-dose. Administration using the 2 different methods was separated by a washout period of at least 6 days.

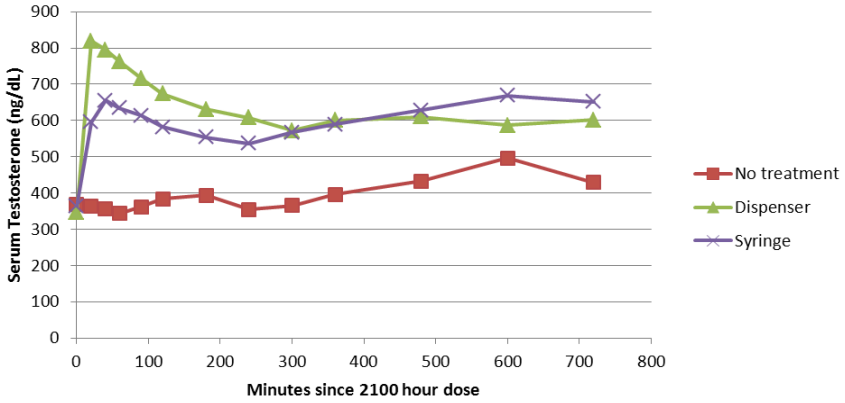
Inclusion criteria included healthy males of 18-45 years with BMI $\leq$ 35 kg/m^2 and normal otorhinolaryngological examination.

Bioanalytical Method:
Bioanalysis for total T was conducted at (b) (4). Human serum samples were analyzed using the same LC-MS/MS method for the determination of total T concentrations in the Phase 3 study, TBS-1-2011-03. Refer to *Bioanalytical Methods* in Section 4.1.1 of this review for detail information on the methods and their validations.

Reviewer Comment: *The acceptance criteria and performance of the total T bioanalytical method is in compliance with the Agency's Bioanalytical Method Validation Guidance. In summary, the method validation and performance of the bioanalytical method in this study are acceptable.*

PK Results:
PK was characterized for all 12 subjects who received TBS-1 in this study. Study participants were healthy men with a mean age of 23.4 years (range: 18-28 years) and had baseline-corrected T concentrations within the normal range (300 to 1050 ng/dL) following administration of TBS-1 using both administration methods. The red curve shows the 12 hour mean baseline (i.e., endogenous) T profile of the subjects (Figure A-4-1).

Figure A-4-1: Multiple-Dose Dispenser vs. Prefilled Syringe: Mean Baseline-Corrected Serum T Concentrations Following a Single Dose of 11 mg TBS-1 in Healthy Men



As shown in Figure A-4-1, the multiple-dose dispenser had higher AUC(0-12) values compared to those with the prefilled syringe, while also having a higher C_{max}. PK parameter values were calculated using baseline-corrected serum T concentrations (post-dose minus endogenous serum T concentration). The total exposures to T, as estimated by the AUC(0-12), after TBS-1 administration using the dispenser or the syringe are summarized in Table A-4-1.

Table A-4-1: Baseline Corrected T PK Parameters Following a Single Dose of 11.0 mg TBS-1 With Either a Multiple-dose Dispenser or a Prefilled Syringe

Parameter [SD]	Method of Administration	
	Multiple-Dose Dispenser (n=12)	Prefilled Syringe (n=12)
AUC_{0-12} (h*ng/dL) [SD]	7484 [1798]	7266 [1360]
t_{max} (h) [SD]	2.751 [3.961]	5.612 [4.736]
C_{max} (ng/dL) [SD]	1028 [283.1]	778.8 [144.1]
C_{min} (ng/dL) [SD]	337.9 [119.7]	355.9 [66.96]
C_{mean} (ng/dL) [SD]	623.6 [149.9]	605.4 [113.2]

Conclusions:

In this study, the multiple-dose dispenser had higher AUC(0-12) values compared to those with the prefilled syringe, while also having a higher C_{max}. One possible explanation for this difference is the more accurate placement of gel in the nasal cavity with the dispenser. Based on this finding, the Sponsor decided to select the multiple-dose dispenser as the proposed commercial method of administration.

4.2 Pharmacometric Review

Office of Clinical Pharmacology:
Pharmacometric Review

4.2.1 Summary of Findings

4.2.1.1 Key Review Questions

The purpose of this review is to address the following key questions.

4.2.1.1.1

Table A-5-1: Number and Percentage of Subjects with C_{avg} (0-24h) Total Testosterone Concentrations within the Normal Range (≥300 ng/dL and ≤1050 ng/dL) on Day 90 for Each Randomized Treatment Arm (by Analysis Population)

Analysis Population	ITT population with LOCF		ITT population with observation at Day 90		PP population	
Treatment	b.i.d. with potential up-titration to t.i.d	t.i.d. Fixed	b.i.d. with potential up-titration to t.i.d	t.i.d. Fixed	b.i.d. with potential up-titration to t.i.d	t.i.d. Fixed
Total number of subjects	(b) (4)	73	(b) (4)	69	(b) (4)	67
Cavg in Normal Range (300≤Cavg≤1050 ng/dL)						
Yes-n	(b) (4)	66		62		61
%		90		90		91
95% CI for Frequency*		(84, 97)		(83, 97)		(84, 98)
Cavg Below Normal Range (Cavg<300 ng/dL)						
Yes-n	(b) (4)	7		7		6
%		10		10		9
Cavg Above Normal Range (Cavg>1050 ng/dL)						
Yes-n	(b) (4)	0		0		0
%		0		0		0

* The CI for the frequency was approximated by a binomial distribution within each treatment.

As shown in Table A-5-2 and Figure A-5-1, the means for C_{avg} (0-24h) total testosterone concentrations were (b) (4) and 420 .9 ng/dL for the b.i.d. without up-titration subgroup, the b.i.d. up-titrated to t.i.d. subgroup, and the fixed t.i.d. treatment group at Day 90 respectively. The Cavg values are generally at (b) (4) for subjects randomized to the b.i.d. treatment arm. Subjects in the b.i.d. initial arm who needed to be titrated up to the t.i.d. regimen were generally (b) (4)

In another words, (b) (4)

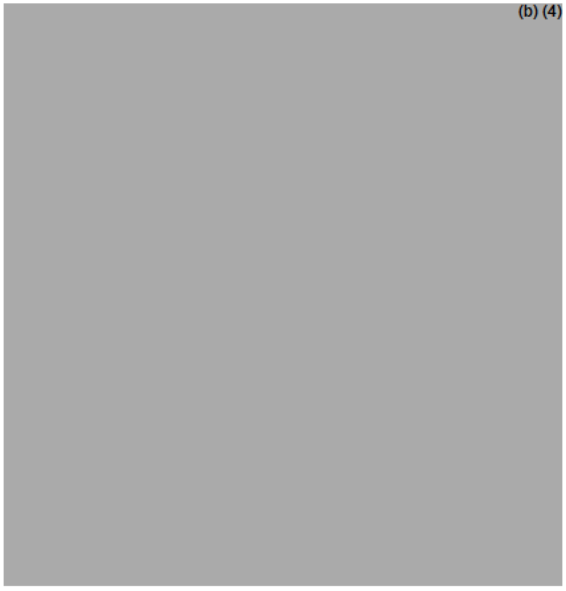
.

Table A-5-2: Mean Cavg for Serum Total Testosterone by Treatment (ITT Population)

Treatment	Baseline		Day 30		Day 90	
	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
b.i.d. Initial	226	(b) (4)				
b.i.d. without up-titration	(b) (4)					
b.i.d. up-titrated to t.i.d.						
t.i.d. Fixed	77	242.9 (7.0)	73	414.8 (13.3)	69	420.9 (14.0)

* The mean Cavg for the b.i.d. up-titrated to t.i.d. subgroup was (b) (4) than that for the general population who were getting the fixed t.i.d. treatment at Day 90 (Tukey test).

Figure A-5-1: Cavg for Serum Total Testosterone at Day 90 by Treatment (ITT Population)

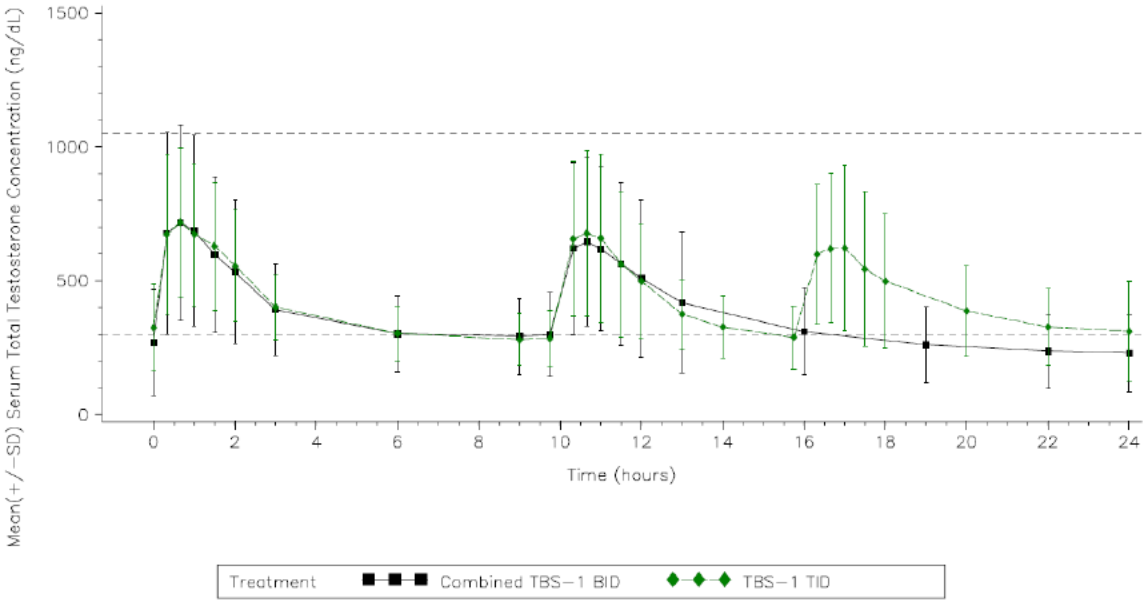


One intuitive solution for the inadequate efficacy problem is to (b) (4). However, one of the secondary efficacy objectives in the trial requires the following for serum total testosterone maximum concentration (C_{max}):

- C_{max} ≤1500 ng/dL in ≥85% of subjects,
- C_{max} 1800 to 2500 ng/dL in <5% of subjects, and
- C_{max} >2500 ng/dL in no subjects;

As shown in Figure A-5-2, the peak-to-trough fluctuation with TBS-1 therapy is wide, and for the (b) (4) the percentage of subjects with C_{max} between 1800 and 2500 ng/dL is about (b) (4) threshold for this range (Table A-5-3). Therefore, (b) (4) not feasible.

