

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205488Orig1s000

MEDICAL REVIEW(S)

Clinical Review
{Roger Wiederhorn MD }
{NDA 205488 }
{Natesto: Testosterone Nasal Gel 4.5%}

CLINICAL REVIEW

Application Type NDA
Application Number(s) 205488
Priority or Standard Standard

Submit Date(s) April 29, 2013
Received Date(s) April 29, 2013
PDUFA Goal Date May 28, 2014

Reviewer Name(s) Roger Wiederhorn MD
Review Completion Date May 20, 2014

Established Name Testosterone Nasal Gel
(Proposed) Trade Name Natesto
Therapeutic Class
Applicant Trimel BioPharma SRL

Formulation(s) Nasal Gel (4.5%)
Dosing Regimen
Indication(s) Testosterone replacement therapy in men with conditions associated with a deficiency in endogenous testosterone due to primary (congenital or acquired) or secondary hypogonadism (e.g, hypogonadotropic hypogonadism) in adult men.

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

It is recommended that NDA 205488 be **APPROVED**.

1.2 Risk Benefit Assessment

A thorough and comprehensive review of NDA 205488 was carried out. This NDA submission provided substantial evidence from an adequate Phase 3 (“pivotal”) study that TBS-1 given as two intranasal administrations per dose (5.5mg of testosterone in each nostril) three times daily (TID) (TID) is safe and effective treatment for replacement therapy in males with conditions associated with a deficiency or absence of endogenous testosterone:

- Primary hypogonadism (congenital or acquired)
- Hypogonadotropic hypogonadism (congenital or acquired)

Efficacy data demonstrates that the pre-determined primary study efficacy objective, the percentage of subjects with serum testosterone time-averaged concentration (Cavg) over the dosing interval of 24 hours within the normal range of 300-1000 ng/dL at Day 112, was achieved for the TID dose administration. In addition, the lower bound of the 95% CI was not to be <65% was also achieved.

Within pivotal Study TBS-1-2011-03 which includes a safety extension to 180 days (SE1) and a second safety extension to 360 days (SE2) and the Phase 2 studies, there was adequate exposure to TBS-1:

- Within the 12-week Phase 3 double-blind population 306 subjects were treated with 142 at the TBS-1 dose of 11 mg BID and 164 at the dose of 11 mg TID.
- Within the Phase 2 studies and the Phase 3 program, 511 subjects were exposed to any dose of TBS-1 (or a similar formulation referred to as “Nasobol”). The Phase 2 studies in hypogonadal men included TBS-1-2011-01, Nasobol-01-2009, MAT0/5, MAT 0/4 and Nasobol-01-2008. Exposures in the Phase 2 studies ranged from 1-28 days.
- Overall 30 healthy men and 306 hypogonadal men were exposed to the to-be-marketed drug at the 4.5% concentration. In all studies, cumulative exposure to TBS-1(4.5%) for hypogonadal men was 430 \geq 1 day, 247 \geq 6 months, 67 \geq 1 year. In the Phase 3 study, (b) (4) patients completed 90 days of BID TBS-1 and 152 patients completed 90 days of TID TBS-1. (b) (4) patients were up-titrated in Study TBS-1-2011-03 from BID TBS-1 to TID dosing at Day 45 of the study.

There were no deaths attributable to TBS-1 in the development program.

1.3 Recommendations for Postmarket Risk Management Activities

There are no recommendations for postmarket risk management activities.

1.4 Recommendations for Postmarket Studies/Clinical Trials

There are no recommendations for postmarket studies or clinical trials.

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2 Introduction and Regulatory Background

Testosterone (T), the active ingredient in TBS-1 is an endogenous androgen which, together with dihydrotestosterone, is responsible for normal growth and development of the male sex organs and the maintenance of secondary male sex characteristics, in addition to playing a role in numerous other normal physiologic and metabolic functions. Normal serum total testosterone concentrations in healthy males is approximately 300 to 1050 ng/dL.

Various administration routes are used in current testosterone replacement therapy include oral, transdermal, buccal, subcutaneous and intramuscular formulations, all of which have associated advantages and disadvantages. The inconvenience of the need for frequent physician visits, application site reactions, and concerns about secondary transfer are among the disadvantages that would be obviated by Natesto, a novel intranasal gel for T replacement.

2.1 Product Information

Testosterone 4.5% intranasal gel (TBS-1) is a bioadhesive testosterone gel for intranasal application proposed for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.

TBS-1 gel is a viscous and thixotropic, oil-based formulation containing testosterone. Three product formulations of TBS-1, containing 3.2%, 4.0%, or 4.5% testosterone, have been tested in clinical studies. The TBS-1 excipients are castor oil, oleoyl polyoxyglycerides, and colloidal silicon dioxide. None of these excipients are of human or animal origin. All excipients are well known and listed in the inactive ingredient list for approved drug products issued by the Food and Drug Administration. as been administered using unit-dose containers, syringes, and multiple-dose dispensers.

The product is provided as a multiple-dose dispenser that employs a finger-actuated dispensing system designed to dispense 5.5 mg of 4.5% intranasal gel per actuation from a non-pressurized container. The commercial dispenser is designed to deliver 30 doses (60 actuations) with an 11-g fill weight. The key components of the multiple-dose dispenser include a barrel, base, pump, piston and actuator, all composed of (b) (4). Each pump actuation dispenses 122.5 mg of drug product, containing 5.5 mg of testosterone.

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2.2 Table of Currently Available Treatment Options for Proposed Indications

Table 1: Currently Available Treatments for Male Primary Hypogonadism and Hypogonadotropic

Formulation	Regimen	Advantages	Disadvantages
Injectables, including T undecanoate, T enanthate, and cypionate	Every 2 weeks to 10 weeks via IM injection depending on formulation (50 mg to 750 mg)	Does not require daily administration.	Requires injections; Peaks and valleys in serum T levels; Pain at injection site; Mood Swings
T transdermal system	1 or 2 patches daily Dose 5-10 mg over 24h	Does not require injections; pK profile resembles diurnal rhythm	Skin site irritation
T gels	5-10g T gel containing 50-100 mg T daily	Does not require injection or patch; flexible dosing; ease of application; good skin tolerability	Potential skin transfer to partner or child
17- α -methyl T	oral tablets	Does not require injection or topical application	Potential liver toxicity
Buccal, bioadhesive T tablets	30 mg controlled release buccal tablet bid	Does not require injection or topical application	Gum-related adverse events
T pellets	4 to 6 200 mg pellets implanted sc	Infrequent dosing schedule	Requires incision to insert; Spontaneous extrusion/infection

Sources: Bhasin S, Cunningham G, et. al., 2006: Testosterone Therapy in Adult Men With Androgen Deficiency Syndromes: An Endocrine Society Clinical Practice Guideline: J of Clin Endocrin and Metab 9 (16): 1995-2010, Clinical Overview TBS-1 (current submission), Pages 7 and 8

2.3 Availability of Proposed Active Ingredient in the United States

Testosterone is readily available in the United States.

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2.4 Important Safety Issues With Consideration to Related Drugs

The important known potential safety issues with testosterone therapy include¹:

- Lipid Alterations
- Erythrocytosis
- Fluid Retention
- Benign Prostatic Hypertrophy
- Prostate Cancer
- Hepatotoxicity
- Sleep Apnea
- Gynecomastia
- Acne or oily skin
- Application site irritation
- Drug interactions: Application site moisturizer lotion or sunscreen, insulin, ACTH, oral anticoagulants, cyclosporine, paclitaxel
- Testicular atrophy or infertility
- Potential for transfer of testosterone by skin contact to partners and children.
- Supraphysiological testosterone levels.

It is not known currently whether testosterone replacement therapy is associated with an increase in serious cardiovascular adverse events. It is also not currently known whether TRT is associated with an increase in prostate cancer, whether in men with or without known prostate cancer.

Appropriate monitoring during testosterone replacement therapy includes: 1) Laboratory assessments of serum total testosterone, serum PSA, hematocrit, and serum lipids 2) Physical exam to include body weight, blood pressure, and rectal examination to assess the prostate. Voiding symptoms can be assessed by history or by the International Prostate Symptom Score (IPSS). A history of sleep apnea should be obtained at baseline.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

A pre-IND Meeting took place on October 18, 2004. On March 22, 2006, the Agency met with Sponsor for a Type C Guidance Meeting. A Type B, End-of-Phase, Teleconference took place on March 14, 2011. Agency Advice Information Requests were conveyed on March 23, 2010, October 31, 2011, September 24, 2012 and March 3, 2013. The key FDA:Sponsor interactions are summarized below:

- Sponsor proposed a single, open-label pivotal study (TBS-1-2011-03) with no comparator or placebo arm. The Division agreed with a single, 12 week, Phase 3 study (with safety extension) and “supportive evidence.” The study should include a 9-month safety extension period to include at least 200 patients treated for ≥ 6 months and at least 50 patients treated for at least ≥ 1 year. Sponsor was cautioned that lacking a placebo control, it will not be possible to determine the independent effect of intranasal TBS-1 on clinical efficacy endpoints. Incorporation of a placebo arm was recommended (October 31, 2011).
- Because the product is associated with a rapid rise and fall in serum testosterone after each dose, PK-based efficacy endpoints alone are not sufficient. Time within normal range

¹ Rhoden E L and Morgentaler A, 2004, Risks of Testosterone-Replacement Therapy and Recommendations for International Prostate Symptoms Score. Any history of sleep apnea should be obtained. Appropriate follow-up to assess changes in any of the above parameters. Monitoring. N Eng J Med; 350: 482-92

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(TWNR) will be incorporated into the analysis and clinical efficacy should demonstrate the adequacy of testosterone replacement with indices of sexual function, hematopoiesis, anthropomorphic evidence, etc (March 14, 2011, March 3, 2013).

- Subjects with intercurrent illnesses (eg, respiratory tract infection, allergic rhinitis) may be excluded (March 14, 2011), but Sponsor agreed to conduct an extrinsic factor and drug interaction study in men with allergic rhinitis. Subjects with asymptomatic seasonal allergic rhinitis will be included in the Phase 3 Study with guidance to Investigators regarding treatment of exacerbation of rhinitis during the study (March 14, 2011).
- Sponsor will enroll a population representative of a heavier U.S. patient population (BMI up to 35 kg/m²) (March 22, 2006)
- Ear, nose and throat (ENT) assessments will be performed for up to 1 year (March 14, 2011).
- Additional regulatory actions that occurred after the initial NDA submission:
 - The Sponsor originally proposed (b) (4) NATESTO (b) (4) 11 mg T two times daily (BID) dosing, (b) (4). However, the Division's analysis of (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 NDA 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.

2.6 Other Relevant Background Information

There is no other relevant background information.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission is of good quality and no concerns have been raised about the integrity of the processes that were used by Sponsor to generate this submission.

3.2 Compliance with Good Clinical Practices

The Sponsor appears to have been compliant with good clinical practices.

3.3 Financial Disclosures

Clinical Investigator Financial Disclosure Review Template

Application Number: 205488

Submission Date(s): April 29, 2013

Applicant: Trimel Pharmaceuticals

Product: Natesto

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Clinical Reviewers: Roger Wiederhorn, Medical Officer and Mark Hirsch, Medical Team Leader

Date of Review: May 5, 2014

Covered Clinical Study (Name and/or Number): TBS-1-2011-03

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>34</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u></p> <p>Significant payments of other sorts: <u>0</u></p> <p>Proprietary interest in the product tested held by investigator: <u>0</u></p> <p>Significant equity interest held by investigator in sponsor of covered study: <u>0</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.² Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)

² See [web address].

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- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

The applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in guidance for industry *Financial Disclosure by Clinical Investigators*. There are no investigators who are employees. There appears to be no lack of disclosure that would affect the approvability of the application.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Chemistry Review states “The applicant of this NDA has provided sufficient CMC information to assure the identity, strength, purity and quality of the drug product.”

4.2 Clinical Microbiology

Microbiology has stated that the submission is acceptable from a product quality microbiology standpoint. It is noted that the gel itself will not support microbial growth (April 10, 2014, Bryan Riley, New Drug Microbiology Staff). In addition, Microbiology concluded that “Wiping the actuator tip with a clean dry swab is reasonable to remove any residual gel that might congeal/dry and clog the applicator and also to remove any contamination (coming) from the patient’s nose” (the biggest source for contamination).

4.3 Preclinical Pharmacology/Toxicology

The Pharmacology/Toxicology review concludes, “The non clinical data support Approval of TBS-1 for the treatment of male hypogonadism.” It is noted that “ In the in vivo local tolerance studies in rats and rabbits and the 3 month repeat dose toxicity study in rabbits, animals were exposed to TBS-1 through the nasal mucosa, the same proposed route of administration for hypogonadal men. Administration of TBS-1 intranasal for three months at doses up to 6-fold the recommended human dose were not associated with any local or systemic toxicity in the organs examined: nasal turbinates, brain, testes, heart, kidneys, and lungs. Local tolerance studies using an ex vivo model and the nasal route of administration in rats and rabbits demonstrated that testosterone in combination with the excipients of the gel (castor oil, oleoyl polyoxylglycerides and colloidal silicon dioxide) was non-irritating.”

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Endogenous androgens, including testosterone and dihydrotestosterone (DHT), are responsible for the normal growth and development of the male sex organs and for the maintenance of secondary sex characteristics. Male hypogonadism is a clinical syndrome that results from insufficient secretion of

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testosterone and is characterized by low serum testosterone. Signs and symptoms that have been reported to be associated with male hypogonadism include erectile dysfunction, decreased sexual desire, fatigue, mood depression, regression of secondary sexual characteristics and osteoporosis.

4.4.2 Pharmacodynamics

While several clinical endpoints are measured in clinical trials (e.g., erectile function and libido questionnaires, mood profiles, body composition indices, and bone mineral density), there are no currently agreed upon pharmacodynamic primary endpoints for Phase 3 studies of testosterone replacement. Therefore, for this NDA and for all previous testosterone replacement applications, the primary efficacy endpoints are pharmacokinetic (i. e., the attainment of testosterone concentrations in the eugonadal range).

4.4.3 Pharmacokinetics

The often used normal reference range for serum testosterone (300 to 1050 ng/dL) was derived by taking the 95% confidence intervals from morning hormone levels measured in normal men between 20 and 65 years of age. Data have shown, according to the Sponsor, that testosterone levels in young eugonadal males are secreted in a pulsatile manner and follow a diurnal pattern. Serum testosterone levels peak in the early morning (approximately between 8 and 9 am) and show a nadir (<300 ng/dL) between 8 and 9 pm.

Intranasal administration of TBS-1 provides transient increases in serum testosterone levels. By carefully timed application of TBS-1, the Sponsor proposes that the normal physiological morning increase in serum testosterone that is seen in eugonadal men can be mimicked. After having reached its peak, the testosterone levels will start to decrease and will approach the lower limit of what is physiologically considered to be normal. While the precise reason for the dynamics of testosterone secretion is unknown, it is suggested that episodic testosterone secretion is required for the operation of the neuroendocrine axis governing testicular function. The Sponsor states that continuous, chronic exposure to testosterone might cause down-regulation of receptors and desensitization of target cells.

TBS-1 4.5% intranasal gel applied TID delivers physiologic amounts of testosterone that produces circulating testosterone concentrations that approximate normal levels (300-1000 ng/dL) seen in healthy men. These average concentrations levels are achieved with a large peak to trough difference. With TID dosing, the peak serum testosterone levels are achieved in approximately 45 minutes and nadir at approximately 6 hours after dosing

There is considerable variation in the half-life of testosterone as reported in the literature ranging from 10 to 100 minutes. Testosterone is metabolized to various 17-keto steroids through two different pathways. The two major metabolites of testosterone are dihydrotestosterone (DHT) and estradiol.

Dihydrotestosterone concentrations increased with increasing testosterone concentrations during during TBS-1 treatment and were within the normal range throughout treatment. The mean steady-state DHT/testosterone (DHT/T) ratio during 90 days of TBS-1 typically remained within normal limits. Following multiple dosing, mean estradiol concentrations were generally within the normal range for all doses tested.

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In regard to the metabolism of TBS-1 4.5%, the information on DHT and estradiol has been summarized above and additional details are shown in the body of this review. Previous studies have shown that about 90% of a dose of testosterone given intramuscularly is excreted in the urine as glucuronic and sulfuric acid conjugates of testosterone and its metabolites; about 6% of a dose is excreted in the feces, mostly in the unconjugated form. Inactivation of testosterone occurs mainly in the liver.

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 5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2: Tabular Listing All Clinical Studies NDA 205488

Type of Study	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Duration of Treatment	Number of Subjects	Healthy Subjects or Diagnosis of Patients
TBS-1-2011-03 Efficacy	Determine 24-hour C_{avg} of serum total testosterone following BID and TID administration; testosterone C_{max} ; serum DHT and serum estradiol; Effect of TBS-1 on body composition, bone mineral density, sexual function, and mood; and Safety	Phase 3, open-label, randomized, 2-arm, parallel	4.5% TBS-1 11.0 mg BID 11.0 mg TID Intranasal	90 days (all patients) 180 days (all patients) 360 days (subset of 75 patients)	280 planned; 306 randomized	Primary or Secondary Hypogonadism
TBS-1-2010-01 PK	Compare PK profile of testosterone and DHT following different doses and regimens of TBS-1; Safety	Phase 2, open-label, randomized, single-dose, 3-arm, parallel-group	4.0% TBS-1 4.5% TBS-1 10.0 mg TID 13.5 mg BID 11.25 mg TID Intranasal	7 days	22 planned; 22 randomized	Primary or Secondary Hypogonadism
Nasobol-01-2009 PK	Compare PK profile of testosterone and DHT following different doses of TBS-1; Safety	Phase 2, open-label, randomized, 4-arm, 4 × 7-day period, crossover with no washout	3.2% TBS-1 Androderm [®] Patch 8.0 mg BID 11.0 mg BID 14.0 mg BID 5.0 mg QD	7 days per period (28 days total)	40 planned; 57 randomized	Primary or Secondary Hypogonadism

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MAT/05 PK	Compare PK profile of testosterone following different doses and regimens of TBS-1 Safety	Phase 2, open-label, randomized, multiple-dose, 3-arm, parallel-group	3.2% TBS-1 Androderm Patch 7.6 mg BID 7.6 mg TID Intranasal	14 days	21 planned; 21 randomized	Primary or Secondary Hypogonadism
MAT/04 PK	Compare PK profile of testosterone following different doses of TBS-1; Safety	Phase 2, open-label, nonrandomized, single-dose, 3-arm, sequential, 3-period, with ≥ 3 -day washout	3.2% TBS-1 7.6 mg QD 15.2 mg QD 22.8 mg QD Intranasal	1 day per period (3 days total)	8 planned; 8 randomized	Primary or Secondary Hypogonadism
Nasobol-01-2008 PK	Compare PK profile of testosterone following different doses and regimen of TBS-1 to testosterone profile in healthy men-safety	Phase 2, open-label, 14-day BID followed by 14 day QD, comparative PK in hypogonadal men vs untreated healthy men	3.2% TBS-1 Healthy men: No treatment 7.6 mg BID 7.6 mg BID 7.6 mg QD	28 days (14 days BID followed by 14 days QD)	16 planned; 16 randomized	Primary or Secondary Hypogonadism and healthy men
TBS-1-2011-01 PK	Compare PK profile of testosterone following administration from a syringe vs multiple dose dispenser	Phase 1, open-label, randomized, 2-group, 2-treatment (crossover with 6-day washout)	4.5% TBS-1 11.0 mg QD Intranasal – syringe vs multiple dose dispenser	1 day per treatment period (2 days total)	12 planned; 12 randomized	Healthy subjects
Extrinsic Factor and Drug Interaction Study	TBS-1-2011-04	Phase 1, open-label, Randomized, 3-group, 3-treatment States, 3-period, crossover with \geq day washout	4.5% TBS 11.0 mg TID Intranasal	1 day per Treatment Period (3 days Total)	18 planned; 18 randomized	Healthy Subjects with seasonal allergies

Source: Table 1: Tabular Listing of Clinical Studies, Page 1 Section 5.2 of Clinical Study Reports

5.2 Review Strategy

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Study TBS-1-2011-03 was, by prior agreement, the single Phase 3 “pivotal” efficacy study. For this study, the results of the total testosterone pharmacokinetic variables, C_{av} and C_{max} , were rigorously analyzed. The major emphasis for safety evaluation of TBS-1 was placed on the safety data from the Phase 3 Study TBS-1-2011-03. Additional safety data was derived from studies TBS-1-2010-01, Nasobol-01-2009, MAT/05, MAT/04, Nasobol 01-2008, TBS-1-2011-01, TBS-1-2011-04 and TBS-1A-2011-01. These studies were the basis of analysis for the Integrated Summary of Safety. The pharmacokinetic variables were separately and jointly reviewed by the Clinical Pharmacology, Biometrics and Clinical disciplines.