Figure A-5-2: Serum Total Testosterone Concentration Time Course at Day 30 by Treatment (ITT Population)



Source: From the sponsor's study report, Figure 2, Page 87.

Table A-5-3: Number (Percentage) of Subjects with Serum Total Testosterone C_{max} in Selected Ranges at Day 90 by Treatment (ITT population)

Treatment	b.i.d. without up-titration	b.i.d. up-titrated to t.i.d.	b.i.d. with potential up-titration to t.i.d	t.i.d. Fixed
Total number of subjects	[redacted] (b) (4)			69
Cmax ≤1500 ng/dL				58 (84.1)
1800 ng/dL ≤ Cmax ≤2500 ng/dL				1 (1.4)
Cmax >2500 ng/dL				0 (0.0)

Therefore, the actual reason for the failure of the [redacted] (b) (4)

As shown in Table A-5-4, there are about [redacted] (b) (4) of subjects in the b.i.d. initial arm who were up-titrated to the t.i.d. regimen. The remained [redacted] (b) (4)% of subjects who stayed with the b.i.d. regimen [redacted] (b) (4)

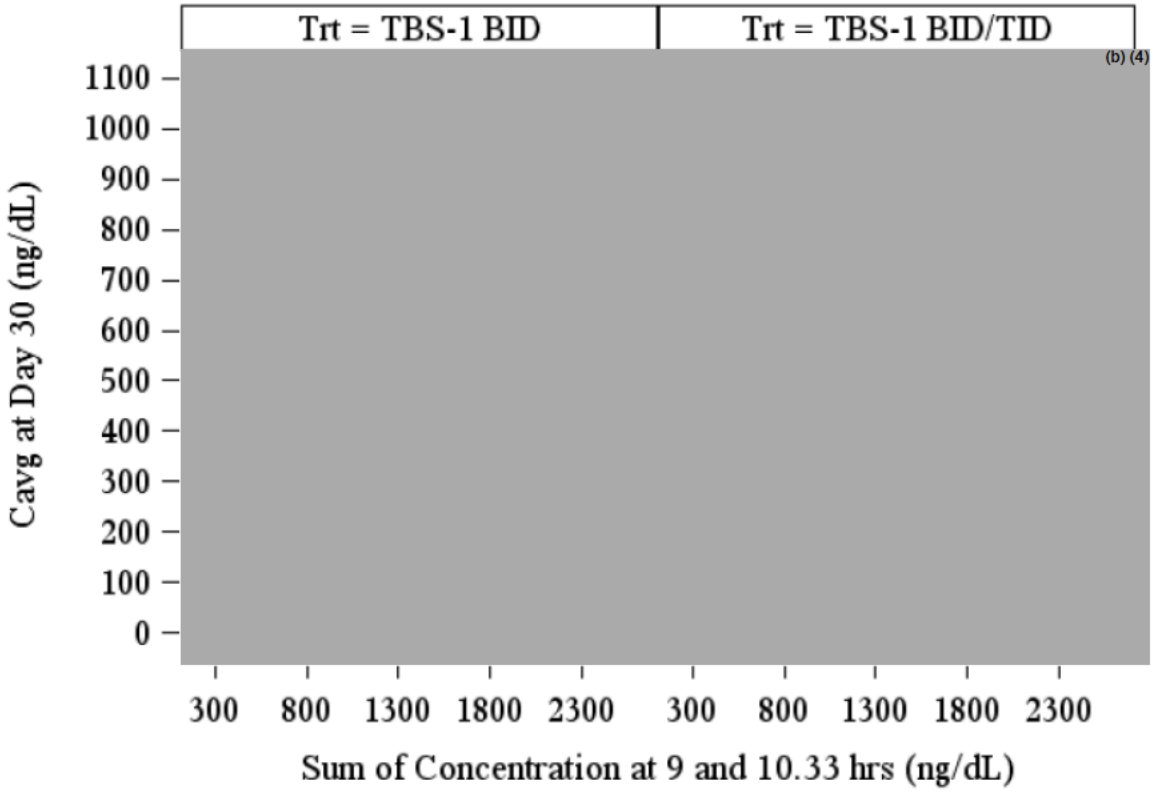
As the efficacy of the t.i.d. regimen has been adequately demonstrated in the trial, a feasible solution is to [redacted] (b) (4)

herefore, the fixed t.i.d. regimen should be considered if the safety had been adequately demonstrated. [redacted] (b) (4)

Table A-5-4: Number and Percentage of Subjects with C_{avg} (0-24h) Total Testosterone Concentrations within the Normal Range (≥300 ng/dL and ≤1050 ng/dL) on Day 90 by the Subgroups with or without up-titration in the b.i.d. Initial Arm (by Analysis Population)

Analysis Population	ITT population with LOCF		ITT population with observation at Day 90		PP population	
Treatment	b.i.d. without up-titration	b.i.d. up-titrated to t.i.d.	b.i.d. without up-titration	b.i.d. up-titrated to t.i.d.	b.i.d. without up-titration	b.i.d. up-titrated to t.i.d.
Total number of subjects	(b) (4)					
Cavg in Normal Range (300≤Cavg≤1050 ng/dL)						
Yes-n	(b) (4)					
%						
95% CI for Frequency						
Cavg Below Normal Range (Cavg<300 ng/dL)						
Yes-n	(b) (4)					
%						
Cavg Above Normal Range (Cavg>1050 ng/dL)						
Yes-n	(b) (4)					
%						

Figure A-5-3: Cavg for Serum Total Testosterone at Day 30 vs. Sum of Concentration at 9 and 10.33 hrs (ITT Population)



4.2.2 Recommendations

The proposed 11 mg b.i.d. dosing regimen for a total daily dose of 22 mg (b) (4) is not acceptable. The fixed t.i.d. regimen should be recommended if adequate safety could be demonstrated (b) (4)

4.3 Clinical Pharmacology Filing Memo

Office of Clinical Pharmacology *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		Information
NDA Number	205488	**Brand Name**	Natesto™
OCP Division	DCP3	**Generic Name**	Testosterone
Medical Division	DBRUP	**Drug Class**	Steroid
OCP Reviewer	Chongwoo Yu, Ph.D	**Indication(s)**	Treatment of male hypogonadism
OCP Team Leader	Myong Jin Kim, Pharm.D.	**Dosage Form**	Gel, T 4.5% (11 mg/dsoe)
Secondary Reviewer	Myong Jin Kim, Pharm.D.	**Dosing Regimen**	Starting dose at 22 mg/day (11 mg BID) (b) (4)
Date of Submission	April 29, 2013	**Route of Administration**	Transdermal
Estimated Due Date of OCP Review	December 29, 2013	**Sponsor**	Trimel BioPharma SRL
PDUFA Due Date	February 28, 2014	**Priority Classification**	Standard
Division Due Date	February 7, 2014		

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	7 methods; 21 studies for 3 analytes		Methods: 10364, 10367,101177, VP0246, VP0227
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		TBS-1A-2011-01
multiple dose:	X	1		TBS-1-2011-01
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	1		TBS-1-2011-04
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	NA			Pediatric waiver request
geriatrics:				
renal impairment:				
hepatic impairment:				

PD:				
Phase 1:				
Phase 2:	X	5		TBS-1-2010-01, Nasobol-01-2009, MAT/05, MAT/04, Nasobol-01-2008
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X	1		TBS-1-2011-03
Population Analyses -				
PK:				
PD:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Immunogenicity profile				
Thorough QT study				
Literature References	X	40		
Total Number of Studies		70		

Other comments

	Comments
QBR questions (key issues to be considered)	1. Dose titration scheme 2. Acceptability of primary efficacy 3. Time within normal T range following Natesto™ (TBS-1) dose 4. OSI inspection on the bioanalytical site 5. Acceptability of bioanalytical method validation and performance
Other comments or information not included above	1. Sponsor needs to submit their justification and additional information on the proposed dose titration method. 2. Sponsor needs to submit the bioanalytical study (i.e., method performance) reports for all clinical studies. 3. Sponsor needs to submit ISR results. 4. A formal OSI consult on the bioanalytical study site will be requested.

Filing Memo

Clinical Pharmacology Review

NDA: 205488
Compound: Natesto™ (TBS-1; Testosterone [T] intranasal gel, 4.5%)
Sponsor: Trimel Biopharma SRL

Date: 6/13/2013
Reviewer: Chongwoo Yu, Ph.D.

Introduction:
Trimel Biopharma SRL submitted 505(b)(2) New Drug Application (NDA) 205488 for Natesto™ (TBS-1; T intranasal gel, 4.5%) on April 29, 2013 to seek an approval for the treatment of primary and hypogonadotropic hypogonadism associated with a deficiency or absence of endogenous T.

Natesto™ (TBS-1) contains 4.5% T for intranasal administration. Natesto™ (TBS-1) is for use in men with hypogonadism. The Sponsor proposes the following dosing and dose adjustment instructions:

The recommended starting dose of Natesto™ (TBS-1) is 2 actuations of 5.5 mg of T (1 actuation per nostril; (b) (4) (b) (4): 11 mg/dose) administered intranasally (b) (4) (b) (4) (b) (4) Natesto™ (TBS-1) should not be administered to other parts of the body including scrotum, penis, abdomen, shoulders, axilla, or upper arms.

Regulatory History
The following meetings were held between the Division of Bone, Reproductive and Urologic Products (DBRUP) and the Sponsor under IND 70512:

- Pre-IND meeting: October 18, 2004
- Type C, guidance meeting: March 22, 2006
- End of Phase 2 meeting: March 14, 2011
- Pre-NDA meeting: Face-to-face meeting request was denied but the Division's written responses to the Sponsor's questions were conveyed to the Sponsor on March 5, 2013

Clinical Development of Natesto™ (TBS-1)
The clinical development of Natesto™ (TBS-1) consists of 9 clinical studies including the pivotal Phase 3 study (Study TBS-1-2011-03) that provides the support for clinical efficacy and safety, the Phase 2 study (Study TBS-1-2010-01), and a Phase 1 drug-drug interaction (DDI) study (Study TBS-1-2011-04) to assess the relative bioavailability (BA), safety, and tolerance of Natesto™ (TBS-1) when administered to patients with seasonal allergic rhinitis in the symptomatic, symptomatic but treated, and asymptomatic states. Of the 9 clinical studies submitted, 4 studies (i.e., Studies TBS-1-2011-03, TBS-1-2010-01, TBS-1-2011-04, and TBS-1-2011-01) were conducted using the to-be-marketed (TBM) formulation. The submitted clinical studies are summarized in Table 1 below:

Table 1: Summary of Clinical Studies Conducted with Natesto™ (TBS-1) in Men

Study/ Sites and Country/ Sponsor	Study Design	Number of Subjects Treated	Duration of Treatment	Formulation (%w/w)	Dose	Total Daily Dose	Subjects Per Treatment
Pivotal Study in Hypogonadal Men							
TBS-1-2011-03 39 centers in the US Trimel	Phase 3, open-label, randomized, 2-arm, parallel	306	90 days (all, efficacy) 180 days (all) 360 days (subset of 75 patients)	4.5%	11.0 mg BID 11.0 mg TID	22.0 mg 33.0 mg	(b) (4)
Other Studies in Hypogonadal Men							
TBS-1-2010-01 3 centers in the US Trimel	Phase 2, open-label, randomized, single-dose, 3-arm, parallel-group	22	7 days	4.0% 4.5% 4.5%	10.0 mg TID 13.5 mg BID 11.25 mg TID	30.0 mg 27.0 mg 33.75 mg	8 7 7
Nasobol-01-2009 6 centers in the US Trimel	Phase 2, open-label, randomized, 4-arm, 4 × 7-day period, crossover with no washout	57	7 days per period (28 days total)	3.2% 3.2% 3.2% Androderm® Patch	8.0 mg BID 11.0 mg BID 14.0 mg BID 5.0 mg QD	16.0 mg 22.0 mg 28.0 mg 5.0 mg	56 56 54 54
MAT/05 1 center in Romania Mattern	Phase 2, open-label, randomized, multiple-dose, 3-arm, parallel-group	21	14 days	3.2% 3.2% 3.2%	7.6 mg BID[b] 7.6 mg BID[c] 7.6 mg TID	15.2 mg 15.2 mg 22.8 mg	7 7 7
MAT/04 1 center in Romania Mattern	Phase 2, open-label, nonrandomized, single-dose, 3-arm, sequential, 3-period, with ≥3-day washout	8	1 day per period (3 days total)	3.2% 3.2% 3.2%	7.6 mg QD 15.2 mg QD 22.8 mg QD	7.6 mg 15.2 mg 22.8 mg	8 8 8
Nasobol-01-2008 1 center in the US Mattern	Phase 2, open-label, 14-day BID followed by 14 day QD, comparative PK in hypogonadal men vs untreated healthy men	16	28 days (14 days BID followed by 14 days QD)	3.2% 3.2% 3.2% *Healthy men:* No treatment	7.6 mg BID[c] 7.6 mg BID[d] 7.6 mg QD None	15.2 mg 15.2 mg 7.6 mg None	8 8 16 16
Study/ Sites and Country/ Sponsor	**Study Design**	**Number of Subjects Treated**	**Duration of Treatment**	**Formulation (%w/w)**	**Dose**	**Total Daily Dose**	**Subjects Per Treatment**
Studies in Healthy Men							
Comparing Methods of Administration							
TBS-1-2011-01 1 center in The Netherlands Trimel	Phase 1, open-label, randomized, 2-group, 2-treatment (multiple-dose dispenser vs syringe) crossover with 6-day washout[a]	12	1 day per treatment arm (2 days total)	4.5%	11.0 mg QD Syringe Dispenser	11.0 mg	 12 12
Men With Seasonal Allergic Rhinitis (Extrinsic Factor and Drug Interaction Study)							
TBS-1-2011-04 1 center in Germany Trimel	Phase 1, open-label, randomized, 3-group, 3-treatment states, 3-period, crossover with ≥4 day washout	18	1 day per treatment arm (3 days total)	4.5%	11.0 mg TID[e] 11.0 mg TID[e] 11.0 mg TID[e]	33.0 mg 33.0 mg 33.0 mg	18 15 17
Study Using TBS-1A Formulation							
TBS-1A-2011-01 1 center in The Netherlands Trimel	Phase 1, open-label, single-dose, 4-way, sequential 4-period, with 6-day washout	15	1 day per treatment arm (4 days total)	4.0% 4.0% TBS-1A 8.0% TBS-1A 4.0% TBS-1A (viscous)	10.0 mg QD 10.0 mg QD 10.0 mg QD 10.0 mg QD	10.0 mg 10.0 mg 10.0 mg 10.0 mg	15 15 15 15

Source: Study TBS-1-2011-03, Study TBS-1-2010-01, Study Nasobol-01-2009, Study MAT/05, Study MAT/04, Study TBS-1-2011-01, Study TBS-1-2011-04, Study Nasobol-01-2008, and Study TBS-1A-2011-01.

[a] Patients were randomized 3:1 to the BID and TID treatment arms. A total of 228 patients were randomized to BID treatment and 78 to TID treatment. (b) patients from BID treatment were titrated up to TID treatment on Day 45. (b) patients completed 90 days of BID treatment and (b) patients completed 90 days of TID treatment.

[b] Dosing times for the first and second 7.6-mg BID groups were 0800 and 1400, and 0800 and 2000, respectively.

[c] Dosing times for the first and second 7.6-mg BID groups were 0700 and 2400, and 0700 and 2200, respectively.

[d] PK samples for this study were drawn 12 hours after dose administration as defined in the protocol.

[e] Subjects in this study were adult men with seasonal allergic rhinitis who were asymptomatic due to the season and were otherwise healthy. Each subject was dosed in a crossover design as asymptomatic, symptomatic untreated, and symptomatic treated (see Module 2.7.2, Section 2.2).

%w/w=percent weight per weight; BID=twice daily; Mattern=Mattern Pharmaceuticals AG (original Sponsor of TBS-1); PK=pharmacokinetic; QD=once daily; TID=three times per day; Trimel=Trimel Biopharma SRL (current Sponsor of TBS-1); US=United States.

Pediatric Waiver Request

This NDA contains a pediatric waiver request. Sponsor states that hypogonadism is a disease that is not applicable to pediatric patients. The signs and symptoms occur in the adult population and there are too few children with the disease/condition to study.

Drug Product Formulation:

The drug product, Natesto™ (TBS-1), is a viscous bioadhesive oil-based formulation containing solubilized T intended for intranasal application. Natesto™ (TBS-1) bulk gel is formulated with the following compendial inactive ingredients: castor oil, oleoyl polyoxylglycerides and colloidal silicon dioxide.

Table 2: Composition of the TBM Formulation of Natesto™ (TBS-1)

Component	Amount (% w/w)	Amount Delivered per Actuation (mg)	Amount Delivered per Dose (mg)	Quantity per Unit[a] (mg)	Function	Quality Standard
Testosterone	4.5%	5.5	11.0	(b) (4)	Active ingredient	USP
Castor oil					(b) (4)	USP
Oleoyl polyoxylglycerides						Ph. Eur./NF
Colloidal silicon dioxide						NF
Total						N/A

[a] Unit is the multiple dose dispenser

Absorption and 24-hr Average Serum T Concentrations

The maximum concentration for T following intranasal administration of Natesto™ (TBS-1) is achieved within 45 minutes of administration and has a half-life of approximately 10 hours. The efficacy and safety of Natesto™ (TBS-1) was evaluated in a multicenter, open-label, 90-day trial that enrolled 306 hypogonadal men at 39 clinical research centers in the US. During the initial Natesto™ (TBS-1) treatment period (Days 1-30), 228 patients were treated with 22 mg of T daily. On Day 45 of the trial, patients were maintained at the same dose or were titrated to three times a day, based on an assessment of 24-hour average serum T concentration (C_{avg}). The primary efficacy variable was the percentage of patients with a serum total T C_{avg} value within the normal range (i.e., 300-1050 ng/dL) on Day 90, with success being defined as ≥ 75% of patients on treatment within the normal serum T concentration range. At the end of the treatment period (Day 90), (b) (4) patients received 22 mg of T daily and (b) (4) patients received 33 mg of T daily.
Of these patients, (b) (4) % of those on 22 mg of T daily and 76% of those on 33 mg of T daily had C_{avg} within the normal range at Day 90. Of the (b) (4) patients who completed the 90-day treatment, (b) (4) patients did so with no deviation from the protocol. Per Sponsor, (b) (4) % of those on 22 mg of T daily and 77% of those on 33 mg of T daily had C_{avg} within the normal T range at Day 90.