The 120 Day Safety-Update, containing the additional safety data from the Phase 3 study TBS-1-2011-03 was received and the data from that Amendment was incorporated into this NDA review.

For this application, particular attention was directed to three issues: 1) With the lack of a placebo and/or a comparator arm, and with the rapid rise and fall in serum testosterone associated with Natesto, analysis of secondary pharmacodynamics (clinical) endpoints was undertaken to assess the changes from baseline in clinical parameters that might suggest adequate testosterone replacement. 2) ENT assessments, and 3) the decrease in exposure when allergic rhinitis occurs or when sympathomimetic drugs are used to treat allergic rhinitis.

The Sponsor is aware of these concerns and has incorporated analysis of these issues into this NDA review to address them.

5.3 Discussion of Individual Studies/Clinical Trials

TBS-1 intranasal testosterone gel has been administered in a total of 9 clinical studies in men. The summary of clinical safety includes safety data for all 9 studies. In the 8 studies other than the pivotal Phase 3 Study TBS-1-2011-03, all had pharmacokinetics (PK) of serum testosterone as their primary endpoint. Five of these studies were in hypogonadal men and 3 studies were in healthy men (of which 1 study was in otherwise healthy men with allergic rhinitis (TBS-1-2011-04). Two studies, while presented in the summary of clinical safety, will not be discussed. They are:

- Study Nasobol-01-2008 analyzed serum testosterone data; however, the analyses were not completed.
- Study TBS-1A-2011-01 was conducted with a development formulation of testosterone intranasal gel that is not the proposed commercial product.

5.3.1 Study TBS-1-2011-03

This “pivotal” Phase 3 study is discussed in the APPENDIX to this NDA Review

5.3.2 Study Nasobol-01-2009

Study Nasobol-01-2009 was a Phase 2, open-label, 4-period crossover study in hypogonadal men with 4 different drug administration schemes: 3 different doses of TBS-1 and an active control arm using the Androderm® 5 mg patch. All patients were randomized to 1 of the 4 treatment groups defining their treatment sequence to receive each of the 3 doses of TBS-1: 8.0 mg BID (total daily dose=16.0 mg), 11.0 mg BID (total daily dose=22.0 mg), and 14.0 mg BID (total daily dose=28.0 mg), and Androderm once per day delivering 5.0 mg/24 hours. Depending on their assigned treatment

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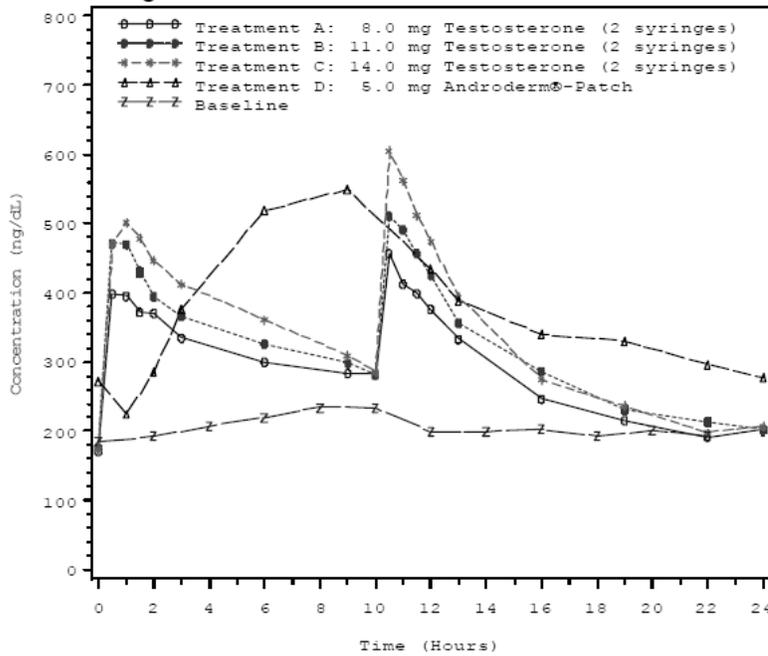
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group, patients administered TBS-1 at 0700 and 2100 hours or applied the Androderm patch at 2100 hours during 7 days for each of the 4 treatment periods. A total of 18 blood samples for the testosterone 24-hour PK analyses were taken for TBS-1 BID doses after the 2100 dose and 12 samples for Androderm taken after the evening application of the patch. Twenty-four-hour PK of serum DHT and estradiol were also analyzed following 7 days of treatment. Inclusion criteria included men between 18 and 80 years; men with primary or secondary hypogonadism with a morning (0900 hour \pm 30 minutes) serum testosterone levels >100 and ≤ 300 ng/dL using samples drawn at least 1 week apart, with the second level drawn just prior to enrollment; body mass index (BMI) between 18.5 and 35 kg/m²; hemoglobin levels ≥ 13.0 g/dL; normal otolaryngological nasal endoscopy examination; normal prostate examination result (no palpable prostatic mass); and serum PSA ≤ 4.0 ng/mL. The study was conducted at 6 centers in the US.

Patients were mostly White (93%) and with a mean age of approximately 52 years (range 20 to 75 years). The PK population consisted of 56 of the 57 patients in the study. These 56 patients completed at least 1 period of the study and had sufficient serum concentration data to calculate the PK parameters. Serum testosterone levels showed increases above baseline, and nonlinear increases in area under the serum concentration-time curve from 0 to 24 hours postdose (AUC_{0-24}) with increasing doses administered. The serum testosterone PK profile with TBS-1 was different from that observed with Androderm; the clearance of serum testosterone was different following evening administration of testosterone compared to the morning administration. This difference is likely the result of endogenous testosterone production, which is elevated in the early morning hours.

Figure 1: Mean Serum Testosterone Concentration Over a 24-hour Dosing Period on Day 7 of TBS-1 Administration in Hypogonadal Men Study Nasobol-01-2009



Source: Study Nasobol-01-2009 CSR, Figure 3

Table 3: Mean (SD) Testosterone PK Parameters Following 7 Days of TBS-1 or Androderm Administration in Hypogonadal Men Study Nasobol-01-2009

PK Parameter	Testosterone Treatment			
	TBS-1			Androderm® Patch
	8.0 mg BID (n=56)	11.0 mg BID (n=56)	14.0 mg BID (n=54)	5.0 mg QD (n=54)
AUC _{0-t} (h*ng/dL)	6890.34 (1834.11)	7599.00 (2134.38)	8066.59 (2418.18)	9230.82 (2471.32)
C _{avg} (ng/dL)	287.10 (76.42)	316.64 (88.93)	336.11 (100.76)	384.62 (102.97)
C _{max} (ng/dL)	557.6 (213.7)	643.9 (224.1)	736.8 (253.1)	621.4 (276.6)
C _{min} (ng/dL)	203.2 (151.4)	202.0 (102.2)	206.8 (96.3)	277.2 (120.6)
t _{max} (h) ^a	10.50	10.00	10.50	9.00

Source: Study Nasobol-01-2009 CSR, Tables 14.2.1.5 through 14.2.1.8.

^a Median.

AUC_{0-t}=area under the serum concentration-time curve from 0 to t hours; 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; QD=once daily; SD=standard deviation; t_{max}=time of maximum concentration.

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The percentage of patients with average serum testosterone concentrations (C_{avg}) within the normal reference range was 36.5%, 49.1%, and 51.9% following TBS-1 8 mg BID, 11 mg BID and 14 mg BID, respectively.

Table 4: Percentage of Patients with Testosterone C_{avg} Within the Normal Range Following 7 Days of TBS-1 Administration in Hypogonadal Men Study Nasobol-01-2009

PK Parameter	TBS-1 Dose		
	8.0 mg BID (n=56)	11.0 mg BID (n=56)	14.0 mg BID (n=54)
% Patients within the normal range (n)	36.5% (19)	49.1% (27)	51.9% (27)
% Patients below the normal range (n)	63.5% (33)	50.9% (28)	48.1% (25)
% Patients above the normal range (n)	0	0	0

Source: Study Nasobol-01-2009 CSR, Table 6

All 3 TBS-1 treatments increased mean serum DHT levels well above mean baseline levels and into the DHT normal range (25.5 to 97.8 ng/dL).

Table 5: Mean (SD) DHT PK Parameters Following 7 Days of TBS-1 Administration in Hypogonadal Men Study Nasobol-01-2009

PK Parameter	TBS-1 Dose		
	8.0 mg BID (n=52)	11.0 mg BID (n=55)	14.0 mg BID (n=52)
AUC _{0-t} (h*ng/dL)	605.65 (204.30)	695.17 (273.90)	738.91 (300.03)
C_{avg} (ng/dL)	25.24 (8.51)	28.97 (11.41)	30.79 (12.50)
C_{max} (ng/dL)	37.02 (15.07)	42.66 (17.99)	48.65 (20.14)
C_{min} (ng/dL)	19.78 (7.74)	22.29 (10.42)	23.25 (10.71)
t_{max} (h) ^a	11.0	10.83	10.58

Source: Study Nasobol-01-2009 CSR, Tables 14.2.2.5 through 14.2.2.8.

For all 3 TBS-1 treatments, the percentage of patients with total testosterone C_{avg} within the normal range was lower than the 75% considered by FDA to demonstrate efficacy. Overall, the 14.0-mg BID dosage of the 3.2% TBS-1 gel administered as 222 μ L BID at 0700 and 2100 hours for a total daily dose of 28.0 mg was efficacious in restoring testosterone to normal levels in 52% of patients. A linear increase in serum testosterone concentration was not achieved with escalating doses (percentage of patients with C_{avg} values within the normal range following administration for 14.0, 11.0, and 8.0 mg BID was 51.9%, 49.1%, and 36.5%, respectively). The lack of linearity suggested to the Sponsor that higher testosterone absorption was limited by the inability of the nasal cavity to hold the highest dose volume of TBS-1 (222 μ L).

Reviewer's Comment: This dose finding study led the Sponsor to conclude that based upon the limited ability of the nasal cavity to hold high volumes of TBS-1, that an increase in

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testosterone concentration in the drug product was warranted. The testosterone concentration in the Nasobol used in this study was 3.2%.

5.3.3 Study TBS-1-2010-01

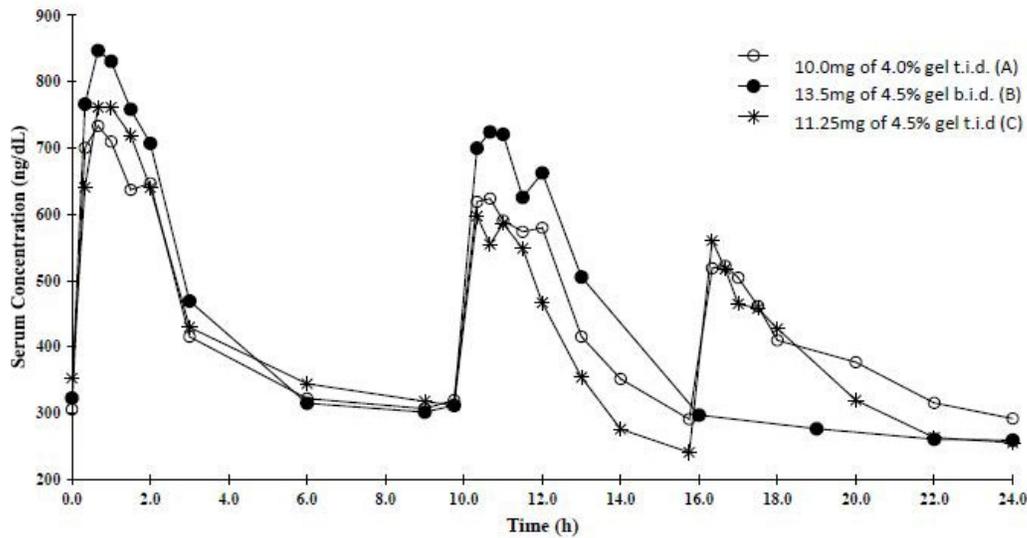
Study TBS-1-2010-01 was a Phase 2, open-label, randomized, parallel-group PK study to determine the absorption of testosterone after administration of 3 different doses of TBS-1 (10.0 mg TID [total daily dose=30.0 mg], 13.5 mg BID [total daily dose=27.0 mg], and 11.25 mg TID [total daily dose=33.75 mg]) for 7 days in hypogonadal men. The investigational product in this study was 4.5% TBS intranasal testosterone gel. The absorption of testosterone was evaluated from the 24-hour testosterone PK profile on Day 7 of daily treatment. Timing of blood draws for testosterone PK determination is listed in Table 16. A total of 20 blood samples were taken following BID treatment, and 26 samples following TID treatment. Twenty-four-hour DHT and estradiol PK were also assessed after 7 days.

Inclusion criteria included men with primary or secondary hypogonadism and a morning serum testosterone level of >100 and ≤ 300 ng/dL in Study Nasobol-01-2009 who demonstrated response to testosterone therapy; a normal otorhinolaryngological nasal endoscopy examination; a normal prostate examination; and a serum prostate specific antigen (PSA) ≤ 4.0 ng/mL. The study was conducted at 3 centers in the US.

Data from 22 patients were included in the PK analysis. The mean age of patients was approximately 53 years (range 35 to 73 years). A similar number of patients received each treatment: 8 patients received 10.0 mg TID, 7 patients received 13.5 mg BID, and 7 patients received 11.25 mg TID.

All 3 TBS-1 treatments showed increases in serum testosterone levels above baseline. The 24-hour average observed concentration (C_{avg}) testosterone level from all the treatment groups met the FDA acceptance criteria for standard testosterone replacement products of at least 75% of patients with C_{avg} in the normal range (a 24-hour C_{avg} value 300 to 1050 ng/dL); 86% to 88% of the patients in each group had C_{avg} within the normal range. Ninety-one percent of patients had a serum testosterone maximum observed concentration (C_{max}) below 1500 ng/dL, and no patients had a C_{max} greater than 1800 ng/dL.

Figure 2: Mean Serum Testosterone Concentration Over a 24-hour Dosing Period on Day 7 of TBS-1 Administration in Hypogonadal Men 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 Testosterone PK Parameters Following 7 Days of TBS-1 Administration in Hypogonadal Men 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.

AUC₀₋₂₄ =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.

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The normal range for DHT is 25.5 to 97.8 ng/dL. Approximately 86% of patients receiving 13.5 mg BID and 11.25 mg TID and approximately 63% of patients receiving 10.0 mg TID had DHT levels within the normal range. No subject had a DHT C_{avg} above the normal range, while approximately 38% of patients receiving 10.0 mg TID and approximately 14% of patients receiving 13.5 mg BID and 11.25 mg TID had a DHT C_{avg} below the normal range.

The normal range for estradiol is 3 to 81 pg/mL. All patients had a C_{avg} estradiol within the normal range.

The relevant clinical guidelines for efficacy of testosterone replacement products of at least 75% of patients achieving a 24-hour C_{avg} value in the normal range (300 to 1050 ng/dL testosterone) was met for all 3 TBS-1 treatments in this study: 10.0 mg TID, 13.5 mg BID, and 11.25 mg TID.

Reviewer's Comment: Using a higher testosterone concentration in the drug product than in Study Nasobol-01-2009, and a three times daily dosing regimen, the clinical efficacy guidelines for efficacy of testosterone replacement were met in this Phase 2 study.

5.2.4 Study TBS-1-2011-01

Study TBS-1-2011-01 was a Phase 1, randomized, crossover study in healthy men, conducted to evaluate the comparability of administration of TBS-1 from a multiple-dose dispenser (the proposed commercial method of administration) compared to administration from prefilled syringes (the method of administration used in several studies earlier in the TBS-1 development program). A 12 hour baseline testosterone profile was performed on each subject to determine their endogenous testosterone levels. PK parameter values were calculated using baseline-corrected serum testosterone concentrations (post-dose minus endogenous serum testosterone level). A total of 13 blood samples were collected for each subject. Treatment was administered at 2100 hours. All subjects were treated with TBS-1 using both the multiple-dose dispenser and prefilled syringes for administration. Administration using the 2 different methods was separated by a washout period of at least 6 days. Comparison of administration efficacy was evaluated from analysis of 12-hour baseline-corrected serum testosterone PK following administration of TBS-1 at 2100 hours. Baseline-corrected values were used for each subject as these corrected values account for endogenous testosterone in these healthy men and reflect the systemic testosterone from the intranasal gel.

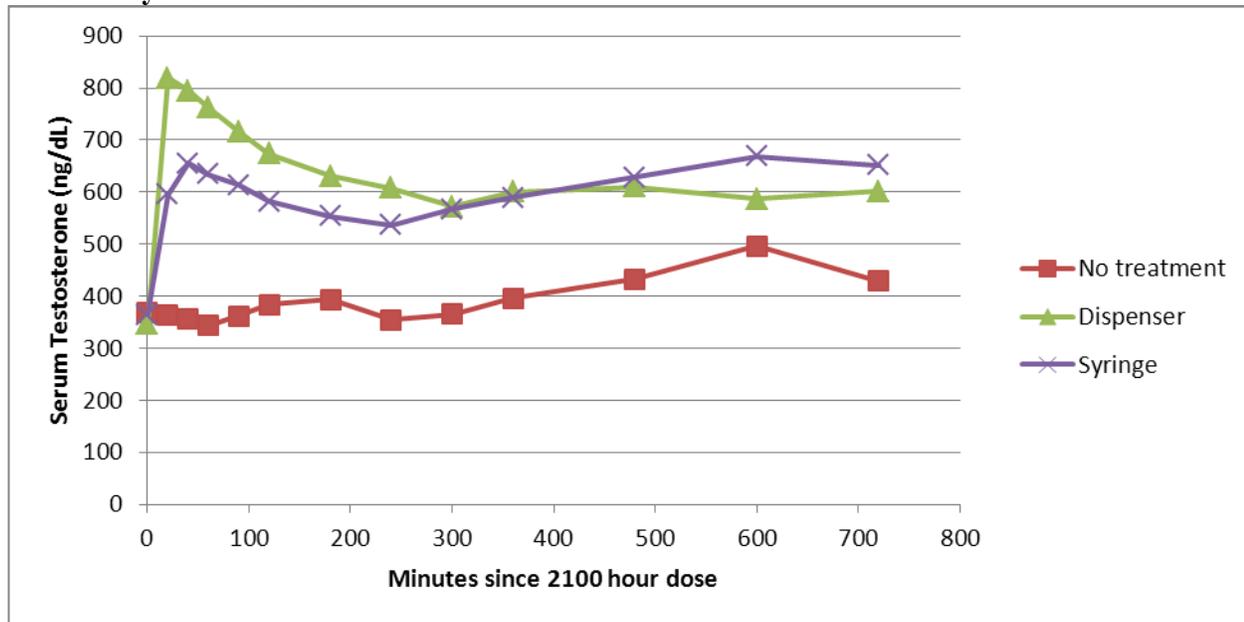
Inclusion criteria included healthy men with BMI ≤ 35 kg/m² and normal otorhinolaryngological examination. The study was conducted at the Centre for Human Drug Research in The Netherlands.