Distribution, Metabolism, and Excretion

No distribution, metabolism, and excretion studies were conducted using Natesto™ (TBS-1) and the Sponsor is proposing to use the available information to support this NDA.

Drug-Drug Interactions:

The effects of allergic rhinitis and the use of oxymetazoline on the absorption of T were investigated in a 3-way cross-over clinical study (i.e., Study TBS-1-2011-04). Eighteen (18) males who suffered from seasonal allergic rhinitis received 3 doses of 11 mg of T intranasally (33 mg/day) while they were in the asymptomatic, symptomatic, and symptomatic but treated (with oxymetazoline) states. Baseline (i.e., pre-dose concentration) corrected AUC_{0-24} and C_{avg} values for T in the symptomatic and the symptomatic but treated states demonstrated a decrease of 21% and 18%, respectively, as compared to the asymptomatic state. The Sponsor proposes the following statement under Section 7, Drug Interactions in the product label: "The relative decrease in bioavailability of TBS-1 in people with symptomatic seasonal rhinitis was neither ameliorated nor aggravated by the administration of the nasal decongestant, oxymetazoline."

Specific Populations and Waiver Request for Pediatrics:

- Pediatric use: No pediatric studies were conducted and pediatric waiver request was submitted

- Geriatric use: Sponsor did not stratify the studies to rule out whether efficacy and safety in those over 65 yr of age would differ from younger subjects. Of the 306 patients enrolled in the Phase 3 clinical study (Study TBS-1-2011-03) conducted using Natesto™ (TBS-1), 60 were 65 years of age or older, and 9 were 75 years of age or older. Additionally, there are insufficient long-term safety data in geriatric patients to assess the potential for increased risks of cardiovascular disease and prostate cancer.
- Renal or hepatic impairment: No studies were conducted in patients with renal or hepatic impairments
- Contraindicated for pregnant or breast feeding women
- Warnings and Precaution for children and women for secondary exposure

Bioanalytical Method Validation:
Serum samples were analyzed for total T, dihydrotestosterone (DHT), and estradiol (E2) using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods. The dynamic range for total T, DHT, and E2 were 0.5-50 ng/mL, 0.1-10 ng/mL, and 5-100 pg/mL, respectively. Bioanalyses were conducted at (b) (4) (b) (4) and (b) (4) All bioanalyses involving studies conducted with the TBM formulation of Natesto™ (TBS-1) (i.e., Studies TBS-1-2011-03, TBS-1-2010-01, TBS-1-2011-04, and TBS-1-2011-01) were conducted at (b) (4)

The Sponsor has submitted the bioanalytical method validation reports but has only submitted bioanalytical study reports for 3 studies (i.e., Studies TBS-1-2011-03, TBS-1-2011-04, and TBS-1-2010-01). Sponsor still needs to submit the bioanalytical study reports for 6 clinical studies. An information request (IR) has been sent to the Sponsor for the bioanalytical study reports. An Office of Scientific Investigations (OSI) consult requesting an inspection of the bioanalytical site of the pivotal Phase 3 study (Study TBS-1-2011-03) will be requested.

Recommendation:
The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Clinical Pharmacology section for NDA 205488 is fileable pending the submission of the missing bioanaytical study reports.

Comments for the Sponsor:

- *Provide your justification and supporting information on your proposed titration method. Specifically, provide the information/your rationale on the following:*
  - *The selection of two sampling time points (i.e., 1 hour pre-dose and 20 minutes post-dose) and the use of its sum to titrate on Day 30.*
  - *The selection of a dose titration recommendation cutoff value (i.e., the sum of total testosterone in two blood samples) of 755 ng/dL.*
  - *The potential effect of deviations from the actual blood draw and its sampling time on the accuracy of C_{ave} prediction.*
  - *A Table with individual testosterone concentrations from the two blood samples including the actual sampling time (e.g., 1 hour pre-dose and 20 minutes post-dose), the sum of these two measurements used in the titration scheme, each patient's C_{ave} value on Days 30 and 90 (based on the 24-hour measurements), the testosterone dose that each patient was on Days 30 and 90, and the time within the normal testosterone range following Natesto™ (TBS-1) dose on Days 30 and 90.*
- *Submit the bioanalytical study (i.e., method performance) reports for all clinical studies.*
- *Incurred sample reanalysis (ISR) is recommended to evaluate the accuracy of the incurred samples analyzed. We note that ISR results were not included in your bioanaylytical study reports. We request that you either submit existing ISR results or conduct ISR and submit the results to ensure the reliability of the data obtained in clinical studies.*
- *The following will be the review issues:*
  - *Effect of body mass index (BMI) on the systemic testosterone exposure*
  - *The dose titration scheme: selection of blood drawing time points, titration criteria (i.e., cutoff value), and the effect of deviations in sampling time on the accuracy of C_{ave} prediction.*
  - *Time within the normal testosterone range following Natesto™ (TBS-1) dose.*

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/s/

CHONGWOO YU
06/17/2013

MYONG JIN KIM
06/18/2013

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHONGWOO YU
04/30/2014

JIANG LIU
04/30/2014

YANING WANG
04/30/2014

MYONG JIN KIM
04/30/2014

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 205488	**Reviewer:** Kelly M. Kitchens, Ph.D.	
Submission Date:	April 29, 2013		
Division:	Division of Bone, Reproductive and Urologic Products	**Team Leader:** Tapash Ghosh, Ph.D.	
Applicant:	Trimel BioPharma SRL	**Acting Supervisor:** Richard Lostritto, Ph.D.	
Trade Name:	---	**Date Assigned:**	September 23, 2013
Established Name:	TBS-1 (Testosterone Nasal Gel)	**Date of Review:**	January 29, 2014
Indication:	Primary hypogonadism (congenital or acquired) in men. Hypogonadotropic hypogonadism (congential or acquired) in men.	**Type of Submission:** NDA 505(b)(2)	
Formulation/ strengths	Nasal Gel/ 5.5 mg per actuation (4.5%)		
Route of Administration	Intranasal		
Type of Review:	In Vitro Release Test Method and Results		

SUMMARY:

Background: The current NDA was submitted per section 505(b)(2) for TBS-1 (testosterone nasal gel) as a testosterone replacement therapy in men for primary and hypogonadotropic hypogonadism. The drug product is a testosterone gel for intranasal administration, and is supplied in a non-aerosol, multiple-dose pump container. The multiple-dose dispenser contains 5.5 mg of testosterone per actuation, and is designed to apply the gel to the nasal mucosa without the need for the patient to handle the gel. One dose consists of two actuations (one per nostril) for a total dose of 11.0 mg of testosterone.

Submission: During development, the procedure to determine the *in vitro* release rate of testosterone from the gel was conducted using the Franz cell system. The Applicant submitted the in vitro release test (IVRT) method validation report, the IVRT method description, and interim IVRT specifications.

Review: The Biopharmaceutics review is focused on the evaluation of the IVRT method and the proposed interim specifications.

RECOMMENDATION:

The following was agreed upon by the Biopharmaceutics team and the Applicant :

(b) (4)

[redacted]

(b) (4)

Overall, the IVRT method and interim *in vitro* release acceptance criteria are acceptable for TBS-1 (testosterone nasal gel). From the Biopharmaceutics perspective, NDA 205488 for TBS-1 (testosterone nasal gel) is recommended for approval.

Signature
Kelly M. Kitchens, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Signature
Tapash Ghosh, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc. RLostritto.

BIOPHARMACEUTICS ASSESSMENT

Drug Product:

TBS-1 is a gel consisting of testosterone USP (4.5%) delivered intranasally as a testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. The target site of TBS-1 is the nasal cavity due to the following advantages of nasal drug delivery:

1. rapid absorption due to a highly permeable nasal epithelium;
2. fast onset of action;
3. avoidance of hepatic first-pass metabolism;
4. avoidance of GIT degradation;
5. ease of administration; and
6. no skin to skin transference of drug can occur as can be the case with transdermal products.

The nominal quantity of TBS-1 gel discharged per pump actuation is 122.5 mg, which equates to a dose volume of (b) (4). The recommended starting dose of TBS-1 is 11.0 mg of testosterone (2 actuations; 1 actuation per nostril) administered intranasally twice daily for a total daily dose of 22.0 mg. The composition of TBS-1 gel is below:

Table 1: Components, Quantity, Quality Standards and Function - TBS-1 Finished Product

Component	Amount (% w/w)	Amount Delivered per Actuation (mg)	Amount Delivered per Dose (mg)	Quantity per Unit[a] (mg)	Function	Quality Standard
Testosterone	4.5%	5.5	11.0	(b) (4)	Active ingredient	USP
Castor oil	(b) (4)					USP
Oleoyl polyoxylglycerides						Ph. Eur./NF
Colloidal silicon dioxide						NF
Total						N/A

[a] Unit is the multiple dose dispenser

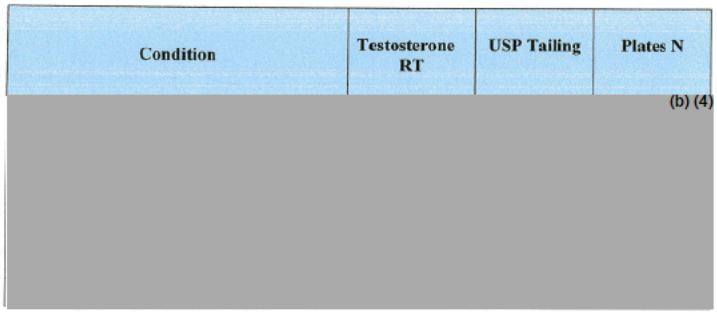
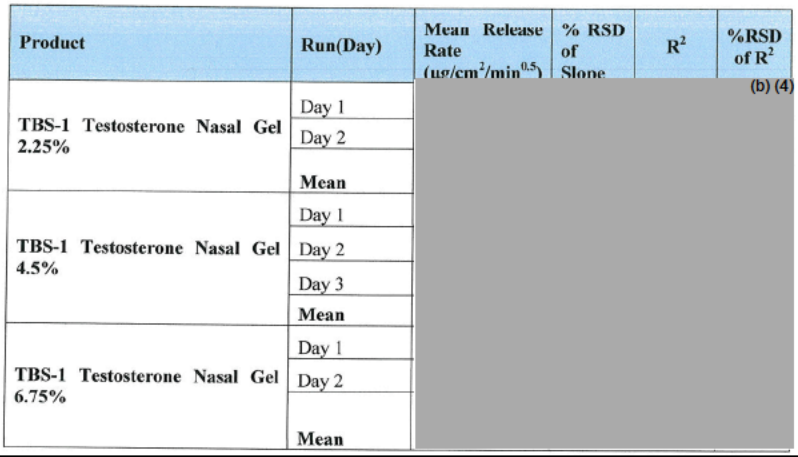
In Vitro Release Testing (IVRT):

IVRT Method Development:

Parameters	Data
Source of data	**Validation of Test Method STM.TBS1.004.00 for *In Vitro* Drug Release of TBS-1 Testosterone Nasal Gel Using Franz Cell** Document No. MV-12-006.00
Membrane	Durapore HV membrane (b) (4) µm pore size, diameter (b) (4) mm) was selected for its reproducibility, pore size, and compatibility with the receptor medium. This membrane also offers low diffusion resistance, high porosity, minimal thickness, and does not exhibit drug binding.
Receptor Medium	Ethanol/water (50:50) was selected to ensure the drug has sufficient solubility in the receptor medium such that the receptor medium does not affect the drug release rate.
Sampling Times	The sampling times, 1, 2, 3, 4, 5, and 6 hours were selected to generate an adequate in vitro release profile to determine the drug release rate.

IVRT Method Validation:

Parameters	Data
Source of data	**Validation of Test Method STM.TBS1.004.00 for *In Vitro* Drug Release of TBS-1 Testosterone Nasal Gel Using Franz Cell** Document No. MV-12-006.00
Analytes	Testosterone
Selectivity	No interference from the chromatograms of blank, placebo, standard, or impurity standards was observed at the Testosterone peak
Standard and Sample Solution Stability	100% standard and sample solutions are stable up to 9 days at room temperature. 1% standard solution is stable up to one day at room temperature (should be freshly diluted on day of use).
System Precision	100% standard: %RSD = (b) (4) (n=5 injections) 1% standard: %RSD = (b) (4) (n=5 injections)
Linearity & Range	r^2 = (b) (4) (b) (4)
Detection Limit	01% standard solution (0.29688 µg/mL), S/N ratio = 3:1
Quantitation Limit	1% standard solution (2.9688 µg/mL)
Method Precision: Repeatability Chemist 1, day 1	% RSD < (b) (4) % (n=6 cells) at each time point
Method Precision: Inter-day Precision Chemist 1, day 2	% RSD < (b) (4) % (n=6 cells) at each time point
Method Precision: Intermediate Precision Chemist 2	% RSD < (b) (4) % (n=6 cells) at each time point

Robustness	
Membrane Binding Treated: membrane immersed in standard soln. for 4 hours Untreated: no membrane immersion	% recovery w/1% standard = (b) (4) % for treated and untreated membranes % recovery w/100% standard = (b) (4) % for treated and untreated membranes
Membrane Resistance	The amount of testosterone released from testosterone solution in ethanol was 6-8 times greater than the amount of testosterone released from testosterone gel.
Precision and Method Sensitivity	
Chromatographic Conditions	Mobile Phase: Methanol:Water (60:40) Column: Poroshell 120EC-C18 Flow Rate: 1.0 mL/min Column Temp.: 40°C Detector: 245 nm Injection Volume: 5 µL Run Time: 5 minutes Retention Time (RT): (b) (4)

In Vitro Release Study Parameters	Data
Source of data	**Validation of Test Method STM.TBS1.004.00 for *In Vitro* Drug Release of TBS-1 Testosterone Nasal Gel Using Franz Cell** Document No. MV-12-006.00
Diffusion Apparatus	Franz diffusion cells: (b) (4) mm orifice diameter
Surface Area	1.7671 cm^2
Diffusion Medium	Ethanol:Water (50:50)
Temperature	37°C ± 0.5°C
Stirring Speed	600 rpm
Pre-soaking of Membrane	≥ 30 min (in diffusion medium)
Medium Volume	20 mL

Aliquot Volume	0.3 mL with medium replacement
Sampling Time (minutes)	60, 120, 180, 240, 300 and 360

Reviewer's comments on IVRT method development and validation:

- The IVRT method development and validation report were provided in the original submission.
- The Applicant provided adequate justification for their IVRT method parameters.
- The validation results demonstrate the specificity, linearity, accuracy, precision, and robustness of the IVRT method.
- The IVRT method development and validation are acceptable.

In Vitro Release Acceptance Criteria

- In the 74-day letter submitted to the Applicant on July 8, 2013, the Agency recommended that the Applicant propose an *in vitro* release acceptance criteria (range) based on the developed IVRT methodology for the drug product at release and during stability as a quality control parameter.
- In the August 1, 2013 response to the 74-day letter comments, the Applicant commented that they have implemented *in vitro* release acceptance criteria (range) that is consistent with the SUPAC-SS guidance based on data generated with the pivotal batches. However, the Applicant still did not propose *in vitro* release acceptance criteria (range). Therefore, the following Information Request (IR) was submitted to the Applicant on September 24, 2013:

  In light of the very tight in vitro release data you obtained from the pivotal batches, we recommend that you propose/implement the in vitro release acceptance criteria (range) for your systemic use product at release and during stability as a quality control parameter.

- On October 4, 2013, the Applicant submitted the following response to this IR:

  The applicant could not find other examples of specifications for drug release for this type of systemic product and the prevailing guideline for drug release, SUPAC (FDA guidance document: Non-sterile semisolid dosage forms: Scale-up and Post Approval Changes: Chemistry, Manufacturing and Controls: *In Vitro* Release Testing and *In Vivo* Bioequivalence Documentation. May 1997) does not recommend that this test be implemented as a quality control parameter. However the applicant appreciates the Agency's request for a specification and has endavoured to provide one. The applicant proposes that this specification be implemented for release and stability testing but for information only until data from 10 batches have been collected. At which time the application will revise the specification as necessary and formalize the specification as a release criteria.

Proposed *in vitro* release acceptance criteria

Trimel proposes the following acceptance criteria for the *in vitro* release:

(b) (4)

- The Agency did not agree with the Applicant's proposal to set specifications for information only, and the proposed specifications were not appropriate for the drug product. Therefore, the following IR was submitted to the Applicant on October 25, 2013:

    - *We request that you commit to setting your proposed in vitro release acceptance criteria as interim specifications and not for information only.*
    - *We recommend you conduct the in vitro release as per the methodology described in SUPAC-SS guidance, and report the specification as a range derived from the slope (in $\mu g/cm^2/hr^{1/2}$) of the linear portion of the cumulative amount released versus $\sqrt{t}$ curve (as opposed to what you proposed as the 3 time-point specifications). We do, however, agree with your proposal to revise the specification if necessary based on in vitro release data collected from 10 batches. You will have the opportunity to submit the information as a PAS following approval of your product.*
    - *Please propose a revised specification along with all the raw data in an electronic format for the Agency to review with proper identification/description of the batches used to generate those data.*

- On October 31, 2013, the Applicant submitted the following response to this IR:

Trimel agrees to conduct the *in vitro* release as per the methodology described in SUPAC-SS guidance and report the specification as a range derived from the slope (in $\mu g/cm^2/hr^{1/2}$) of the linear portion of the cumulative amount released versus $\sqrt{t}$ curve.

Table 1 and Figure 1 summarize the results for amount released versus $\sqrt{}$time for all five pivotal batches presented in Section 3.2.P.8.3.1 in the NDA. The raw data for these batches is provided in electronic format with this submission.

The SUPAC-SS guidance provides for a measure of sameness based on the slope (in $\mu g/cm^2/hr^{1/2}$) of the linear portion of the cumulative amount released versus $\sqrt{t}$ curve falling within the range of 75% to 133.33% of the reference. The sponsor has set the specifications based on the definition of sameness in SUPAC-SS as follows:

Stage 1:

The Slope of the mean results of six cells ranges from (b) (4)

If the test does not pass Stage 1 then proceed to Stage 2.

Stage 2:

Test two additional runs of the (six cells) *in vitro* apparatus should be carried out, yielding twelve additional results for a total of 18 (including the first stage results).