PK data are summarized for all 12 subjects who received TBS-1 in this study. The mean age of subjects was 23.4 years (range, 18 to 28 years).

All subjects were healthy men and had baseline-corrected testosterone levels within the normal range (300 to 1050 ng/dL) following administration of TBS-1 using both administration methods. The brown curve shows the 12 hour mean endogenous testosterone profile of the subjects. Their

testosterone profile shows the slow circadian fluctuations in testosterone levels expected in a young, healthy population, with the highest levels in the early morning (Figure 5).

Figure 3: Multiple-Dose Dispenser Versus Prefilled Syringe: Individual and Mean Baseline-Corrected Serum Testosterone Concentrations Following a Single Dose of TBS-1 in Healthy Men Study TBS-1-2011-01



Source: Study TBS-1-2011-01 Figure 5.

PK parameter values were calculated using baseline-corrected serum testosterone concentrations. The total exposure to testosterone, as estimated by the mean area under the serum concentration-time curve from 0 to 12 hours (AUC₀₋₁₂ in h*ng/dL), was higher after TBS-1 administration using the dispenser or syringe (Table 10) than endogenous levels alone (mean [standard deviation (SD)] of 7484 [1798] and 7266 [1360] h*ng/dL, respectively, versus 4911 h*ng/dL). The mean time after dose at which the maximum testosterone concentration occurred (time of maximum concentration [t_{max}]) was shorter following administration using the dispenser compared to the syringe (mean [SD] of 2.751 [3.961] versus 5.612 [4.736] hours, respectively).

Table 7: Testosterone PK Parameters Following a Single 11.0 mg Administration of TBS with Either a Multiple-dose Dispenser or a Prefilled Syringe Study TBS-1-2011-01

Parameter [SD]	Method of Administration	
	Multiple-Dose Dispenser (n=12)	Prefilled Syringe (n=12)
AUC0-12 (h*ng/dL) [SD]	7484 [1798]	7266 [1360]
tmax (h) [SD]	2.751 [3.961]	5.612 [4.736]
Cmax (ng/dL) [SD]	1028 [283.1]	778.8 [144.1]
Cmin (ng/dL) [SD]	337.9 [119.7]	355.9 [66.96]
Cmean (ng/dL) [SD]	623.6 [149.9]	605.4 [113.2]

Source: Study TBS-1-2011-01.

AUC0-12=area under the serum concentration-time curve from 0 to 12 hours; Cmax=maximum observed concentration; Cmean=mean concentration; Cmin=minimum observed concentration; n=number of subjects in the study; PK=pharmacokinetic; SD=standard deviation; tmax=time of maximum concentration.

The study conclusion was that the use of a multiple-dose dispenser is a feasible administration method compared to prefilled syringes. In this study, the multiple-dose dispenser demonstrated testosterone AUC0-12 values comparable to those with the prefilled syringe, while peak concentrations were higher after administration with the multiple-dose dispenser than after administration using a syringe. One possible explanation for this difference is the more accurate placement of gel in the nasal cavity with the dispenser. This does not, however, seem to lead to lower total absorption because the AUCs were comparable between the 2 methods of administration.

Reviewer's Comment: This study demonstrated that the use of a multiple-dose dispenser is a feasible administration method compared to prefilled syringes.

5.2.5 Study MAT/04

Study MAT/04 was a Phase 2, open-label, nonrandomized, sequential, 3-period, dose-ranging study in hypogonadal men to determine the testosterone 24-hour PK following administration of 3 different doses of TBS-1. The lowest dose administered in the study was 7.6 mg QD. In order to describe the single-dose PK at different doses, the recommended single dose was doubled (15.2 mg QD) and tripled (22.8 mg QD).

Therefore, patients each received a 7.6, 15.2, and 22.8mg QD TBS-1, sequentially ordered, with a washout period of at least 3 days between each treatment. Each subject received TBS-1 between 0700 and 0830 hours. A total of 20 blood samples were taken as listed in Table 16.

Inclusion criteria included men with serum testosterone levels <300 ng/dL as measured on 2 occasions; no androgen treatment within the 2 weeks prior to the study (oral, buccal, or topical), 4 weeks (intramuscular), or 12 months (implant) prior to the study; and normal otorhinolaryngological examination prior to the study. The study was conducted at 1 site in Romania.

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Data from 8 patients were included in the PK analyses. The mean age of patients in the study was approximately 39 years (range, 22 to 62 years).

Testosterone was well absorbed after intranasal administration of different doses of TBS-1. Absorption of testosterone as determined from AUC_{0-24} was seen to increase with dose, although the increase was not dose-proportional (mean AUC_{0-24} was 5591, 7563, and 7462 h*ng/dL for the 7.6, 15.2, and 22.8 mg QD doses, respectively). C_{max} also increased non-dose-proportionally, and the mean C_{max} at the highest dose (22.8 mg QD) did not exceed the upper limit of the normal testosterone range. The $t_{1/2}$ was approximately 10 hours (mean $t_{1/2}$ was 11.7, 8.19, and 10.5 hours for the 7.6, 15.2, and 22.8 mg QD doses, respectively).

Table 8: Testosterone PK Parameters Following a Single Dose of TBS-1 in Hypogonadal Men Study MAT/04

PK Parameter	Statistic	7.6 mg QD (n=8)	15.2 mg QD (n=8)	22.8 mg QD (n=8)
AUC_{0-24} (ng*h/dL)	Geometric mean	5591	7563	7462
	95% CI (lower limit, upper limit)	(3442, 9081)	(5479, 10440)	(4963, 11220)
C_{max} (ng/dL)	Geometric mean	739	925	952
	95% CI (lower limit, upper limit)	(593, 921)	(672, 1273)	(695, 1305)
t_{max} (h)	Mean (SD)	1.02 (0.759)	1.40 (0.943)	1.02 (0.68)
$t_{1/2}$ (h)	Mean (SD)	11.7 (7.18)	8.19 (5.03)	10.5 (5.43)

Source: Study MAT/04.

AUC_{0-24} =area under the serum concentration-time curve from 0 to 24 hours postdose; CI=confidence interval; C_{max} =maximum observed concentration; n=number of patients included in the PK Population; PK=pharmacokinetic; QD=once daily; SD=standard deviation; $t_{1/2}$ =elimination half-life; t_{max} =time of maximum concentration.

Testosterone was well and rapidly absorbed for all 3 of the doses administered. The PK results indicated that the relative bioavailability decreased with dose, the elimination of testosterone was not dependent on the dose administered, and the PK of testosterone after TBS-1 intranasal administration was not dose proportional. The 22.8-mg dose did not exceed the upper limit of normal.

Reviewer's Comment: Only a study synopsis is provided and I cannot specifically discern the testosterone concentration in this study, but in previous studies the concentration was 3.2%. If this study used a 3.2% formulation, then the results and conclusions do not add directly relevant information to evaluate the 4.5% product in this NDA. I presume the testosterone concentration is 3.2% in this study, the same as it was in the Study Nasobol-01-2009.

5.2.6 Study MAT/05

A study synopsis only is provided. Study MAT/05 was a Phase 2, randomized, open-label, multiple-dose, parallel-group, dose-finding study in hypogonadal men to evaluate the optimum dosage of TBS-1 among 3 different treatment schedules administered for 14 consecutive days: 7.6 mg BID at 0800 and 1400 hours (total daily dose=15.2 mg); 7.6 mg BID at 0800 and 2000 hours (total daily dose=15.2 mg); and 7.6 mg TID at 0800, 1400, and 2000 hours (total daily dose=22.8 mg).

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Efficacy was determined from the 24-hour serum testosterone PK profiles following 14 consecutive days of treatment. The Aging Males' Symptoms (AMS) questionnaire and Clinical Global Score (CGS) based on physician's evaluation using a visual analog score were also evaluated.

Inclusion criteria included men with serum testosterone levels <300 ng/dL as measured on 2 occasions; no androgen treatment within the 2 weeks prior to the study (oral, buccal, or topical), 4 weeks (intramuscular), or 12 months (implant) prior to the study; and normal otorhinolaryngological examination prior to the study. The study was conducted at 1 site in Romania. A total of 21 hypogonadal men with a mean age of approximately 33 years (range, 19 to 57 years) were randomized, 7 to each of the 3 treatment regimens.

Serum testosterone C_{avg} was within the normal range for both BID treatments and for the TID treatment, but the 95% CI was completely within the normal range only for TID administration. There were several individual C_{max} values that exceeded the upper limit of the normal range. The elimination half-life ($t_{1/2}$) under steady-state conditions was comparable to that estimated after single-dose administration. These results indicate that testosterone did not accumulate in the body. The percentage of patients with C_{avg} within the normal range was not calculated in this study.

Table 9: Testosterone PK Following 14 Days of TBS-1 Administration in Hypogonadal Men Study MAT/05

PK Parameter	Statistic	7.6 mg BID 0800 and 1400 hours (n=7)	7.6 mg BID 0800 and 2000 hours (n=7)	7.6 mg TID 0800, 1400, and 2000 hours (n=7)
AUC ₀₋₂₄ (ng*h/dL)	Mean (95% CI)	7545 (5785, 9840)	7846 (5206, 11 824)	11327 (7984, 16 071)
C_{avg} (ng/dL)	Mean (95% CI)	314 (236, 419)	327 (210, 509)	472 (323, 689)
C_{min} (ng/dL)	Mean (95% CI)	102 (55, 189)	157 (98, 251)	220 (116, 419)
C_{max} (ng/dL)	Mean (95% CI)	859 (632, 1167)	854 (465, 1570)	1137 (895, 1444)
$t_{1/2}$ (h)	Mean (SD)	14.29 (12.86)	8.74 (5.65)	11.92 (3.62)

Source: Study MAT/05.

AUC₀₋₂₄ =area under the serum concentration-time curve from 0 to 24 hours postdose; BID=twice daily; C_{avg} =average observed concentration; CI=confidence interval; 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; $t_{1/2}$ =elimination half-life.

All 3 TBS-1 dosing regimens showed increases in serum testosterone levels above baseline. The mean C_{avg} achieved the physiological range in all 3 treatment groups. The highest area under the serum concentration-time curve (AUC) was observed after TID administration. In each group, there was a single subject who had a C_{max} value that exceeded the upper limit of the normal range (1050 ng/dL).

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Reviewer's Comment: The results of this study are not directly relevant to Natesto, as drug product under investigation was Nasobol, a slightly different formulation. Nonetheless, the results suggest that BID intranasal dosing may not be sufficient.

5.2.7 Study TBS-1-2011-04

Study TBS-1-2011-04 was a randomized, crossover study conducted in healthy men who suffer from seasonal allergic rhinitis. Subjects received TBS-1 (4.5%) when they were asymptomatic, symptomatic and untreated, and symptomatic and treated with oxymetazoline nasal spray (a selective alpha-1 and partial alpha-2 adrenergic agonist [sympathomimetic] topical decongestant). The symptomatic state was induced by exposure to *Dactylis glomerata* pollen in an environmental challenge chamber (ECC). The symptomatic state was defined by a positive case history, a positive skin prick and/or intradermal test for *Dactylis glomerata* pollen allergen, a Total Nasal Symptom Score (TNSS) of $\geq 6/12$, and a congestion score of $\geq 2/3$.

The objectives of the study were (1) to evaluate whether intranasal application of testosterone is a reliable route of administration during naturally occurring nasal inflammation, such as allergic rhinitis; and (2) to investigate the potential interaction of TBS-1 with the common over-the-counter nasal decongestant spray, oxymetazoline [Nasivin®], in the presence of swelling of the nasal mucosa, as it occurs during allergic rhinitis. Absorption of testosterone and drug interaction was assessed from the relative bioavailability of baseline-corrected serum testosterone concentrations and determination of bioequivalence using threshold values for bioequivalence of 0.8 to 1.25. If the 90% CI for the ratio point estimates of AUC_{0-24} , C_{max} , and C_{avg} was contained within the 80% to 125% range (0.80 to 1.25), then bioequivalence would be inferred, as indicated in the EMEA's 2010 Guideline on the Investigation of Bioequivalence.

Subjects each received TBS-1 11.0 mg TID for 1 day, while in each of the 3 treatment states: the asymptomatic state, the symptomatic and untreated state, and the symptomatic and treated with oxymetazoline state. TBS-1 doses were administered at 0700, 1300, and 2100 hours.

Prior to randomization, a 24-hour total serum testosterone profile was collected from all subjects while in the ECC. Subjects were randomized to 3 groups and treatments were administered in 3 dose sequences (Table 11). Treatment 1, 2, or 3 was allocated according to the predefined state of symptoms (Treatment 1: symptomatic and untreated state; Treatment 2: symptomatic and treated state; and Treatment 3: asymptomatic state). Treatment periods were separated by a 4-day washout period.

Table 10: TBS-1 Treatment Dose Sequences in Study TBS-1-2011-04

Sequence	PERIOD I Visit 3	PERIOD II Visit 4	PERIOD III Visit 5
Group A	Treatment 1 ^a	Treatment 2 ^a	Treatment 3 ^b
Group B	Treatment 2 ^a	Treatment 3 ^b	Treatment 1 ^a
Group C	Treatment 3 ^b	Treatment 1 ^a	Treatment 2 ^a

Source: Study TBS-1-2011-04 CSR, Table 1.

^a Subjects in the symptomatic state (Treatment 1) and symptomatic but treated state (Treatment 2) had to get up between 0240 and 0315 to enter the pollen chamber between 0420 and 0445.

^b Subjects in the asymptomatic state (Treatment 3) had to get up at between 0530 and 0600, as no “priming” in the environmental challenge chamber was required.

Symptomatic state subjects completed diary cards every 15 minutes for 4 hours showing at least 6/12 for TNSS and 2/3 for the congestion score on at least 1 of the 4 diary cards within the 2 hours prior to the 0700 hour dose. In the symptomatic and treated state, subjects were treated with oxymetazoline 30 minutes prior to the 0700 hour dose and were treated with oxymetazoline again 12 hours after the first administration.

Absorption of testosterone and any drug interaction was evaluated from 24-hour baseline-corrected serum testosterone PK parameters. Blood samples were drawn after the 2100 dose administration. A total of 26 blood samples were taken.

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 (ie, count and percentages). All baseline-corrected PK parameters were tested regarding bioequivalence by analysis of variance.

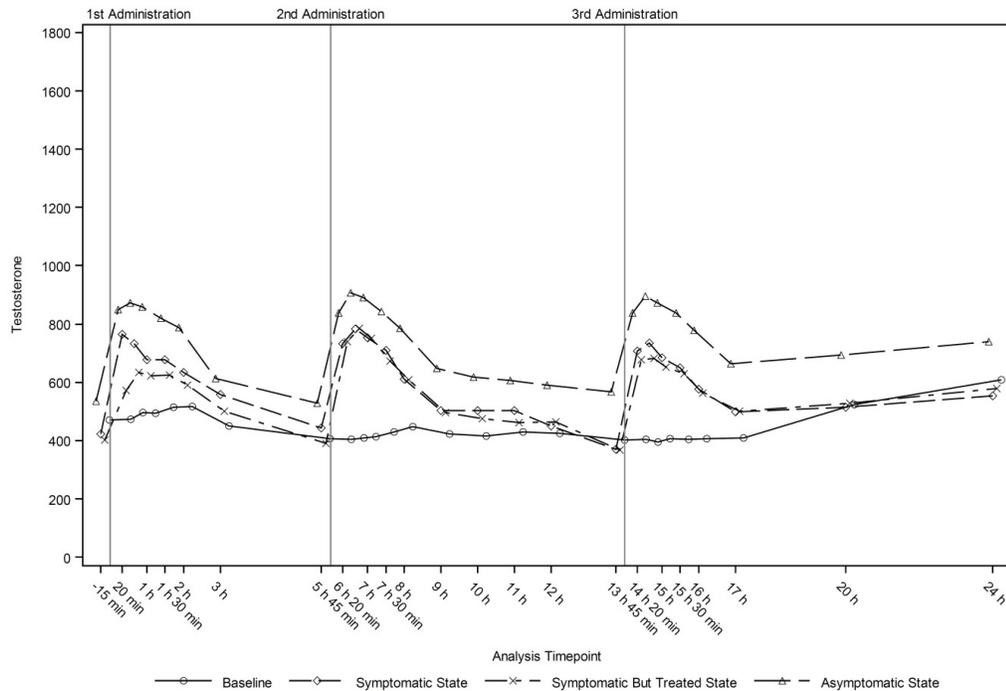
The study was conducted at a single site, the Fraunhofer Institute for Toxicology and Experimental Medicine in Germany.

The number of subjects completing each of the 3 treatment states was: asymptomatic (N=18), symptomatic but treated (N=17), and symptomatic untreated (N=15). The subjects were aged between 27 and 44 years. Fourteen subjects had pharmacokinetically evaluable profiles for all treatment periods and were included in the PK and the bioequivalence analysis.

According to Sponsor, neither sequence nor period of treatment had an effect on serum testosterone levels; therefore, data were pooled from the 3 different sequence groups for each treatment state.

Mean baseline levels of testosterone fluctuated between 403 and 608 ng/dL before reaching their peak 24 hours after the 0700 hour as expected in the normal diurnal dynamics of testosterone levels in healthy young men. After each administration of TBS-1 at t=0, t=6, and t=14 hours, serum testosterone levels increased for subjects in all treatment states, so that 3 peaks occurred within the observation time of 24 hours (see Figure below).

Figure 4: Mean Serum Testosterone Concentration versus Time Curve Following a Single Dose of TBS-1 in Healthy Men with Seasonal Allergic Rhinitis, by Treatment State (n=14) Study TBS-1-2011-04



Source: Study TBS-1-2011-04 CSR, Figure 1.

The testosterone exposure as estimated by the mean baseline-corrected AUC_{0-24} was higher for subjects in the asymptomatic state than for the symptomatic and untreated and the symptomatic and treated states (mean [SD] of 5797.1 [2643.1], 2267.5 [2172.6], and 1828.4[1889.1]h*g/d/L [1889.1]h*g/dL, respectively).

The difference in baseline-corrected AUC_{0-24} between the symptomatic and untreated and the symptomatic and treated states was small, indicating that administration of oxymetazoline did not relevantly affect the absorption of TBS-1 by the Sponsor's analysis.

Table 11: Baseline-Corrected Testosterone 24-hour PK in Healthy Men with Seasonal Allergic Rhinitis, by Treatment State (n=14) Study TBS-1-2011-04

PK Parameter	Treatment Condition ^a	Mean (SD)	CV%
AUC (h*ng/dL)	Asymptomatic	5797.1 (2643.1)	45.6
	Symptomatic and Untreated	2267.5 (2172.6)	95.8
	Symptomatic and Treated	1828.4 (1889.1)	103.3
C _{avg} (ng/dL)	Asymptomatic	239.1 (112.7)	47.2
	Symptomatic and Untreated	92.8 (91.6)	98.8
	Symptomatic and Treated	75.7 (79.1)	104.5
C _{max} (ng/dL)	Asymptomatic	431.8 (147.2)	34.1
	Symptomatic and Untreated	278.5 (163.3)	58.6
	Symptomatic and Treated	240.6 (211.6)	88.0
C _{min} (ng/dL)	Asymptomatic	468.1 (93.7)	20.0
	Symptomatic and Untreated	344.4 (114.0)	33.1
	Symptomatic and Treated	345.1 (92.6)	26.8

Source: Study TBS-1-2011-04 CSR, Table 12.