The Slope of the mean results of twelve cells ranges from (b) (4)

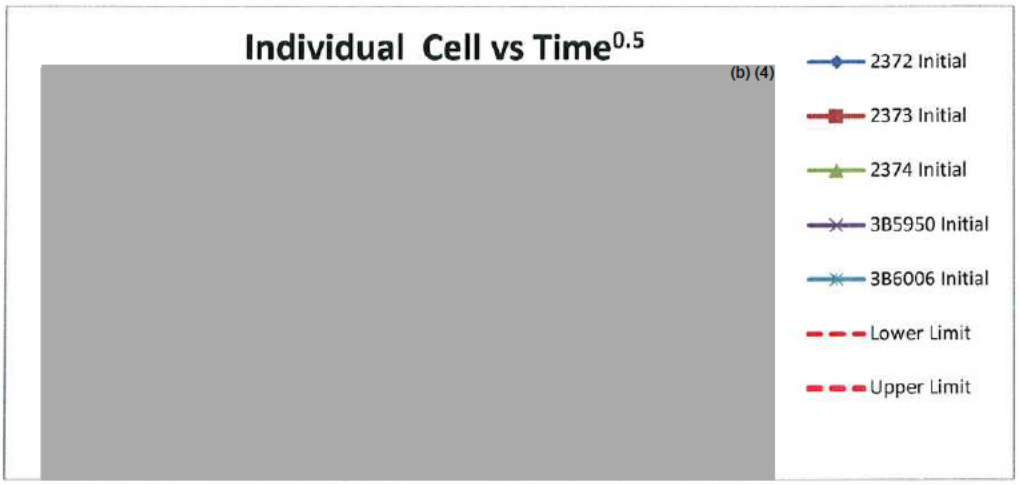
Trimel agrees to introduce the proposed *in vitro* release acceptance criteria as interim specifications. The *in vitro* specification will be re-assessed and revised if necessary based on *in vitro* release data collected from 10 batches via a PAS.

Table 1: Calculated Minimum (at 75%) and Maximum (at 133.33%) ranges for the mean amount released for TBS-1 Testosterone Nasal Gel 11.0mg/dose, batch 2372, 2373, 2374, 3B5950 and 3B6006

Actual Amount of Active Released ($\mu g/cm^2$) vs $Time^{0.5}$								
Amount of Active Released (µg/cm2)								
	2372	2373	2374	3B5950	3B6006	Mean of 5 pivotal batches	Minimum at 75% Mean	Minimum at 133.33% Mean
	Time 0	Time 0	Time 0	Time 0	Time 0			
√Times	Mean 1-6	Mean 1-6	Mean 1-6	Mean 1-6	Mean 1-6			
(b) (4)								
SLOPE								(b) (4)
r^2								

Reviewer's Note: "Time 0" is the initial release time point (0 months)

Figure 1: **Calculated Minimum (at 75%) and Maximum (at 133.33%) ranges for the amount released for TBS-1 Testosterone Nasal Gel 11.0 mg/dose, batch 2372, 2373, 2374, 3B5950 and 3B6006**



- Per the raw data submitted by the Applicant, the *in vitro* release rates (slopes) of the pivotal batches are summarized in the following table:

Testosterone Release Rates (slopes of amount released vs. √time) µg/cm²/hr^1/2	
Batch No.	**Mean Slopes (n=6)**
2372 (initial release)	(b) (4)
2372 (3 months 25°C/60% RH)	
2372 (6 months 25°C/60% RH)	
2372 (9 months 25°C/60% RH)	
2372 (12 months 25°C/60% RH)	
2372 (18 months 25°C/60% RH)	
2372 (3 months 40°C/75% RH)	
2372 (6 months 40°C/75% RH)	
2373 (initial release)	
2373 (3 months 25°C/60% RH)	
2373 (6 months 25°C/60% RH)	
2373 (9 months 25°C/60% RH)	
2373 (12 months 25°C/60% RH)	
2373 (18 months 25°C/60% RH)	
2373 (3 months 40°C/75% RH)	
2373 (6 months 40°C/75% RH)	
2374 (initial release)	
2374 (3 months 25°C/60% RH)	
2374 (6 months 25°C/60% RH)	
2374 (9 months 25°C/60% RH)	
2374 (12 months 25°C/60% RH)	
2374 (18 months 25°C/60% RH)	
2374 (3 months 40°C/75% RH)	
2374 (6 months 40 °C/75% RH)	

- The proposed *in vitro* release specification (range) is too liberal based on the submitted data. Therefore, the following IR was submitted to the Applicant on December 18, 2013:
    - *We believe your slope will be in the unit of µg/cm^2/min^{½}. Please verify and confirm. Change your in vitro release profiles in the submission (legends etc.) accordingly.*
    - *In the future, include the time points in correct units (minutes, hours, etc.), which are used in evaluating the in vitro release rates, in your datasets.*
    - *Your proposed in vitro release interim acceptance criterion (range) of* (b) (4) *is too liberal. Per the submitted data and based on our calculations, the Agency recommends the acceptance criterion (range) of* (b) (4) .
    - *Your proposed approach for setting the acceptance criterion per the SUPAC-SS Guidance is not appropriate. SUPAC-SS statistical approach is applicable to bridge semisolid products under different circumstances as described in the guidance, NOT to set up regulatory acceptance criterion.*
    - *Based on reanalysis of your submitted data, the Agency proposes the following 2-level Regulatory acceptance criteria for both at release and during stability:*
        - ***Level 1 (n = 6)***
          Each individual slope will fall within (b) (4)
        - ***Level 2 (n=12)***
          The average value of 12 slopes (L1 + L2) lies within the stated range (b) (4) *No individual value is outside of the stated range by more than* (b) (4) *% of the average stated range* (b) (4)

- On December 23, 2013, the Applicant submitted the following response to this IR via e-mail (formal response submitted on January 13, 2014):
    - Trimel can confirm that the unit for the product slope will be µg/cm^2/min^{½} and has revised the *in-vitro* release profiles accordingly to include the unit of µg/cm^2/min^{½}.
    - Trimel is not in agreement with the proposed specifications from the Agency. SUPAC-SS is the only guidance available to set appropriate acceptance criteria for this type of drug release test on a semi-solid product such as TBS-1. Trimel has proposed specifications based on the limited amount of data collected to date on the product and the guidance provided by SUPAC-SS. In reviewing the release and stability data from the submission batches, the specifications proposed by the Agency would lead to a significant amount of L2 testing as there are a number of individual profiles that do not meet the L1 criteria proposed by the Agency, these are summarized in the table below.

Sample	Time point/condition	Slope value
2373 (TBP-108)	(b) (4)	(b) (4)
2373 (TBP-108)		
2373 (TBP-108)		
2374 (TBP-109)		
2374 (TBP-109)		

Consistent with the data from the submission batches, Trimel is proposing an acceptance criterion (range) of (b) (4) and the following 2-level Regulatory acceptance criteria for both release and during stability:

- **Level 1 (n = 6)**
  Each individual slope will fall within (b) (4)
- **Level 2 (n = 12)**
  The average value of 12 slopes (L1 + L2) lies within the stated range (b) (4) No individual value is outside of the stated range by more than (b) (4) % of the average stated range (b) (4)

We trust that the Agency will find this proposal acceptable. Upon confirmation we will send the official submission which will include the revised *in-vitro* plots as requested.

- On January 16, 2014, a teleconference was held with the Applicant to discuss the proposed acceptance criteria. The following was agreed upon by the Biopharmaceutics team and the Applicant (formal response was submitted on January 23, 2014):
  - As agreed with your Biopharmaceutics team, the L1 and L2 acceptance criteria for both release and during stability testing for the Drug Release test are as follows:
    - *Level 1 (n = 6)*
      Each individual slope will fall within (b) (4)
    - *Level 2 (n = 12)*
      The average value of 12 slopes (L1 + L2) lies within the stated range (b) (4) *No individual value is outside of the stated range by more than* (b) (4) *% of the average stated range* (b) (4)

Based on future product performance understanding from data from more batches, we may have to change the *in-vitro* release acceptance criteria in future.

Reviewer's comments on the *in vitro* release acceptance criteria:

- The Applicant's proposed acceptance criteria are acceptable.
- The Applicant's approach to re-assess and revise the *in vitro* release acceptance criteria, if necessary, based on *in vitro* release data collected from 10 batches via a Post-Approval Supplement (PAS) is acceptable.

Recommendation:

Overall, the IVRT method and interim *in vitro* release acceptance criteria are acceptable for TBS-1 (testosterone nasal gel). From the Biopharmaceutics perspective, NDA 205488 for TBS-1 (testosterone nasal gel) is recommended for approval.