^a Asymptomatic=state at study enrollment; Symptomatic=state after pollen challenge in ECC; Symptomatic and Treated=state after pollen challenge in ECC and treatment with oxymetazoline.

AUC=area under the serum concentration-time curve; C_{avg}=average observed concentration; C_{max}=maximum observed concentration; C_{min}=minimum observed concentration; CV%=coefficient of variation; ECC=environmental challenge chamber; n=number of subjects included in the PK Population; PK=pharmacokinetic; SD=standard deviation.

Bioequivalence of baseline-corrected serum testosterone was evaluated for all pairs of the 3 treatment states (asymptomatic, symptomatic and untreated, and symptomatic and treated with the decongestant nasal spray, oxymetazoline). Bioequivalence was assumed if the CIs of the ratio point estimates were contained within the 80% to 125% range (0.80 to 1.25). The point estimates (ratio of central value of Treatment 1 to central value of Treatment 2) for the baseline-corrected values of AUC₀₋₂₄, C_{avg}, and C_{max} and the respective CIs are presented in the table below.

The Sponsor concludes that bioequivalence was not demonstrated between the asymptomatic and the symptomatic and untreated states and between the asymptomatic and the symptomatic and treated states. The high values for the point estimate indicate that the bioavailability of intranasally administered TBS-1 was reduced during the symptomatic treatment state, and this effect was not ameliorated by the administration of oxymetazoline.

A comparison of the baseline-corrected AUC₀₋₂₄ between the symptomatic and untreated and the symptomatic and treated states revealed that these 2 treatment conditions were not bioequivalent. However, given that the point estimates were close to 1 (1.0903), the failure to show bioequivalence may be due to large interindividual variations. These large variations led to wide CIs, which exceed the threshold values for bioequivalence of 0.8 to 1.25.

Table 12: Bioequivalence of Baseline-Corrected Testosterone PK in Healthy Men with Seasonal Allergic Rhinitis, by Treatment State Study TBS-1-2011-04 (n=14)

Treatment States Tested ^a	PK Parameter ^b	Point Estimate ^c	90% CI	
			LL	UL
Asymptomatic vs symptomatic	AUC ₀₋₂₄	2.6249	1.7570	3.9215
	C _{avg}	2.8249	1.6961	4.7048
	C _{max}	2.1512	1.3035	3.5503
Asymptomatic vs symptomatic and treated	AUC ₀₋₂₄	2.8620	1.8828	4.3504
	C _{avg}	2.7897	1.6396	4.7464
	C _{max}	2.0331	1.2170	3.3964
Symptomatic vs symptomatic and treated	AUC ₀₋₂₄	1.0903	0.6991	1.7005

Source: Study TBS-1-2011-04 CSR, Table 14.

^a Asymptomatic=state at study enrollment; Symptomatic=state after pollen challenge in ECC; Symptomatic and Treated=state after pollen challenge in ECC and treatment with oxymetazoline.

^b PK parameters for 0 to 24 hours, baseline corrected.

^c Bioequivalence threshold values were 0.8 to 1.25.

AUC₀₋₂₄=area under the serum concentration-time curve from 0 to 24 hours postdose; C_{avg}=average observed concentration; CI=confidence interval; C_{max}=maximum observed concentration; ECC=environmental challenge chamber; LL=lower limit; n=number of subjects; PK=pharmacokinetic; UL=upper limit; vs=versus.

Additional exploratory analyses revealed that different treatment conditions influenced the predose testosterone concentrations (see Study TBS-1-2011-04, Section 11.7). The Student t-test showed significant differences in the predose testosterone between the asymptomatic treatment conditions (subjects not exposed to pollen in the ECC) compared to the symptomatic and the symptomatic and treated condition. A post-hoc analysis confirmed that the pre-dose serum total testosterone levels were significantly lower at the baseline and both symptomatic states as compared to the corresponding point for the asymptomatic treatment state. The average baseline, symptomatic and symptomatic but treated condition pre-dose serum testosterone levels of 470.8, 422.9 and 401.5 ng/dL, respectively, were 12, 21 and 25% lower than the average pre-dose testosterone level of 535.9 ng/dL for the asymptomatic treatment condition. It is hypothesized that the earlier wake-up time and/or stress caused by procedures associated with confinement in the Environmental Challenge Chamber may have led to lower testosterone values at baseline and in both symptomatic states compared to the asymptomatic state. The additional analysis corrected for this difference by using predose values instead of correction by 24-hour baseline profile. As expected, the differences between asymptomatic and both symptomatic treatment conditions were less pronounced with respect to baseline-corrected AUC, C_{avg} and C_{max}.

Pre-dose corrected AUC_{0-24h} and C_{avg} values for testosterone in the symptomatic and the symptomatic but treated states demonstrated a decrease of 21% and 18%, respectively, as compared to the asymptomatic state. This decrease was comparable to the 21% and 25% decrease in pre-dose testosterone concentrations and to a 21% and 24% reduction in the uncorrected AUC_{0-24h} and C_{avg} for the same treatment states, suggesting that the use of the 24-hour baseline profile for correction purposes was not truly representative of the non-treated state.

Therefore, in the Sponsor's opinion, the maximum relative 21% decrease in serum total testosterone 24-hour average concentration post-dose in both symptomatic states was more

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likely influenced by the comparably lower pre-dose testosterone level than by the allergic rhinitis symptoms.

Administration of TBS-1 under asymptomatic, symptomatic and untreated, and symptomatic and treated states of allergic rhinitis demonstrated a reliable increase in testosterone serum concentrations under all 3 treatment conditions. The baseline-corrected AUC_{0-24} exposure to testosterone was higher in the asymptomatic state compared to both the symptomatic and untreated and symptomatic and treated state. An analysis of variance did not demonstrate bioequivalence between the asymptomatic state and either symptomatic or symptomatic and treated states.

A comparison between symptomatic and untreated and symptomatic and treated baseline-corrected AUC_{0-24} showed that these 2 treatment conditions are not bioequivalent. However, given that the point estimates were close to 1 (1.0903 for testosterone and 0.9944 for DHT), the failure to show bioequivalence may have been due to large interindividual variations. These large variations led to wide CIs, which exceeded the threshold values for bioequivalence of 0.8 to 1.25. The relative decrease in bioavailability of TBS-1 in symptomatic seasonal rhinitis subjects was neither ameliorated nor aggravated by the administration of the nasal decongestant oxymetazoline.

The post-hoc analysis showed that the pre-dose serum total testosterone levels were significantly higher for the asymptomatic treatment condition compared to the baseline and symptomatic and symptomatic but treated condition. It is hypothesized that the earlier wake up time and/or stress caused by procedures associated with confinement in the ECC may have led to lower total testosterone values in baseline and both symptomatic states compared to the asymptomatic state. The additional analysis corrected for this difference by using the pre-dose values instead of correcting using the 24-hour baseline profile and showed the differences between asymptomatic and both symptomatic treatment conditions were less pronounced with respect to baseline-corrected AUC, C_{avg} , and C_{max} . Therefore, the maximum relative 21% decrease in serum total testosterone 24h average concentration post-dose in both symptomatic states was more likely influenced by the comparably lower pre-dose serum total testosterone level than by the allergic rhinitis symptoms.

Reviewer's Comment: This result is, in the Sponsor's analysis, a worst case scenario with the maximum relative decrease of 21% in serum testosterone 24h average concentrations in both symptomatic states. While this finding should be in labeling, if Sponsor's interpretation is correct and Clinical Pharmacology concurs, it has minimal import with regard to efficacy, in my opinion.

Summary: Overall, the aim of the early development program for TBS-1 was to develop a formulation that, when applied intranasally, would restore testosterone levels to normal physiological levels (300 to 1050 ng/dL) in men with a condition associated with a deficiency or absence of endogenous testosterone. The TBS-1 clinical development program included administration of 4 different formulations of TBS-1 containing 3.2%, 3.5%, 4.0%, or 4.5% testosterone using unit-dose containers, prefilled syringes, or a multiple-dose dispenser. Clinical studies were conducted in hypogonadal and healthy men. Later in the development program, TBS-1 was administered as 11 mg twice-daily (BID) and three times daily (TID) doses using a multiple-dose dispenser, which is the proposed commercial product and administration method.

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6 Review of Efficacy

Efficacy Summary

The primary efficacy variable for Study TBS-1-2011-03 was the percentage of subjects with total testosterone C_{avg} within the normal range on Day 112. C_{avg} results were required to fall within the normal range of 300-1050 ng/dL, with success being defined as $\geq 75\%$ of subjects on active treatment within the normal serum testosterone concentration range (300-1050ng/dL) and the lower bound of the 95% CI was to be not less than 65% based on the Day 112 results.

The key secondary efficacy success criteria required the individual C_{max} results to be within the following ranges:

- ≤ 1500 ng/dL in $\geq 85\%$ of the subjects
- between 1800-2500 in $\leq 5\%$ of the subjects and
- >2500 in none of the subjects.

Following discussions with the Division concerning the study results, the Sponsor is seeking approval for the TID dose of TBS-1 only. Therefore, this discussion of efficacy will consider only the TID dose. There were 77 patients randomized to the TID dose of TBS-1. At Day 90, 69 TID-only patients had a C_{avg} determination. At Day 90, 62 of 69 TID-only patients (90%), had a testosterone C_{avg} in the normal range ($300 \leq C_{avg} \leq 1050$ ng/dL). The 95% CI for frequency of responders was (83, 97). In the ITT population using LOCF (e.g., if Day 90 data was missing, Day 30 was carried forward), 66 of 73 (90%) had a testosterone C_{avg} in the normal range ($300 \leq C_{avg} \leq 1050$ ng/dL). The 95% CI for frequency of responders was (84, 97). At Day 30, there were 73 TID-only patients who had a C_{avg} determination. 61 of these 73 TID-only patients (84%) had a testosterone C_{avg} in the normal range ($300 \leq C_{avg} \leq 1050$ ng/dL) on Day 30. The 95% CI for frequency was (75, 92).

In the ITT sample, 69 TID-only subjects had a C_{max} at Day 90. 58 of 69 subjects (84.1%) had a serum total testosterone ≤ 1500 ng/dL. In the Per Protocol population (N=67), 67 subjects had a C_{max} at Day 90, and of these 56 of 67 (83.6%) had C_{max} below <1500 ng/dL. The pre-determined criterion for success was not less than 85% of subjects with $C_{max} < 1500$ ng/dL. This reviewer does not feel that this minor discrepancy raises an efficacy or safety concern that would preclude approval. One (1) of 69 TID-only subjects had a serum total testosterone C_{max} between 1800 and ≤ 2500 ng/dL at Day 90. No TID dose subject had a $C_{max} >2500$ ng/dL at Day 90.

At Day 30, there was one TID subject with a total serum testosterone > 2500 ng/dL. At Day 90, this subject's C_{max} was 2260 ng/dL.

Overall 1 of 69 (1.4%) TID-only subjects with C_{max} determinations at Day 30 and Day 90 had total serum testosterone C_{max} between 1800 and ≤ 2500 ng/dL. This one instance occurred on PK Day 30.

Only 1 (1.4%) of 73 TID-only patients had a total serum testosterone >2500 ng/dL at Day 30 and 0 (0.0%) of 67 TID-only patients had a total serum testosterone >2500 ng/dL at Day 90. In

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both safety extension periods there was one subject (taking the BID dose) with a total serum testosterone >2500 ng/dL. This patient did not have similar elevation in the treatment period.

The observed PK profile for DHT on Days 30 and 90 were consistent with dosing with testosterone. DHT values remained within normal limits as did the DHT/T ratio.

The mean change from baseline to Day 90 in the IIEF-EF domain in TID-only patients was 6.2 points (SD 9.33, p-value<0.001). The mean change-from-baseline to Day 90 in the IIEF total score in TID-only subjects was 14.4 (SD 18.35, p-value <0.001). In the absence of a placebo arm, it is not possible to determine the actual treatment effect, but there appears to have been a clinically meaningful change suggestive of efficacy. The PANAS (mood) scores appears to demonstrate improvement with treatment both in the positive and negative mood spheres. Again, the lack of a placebo arm counfounds interpretation of these results. Changes in bone mineral density and lean body mass and fat mass changes were too small to allow a supportive conclusion. A placebo arm possibly would have allowed a supportive conclusion. For more thorough discussion of these endpoints see **Section 6.1.7.5**.

TBS-1 4.5% (Natesto), in 11.00 mg TID dosing was found to be efficacious in the treatment of male hypogonadism as measured by the Primary Endpoint. Two of three critical endpoints were achieved for TID dosing. The third critical endpoint of total serum testosterone ≤ 1500 ng/dL in $\geq 85\%$ of the subjects at Day 90 was 84.1%. I do not feel that this minor discrepancy precludes approval. The secondary variables of the IIEF and its domains and PANAS (mood) PRO support the primary efficacy endpoints for Natesto.

6.1 Indication

TBS-1 is indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone:

- Primary hypogonadism (congenital or acquired)
- Hypogonadotropic hypogonadism (congenital or acquired)

Examples of causative conditions or agents for primary (hypergonadotropic) hypogonadism include: testicular failure due to cryptorchidism, bilateral testicular torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals.

Examples of causative conditions or agents for secondary (hypogonadotropic) hypogonadism include: idiopathic gonadotrophin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma or radiation.

6.1.1 Methods

In support of this application, the Sponsor provided efficacy results from one Phase 3 (TBS-1-2-11-03) study which was a 90-day, randomized, dose-ranging study without a placebo arm. In an Advice/Information Request letter dated October 3, 2011, the Division agreed that a single, 12-week, Phase 3 study with safety extension and "supportive evidence" evaluating the efficacy and

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safety and of intranasal testosterone gel would be sufficient to file the application for review.

This review of efficacy is based on review of Protocol TBS-1-2-11-03 . Of note, additional multiple-dose pharmacokinetic data for intranasal testosterone gel was collected in several Phase 1 and Phase 2 studies, including dose-ranging studies.

The efficacy of TBS-1 in males with primary or secondary hypogonadism is determined by the pharmacokinetic (PK) profile in this population.

6.1.2 Demographics

For the single Phase 3 Study TBS-1-2011-03:

Initiation Date: 23 September 2011

90-day Treatment Period Completion Date: 12 October 2012

Safety Extension Period 1 Completion Date: 09 January 2013

Safety Extension Period 2 Completion Date: 11 March 2013

In total, there were 306 (100.0%) male subjects. 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. The mean weight at screening was 93.34 kg, mean height was 177.1 cm, and mean BMI was 29.69 kg/m². 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 testosterone replacement therapy at screening. Subjects who did not require a wash-out were either naïve (73.2%) or discontinued their previous treatment with testosterone prior to enrollment in the study. The mean qualifying fasting serum total testosterone concentration was 201 ng/dL, representing values considerably below the lower end of the eugonadal range of 300-1050 ng/dL. Mean DHT at screening was 19.2 ng/dL and also well below the range of normal (25.5-97.8 ng/dL). Mean screening estradiol was 18.2 pg/mL, and toward the lower end of the normal range for men of 3-81 pg/mL. In general, the treatment groups were comparable with respect to demographic and baseline characteristics.

Reviewer's Comment:

- *Sponsor did enroll a representative, heavier population based on the US (BMI up to 35 kg/m²)*
- *Sponsor did enroll 49 patients with the condition of seasonal allergies (Listing 7.2 of CSR)*

Table 13: Demographics of Hypogonadal Patients in Phase III Safety Sample (TBS-1-2011-03)

Randomized Treatment Assignment	Randomized to TBS-1 BID			Randomized to TBS-1 TID	
Treatment Group Characteristic Category/Statistic	TBS-1 BID (N=142)	TBS-1 BID/TID[5] (N=86)	Combined TBS-1 BID (N=228)	TBS-1 TID (N=78)	Total (N=306)
Age (years)					
n	142	86	228	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	121 (85.2)	64 (74.4)	185 (81.1)	61 (78.2)	246 (80.4)
≥65 years	21 (14.8)	22 (25.6)	43 (18.9)	17 (21.8)	60 (19.6)
Ethnicity - n (%)					
Hispanic or Latino	24 (16.9)	8 (9.3)	32 (14.0)	9 (11.5)	41 (13.4)
Not Hispanic or Latino	118 (83.1)	78 (90.7)	196 (86.0)	69 (88.5)	265 (86.6)
Race - n (%)					
Asian	7 (4.9)	6 (7.0)	13 (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)	0 (0.0)
Black/African or African American	7 (4.9)	7 (8.1)	14 (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)	0 (0.0)
White/Caucasian	128 (90.1)	73 (84.9)	201 (88.2)	70 (89.7)	271 (88.6)
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.3)
Weight at Screening (kg)					
n	142	86	228	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	142	86	228	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	142	86	228	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	78 (54.9)	44 (51.2)	122 (53.5)	43 (55.1)	165 (53.9)
BMI ≥30 kg/m ²	64 (45.1)	42 (48.8)	106 (46.5)	35 (44.9)	141 (46.1)
Hypogonadism Etiology - n (%)					
Primary	110 (77.5)	57 (66.3)	167 (73.2)	52 (66.7)	219 (71.6)
Secondary	32 (22.5)	29 (33.7)	61 (26.8)	26 (33.3)	87 (28.4)

Source: Table 7, CSR TBS-1-2011-03, page 71

Table 14: Endocrinological Baseline Characteristics Phase III Randomized Population (TBS-1-2011-03)

Randomized Treatment Assignment	Randomized to TBS-1 BID			Randomized to TBS-1 TID	Total (N=306)	
	TBS-1 BID	TBS-1 BID/TID[5]	Combined TBS-1 BID (b) (4)			TBS-1 TID (N=78)
Testosterone Therapy at					(b) (4)	
Naïve						56 (71.8)
Injection						10 (12.8)
Oral						2 (2.6)
Topical						10 (12.8)
Buccal						0 (0.0)
Previous Treatment for					(b) (4)	
None						32 (41.0)
Injection						11 (14.1)
Oral						1 (1.3)
Topical						13 (16.7)
Buccal						1 (1.3)
Duration of Hypogonadi					(b) (4)	
n						78
Mean (SD)						5.0 (5.67)
Qualifying Fasting Seru					(b) (4)	
n						78
Mean (SD)						210.35 (51.510)
Estradiol (nl range 5-81					(b) (4)	
n						76
Mean (SD)						19.58 (7.460)
DHT (nl range 25.5-97.8					(b) (4)	
n						76
Mean (SD)						20.54 (8.980)

Source: Table 7, CSR TBS-1-2011-03, page 72 *Naïve means not being treated at time screening

6.1.3 Subject Disposition

For the single Phase 3 Study TBS-1-2011-03:

Number of Subjects:

Planned: Approximately 280 subjects (210 subjects randomized to the BID treatment group; 70 subjects randomized to the TID treatment group)

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(b) (4)

Source: Figure 1, CSR TBS-1-2011-03, page 65

In total, 306 subjects were randomized: 228 subjects to the TBS-1 BID group and 78 subjects to the TBS-1 TID group. After 45 days of treatment, (b) (4) of 228 subjects from the BID group were titrated up to the TID regimen (this group is referred to as the TBS-1 BID/TID group) and (b) (4) subjects continued with their drug administrations twice daily. Subject 010-005 did not uptitrate to the TID regimen until after Day 90. This subject is included in the TBS-1 BID/TID group, but in the efficacy and safety tables he is included in the TBS-1 BID group up until Day 90. There were (b) (4)% subjects who discontinued the study during the Treatment Period ((b) (4)%] subjects randomized to TBS-1 BID and 9 [11.5%] subjects

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randomized to TBS-1 TID). The primary reason for discontinuation during the Treatment Period was withdrawal of consent (18 [5.9%] subjects). The discontinuation rate during the Treatment Period due to adverse events was low (5 [1.6%] subjects). A total of (b) (4) % subjects completed the Treatment Period (b) (4) subjects randomized to TBS-1 BID and 69 subjects randomized to TBS-1 TID).

Table 15: Subject Disposition-Treatment Period (Day 1-Day 90) Randomized Population TBS-1-2011-03

	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	(b) (4)	69 (88.5)	(b) (4)
Discontinued During the Treatment Period		9 (11.5)	
Withdraw 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: Table 4, CSR TBS-1-2011-03, page 66

In total, 274 subjects entered Safety Extension Period 1: 122 subjects from the TBS-1 BID group and 152 subjects from the TBS-1 BID/TID group and TBS-1 TID group. There were 29 (10.6%) subjects who discontinued the study during Safety Extension Period 1 (15 [12.3%] subjects in the TBS-1 BID group and 14 [9.2%] subjects in the TBS-1 TID group). The primary reason for discontinuation during Safety Extension Period 1 was withdrawal of consent (11 [4.0%] subjects). The discontinuation rate during Safety Extension Period 1 due to adverse events was low (3 [1.1%] subjects). A total of 245 (89.4%) subjects completed Safety Extension Period 1.

In total, 75 subjects entered Safety Extension Period 2 (35 subjects in the TBS-1 BID group and 40 subjects in the TBS-1 TID group). There were 8 (10.7%) subjects who discontinued the study during Safety Extension Period 2 (5 [14.3%] subjects in the TBS-1 BID group and 3 [7.5%] subjects in the TBS-1 TID group). The primary reason for discontinuation during Safety Extension Period 2 was withdrawal of consent (6 [8.0%] subjects). Only 1 (1.3%) subject (in the TBS-1 TID group) discontinued during Safety Extension Period 2 due to an adverse event. A total of 67 (89.3%) subjects completed Safety Extension Period 2 (30 [85.7%] subjects in the

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TBS-1 BID group and 37 [92.5%] subjects in the TBS-1 TID group).

Table 16: Subject Disposition-Safety Extension Periods-Study TBS-1-2011-03

	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	30 (85.7)	37 (92.5)	67 (89.3)
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: Table 5, CSR TBS-01-2011-03, page 67

56 patients are listed as withdrawing consent during the duration of the protocol. Seven (7) of these patients withdrew during screening. 23 of the remaining 49 patients did not have an adverse event or reaction. Of the remaining 26 patients, 13 had adverse events referable to the nasal or upper respiratory tracts. Eight of these patients had events localized to the nasal tract including cold, nasal crusting, nasal pain, rhinorrhea, URI, difficult to breathe and sneezing.

Reviewer's Comment: Based upon withdrawals, nasal tolerability appears adequate.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy parameter was the percentage of subjects with serum testosterone time-averaged concentration (C_{avg}) over the dosing interval of 24 hours within the normal range of 300-1050 ng/dL at Day 112.

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Success in the study was defined as $\geq 75\%$ of subjects on active treatment within the normal serum testosterone concentration range of 300-1050 ng/dL. In addition, the lower bound of the 95% CI was not to be $< 65\%$.

Table 17: Number and Percentage of Subjects by Serum Total Testosterone C_{avg} Category at Day 90- Intent to Treat Population TBS-1-2011-03

	TBS-1 BID (N ^{(b) (4)})	TBS-1 BID/TID (N ^{(b) (4)})	TBS-1 TID (N=77)	Combined TBS-1 TID (N ^{(b) (4)})	Total (N ^{(b) (4)})
C_{avg} in Normal Range (300 ≤ C_{avg} ≤ 1050 ng/dL)					
N'		(b) (4)	69	(b) (4)	(b) (4)
Yes - n			62		
%			90		
95% CI for Frequency [1]			(83, 97)		
C_{avg} Below Normal Range (C_{avg} < 300 ng/dL)					
N'		(b) (4)	69	(b) (4)	
Yes - n			7		
%			10		
C_{avg} Above Normal Range (C_{avg} > 1050 ng/dL)					
N'		(b) (4)	69	(b) (4)	
Yes - n			0		
%			0		
Note: N' is the number of subjects who had a C _{avg} at Day 90. % = n/N'. 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 6.1.1					

At Day 90 LOCF, there were ^{(b) (4)} subjects in the ITT Population with valid 24-hour serum total testosterone C_{avg}.

According to the Sponsor's analyses, on Day 90, using LOCF methodology, ^{(b) (4)} of subjects on the Combined TBS-1 TID regimen and ^{(b) (4)} of subjects on the BID regimen had C_{avg} in the target total testosterone range. Individual treatment group analyses demonstrated that the highest percentage of subjects achieving C_{avg} in the target total testosterone range was in the TBS-1 TID group, 90% (95% CI = 84 to 97%), followed by ^{(b) (4)}

In the full ITT Population sample at Day 90 LOCF, 26% of subjects had C_{avg} below the target range. There ^{(b) (4)} in the TBS-1 BID group ^{(b) (4)} that was slightly above the normal range.

The table below shows the Sponsor's analysis of the proportion of subjects having serum total testosterone C_{avg} within the normal range on Day 90.

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Table 18: Proportion of Subjects with Serum Total Testosterone C_{avg} within the Normal Range Day 90 Treatment TBS-1-2011-03

Serum Total Testosterone C _{avg} in Normal Range on Day 90	ITT Population (N = (b) (4))	Per-Protocol Population (N = (b) (4))
Both TBS-1 treatment regimens	73%	76%
N'	(b) (4)	
95% CI for frequency [1]		
Combined TBS-1 TID (33.0 mg)	(b) (4)	
N'		
95% CI for frequency [1]	(b) (4)	
TBS-1 BID (22.0 mg)		
N'	(b) (4)	
95% CI for frequency [1]		

Note: N' is the number of subjects who had a C_{avg} at Day 90. % = n/N'.
 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; ITT = Intent-to-Treat; TID = three times daily.

Source: Post Text tables 6.1.1-6.2.2 CSR TBS-1-2011-03

According to the Sponsor, the primary efficacy endpoint success criterion was met by the TBS-1 TID dose regimen for both study populations analyzed (ITT and PP). In this group the percentage of subjects achieving C_{avg} in the target total testosterone range was 90% (95% CI = 83 to 97).

However, in FDA's analysis, we determined that (b) (4) were successful in achieving the primary efficacy criteria. The reader is referred to Table 20 of this review for data for these failed groups.

Reviewer's Comment: Based on these results, after considering feedback from the Division during a December 9, 2013, telephone conference, the Sponsor elected to seek approval just for the three times daily (TID)-only dose of TBS-1.

On January 7, 2014, the Sponsor submitted a major amendment to the NDA seeking approval just for the TID-only dosing regimen of Natesto. Therefore, the primary efficacy cohort from the pivotal Phase III study TBS-1-2011-03 for the 11 mg TID dose now consists of 73 patients in the ITT LOCF group, 69 patients in the ITT group and 67 patients in the Per Protocol Group (PP). In the table below are the number of men that achieved the agreed upon endpoint in those three categories:

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Table 19: Day 90 Number and Percentage of Patients With Serum Total Testosterone in the Normal Range (ITT Population, LOCF and PP Population Dosed Exclusively TID with TBS-1)-Treatment Period

Patient Population (n)	C _{avg} in Normal Range (300 ≤ C _{avg} ≤ 1050 ng/dL)		95% CI for Frequency
	Number	Percentage	
ITT LOCF (73)	66	90%	(84-97)
ITT (69)	62	90%	(83-97)
PP (67)	61	91%	(84-98)

Source: Table 1, page 2 of January 7, 2014, major amendment to NDA

The Sponsor states the primary efficacy population has a sufficient number of subjects to estimate the success rate.

The following table provides an analysis of the primary efficacy criterion in three failed dose groups: BID-only, BID to TID, and BID-only *plus* BID to TID.

Table 20: Number and Percentage of Subjects in the ITT Population by Serum Total 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)	(b) (4)	(b) (4)	73	(b) (4)
C _{avg} in normal range (300 < C _{avg} < 1050 ng/dL)					
Yes	(b) (4)	(b) (4)	(b) (4)	66	(b) (4)
%	(b) (4)	(b) (4)	(b) (4)	90	(b) (4)
95% CI for frequency*	(b) (4)	(b) (4)	(b) (4)	(84, 97)	(b) (4)
C _{avg} below normal range (C _{avg} < 300 ng/dL)					
Yes	(b) (4)	(b) (4)	(b) (4)	7	(b) (4)
%	(b) (4)	(b) (4)	(b) (4)	10	(b) (4)
C _{avg} above normal range (C _{avg} > 1050 ng/dL)					
Yes	(b) (4)	(b) (4)	(b) (4)	0	(b) (4)
%	(b) (4)	(b) (4)	(b) (4)	0	(b) (4)

*The CI for frequency is based on the binomial distribution within each treatment.

Source: Page 48 of the Clinical Pharmacologist's Review of NDA 205488 (Natesto).

Reviewer's Comment: For the result of the primary efficacy success rate for the combined TBS-1 BID to TID plus TBS-1 TID-only group, refer to Table 17.

The results in Table 20 show that the BID dosage

(b) (4)

However, the TID-only regimen reliably

met the primary efficacy criterion.

Reviewer’s Comment: This data are sufficient to support the primary efficacy endpoint for the TID-only regimen. The narrow confidence limits confirm the accuracy of the point estimates. Additional efficacy data from Phase 2 and dose-response data from other studies serve as supportive evidence.

6.1.5 Analysis of Secondary Endpoints(s)

The key (mandatory) secondary endpoint was the number and percentage of subjects with a serum total testosterone C_{max} in the following ranges on Day 90:

- ≤ 1500 ng/dL in $\geq 85\%$ of subjects,
- ≥ 1800 and ≤ 2500 ng/dL in $< 5\%$ of subjects, and
- > 2500 ng/dL in no subjects

Overall, (b) (4)% of the subjects in the ITT Population, regardless of their TBS-1 dose, had serum total testosterone $C_{max} \leq 1500$ ng/dL at Day 90. Only 9 (b) (4)% subjects in the ITT Population (b) (4) subjects in the TBS-1 BID group and (b) (4) subjects in the Combined TBS-1 TID group) had serum total testosterone C_{max} between 1800 ng/dL and 2500 ng/dL at Day 90. (b) (4) subject (b) (4) in the TBS-1 BID group) had serum total testosterone $C_{max} > 2500$ ng/dL at Day 90. This subject’s high serum total testosterone C_{max} value of 3570 ng/dL could be attributed to a possible continuing post-treatment effect of finasteride (a 5 α -reductase inhibitor) on hormone metabolism. This is supported by the subject’s low DHT/T ratio of 0.06. No safety concerns were identified for this subject during the study otherwise.

Table 15. Number and Percentage of Subjects With Serum Total Testosterone Cmax in Selected Ranges at Day 90 by Treatment –Intent-to-Treat Population – Treatment Period

	TBS-1 BID (N=(b) (4)) n (%)	TBS-1 BID/TID (N=(b) (4)) n (%)	TBS-1 TID (N=77) n (%)	Combined TBS-1 TID (N=(b) (4)) n (%)	Total (N=(b) (4)) n (%)
Day 90	(b) (4)		N'=69	(b) (4)	
$C_{max} \leq 1500$ ng/dL	(b) (4)		58 (84.1)	(b) (4)	
1800 ng/dL \leq $C_{max} \leq 2500$ ng/dL	(b) (4)		1 (1.4)	(b) (4)	
$C_{max} > 2500$ ng/dL	(b) (4)		0 (0.0)	(b) (4)	

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

Reviewer’s Comment: A similar result was demonstrated in the Per Protocol Population. There is a satisfactory explanation for outlier Subject 052-024. This secondary endpoint has been achieved, in my opinion.

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Another secondary endpoint (non-mandatory) was the number and percentage of subjects with a serum total testosterone C_{avg} in the normal range (≥ 300 ng/dL and ≤ 1050 ng/dL) on Day 30:

On Day 30, 84% of subjects on the TID regimen and (b) (4)% of subjects on the BID regimen had C_{avg} in the target total testosterone range. Individual treatment group analyses demonstrated that the highest percentage of subjects achieving C_{avg} in the target total testosterone range was in the TBS-1 TID group, 84%, followed by (b) (4)% of subjects in the TBS-1 BID group, (b) (4)% of subjects in the Combined TBS-1 BID group, and (b) (4)% of subjects in the TBS-1 BID/TID group.

In the full ITT Population sample, 30% of subjects had C_{avg} below the target range on Day 30. There were (b) (4) subjects in the TBS-1 BID group who had C_{avg} above the target range:



Table 21: Number and Percentage of Subjects by Serum Testosterone C_{avg} Category at Day 30 Intent-to-Treat Population TBS-1-2011-03

	TBS-1 BID (N (b) (4)) n (%)	TBS-1 BID/TID (N (b) (4)) n (%)	Combined TBS-1 BID (N (b) (4)) n (%)	TBS-1 TID (N=77) n (%)	Total (N=303) n (%)
C_{avg} in Normal Range ($300 \leq C_{avg} \leq 1050$ ng/dL)					
N ¹			(b) (4)	73	(b) (4)
Yes - n				61	
%				84	
95% CI for Frequency [1]				(75.06, 92.06)	
C_{avg} Below Normal Range ($C_{avg} < 300$ ng/dL)					
N ¹			(b) (4)	73	
Yes - n				12	
%				16	
C_{avg} Above Normal Range ($C_{avg} > 1050$ ng/dL)					
N ¹			(b) (4)	73	
Yes - n				0	
%				0	

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

Reviewer's Comment: At 30 days, TBS-1 TID-only achieved the primary efficacy parameters for achieving normal testosterone ranges.

Another non-mandatory secondary endpoint was the number and percentage of subjects with a serum total testosterone C_{max} in the following ranges on Day 30:

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- ≤1500 ng/dL,
- ≥1800 and ≤2500 ng/dL, and
- >2500 ng/dL;

Overall, 92.4% of the subjects in the study, regardless of their TBS-1 dose, had serum total testosterone C_{max} ≤1500 ng/dL at Day 30. In total, (b) (4) % subjects in the study (all (b) (4) had serum total testosterone C_{max} between 1800 ng/dL and 2500 ng/dL at Day 30. Only (b) (4) % subjects had serum total testosterone C_{max} >2500 ng/dL at Day 30: (b) (4) and 1 (1.4%) (b) (4) subject in the TBS-1 TID group (Subject 013-008). Subject

All (b) (4) subjects completed the Treatment

Period with Day 90 C_{max} values <2500 ng/dL (i.e., 2260 ng/dL for Subject 013-008, (b) (4) , and without any safety concerns identified.

Table 22: Number and Percentage of Subjects with Serum Total Testosterone C_{max} in Selected Ranges at Day 30 by Treatment Intent-to-Treat Population TBS-1-2011-03

	TBS-1 BID	TBS-1 BID/TID	Combined TBS-1 BID	TBS-1 TID (N=77) n (%)	Total (N=(b) (4)) n (%)
Day 30	(b) (4)			N=73	N=(b) (4)
C_{max} ≤1500 ng/dL	(b) (4)			69 (94.5)	(b) (4)
1800 ng/dL ≤ C_{max} ≤2500 ng/dL	(b) (4)			0 (0.0)	(b) (4)
C_{max} >2500 ng/dL	(b) (4)			1 (1.4)	(b) (4)

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

Reviewer's Comment: These results indicate that testosterone levels at Day 30 are below 2500 ng/dL in the vast majority of patients which is useful as an indicator of safety.

The following is a focused analysis of patients with serum total testosterone C_{max} > 2500 ng/dL: (See Table 23 below):

In each patient with a total serum testosterone value >2500 ng/dL, the abnormal value was bracketed by elevated total serum testosterone levels that were above 1800 ng/dL in all cases, making a chance variation unlikely. The Sponsor explained the elevation noted in the single Day 90 patient with a serum total testosterone >2500 ng/dL (052-024) as being secondary to the use of finasteride which was stopped May 5, 2012. Patient treatment was commenced with TBS-1 on July 10, 2012. The Sponsor cites the low DHT/T ratio as indicative of a persistent 5-alpha

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reductase effect; however, on Day 30, the highest total serum testosterone level in this patient was 1390 ng/dL. If there was a residual finasteride effect, one could postulate that it should have been worse on Day 30 than on Day 90.

Reviewer's Comment: All 4 subjects had low DHT/Testosterone ratios. This observation can sometimes be seen with specimen or skin venipuncture site contamination from testosterone. None of the patients had clinical adverse reactions that could be attributed to testosterone excess. In light of the possibility of venipuncture site skin contamination, the additional possibility of residual 5-alpha reductase inhibition, and the fact that only 1 patient had a total serum testosterone concentration >2500 ng/dL, I do not consider the data to indicate a safety concern that needs further consideration.

Table 23: Summary of Patients with Serum Testosterone > 2500 ng/dL at either Day 30 or Day 90 Study TBS-1-2013-03

Subject Number	Dose (11 mg testosterone)	Day	Timepoint After Dosing	Total Testosterone (ng/dL)	DHT (ng/dL) Highest level	DHT/T Ratio (95% interval)	E2 (pg/mL) Peak level & time	Comments Narrative Analysis	Number of Pump Actuations by 30 or 90 Day Visit*
Normal Range				300-1070 ng/dL	25.5-97.8 ng/dL	(0.074-0.33)	5-81 pg/mL		
C_{max} of Testosterone >2500 ng/dL at Day 90									
052-024	BID	90	0.66 hrs	3570	27.9	0.007	29.4 @ 2 hrs		287 pump actuations
C_{max} of Testosterone >2500 ng/dL at Day 30									
014-010	BID	30	1.0 hour	2660	12.1	0.005	69 @11 hrs	Cmax @ 90 days: 1160	128 pump actuations(32 days V1-V4)
047-003	BID	30	12.0 hours	3070	78.2	0.025	32.7 @16 hrs	Cmax@ 11.5 hrs: 2320	104 pump actuations (30 days V1-V4)
013-008	TID	30	17.0 hours	2520	117	0.046	70.2 @20 hrs	Cmax@ 1.5 hrs: 2260	199 pump actuations (33 days V1-V4)

Source: Listings 9, 10.1, 10.2, 10.3 of CSR TBS-1-2011-03. *For BID dosage there are 4 pump actuations per day and for TID dosage there are 6 pumps per day.

There is one additional serum testosterone concentration of note. In safety extension 1 (SE1), another BID-dosed subject (043-007) had a total serum testosterone of 2870 ng/dL on Day 180. His baseline total serum testosterone at entry into SE1 was 341 ng/dL. Testosterone at Visit 1 was 108 ng/dL.

Another secondary (non-mandatory) endpoint analysis was for the mean complete PK profile (including mean C_{avg}, the mean minimum concentration [C_{min}], mean C_{max}, and mean time to maximum concentration [T_{max}]) of serum total testosterone on Days 30 and 90:

The mean PK profiles for the TID-only group as well as the combined BID-only plus Day 30 BID-dosed patients from the BID to TID group are shown in Figure 6 below.