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/s/

KELLY M KITCHENS
04/02/2014

TAPASH K GHOSH
04/02/2014

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	The to-be-marketed formulation was used in the pivotal Phase 3 trial
2	Has the applicant provided metabolism and drug-drug interaction information?			x	Refers to distribution, metabolism, and excretion information publically available
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			All bioanalytical method validation reports and bioanaytical study (i.e., method performance) reports from 3 studies were submitted but the Sponsor still needs to submit the missing bioanalytical study reports for the remaining 6 clinical studies (pending).
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	Pediatric waiver submitted
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	Pediatric waiver submitted
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? ___Yes (pending)___

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- *Provide your justification and supporting information on your proposed titration method. Specifically, provide the information/your rationale on the following:*
  - *The selection of two sampling time points (i.e., 1 hour pre-dose and 20 minutes post-dose) and the use of its sum to titrate on Day 30.*
  - *The selection of a dose titration recommendation cutoff value (i.e., the sum of total testosterone in two blood samples) of 755 ng/dL.*
  - *The potential effect of deviations from the actual blood draw and its sampling time on the accuracy of C_{ave} prediction.*
  - *A Table with individual testosterone concentrations from the two blood samples including the actual sampling time (e.g., 1 hour pre-dose and 20 minutes post-dose), the sum of these two measurements used in the titration scheme, each patient's C_{ave} value on Days 30 and 90 (based on the 24-hour measurements), the testosterone dose that each patient was on Days 30 and 90, and the time within the normal testosterone range following Natesto™ (TBS-1) dose on Days 30 and 90.*
- *Submit the bioanalytical study (i.e., method performance) reports for all clinical studies.*
- *Incurred sample reanalysis (ISR) is recommended to evaluate the accuracy of the incurred samples analyzed. We note that ISR results were not included in your bioanayltical study reports. We request that you either submit existing lSR results or conduct ISR and submit the results to ensure the reliability of the data obtained in clinical studies.*
- *The following will be the review issues:*
  - *Effect of body mass index (BMI) on the systemic testosterone exposure*
  - *The dose titration scheme: selection of blood drawing time points, titration criteria (i.e., cutoff value), and the effect of deviations in sampling time on the accuracy of C_{ave} prediction.*
  - *Time within the normal testosterone range following Natesto™ (TBS-1) dose.*

Chongwoo Yu — 6/13/2013

Reviewing Clinical Pharmacologist — Date

Myong Jin Kim — 6/13/2013

Team Leader/Supervisor — Date

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Filing Memo

Clinical Pharmacology Review

NDA: 205488
Compound: Natesto™ (TBS-1; Testosterone [T] intranasal gel, 4.5%)
Sponsor: Trimel Biopharma SRL

Date: 6/13/2013
Reviewer: Chongwoo Yu, Ph.D.

Introduction:
Trimel Biopharma SRL submitted 505(b)(2) New Drug Application (NDA) 205488 for Natesto™ (TBS-1; T intranasal gel, 4.5%) on April 29, 2013 to seek an approval for the treatment of primary and hypogonadotropic hypogonadism associated with a deficiency or absence of endogenous T.

Natesto™ (TBS-1) contains 4.5% T for intranasal administration. Natesto™ (TBS-1) is for use in men with hypogonadism. The Sponsor proposes the following dosing and dose adjustment instructions:

The recommended starting dose of Natesto™ (TBS-1) is 2 actuations of 5.5 mg of T (1 actuation per nostril; (b) (4) (b) (4); 11 mg/dose) administered intranasally (b) (4) Natesto™ (TBS-1) should not be administered to other parts of the body including scrotum, penis, abdomen, shoulders, axilla, or upper arms.

Regulatory History
The following meetings were held between the Division of Bone, Reproductive and Urologic Products (DBRUP) and the Sponsor under IND 70512:

- Pre-IND meeting: October 18, 2004
- Type C, guidance meeting: March 22, 2006
- End of Phase 2 meeting: March 14, 2011
- Pre-NDA meeting: Face-to-face meeting request was denied but the Division's written responses to the Sponsor's questions were conveyed to the Sponsor on March 5, 2013

Clinical Development of Natesto™ (TBS-1)
The clinical development of Natesto™ (TBS-1) consists of 9 clinical studies including the pivotal Phase 3 study (Study TBS-1-2011-03) that provides the support for clinical efficacy and safety, the Phase 2 study (Study TBS-1-2010-01), and a Phase 1 drug-drug interaction (DDI) study (Study TBS-1-2011-04) to assess the relative bioavailability (BA), safety, and tolerance of Natesto™ (TBS-1) when administered to patients with seasonal allergic rhinitis in the symptomatic, symptomatic but treated, and asymptomatic states. Of the 9 clinical studies submitted, 4 studies (i.e., Studies TBS-1-2011-03, TBS-1-2010-01, TBS-1-2011-04, and TBS-1-2011-01) were conducted using the to-be-marketed (TBM) formulation. The submitted clinical studies are summarized in Table 1 below:

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Table 1: Summary of Clinical Studies Conducted with Natesto™ (TBS-1) in Men

Study/ Sites and Country/ Sponsor	Study Design	Number of Subjects Treated	Duration of Treatment	Formulation (%w/w)	Dose	Total Daily Dose	Subjects Per Treatment
Pivotal Study in Hypogonadal Men							
TBS-1-2011-03 39 centers in the US Trimel	Phase 3, open-label, randomized, 2-arm, parallel	306	90 days (all; efficacy) 180 days (all) 360 days (subset of 75 patients)	4.5%	11.0 mg BID 11.0 mg TID	22.0 mg 33.0 mg	(b) (4)
Other Studies in Hypogonadal Men							
TBS-1-2010-01 3 centers in the US Trimel	Phase 2, open-label, randomized, single-dose, 3-arm, parallel-group	22	7 days	4.0% 4.5% 4.5%	10.0 mg TID 13.5 mg BID 11.25 mg TID	30.0 mg 27.0 mg 33.75 mg	8 7 7
Nasobol-01-2009 6 centers in the US Trimel	Phase 2, open-label, randomized, 4-arm, 4 × 7-day period, crossover with no washout	57	7 days per period (28 days total)	3.2% 3.2% 3.2% Androderm® Patch	8.0 mg BID 11.0 mg BID 14.0 mg BID 5.0 mg QD	16.0 mg 22.0 mg 28.0 mg 5.0 mg	56 56 54 54
MAT/05 1 center in Romania Mattern	Phase 2, open-label, randomized, multiple-dose, 3-arm, parallel-group	21	14 days	3.2% 3.2% 3.2%	7.6 mg BID[b] 7.6 mg BID[b] 7.6 mg TID	15.2 mg 15.2 mg 22.8 mg	7 7 7
MAT/04 1 center in Romania Mattern	Phase 2, open-label, nonrandomized, single-dose, 3-arm, sequential, 3-period, with ≥3-day washout	8	1 day per period (3 days total)	3.2% 3.2% 3.2%	7.6 mg QD 15.2 mg QD 22.8 mg QD	7.6 mg 15.2 mg 22.8 mg	8 8 8
Nasobol-01-2008 1 center in the US Mattern	Phase 2, open-label, 14-day BID followed by 14 day QD, comparative PK in hypogonadal men vs untreated healthy men	16	28 days (14 days BID followed by 14 days QD)	3.2% 3.2% 3.2% *Healthy men:* No treatment	7.6 mg BID[c] 7.6 mg BID[c] 7.6 mg QD None	15.2 mg 15.2 mg 7.6 mg None	8 8 16 16
Study/ Sites and Country/ Sponsor	**Study Design**	**Number of Subjects Treated**	**Duration of Treatment**	**Formulation (%w/w)**	**Dose**	**Total Daily Dose**	**Subjects Per Treatment**
Studies in Healthy Men							
Comparing Methods of Administration							
TBS-1-2011-01 1 center in The Netherlands Trimel	Phase 1, open-label, randomized, 2-group, 2-treatment (multiple-dose dispenser vs syringe) crossover with 6-day washout[d]	12	1 day per treatment arm (2 days total)	4.5%	11.0 mg QD Syringe Dispenser	11.0 mg	 12 12
Men With Seasonal Allergic Rhinitis (Extrinsic Factor and Drug Interaction Study)							
TBS-1-2011-04 1 center in Germany Trimel	Phase 1, open-label, randomized, 3-group, 3-treatment states, 3-period, crossover with ≥4 day washout	18	1 day per treatment arm (3 days total)	4.5%	11.0 mg TID[e] 11.0 mg TID[e] 11.0 mg TID[e]	33.0 mg 33.0 mg 33.0 mg	18 15 17
Study Using TBS-1A Formulation							
TBS-1A-2011-01 1 center in The Netherlands Trimel	Phase 1, open-label, single-dose, 4-way, sequential 4-period, with 6-day washout	15	1 day per treatment arm (4 days total)	4.0% 4.0% TBS-1A 8.0% TBS-1A 4.0% TBS-1A (viscous)	10.0 mg QD 10.0 mg QD 10.0 mg QD 10.0 mg QD	10.0 mg 10.0 mg 10.0 mg 10.0 mg	15 15 15 15

Source: Study TBS-1-2011-03, Study TBS-1-2010-01, Study Nasobol-01-2009, Study MAT/05, Study MAT/04, Study TBS-1-2011-01, Study TBS-1-2011-04, Study Nasobol-01-2008, and Study TBS-1A-2011-01.

[a] Patients were randomized 3:1 to the BID and TID treatment arms. A total of 228 patients were randomized to BID treatment and 78 to TID treatment; (b) patients from BID treatment were titrated up to TID treatment on Day 45; (b) patients completed 90 days of BID treatment and (b) patients completed 90 days of TID treatment.

[b] Dosing times for the first and second 7.6-mg BID groups were 0800 and 1400, and 0800 and 2000, respectively.

[c] Dosing times for the first and second 7.6-mg BID groups were 0700 and 2400, and 0700 and 2200, respectively.

[d] PK samples for this study were drawn 12 hours after dose administration as defined in the protocol.

[e] Subjects in this study were adult men with seasonal allergic rhinitis who were asymptomatic due to the season and were otherwise healthy. Each subject was dosed in a crossover design as asymptomatic, symptomatic untreated, and symptomatic treated (see Module 2.7.2, Section 2.2).

%w/w=percent weight per weight; BID=twice daily; Mattern=Mattern Pharmaceuticals AG (original Sponsor of TBS-1); PK=pharmacokinetic; QD=once daily; TID=three times per day; Trimel=Trimel Biopharma SRL (current Sponsor of TBS-1); US=United States.