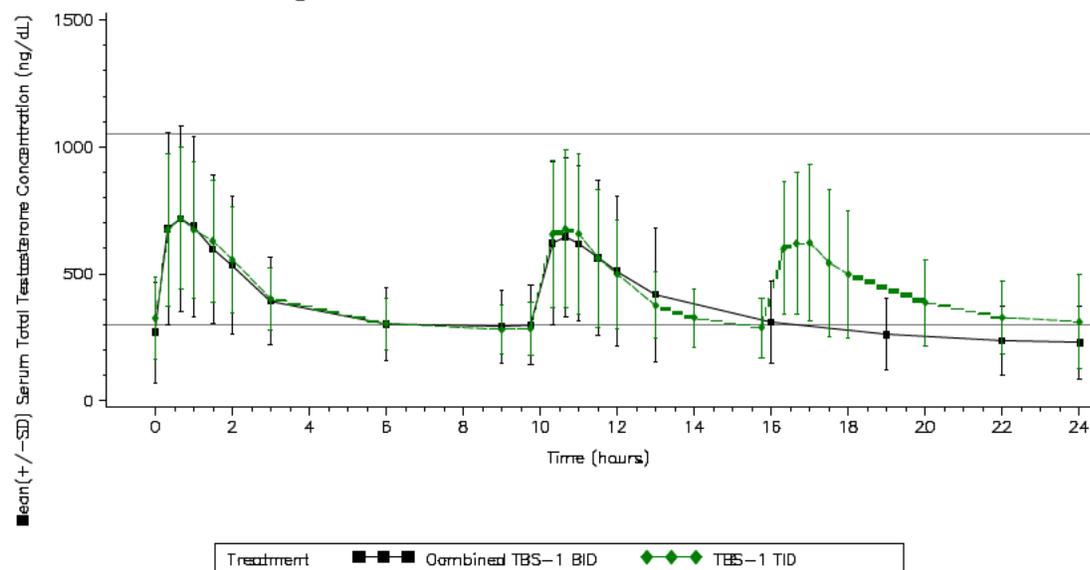
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Figure 6: Serum Total Testosterone Concentration by Treatment and Time Point at Day 30 Intent to Treat Population TBSD-1-2011-03



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

Source: Figure 2, CSR TBS-1-2011-03, page 85

At Day 30, the geometric mean $AUC_{(0-24)}$ of serum total testosterone was (b) (4) ng•hr/dL in the Combined TBS-1 BID group and 9619.56 ng•hr/dL in the TBS-1 TID group. According to the Sponsor, the mean C_{avg} values were within the normal range of 300-1050 ng/dL in all treatment groups and were reported as (b) (4) ng/dL in the Combined TBS-1 BID group and 414.83 ng/dL in the TBS-1 TID group. C_{min} geometric means were (b) (4) ng/dL in the Combined TBS-1 BID group and 198.15 ng/dL in the TBS-1 TID group. The geometric mean C_{max} values did not exceed the upper limit of normal (ULN) in any of the treatment groups and were reported as (b) (4) ng/dL in the Combined TBS-1 BID group and 861.07 ng/dL in the TBS-1 TID group. Median T_{max} was (b) (4) hrs in the Combined TBS-1 BID group and 0.70 hrs in the TBS-1 TID group.

Reviewer's Comment: The Combined BID group includes the BID-only group combined with the Day 30 BID experience from the BID to TID group. This is considered an exploratory analysis.

Figure 7 below shows the mean PK concentration-time profiles for patients taking TBS-1 TID and BID on Day 90.

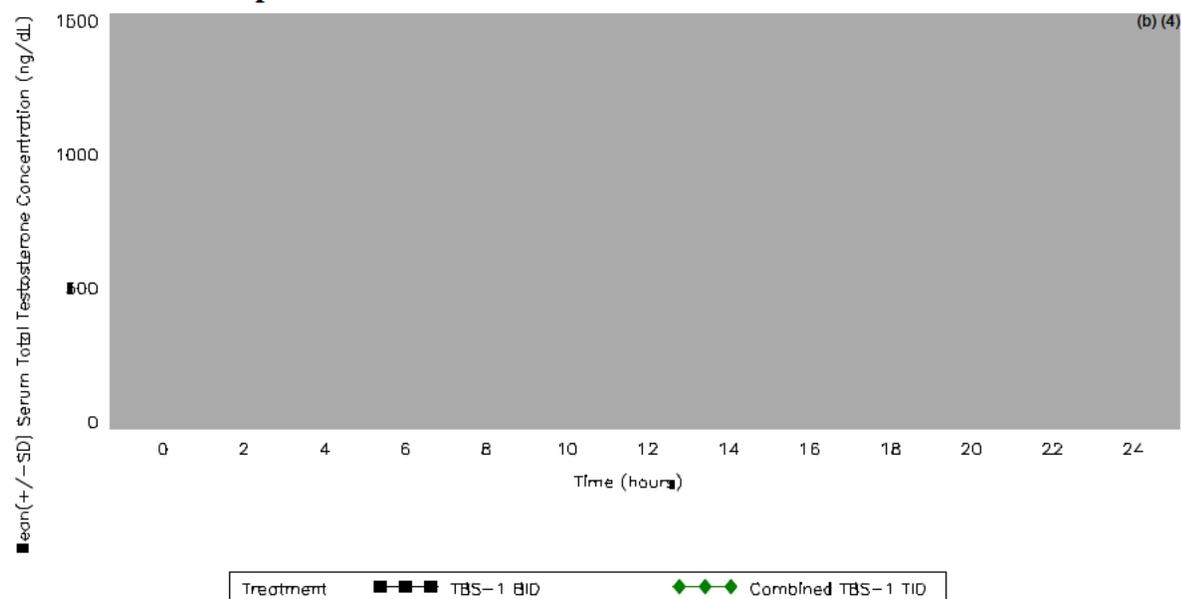
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**Figure 7: Serum Total Testosterone Concentration by Treatment and Timepoint at Day 90
Intent to Treat Population TBS-1-2011-03**



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

Source: Figure 3, CSR TBE-1-2011-03, page 86

According to the Sponsor's analysis, at Day 90, the geometric mean $AUC_{(0-24)}$ of serum total testosterone was (b) (4) ng·hr/dL in the TBS-1 BID group and (b) (4) ng·hr/dL in the Combined TBS-1 TID group. Mean C_{avg} values increased slightly from Day 30 in the TBS-1 TID group, but remained within the normal range in all treatment groups. Mean C_{avg} was reported as (b) (4) ng/dL in the TBS-1 BID group and (b) (4) ng/dL in the Combined TBS-1 TID group. C_{min} Geometric mean was (b) (4) ng/dL in the TBS-1 BID group and (b) (4) ng/dL in the Combined TBS-1 TID group. The geometric mean C_{max} showed an increase from Day 30 in the TBS-1 TID group, but did not exceed the ULN. Geometric mean C_{max} was reported as (b) (4) ng/dL in the TBS-1 BID group and (b) (4) in the Combined TBS-1 TID group. Median T_{max} was (b) (4) hrs in the TBS-1 BID and Combined TBS-1 TID groups and 0.65 hrs in the TBS-1 TID group.

Reviewer's Comment: The combined TBS-1 TID group includes both the TID-only group and the BID to TID group. This is considered an exploratory analysis.

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Table 24: Summary of Pharmacokinetic Parameters for Serum Total Testosterone at Day 30 and Day 90 by Treatment Intent-to-Treat Population TBS-1-2011-03

Visit Treatment Statistic	AUC ₍₀₋₂₄₎ (ng•hr/dL)	C _{avg} (ng/dL)	C _{min} (ng/dL)	C _{max} (ng/dL)	T _{max} (hr)
Day 30					
Combined TBS-1 BID (N=226)					
n	(b) (4)				
Mean (SD)					
CV%					
Geometric mean					
Median					
Min, Max					
TBS-1 TID (N=77)					
n	73	73	73	73	73
Mean (SD)	9956.00 (2726.98)	414.83 (113.62)	210.97 (73.21)	912.71 (342.85)	1.16 (1.37)
CV%	27.4	27.4	34.7	37.6	117.8
Geometric mean	9619.56	400.82	198.15	861.07	0.84
Median	9756.02	406.50	199.00	807.00	0.70
Min, Max	5476.4, 21335.1	228.2, 889.0	63.9, 441.0	426.0, 2520.0	0.3, 8.0
Day 90					
TBS-1 BID (N=141)					
n	(b) (4)				
Mean (SD)					
CV%					
Geometric mean					
Median					
Min, Max					
Combined TBS-1 TID (N=151)					
n	151	151	151	151	151
Mean (SD)	(b) (4)				
CV%					
Geometric mean					
Median					
Min, Max					
Min, Max					

AUC₍₀₋₂₄₎ = area under the plasma concentration-time curve from time zero to 24 hours post-dose;
 BID = twice daily; C_{avg} = average concentration; C_{min} = minimum concentration;
 C_{max} = maximum concentration; CV% = percent coefficient of variation; Min = minimum; Max = maximum;

SD = standard deviation; TID = three times daily; T_{max} = time to maximum concentration.

Source: Table 19, CSR TBS-1-2011-03, page 87

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Reviewer's Comment: In this table, the combined TBS-1 TID group ($n = (b) (4)$) includes both the TID-only group and the BID to TID group. This is considered an exploratory analysis.

The Sponsor observes that among the subjects with C_{avg} in the normal range at Day 90, mean C_{avg} values of $(b) (4)$ ng/dL and $(b) (4)$ ng/dL for the BID and Combined TID treatment regimens, respectively, were consistent with the total testosterone C_{avg} value of 418 ng/dL reported by Litman et al in normal, healthy males in a large -scale, population-based epidemiological survey (*J Clin Endocrinol Metab.* 2006;91:4326-4334).

Reviewer's Comment: There was one Day 90 TID patient with elevation of total serum testosterone > 2500 ng/dL. There were no TID dosed patients with such elevations in the safety extension SE1 and SE2, indicating relative long-term safety for this product with respect to this parameter. This single outlier on Day 90 should not preclude approval, in my opinion.

Another secondary (non-mandatory) endpoint was the time within the normal range (TWNR) for serum total testosterone based on the PK profile on Day 30 and Day 90:

The mean daily hours during which serum total testosterone concentrations were within the normal range at Day 90 for the ITT Population were as follows: $(b) (4)$ hours for the TBS-1 BID group, $(b) (4)$ hours for the TBS-1 BID/TID group, 15.9 hours for the TBS-1 TID group, and $(b) (4)$ hours for the Combined TBS-1 TID group.

For subjects with Day 90 $C_{avg} \geq 300$ ng/dL in the ITT Population, the mean daily hours during which serum total testosterone concentrations were within the normal range at Day 90 were higher than in the ITT Population and reported as follows: $(b) (4)$ hours for the TBS-1 BID group, $(b) (4)$ hours for the TBS-1 BID/TID group, 17.1 hours for the TBS-1 TID group, and $(b) (4)$ hours for the Combined TBS-1 TID group.

Reviewer's Comment: In no subject group was TWNR less than 12 hours, and in those subject who received TID dosing on Days 30 and 90, the TWNR was approximately 15 and 17 hours, respectively. While of interest, TWNR is considered an exploratory endpoint.

An important secondary endpoint was the mean PK profile of serum estradiol on Day 30 and Day 90:

The complete estradiol PK profile (including $AUC_{(0-24)}$, C_{avg} , C_{min} , C_{max} , and T_{max}) was determined at Baseline, on Day 30 and on Day 90. At Baseline (screening), the mean estradiol value was within the normal range for all treatment groups and reported as $(b) (4)$ pg/mL for the TBS-1 BID group, $(b) (4)$ pg/mL for the Combined TBS-1 BID group, and 19.6 pg/mL for the TBS-1 TID group. Observed increases in serum estradiol concentrations were consistent with dosing with testosterone in the Sponsor's opinion.

At Day 30, geometric mean $AUC_{(0-24)}$ of serum estradiol was $(b) (4)$ pg•hr/mL in the Combined TBS-1 BID group and 605 pg•hr/mL in the TBS-1 TID group. Mean C_{avg} was

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within the normal range of 3 - 81 pg/mL and reported as (b) (4) pg/mL in the Combined TBS-1 BID group and 27 pg/mL in the TBS-1 TID group. Geometric mean C_{\min} values were also within the normal range and reported as (b) (4) pg/mL in the Combined TBS-1 BID group and 16 pg/mL in the TBS-1 TID group. Geometric mean C_{\max} did not exceed the ULN and was (b) (4) pg/mL in the Combined TBS-1 BID group and 40 pg/mL in the TBS-1 TID group. Median estradiol T_{\max} was (b) (4) hrs for the Combined TBS-1 BID group and 1.6 hrs for the TBS-1 TID group.

At Day 90, geometric mean $AUC_{(0-24)}$ of serum estradiol was 680.3pg•hr/mL in the TBS-1 TID-only group. Mean estradiol C_{avg} remained within the normal range in all groups and was reported as 28.3pg/mL in the TBS-1 TID-only group (n=67). Geometric mean estradiol C_{\min} was 18.9pg/mL in the TBS-1 TID-only group (n=67) . Geometric mean estradiol C_{\max} was reported as 45.9pg/mL pg/mL in the TBS-1TID group (n=67). This values were within normal limits. Mean estradiol T_{\max} was 2.1 hours.

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Table 25: Summary of Pharmacokinetic Parameters for Serum Estradiol at Day 30 and Day 90 by Treatment Intent-to-Treat

Visit Treatment Statistic	AUC ₍₀₋₂₄₎ (pg•hr/mL)	C _{avg} (pg/mL)	C _{min} (pg/mL)	C _{max} (pg/mL)	T _{max} (hr)
Day 30					
Combined TBS-1 BID (N=226)					
n	(b) (4)				
Mean (SD)	(b) (4)				
CV%	(b) (4)				
Geometric mean	(b) (4)				
Median	(b) (4)				
Min, Max	(b) (4)				
TBS-1 TID (N=77)					
n	73	73	73	73	73
Mean (SD)	647.55 (237.36)	26.98 (9.89)	17.84 (7.33)	43.28 (15.69)	2.22 (1.96)
CV%	36.7	36.7	41.1	36.3	88.6
Geometric mean	605.39	25.22	16.41	40.33	1.60
Median	602.84	25.12	16.70	40.80	1.58
Min, Max	279.3, 1226.7	11.6, 51.1	5.3, 41.4	15.8, 76.1	0.3, 9.7
Day 90					
TBS-1 BID (N (b) (4))					
n	(b) (4)				
Mean (SD)	(b) (4)				
CV%	(b) (4)				
Geometric mean	(b) (4)				
Median	(b) (4)				
Min, Max	(b) (4)				
Combined TBS-1 TID (N (b) (4))					
n	(b) (4)				
Mean (SD)	(b) (4)				
CV%	(b) (4)				
Geometric mean	(b) (4)				
Median	(b) (4)				
Min, Max	(b) (4)				
AUC ₍₀₋₂₄₎ = area under the plasma concentration-time curve from time zero to 24 hours post-dose; BID = twice daily; C _{avg} = average concentration; C _{min} = minimum concentration; C _{max} = maximum concentration; CV% = percent coefficient of variation; Min = minimum; Max = maximum;					

SD = standard deviation; TID = three times daily; T_{max} = time to maximum concentration.

Source: Table 21, CSR TBS-1-2011-03, page 92

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Reviewer's comment: The assessments of serum estradiol concentrations in the Combined TBS-1 TID group is considered exploratory. The serum estradiol concentrations in the TID-only group on Day 90 are relevant to the to-be-marketed regimen and these are well within the normal range.

Another secondary endpoint in this study was the mean PK profile of serum dihydrotestosterone (DHT) on Day 30 and Day 90:

The complete serum DHT PK profile (including $AUC_{(0-24)}$, C_{avg} , C_{min} , C_{max} , and T_{max}) was determined at Baseline and on Day 30 and Day 90. The mean DHT value at Baseline (screening) was below the lower limit of normal (LLN) and reported as 20.5 ng/dL for the TBS-1 TID group. Observed increases in serum DHT concentrations were consistent with dosing with testosterone, in the Sponsor's opinion.

At Day 90, geometric mean $AUC_{(0-24)}$ of serum DHT was 961.5ng•hr/dL in the TBS-1 TID-only group. Mean DHT C_{avg} at Day 90 in the TBS-1 TID-only group (n=69) was 40.1 ng/dL. Geometric mean DHT C_{min} at 90 days was 26.5ng/dL in the TBS-1 TID-only group (n=69). Mean DHT C_{max} in the TBS-1 TID group (n=69) was 64.9 ng/dL at Day 90. Mean DHT T_{max} was 2.1hours in the TID-only group.

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Table 26: Summary of Pharmacokinetic Parameters for Serum Dihydrotestosterone at Day 30 and Day 90 by Treatment Intent-to-Treat TBS-1-2011-03

Visit Treatment Statistic	AUC ₍₀₋₂₄₎ (ng•hr/dL)	C _{avg} (ng/dL)	C _{min} (ng/dL)	C _{max} (ng/dL)	T _{max} (hr)
Day 30					
Combined TBS-1 BID (N=226)					
n	(b) (4)				
Mean (SD)	(b) (4)				
CV%	(b) (4)				
Geometric mean	(b) (4)				
Median	(b) (4)				
Min, Max	(b) (4)				
TBS-1 TID (N=77)					
n	73	73	73	73	73
Mean (SD)	934.05 (333.36)	38.92 (13.89)	26.09 (10.15)	61.58 (22.08)	2.13 (1.72)
CV%	35.7	35.7	38.9	35.9	80.6
Geometric mean	882.37	36.77	24.33	58.27	1.66
Median	849.26	35.39	23.20	55.80	1.55
Min, Max	450.9, 2092.8	18.8, 87.2	11.3, 61.3	29.1, 160.0	0.3, 9.0
Day 90					
TBS-1 BID (N= (b) (4))					
n	(b) (4)				
Mean (SD)	(b) (4)				
CV%	(b) (4)				
Geometric mean	(b) (4)				
Median	(b) (4)				
Min, Max	(b) (4)				
Combined TBS-1 TID (N= (b) (4))					
n	(b) (4)				
Mean (SD)	(b) (4)				
CV%	(b) (4)				
Geometric mean	(b) (4)				
Median	(b) (4)				
Min, Max	(b) (4)				
AUC ₍₀₋₂₄₎ = area under the plasma concentration-time curve from time zero to 24 hours post-dose; BID = twice daily; C _{avg} = average concentration; C _{min} = minimum concentration; C _{max} = maximum concentration; CV% = percent coefficient of variation; Min = minimum; Max = maximum; SD = standard deviation; TID = three times daily; T _{max} = time to maximum concentration.					

Source: Table 20, CSR TBS-1-2011-03, Page 90

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Reviewer's comment: The assessments of serum DHT concentrations in the Combined TBS-1 TID group is considered exploratory. The serum DHT concentrations in the TID-only group on Day 90 are relevant to the to-be-marketed regimen and these are well within the normal range.

Another secondary efficacy endpoint in this study was the ratio of DHT to total testosterone on Day 30 and Day 90:

The mean ratios of DHT C_{avg} to serum total testosterone C_{avg} at Day 90 did not exceed the normal limit (approximately 0.100) in any treatment group and ranged from (b) (4) for the TBS-1 BID group to (b) (4) for the Combined TBS-1 TID group.²⁴ The mean ratios of DHT C_{avg} to serum total testosterone C_{avg} at Day 30 were also similar across treatment groups and ranged from (b) (4) for the TBS-1 BID group to 0.095 for the TBS-1 TID group.