Pediatric Waiver Request

This NDA contains a pediatric waiver request. Sponsor states that hypogonadism is a disease that is not applicable to pediatric patients. The signs and symptoms occur in the adult population and there are too few children with the disease/condition to study.

Drug Product Formulation:

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The drug product, Natesto™ (TBS-1), is a viscous bioadhesive oil-based formulation containing solubilized T intended for intranasal application. Natesto™ (TBS-1) bulk gel is formulated with the following compendial inactive ingredients: castor oil, oleoyl polyoxylglycerides and colloidal silicon dioxide.

Table 2: Composition of the TBM Formulation of Natesto™ (TBS-1)

Component	Amount (% w/w)	Amount Delivered per Actuation (mg)	Amount Delivered per Dose (mg)	Quantity per Unit[a] (mg)	Function	Quality Standard
Testosterone	4.5%	5.5	11.0	(b) (4)	Active ingredient	USP
Castor oil					(b) (4)	USP
Oleoyl polyoxylglycerides						Ph. Eur./NF
Colloidal silicon dioxide						NF
Total						N/A

[a] Unit is the multiple dose dispenser

Absorption and 24-hr Average Serum T Concentrations

The maximum concentration for T following intranasal administration of Natesto™ (TBS-1) is achieved within 45 minutes of administration and has a half-life of approximately 10 hours. The efficacy and safety of Natesto™ (TBS-1) was evaluated in a multicenter, open-label, 90-day trial that enrolled 306 hypogonadal men at 39 clinical research centers in the US. During the initial Natesto™ (TBS-1) treatment period (Days 1-30), 228 patients were treated with 22 mg of T daily. On Day 45 of the trial, patients were maintained at the same dose or were titrated to three times a day, based on an assessment of 24-hour average serum T concentration (C_{avg}). The primary efficacy variable was the percentage of patients with a serum total T C_{avg} value within the normal range (i.e., 300-1050 ng/dL) on Day 90, with success being defined as ≥ 75% of patients on treatment within the normal serum T concentration range. At the end of the treatment period (Day 90), (b) (4) patients received 22 mg of T daily and 151 patients received 33 mg of T daily.

Of these patients (b) (4)% of those on 22 mg of T daily and 76% of those on 33 mg of T daily had C_{avg} within the normal range at Day 90. Of the (b) (4) patients who completed the 90-day treatment (b) (4) patients did so with no deviation from the protocol. Per Sponsor, (b) (4)% of those on 22 mg of T daily and 77% of those on 33 mg of T daily had C_{avg} within the normal T range at Day 90.

Distribution, Metabolism, and Excretion

No distribution, metabolism, and excretion studies were conducted using Natesto™ (TBS-1) and the Sponsor is proposing to use the available information to support this NDA.

Drug-Drug Interactions:

The effects of allergic rhinitis and the use of oxymetazoline on the absorption of T were investigated in a 3-way cross-over clinical study (i.e., Study TBS-1-2011-04). Eighteen (18) males who suffered from seasonal allergic rhinitis received 3 doses of 11 mg of T intranasally (33 mg/day) while they were in the asymptomatic, symptomatic, and symptomatic but treated (with oxymetazoline) states. Baseline (i.e., pre-dose concentration) corrected AUC_{0-24} and C_{avg} values for T in the symptomatic and the symptomatic but treated states demonstrated a decrease of 21% and 18%, respectively, as compared to the asymptomatic state. The Sponsor proposes the following statement under Section 7, Drug Interactions in the product label: "The relative decrease in bioavailability of TBS-1 in people with symptomatic seasonal rhinitis was neither ameliorated nor aggravated by the administration of the nasal decongestant, oxymetazoline."

Specific Populations and Waiver Request for Pediatrics:

- Pediatric use: No pediatric studies were conducted and pediatric waiver request was submitted

- Geriatric use: Sponsor did not stratify the studies to rule out whether efficacy and safety in those over 65 yr of age would differ from younger subjects. Of the 306 patients enrolled in the Phase 3 clinical study (Study TBS-1-2011-03) conducted using Natesto™ (TBS-1), 60 were 65 years of age or older, and 9 were 75 years of age or older. Additionally, there are insufficient long-term safety data in geriatric patients to assess the potential for increased risks of cardiovascular disease and prostate cancer.
- Renal or hepatic impairment: No studies were conducted in patients with renal or hepatic impairments
- Contraindicated for pregnant or breast feeding women
- Warnings and Precaution for children and women for secondary exposure

Bioanalytical Method Validation:
Serum samples were analyzed for total T, dihydrotestosterone (DHT), and estradiol (E2) using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods. The dynamic range for total T, DHT, and E2 were 0.5-50 ng/mL, 0.1-10 ng/mL, and 5-100 pg/mL, respectively. Bioanalyses were conducted at (b) (4) (b) (4) and (b) (4) All bioanalyses involving studies conducted with the TBM formulation of Natesto (TBS-1) (i.e., Studies TBS-1-2011-03, TBS-1-2010-01, TBS-1-2011-04, and TBS-1-2011-01) were conducted at (b) (4)

The Sponsor has submitted the bioanalytical method validation reports but has only submitted bioanalytical study reports for 3 studies (i.e., Studies TBS-1-2011-03, TBS-1-2011-04, and TBS-1-2010-01). Sponsor still needs to submit the bioanalytical study reports for 6 clinical studies. An information request (IR) has been sent to the Sponsor for the bioanalytical study reports. An Office of Scientific Investigations (OSI) consult requesting an inspection of the bioanalytical site of the pivotal Phase 3 study (Study TBS-1-2011-03) will be requested.

Recommendation:
The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Clinical Pharmacology section for NDA 205488 is fileable pending the submission of the missing bioanaytical study reports.

Comments for the Sponsor:

- *Provide your justification and supporting information on your proposed titration method. Specifically, provide the information/your rationale on the following:*
  - *The selection of two sampling time points (i.e., 1 hour pre-dose and 20 minutes post-dose) and the use of its sum to titrate on Day 30.*
  - *The selection of a dose titration recommendation cutoff value (i.e., the sum of total testosterone in two blood samples) of 755 ng/dL.*
  - *The potential effect of deviations from the actual blood draw and its sampling time on the accuracy of C_{ave} prediction.*
  - *A Table with individual testosterone concentrations from the two blood samples including the actual sampling time (e.g., 1 hour pre-dose and 20 minutes post-dose), the sum of these two measurements used in the titration scheme, each patient's C_{ave} value on Days 30 and 90 (based on the 24-hour measurements), the testosterone dose that each patient was on Days 30 and 90, and the time within the normal testosterone range following Natesto™ (TBS-1) dose on Days 30 and 90.*
- *Submit the bioanalytical study (i.e., method performance) reports for all clinical studies.*
- *Incurred sample reanalysis (ISR) is recommended to evaluate the accuracy of the incurred samples analyzed. We note that ISR results were not included in your bioanayltical study reports. We request that you either submit existing lSR results or conduct ISR and submit the results to ensure the reliability of the data obtained in clinical studies.*
- *The following will be the review issues:*
  - *Effect of body mass index (BMI) on the systemic testosterone exposure*
  - *The dose titration scheme: selection of blood drawing time points, titration criteria (i.e., cutoff value), and the effect of deviations in sampling time on the accuracy of C_{ave} prediction.*
  - *Time within the normal testosterone range following Natesto™ (TBS-1) dose.*

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**205488**	**Brand Name**	**Natesto™**
OCP Division	**DCP3**	**Generic Name**	**Testosterone**
Medical Division	**DBRUP**	**Drug Class**	**Steroid**
OCP Reviewer	**Chongwoo Yu, Ph.D**	**Indication(s)**	**Treatment of male hypogonadism**
OCP Team Leader	**Myong Jin Kim, Pharm.D.**	**Dosage Form**	**Gel, T 4.5% (11 mg/dsoe)**
Secondary Reviewer	**Myong Jin Kim, Pharm.D.**	**Dosing Regimen**	**Starting dose at 22 mg/day (11 mg BID)** (b) (4) [redacted]
Date of Submission	**April 29, 2013**	**Route of Administration**	**Transdermal**
Estimated Due Date of OCP Review	**December 29, 2013**	**Sponsor**	**Trimel BioPharma SRL**
PDUFA Due Date	**February 28, 2014**	**Priority Classification**	**Standard**
Division Due Date	**February 7, 2014**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	7 methods; 21 studies for 3 analytes		Methods: **10364, 10367**,101177, VP0246, VP0227
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		TBS-1A-2011-01
multiple dose:	X	1		**TBS-1-2011-01**
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	1		**TBS-1-2011-04**
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	NA			Pediatric waiver request
geriatrics:				
renal impairment:				
hepatic impairment:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
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PD:				
Phase 1:				
Phase 2:	X	5		**TBS-1-2010-01**, Nasobol-01-2009, MAT/05, MAT/04, Nasobol-01-2008
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X	1		**TBS-1-2011-03**
Population Analyses -				
PK:				
PD:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Immunogenicity profile				
Thorough QT study				
Literature References	X	40		
Total Number of Studies		70		

Other comments

	Comments
QBR questions (key issues to be considered)	1. Dose titration scheme 2. Acceptability of primary efficacy 3. Time within normal T range following Natesto™ (TBS-1) dose 4. OSI inspection on the bioanalytical site 5. Acceptability of bioanalytical method validation and performance
Other comments or information not included above	1. Sponsor needs to submit their justification and additional information on the proposed dose titration method. 2. Sponsor needs to submit the bioanalytical study (i.e., method performance) reports for all clinical studies. 3. Sponsor needs to submit ISR results. 4. A formal OSI consult on the bioanalytical study site will be requested.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHONGWOO YU
06/17/2013

MYONG JIN KIM
06/18/2013