Table 27: Ratio of Dihydrotestosterone C_{avg} to Serum Total Testosterone C_{avg} by Treatment and Visit Intent -to-Treat Population TBS-1-2011-03

Visit Statistic	TBS-1 BID	TBS-1 BID/TID	Combined TBS-1 BID	TBS-1 TID (N=77)	Combined TBS-1 TID (N=(b) (4))	Total (N=(b) (4))
Day 30			(b) (4)			
n				73		(b) (4)
Mean (SD)				0.095 (0.0261)		
Median				0.089		
Min, Max				0.05, 0.21		
Day 90						
n				69		
Mean (SD)				0.094 (0.0296)		
Median				0.089		
Min, Max				0.05, 0.22		

Note: Ratio = DHT C_{avg} / Serum Total Testosterone C_{avg}.
BID = twice daily; C_{avg} = average concentration; DHT= dihydrotestosterone; Min = minimum; Max = maximum; SD = standard deviation; TID = three times daily.
Source: Table 22, CRF TBS-1-2011-03, Page 93

Reviewer's comment: The assessments of serum DHT:T concentration ratios in the Combined TBS-1 TID group is considered exploratory. The serum DHT:T concentration ratio in the TID-only group on Day 90 (n=69) is relevant to the to-be-marketed regimen and is within the normal range.

Additional secondary endpoints including measurements of change from baseline in selected pharmacodynamics (clinical) endpoints. These include scores from the International Index of Erectile Function (IIEF) questionnaire at Baseline and on Days 30, 60, and 90:

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Table 28: Summary of IIEF Questionnaire: Erectile Function (EF) Domain Scores by Treatment and Visit ITT Population TBS-1-2011-03

Variable Statistic	TBS-1 BID (N (b) (4))	TBS-1 BID/TID (N (b) (4))	Combined TBS-1 BID (N= (b) (4))	TBS-1 TID (N=77)	Combined TBS-1 TID (N= (b) (4))	Total (N (b) (4))
Change from Baseline to Day 30						
n [1]			(b) (4)	73		(b) (4)
Mean (SD)				5.0 (8.08)		
p-value [2]				<0.0001		
Combined TBS-1 BID vs. TBS-1 TID						
Mean (p-value) [2]						
Change from Baseline to Day 60						
n [1]			(b) (4)	69		(b) (4)
Mean (SD)				5.7 (9.42)		
p-value [2]				<0.0001		
TBS-1 BID vs. Combined TBS-1 TID						
Mean (p-value) [2]						0.3 (0.7524)
Change from Baseline to Day 90						
n [1]			(b) (4)	69		(b) (4)
Mean (SD)				6.2 (9.33)		
p-value [2]				<0.0001		
TBS-1 BID vs. Combined TBS-1 TID						
Mean (p-value) [2]						
Note: Baseline was the Day 1 value. If missing, the last value prior to the first dose of study medication was used. The score for the erectile function domain was the sum of the results from questions 1, 2, 3, 4, 5, and 15 from the IIEF questionnaire.						
1. n is the number of subjects with both baseline and endpoint measurements.						
2. t-test was used for the p-value calculation of change from baseline within treatment group and between treatment groups.						
BID = twice daily; IIEF = International Index of Erectile Function; SD = standard deviation; TID = three times daily.						

Source: Table 23, CSR TBS-1-2011-03, Page 94

Reviewer's Comment: Although the study did not include a placebo control, change from baseline in the EF domain score for the TID-only group on Day 90 was 6.2 points, a clinically significant improvement. In a large number of clinical trials of ED products, the placebo response for the IIEF EF domain in subjects with baseline erectile dysfunction (ED) has been reported to be negligible, suggesting a positive clinical effect of Natesto in this study.

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Table 29: Summary of IIEF Questionnaire Total Score by Treatment and Visit ITT Population TBS-1-2011-03

Variable Statistic	TBS-1 BID (N= (b) (4))	TBS-1 BID/TID (N= (b) (4))	Combined TBS-1 BID (N= (b) (4))	TBS-1 TID (N=77)	Combined TBS-1 TID (N= (b) (4))	Total (N= (b) (4))
Change from Baseline to Day 30						
n [1]				73		
Mean (SD)				11.0 (15.54)		
p-value [2]				<0.0001		
Combined TBS-1 BID vs. TBS-1 TID						
Mean (p-value) [2]						
Change from Baseline to Day 60						
n [1]				69		
Mean (SD)				12.3 (18.00)		
p-value [2]				<0.0001		
TBS-1 BID vs. Combined TBS-1 TID						
Mean (p-value) [2]						
Change from Baseline to Day 90						
n [1]				69		
Mean (SD)				14.4 (18.35)		
p-value [2]				<0.0001		
TBS-1 BID vs. Combined TBS-1 TID						
Mean (p-value) [2]						
Note: Baseline was the Day 1 value. If missing, the last value prior to the first dose of study medication was used. The total score was the sum of the results across all domains from the IIEF questionnaire.						
1. n is the number of subjects with both baseline and endpoint measurements.						
2. t-test was used for the p-value calculation of change from baseline within treatment group and between treatment groups.						
BID = twice daily; IIEF = International Index of Erectile Function; SD = standard deviation; TID = three times daily.						

Source: Table 28, CSR TBS-1-2011-03, Page 99

Reviewer's Comment: Although there is no placebo control, the mean changes from baseline in total IIEF score (14.4 points) and the EF domain score (6.2 points) suggest a positive treatment effect in this clinical study. Other than the EF domain score, the remaining IIEF domains may not be reliable and fit for use in labeling claims but these results are included in this review as supportive evidence of efficacy. The lack of a placebo control arm in this study also limits interpretation.

Reviewer's Comment: The IIEF also includes a sexual desire domain, which, while not validated as a stand-alone patient reported outcome, (b) (4). In this clinical study, there were positive mean changes in the sexual desire domain of the IIEF (see Table 29).

Table 30: Summary of IIEF Questionnaire: Sexual Desire Domain by Treatment and Visit ITT Population TBS-1-2011-03

Variable Statistic	TBS-1 BID (N ^{(b) (4)})	TBS-1 BID/TID (N ^{(b) (4)})	Combined TBS-1 BID (N ^{(b) (4)})	TBS-1 TID (N=77)	Combined TBS-1 TID (N ^{(b) (4)})	Total (N ^{(b) (4)})
Change from Baseline to Day 30						
n [1]				73		
Mean (SD)				1.3 (2.10)		
p-value [2]				<0.0001		
Combined TBS-1 BID vs. TID						
Mean (p-value) [2]						
Change from Baseline to Day 60						
n [1]				69		
Mean (SD)				1.4 (2.07)		
p-value [2]				<0.0001		
TBS-1 BID vs. Combined TBS-1 TID						
Mean (p-value) [2]						
Change from Baseline to Day 90						
n [1]				69		
Mean (SD)				1.6 (2.16)		
p-value [2]				<0.0001		
TBS-1 BID vs. Combined TBS-1 TID						
Mean (p-value) [2]						
Note: Baseline was the Day 1 value. If missing, the last value prior to the first dose of study medication was used. The score for the sexual desire domain was the sum of the results from questions 11 and 12 from the IIEF questionnaire.						
1. n is the number of subjects with both baseline and endpoint measurements.						
2. t-test was used for the p-value calculation of change from baseline within treatment group and between treatment groups.						
BID = twice daily; IIEF = International Index of Erectile Function; SD = standard deviation; TID = three times daily.						

Source: Table 26, CSR TBS-1-2011-03, Page 97

Reviewer's Comment: Although there was no placebo group in the study, all domains of the IIEF demonstrated positive changes from baseline (see Table below). The EF domain demonstrates a clinically meaningful mean change-from baseline in a population with erectile dysfunction at baseline, where little placebo effect is expected.

Table 31: Change in IIEF Questionnaire Domain Scores: Mean Total Baseline vs. Mean Total Day 90 LOCF ITT Population TBS-1-2011-03

IIEF Domain	Mean Total Baseline Score	Mean Total Day 90 LOCF Score	Mean Score Range for Normal Healthy Controls*	Maximum Score
Erectile Function	14.6	20.1	25.8 - 26.9	30
Orgasmic function	5.4	6.9	8.8 - 9.5	10
Sexual desire	5.3	6.8	7.0	10
Intercourse satisfaction	5.6	8.0	10.6- 10.8	15
Overall satisfaction	4.7	6.5	8.6 - 9.0	10
IIEF = International Index of Erectile Function; LOCF = last observation carried forward.				
Source: Table 29, CSR TBS-1-2011-03, Page 100				

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An additional pharmacodynamic (clinical) endpoint in this study was the assessment of mood, using scores from the Positive and Negative Affect Schedule (PANAS) at Baseline, Day 30, Day 60, and Day 90:

The PANAS questionnaire consists of two 10-item scales that assess subject mood. The PANAS questionnaire was administered during the Treatment Period (Visit 3 [Day 1], Visit 4 [Day 30/31], Visit 5 [Day 60], and Visit 6 [Day 90/91]), and at Early Termination (if the subject terminated before Visit 6 [Day 90]). Positive Affect Score was found by adding the scores from items 1, 3, 5, 9, 10, 12, 14, 16, 17, and 19. Negative Affect Score was found by adding the scores from items 2, 4, 6, 7, 8, 11, 13, 15, 18, and 20. A separate summary was performed to summarize the PANAS scores based on how the subject “felt over the past week,” not including those scores based on how the subject “feels right now” (both are endpoints in the PRO).

According to the Sponsor, there were improvements in in the Positive and Negative Affect Scores from baseline to Day 90 in all treatment groups.

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Table 32: Summary of PANAS Questionnaire: Affect Scores by Treatment and Visit - ITT Population TBS-1-2011-03

Parameter Variable Statistic	TBS-1 BID (N=(b)(4))	TBS-1 BID/TID (N=(b)(4))	Combined TBS-1 BID (N=(b)(4))	TBS-1 TID (N=77)	Combined TBS-1 TID (N=(b)(4))	Total (N=(b)(4))
Positive Affect Score [1]						
Change from Baseline to Day 30						
n [3]	(b)(4)			73	(b)(4)	
Mean (SD)	(b)(4)			3.0 (8.52)	(b)(4)	
p-value [4]	(b)(4)			0.0033	(b)(4)	
Combined TBS-1 BID vs. TBS-1 TID						
Mean (p-value) [4]						
Change from Baseline to Day 60						
n [3]	(b)(4)			69	(b)(4)	
Mean (SD)	(b)(4)			4.3 (9.09)	(b)(4)	
p-value [4]	(b)(4)			0.0002	(b)(4)	
TBS-1 BID vs. Combined TBS-1 TID						
Mean (p-value) [4]						
Change from Baseline to Day 90						
n [3]	(b)(4)			69	(b)(4)	
Mean (SD)	(b)(4)			4.0 (9.38)	(b)(4)	
p-value [4]	(b)(4)			0.0008	(b)(4)	
TBS-1 BID vs. Combined TBS-1 TID						
Mean (p-value) [4]						
Negative Affect Score [2]						
Change from Baseline to Day 30						
n [3]	(b)(4)			73	(b)(4)	
Mean (SD)	(b)(4)			-3.0 (4.91)	(b)(4)	
p-value [4]	(b)(4)			<0.0001	(b)(4)	
Combined TBS-1 BID vs. TBS-1 TID						
Mean (p-value) [4]						
Note: Baseline was the Day 1 value. If missing, the last value prior to the first dose of study medication was used.						
1. The Positive Affect Score was found by adding the scores from the following feelings/emotions: Interested, Excited, Strong, Enthusiastic, Proud, Alert, Inspired, Determined, Attentive, and Active. Higher scores represented higher levels of positive affect.						
2. The Negative Affect Score was found by adding the scores from the following feelings/emotions: Distressed, Upset, Guilty, Scared, Hostile, Irritable, Ashamed, Nervous, Jittery, and Afraid. Lower scores represented lower levels of negative affect.						
3. n is the number of subjects with both baseline and endpoint measurements.						
4. t-test was used for the p-value calculation of change from baseline within treatment group and between treatment groups.						
BID = twice daily; PANAS = Positive and Negative Affect Schedule; SD = standard deviation; TID = three times daily.						

Source: Table 30, CSR TBS-1-2011-03, Page 101

Table 34 Continued

Parameter Variable Statistic	TBS-1 BID (N=(b)(4))	TBS-1 BID/TID (N=(b)(4))	Combined TBS-1 BID (N=(b)(4))	TBS-1 TID (N=77)	Combined TBS-1 TID (N=(b)(4))	Total (N=(b)(4))
Negative Affect Score [2]						

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Change from Baseline to Day 60		
n [3]	(b) (4)	69 (b) (4)
Mean (SD)		-3.7 (5.93)
p-value [4]		<0.0001
TBS-1 BID vs. Combined TBS-1 TID		
Mean (p-value) [4]		
Change from Baseline to Day 90		
n [3]	(b) (4)	69 (b) (4)
Mean (SD)		-3.0 (5.76)
p-value [4]		<0.0001
TBS-1 BID vs. Combined TBS-1 TID		
Mean (p-value) [4]		

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Table 33: Summary of PANAS Questionnaire: Affect Scores Over the Past Week by Treatment and Visit ITT Population TBS-1-2011-03

Parameter Variable Statistic	TBS-1 BID (N (b) (4))	TBS-1 BID/TID (N (b) (4))	Combined TBS-1 BID (N= (b) (4))	TBS-1 TID (N=77)	Combined TBS-1 TID (N (b) (4))	Total (N (b) (4))
Positive Affect Score [1]						
Change from Baseline to Day 30						
n [3]	(b) (4)			66	(b) (4)	
Mean (SD)	(b) (4)			3.4 (8.72)	(b) (4)	
p-value [4]	(b) (4)			0.0025	(b) (4)	
Combined TBS-1 BID vs. TBS-1 TID						
Mean (p-value) [4]	(b) (4)				(b) (4)	
Change from Baseline to Day 60						
n [3]	(b) (4)			61	(b) (4)	
Mean (SD)	(b) (4)			4.5 (9.13)	(b) (4)	
p-value [4]	(b) (4)			0.0003	(b) (4)	
TBS-1 BID vs. Combined TBS-1 TID						
Mean (p-value) [4]	(b) (4)				(b) (4)	
Change from Baseline to Day 90						
n [3]	(b) (4)			62	(b) (4)	
Mean (SD)	(b) (4)			3.6 (9.73)	(b) (4)	
p-value [4]	(b) (4)			0.0045	(b) (4)	
TBS-1 BID vs. Combined TBS-1 TID						
Mean (p-value) [4]	(b) (4)				(b) (4)	
Negative Affect Score [2]						
Change from Baseline to Day 30						
n [3]	(b) (4)			66	(b) (4)	
Mean (SD)	(b) (4)			-3.0 (4.78)	(b) (4)	
p-value [4]	(b) (4)			<0.0001	(b) (4)	
Combined TBS-1 BID vs. TBS-1 TID						
Mean (p-value) [4]	(b) (4)				(b) (4)	
Note: Baseline was the Day 1 value. If missing, the last value prior to the first dose of study medication was used.						
1. The Positive Affect Score was found by adding the scores from the following feelings/emotions: Interested, Excited, Strong, Enthusiastic, Proud, Alert, Inspired, Determined, Attentive, and Active. Higher scores represent higher levels of positive affect.						
2. The Negative Affect Score was found by adding the scores from the following feelings/emotions: Distressed, Upset, Guilty, Scared, Hostile, Irritable, Ashamed, Nervous, Jittery, and Afraid. Lower scores represented lower levels of negative affect.						
3. n is the number of subjects with both baseline and endpoint measurements.						
4. t-test was used for the p-value calculation of change from baseline within treatment group and between treatment groups.						
BID = twice daily; PANAS = Positive and Negative Affect Schedule; SD = standard deviation; TID = three times daily.						

Source: Table 31, CSR TBS-1-2011-03, Page 103

Table 35 Continued

Parameter Variable Statistic	TBS-1 BID (N=(b) (4))	TBS-1 BID/TID (N=(b) (4))	Combined TBS-1 BID (N=(b) (4))	TBS-1 TID (N=77)	Combined TBS-1 TID (N=(b) (4))	Total (N=(b) (4))
Negative Affect Score [2]						
Change from Baseline						
n [3]	(b) (4)			61	(b) (4)	
Mean (SD)	(b) (4)			-3.7 (6.10)	(b) (4)	
p-value [4]	(b) (4)			<0.0001	(b) (4)	
TBS-1 BID vs. Combined TBS-1 TID						
Mean (p-value) [4]						
Change from Baseline to Day 90						
n [3]	(b) (4)			62	(b) (4)	
Mean (SD)	(b) (4)			-3.0 (5.85)	(b) (4)	
p-value [4]	(b) (4)			0.0002	(b) (4)	
TBS-1 BID vs. Combined TBS-1 TID						
Mean (p-value) [4]						

Table 34: Mean Positive and Negative Affect Scores and Percentiles at Baseline and Day 90 LOCF ITT Population TBS-1-2011-03

Domain	Mean Total Baseline	Mean Total Day 90 LOCF	Average Male Population
Mean Positive Affect Score	30.2	33.6	32
Mean Negative Affect Score	16.6	14.6	14
Percentile Positive Affect Score/Negative Affect Score based on mean	41/69	62/55	52/47
LOCF = last observation carried forward.			

Source: Table 32, CSR TBS-1-2011-03, Page 105

The Sponsor notes in the full ITT sample, noticeable changes in mean total domain scores from baseline were observed in both Positive and Negative Affect Scores. According to the Sponsor’s analysis, Positive Affect Scores increased to the average male population score on Day 90 LOCF. Similar improvement was demonstrated for Negative Affect Scores. The improvement in Positive and Negative Affect Scores was consistent in all groups, with no significant difference demonstrated for between-group comparisons, which, according to the Sponsor, suggests that the treatment was effective for all TBS-1 doses.

Reviewer’s Comment: The PANAS scores appear to document improvement with treatment in both the positive spheres and negative spheres, although the standard deviations are large. This is a non-validated instrument and the results should not be included in labeling. A lack of a placebo arm confounds result interpretation.

Another pharmacodynamic endpoint was the change in bone mineral density from baseline to Day 180 and from baseline to Day 360 in bone mineral density:

There were no statistically significant changes in bone mineral density for any of the treatment group at either Day 180 or Day 360 as measured by DEXA scans. However, at Day 360, there was a trend observed towards increasing bone mineral density values from baseline

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in both total lumbar spine and total hip measurements. The total spine and hip bone mineral density values increased from 1.131 g/cm² and 1.022 g/cm² at baseline, respectively, to 1.137 g/cm² and 1.026 g/cm², respectively, at Day 360. Over time, the number of these subjects decreased dramatically. For example, for lumbar spine BMD, there were (b) (4) subjects at day 180 and (b) (4) subjects at Day 360. The confidence intervals for these small changes from baseline cross zero.

Reviewer's Comment: The Sponsor notes the absence of significant changes was not unexpected given the relatively short treatment duration. Commonly, an average timeframe of 36 months is required for noticeable changes in bone mineral density (via DEXA) to occur.

Table 35: Lumbar Spine Bone Mineral Density Changes

**Study TBS-1-2011-03: Summary of Lumbar Spine Bone Mineral Density* (BMD) by Treatment and Visit
(All ITT Subjects with Both Baseline and Post-Baseline Values at Each Time Point)**

Treatment Group	BMD (g/cm ²) Mean Change from Baseline (95% C.I.)			
	n	At Day 180	n	At Day 360
BID group	(b) (4)			
BID to TID group				
TID group	57	-0.010 (-0.028, 0.008)	12	0.009 (-0.019, 0.036)

Source: Statistical Reviewer's listing. 95% confidence interval based on t-test.

* BMD value based on the total adequate BMD value.

Reviewer's Comment: Without a placebo arm, the results are difficult to interpret.

An additional pharmacodynamics endpoint was 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:

Baseline values for lean body mass, fat mass, and percent fat were 58.9 kg, 30.7 kg, and 32.5%, respectively.

The increase in lean body mass of 0.31 kg following 180 days of treatment, and this change was statistically significant from baseline. A similar increase of 0.18 kg was observed at Day 360, but this was not statistically significant (p= 0.5676), perhaps due to smaller sample size on Day 360. The observed decreases in fat mass and percent fat after 180 days of TBS-1 treatment were 0.15 kg and 0.22%, respectively, and these changes continued onto Day 360 (0.57 kg and 0.62%, respectively). Over time, the number of these subjects decreased dramatically. The changes on Day 360 were not statistically significant from baseline (p-values= 0.4297, 0.1641 [Day 180]; 0.2579, 0.1005 [Day 360]),

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respectively), but were qualitatively consistent with testosterone replacement therapy in showing appropriate changes for these body composition parameters.

Statistically significant changes were observed in single body composition parameters as follows:

- Increase in lean body mass from baseline to Day 180 for the trunk for the TBS-1 TID group
- Decrease in fat mass from baseline to Day 180 for the left leg for the TBS-1 TID group.
- Decreases in percent fat from baseline to Day 180 for the left arm and arms for the TBS-1 TID group.
- Decrease in percent fat from baseline to Day 360 in the left arm for the TBS-1 TID group.

Table 36: Lean Body Mass Changes

**Study TBS-1-2011-03: Summary of Lean Body Mass (LBM) by Treatment and Visit
(All ITT Subjects with Both Baseline and Post-Baseline Values at Each Time Point)**

Treatment Group	LBM (kg) Mean Change from Baseline (95% C.I.)			
	n	At Day 180	n	At Day 360
BID group	(b) (4)			
BID to TID group				
TID group	54	0.21 (-0.50, 0.92)	10	0.60 (-0.89, 2.10)

Source: Statistical Reviewer's listing. 95% confidence interval based on t-test.

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Table 37: Fat Body Mass Changes

**Study TBS-1-2011-03: Summary of Fat Mass (FM) by Treatment and Visit
 (All ITT Subjects with Both Baseline and Post-Baseline Values at Each Time Point)**

Treatment Group	FM (kg) Mean Change from Baseline (95% C.I.)			
	n	At Day 180	n	At Day 360
BID group	(b) (4)			
BID to TID group				
TID group	54	-0.16 (-0.82, 0.51)	10	0.09 (-1.42, 1.60)

Source: Statistical Reviewer's listing. 95% confidence interval based on t-test.

Reviewer's Comment: The Sponsor concludes that "Overall, treatment with TBS-1 for 180 and 360 days resulted in positive trends in body composition parameters for all doses." It is notable that some of the changes in some of the endpoints were not statistically significant at 180 days and others at 360 days. For these small changes, almost all of the confidence intervals crossed zero. While in totality, the results provide some supporting evidence of a treatment effect, the lack of a placebo arm (which could show worsening of some parameters) makes interpretation of these results difficult.

6.1.7 Subpopulations

6.1.7.1 Allergic Rhinitis

The reader is referred to the review of Study TBS-1-2011-04 in Section 5.2.7 of this review. The maximum relative 21% decrease in serum total testosterone 24-hour average concentration post-dose in both symptomatic states (treated and untreated) may have been the result of comparably lower pre-dose testosterone level and not the allergic rhinitis symptoms. Overall, in Phase 3 Study TBS-1-2011-03, 59 patients reported a medical history of either allergic rhinitis or seasonal allergies/hay fever, 49 patients indicated allergies as an ongoing condition. The incidence of allergic symptoms and/or allergy exacerbations reported as an adverse event in this group of patients during the study was low, even though the study period covered at least one to two allergy seasons. Of the 59 patients with this medical history, only 3 patients (5.1%) reported exacerbations of allergic rhinitis. A medical history of either allergic rhinitis or seasonal allergies as well as rare exacerbations of this condition did not affect patients' response to testosterone supplementation. On Day 90, the percentages of patients with a medical history of allergies in whom serum total testosterone within the normal range were 83% and (b) (4) % in TID and BID groups, respectively.

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 6.1.7.2 *Body Mass Index*

Sponsor did not formally do subgroup analysis for this subgroup but was asked to include subjects with high BMI in the Phase 3 study. Below are the percentage of subjects with normal range serum total testosterone by body mass index at Day 90. These efficacy results were prepared by the Office of Biometrics.

Table 38: Percentage of Subjects with Serum Total Testosterone Level in the Normal Range [≥ 300 ng/dL and ≤ 1050 ng/dL] by Body Mass Index (BMI) at Day 90 (Biometric's Reviewer's Definition of ITT Population*, LOCF)

TBS-1 Treatment Group**	n	Normal Level	Percentage (95% CI)
BMI < 30 kg/m²			
BID group			(b) (4)
BID-to-TID group			
BID group plus the BID-to-TID group			
TID group	43	33	76.7 (83.7, 97.2)
BMI ≥ 30 kg/m²			
BID group			(b) (4)
BID-to-TID group			
BID group plus the BID-to-TID group			
TID group	35	33	94.3 (80.1, 99.3)

Source: Statistical Reviewer's calculations

* ITT population are those subjects with a serum total testosterone level at any time, including baseline. Subjects with missing Day 30 and Day 90 data had baseline value used for LOCF. Baseline value was below normal, as per baseline inclusion criteria.

** BID = twice daily; C_{avg} = average concentration; CI = confidence interval; TID = three times daily.

Reviewer's Comment: TID dosing achieved primary efficacy endpoint in both low and high BMI groups. Efficacy does not appear to be affected by high or low BMI.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Study TBS-1-2011-03 was designed to randomly assign patients to a 22.0 mg or 33.0 mg daily dose (administered as 11.0 mg BID or TID respectively). The larger patient population in the BID treatment allowed for an evaluation of the effectiveness of the titration plan, as outlined in the protocol, after 30 days of treatment.

Within the group of patients who were titrated from BID to TID, referred to as the BID/TID group, an increase was observed in the number of patients who received effective testosterone replacement from the additional 11.0 mg of testosterone daily. Following 90 days of treatment the percentage of patients with serum testosterone levels within the normal range was (b) (4) % compared to (b) (4) % for this same group of patients following 30 days of treatment. The increase in the percentage of patients meeting the primary endpoint is consistent with the observed increase in mean C_{avg} within the BID/TID group between treatment Day 30 and Day 90. Following 30 days of treatment, the mean C_{avg} in the BID/TID group was (b) (4) ng/dL and was

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increased to (b) (4) ng/dL following titration to TID dosing at Day 90 . The increase in C_{avg} for the BID/TID group, (b) (4) ng/dL, is consistent with the addition of 11.0 mg of testosterone daily. Despite these increases, the BID/TID regimen was not successful in achieving the primary endpoint criterion, nor was the BID-only dose regimen.

Reviewer's Comment: Some of the patients who were up-titrated but still didn't achieve normal range average T concentrations could have been "non-responders" in the Sponsor's opinion.

(b) (4)

Reviewer's Comment:

(b) (4)

(b) (4) dose regimens other than the TBS-1 11.0 mg three times daily dosing regimen in their application.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Neither persistence nor tolerance was formally assessed in the TBS-1 clinical program (SCS page 67). However, in the March 7, 2014, Information Request response, the fasting serum testosterone in 59 TID-only subjects at Day 180 was 562 ng/dL while at Day 360 in 15 TID-only subjects the fasting serum testosterone was 671 ng/dL, not indicative of tolerance or lack of persistence of efficacy.

6.1.10 Additional Efficacy Issues/Analyses

There were no additional efficacy issues or efficacy analyses.

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7 Review of Safety

Safety Summary

The studies performed by the Sponsor are adequate to assess the safety of TBS-1[4.5%] (Natesto). 350 patients have been exposed to Natesto [4.5%] testosterone. There were no deaths, SAEs, or discontinuations due to AEs reported across the 5 Phase 2 studies in hypogonadal men or the 3 Phase 1 studies in healthy men. In Study TBS-1-2011-03, the single Phase 3 study, one death was reported due to a motorcycle accident. The adverse event profile in the Phase 3 was similar to other drugs in its class except for mild to moderate nasal adverse reactions (See **Section 2.4** Important Safety Issues With Consideration to Related Drugs). With respect to SAEs, there appeared to be no repetitive occurrence pattern, and there was lack of attribution of any SAE to the study drug.

In the double-blind period (Treatment Period) of the Phase 3 study, all adverse events that led to study discontinuation occurred as single events, with the exception of increased PSA, a cause of withdrawal in a total of 2 subjects (one in each of the safety extension periods). Two subjects withdrew from the treatment period with what may have been possible allergic or hypersensitivity reactions, these were: Subject 043-044 (angioedema) and Subject 021-014 (joint pain, arthralgia, fever, petechiae). For further discussion of these events see **Section 7.3.3**.

A total of 10 (3.3%) study subjects had a TEAE of increased PSA: 4 subjects in the TBS-1 BID/TID group and 4 subjects in the TBS-1 TID-only group.

Among 49 subjects with an active medical history of either allergic rhinitis or seasonal allergies, only 3 (6.1%) subjects reported exacerbations of allergies during the study, even though the study period covered at least one to two allergy seasons. An incidence of other nasal adverse events. These data are from the overall study population.

The following is a summary of drug-related adverse events and safety issues of special interest or class-related safety issues

Intranasal Route of Administration (Local Tolerance):

Evaluation of nasal symptoms and findings were performed by the investigator via monthly ENT examinations. At Day 90, 89.0% of subjects had no ENT symptoms. Of those who did report nasal signs or symptoms, the most common ENT symptom reported was "Other - Symptom not specified" (18 [6.6%] subjects). Among treatment-related symptoms, altered sense of smell (7 [2.6%] subjects) was the most frequent. A total of 97.4% of subjects had no ENT physical examination findings, and the only findings were "Other - Findings not specified (7 [2.6%] subjects). Otorhinolaryngological physical examination results were similar for the Safety Extension Periods. At Day 180, 92.6% of subjects did not report ENT symptoms and 96.3% of subjects had no ENT physical examination findings. At Day 360, 93.9% of subjects had no ENT symptoms. In those who did report

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ENT symptoms, the otorhinolaryngological symptoms reported were nasal dryness, nasal bleeding, nasal pain, and altered sense of smell (1 [1.5%] subject each). “Other - Symptom not specified” (1 [1.5%] subject) was also reported. There were no ENT physical examination findings for any subject at Day 360. These data are from the overall study population.

The most common system organ class of TEAEs during all periods was “Respiratory, Thoracic, and Mediastinal disorders” (24.2% for Day 90, 13.6% for Day 180, and 18.9% for Day 360). The most frequently reported TEAEs from this system organ class during all periods of the study were the events that can be attributed to and expected for the intranasal route of administration. For the TBS-1 BID group, the most frequently reported TEAEs from this system organ class during all periods of the study were rhinorrhea and nasal discomfort (7% each), and epistaxis (6.3%). Similarly, for the Combined TBS-1 TID group during all periods of the study, such events were rhinorrhea (8.5%) and epistaxis (6.7%). These data are from the overall study population and were not restricted to TID-only patients as the larger number of subjects included gives a reasonable perspective on product tolerability, in my opinion. No increase with treatment duration in the proportion of these nasal local tolerance events was observed during the study across the 3 study periods. The tolerance for this route of administration was acceptable, in my opinion.

Overall, 59 patients reported a medical history of either allergic rhinitis or seasonal allergies/hay fever, and 49 patients indicated allergies as an ongoing condition. The incidence of allergic symptoms and/or allergy exacerbations reported as an AE in this group of patients during the study was low, even though the study period covered at least 1 to 2 allergy seasons. Of the 59 patients with this medical history, 3 patients (5.1%) reported exacerbations of allergic rhinitis. A total of 19 patients (32.2%) in this group reported the following nasal AEs (without allergic etiology specified): parosmia, epistaxis, nasal discomfort, nasal congestion, and/or rhinorrhea. The majority of these events were mild in intensity and did not require intervention. The incidence of these nasal AEs in this subset of patients was as follows: parosmia 6 patients (10.2%), epistaxis 6 patients (10.2%), nasal discomfort 5 patients (8.5%), nasal congestion 3 patients (5.1%), and rhinorrhea 4 patients (6.8%). The incidence of these nasal AEs in this subset of patients with a history of either allergic rhinitis or seasonal allergies/hayfever was either slightly higher or comparable to the full study Safety Population (ie, the incidence of epistaxis in the full study Safety Population was 6.5%, nasal discomfort 5.9%, nasal congestion 3.9%, and rhinorrhea 7.8%). Parosmia was the only event with a noticeably higher incidence than the general Safety Population (5.2%). Parosmia is a symptom that is often associated with allergic rhinitis. The lack of a placebo arm does not permit drug or disease attribution, in my opinion. Overall, the nasal route of TBS-1 administration is generally well tolerated.

Transfer Issue:

Transfer exposure has been a safety issue for topically applied testosterone replacement products. There has been no secondary exposure documented to occur with intranasal application of TBS-1.

Sporadic Testosterone Levels >2500 ng/dL:

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{NDA 205488 }

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Only 1 (0.4%) subject (Subject 052-024 in the TBS-1 BID group) had serum total testosterone C_{max} >2500 ng/dL at Day 90. No subject in the TID dose group had a testosterone C_{max}>2500 ng/dL at Day 90 or at the end of SE1 or SE2. One BID subject (043-007 at Day 180 endpoint) had a fasting total serum testosterone of 2870 ng/dL. In addition, Subject 052-024 had a serum total testosterone C_{max} value of 3570 ng/dL that Sponsor attributed to a possible continuing post-treatment effect of finasteride (a 5 α -reductase inhibitor) on hormone metabolism. The events of elevations of testosterone consist of only two endpoint events which did not appear to be associated with increased morbidity, one of which may be related to a concomitant medication. They did not involve TID dosed patients. From a safety standpoint, I see no reason why these events should preclude approval.

Increased Hematocrit:

Testosterone is known to increase red cell production. In some patients, hematocrit can increase. Androgen labeling advises periodic measurements of hematocrit. A total of 8 subjects in this NDA had hematocrit values \geq 54% during the Phase 3 study: 3 (2.1%) subjects in the TBS-1 BID dose group, and 5 (3.0%) in the Combined TBS-1 TID dose group (2 were in the TID dose group). No subject had a hematocrit above 58% (the pre-determined level of clinical significance in the protocol). None of these subjects had a total serum testosterone \geq 1500 ng/dL at any time during their study participation and all had baseline hematocrits above the mean for their dose groups. The 90 Day mean mean changes from baseline in hematocrit were -0.4 (3.3 SD) and -0.2 (3.1 SD) for TID (N=78) and Combined TID (N=163) dosing respectively in the treatment period. In the treatment period , one BID subject had an hematocrit increase from 51% at baseline to 54% at Day 30, then back to 51% at Day 90 and 1 TID subject had a hematocrit increase from 48% at baseline to 55% at Day 90 measured again as 55% at Day 180. There were 3 BID/TID subjects and 1 BID subject who had hematocrit increases at Days 180 and 270 (See Table 60). At Day 180, the mean change in hematocrit for TID subjects (N=152) was 1.0 (3.3 SD) and 0.9 (2.2 SD) at Day 360. Increased hematocrit was not a reason for discontinuation in Study TBS-1-2011-03. There were no thromboembolic events noted at any period in the study. No new safety signal or change in pattern was detected. Appropriate labeling is present in the proposed product label (**Section 5.2**).

Increased PSA:

Testosterone replacement can increase PSA. Subjects were included in the study if their PSA was < 4.0 ng/dL. Per protocol, subjects were discontinued from the study if their PSA increased from Baseline by greater than 1.4 ng/dL.

PSA values for the Safety Population overall demonstrated mean increases from baseline of 0.10 ng/mL after 3 months of treatment at Day 90, 0.06 ng/mL at Day 180, and 0.14 ng/mL at Day 360. PSA values for the TBS-1 BID group demonstrated mean increases from baseline of 0.06 ng/mL after 3 months of treatment at Day 90, 0.01 ng/mL at Day 180, and 0.06 ng/mL at Day 360. PSA values for the Combined TBS-1 TID group demonstrated mean increases from baseline of 0.13 ng/mL after 3 months of treatment at Day 90, 0.09 ng/mL at Day 180, and 0.21 ng/mL at Day 360.

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{NDA 205488 }

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A total of 6 (3.7%) subjects from the Combined TBS-1 TID group, 0 (0.0) from the BID dose group and 4 (5.1 %) from the TID group in the treatment period had a TEAE of increased PSA, as defined by pre-determined , per-protocol changes in serum PSA (PSA > 4 ng/mL or PSA increase > 1.4 ng/mL). In Safety Extension Period 1, 4.2% of BID dosed patients (n=5) and 2.9% of TID patients (n=2) had a TEAE of increased PSA. In Safety Extension Period 2, there were no patients with a TEAE of PSA increased. Elevation of PSA values above the ULN (4 ng/mL) was reported in 5 cases; the remainder of the events were due to elevation of PSA by >1.4 ng/mL. Only 2 subjects were discontinued from the study due to this adverse event (Subject 001-049 and Subject 011-016), per the Investigator's decision. Both subjects' PSA values were monitored after TBS-1 discontinuation. A relatively rapid decrease in PSA values was reported for both subjects, with a resolution of the adverse event within an average of 60 days. One subject (Subject 028-005) interrupted TBS-1 administration for 2 weeks after an increase in PSA and then was re-challenged. His PSA initially increased from 0.65 ng/mL at baseline to 3.15 ng/mL at Visit 6, but returned to the baseline value after de-challenge. All of the subject's post-re-challenge PSA measurements were at baseline level, and the subject successfully completed the study (Safety Extension Period 2).

This AE requires mention in labeling.

Prostate Cancer:

It is not known whether replacement of T in men with hypogonadism increases the risk of prostate cancer. This potential risk and advice to monitor serum PSA is shown in androgen product labeling. No case of prostate cancer occurred in Study TBS-1-2011-03. This potential risk is a standard part of testosterone class labeling.

Hypertension:

Hypertension, as result of fluid retention and increased red blood cell mass, is a potential adverse reaction to testosterone. Hypertension was reported as a TEAE in 1.4% of the BID dosed patients (2/142) and 1.8% of the Combined TBS-1 doses patients (1/85 in BID/TID dose group and 1/78 in the TID-only dose group). The mean change from baseline in systolic blood pressure noted at Day 90 was -0.4 mm Hg for the 143 BID dosed patients and -0.7 mm Hg for the 78 TID-only dosed patients and -0.6 mm Hg for the 163 combined dose (BID/TID) patients. By Day 180 the mean change in systolic blood pressure was -2.7 mm Hg mm Hg for the 107 BID dose patients and -3.1 mm Hg for the 132 TID dose patients. While the 360 day results also showed decreases in blood pressure, the sample sizes on that day were small. In the 90-Day treatment period, hypertension was reported as a TEAE in 1/143 BID dose group patient, 1/85 BID/TID dose group patient and 1/78 TID dose group patient. In Safety Extension Period 1, hypertension was reported as a TEAE in 1/120 BID dose patient, 0/83 combined dose group patient and 0/69 TID dose group patient. In Safety Extension Period 2, hypertension was reported as a TEAE in 0/34 BID dose patients and 1/18 TID dose group patients. Hypertension was not a reason for study withdrawal.

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Thus, in the Phase 3 study, there was no evidence of a signal for hypertension. Therefore, the risk of hypertension is small, not dose related and, not time dependent, in my opinion. There were not discernible study population trends regarding blood pressure.

Correlation of Adverse Events with Peak Testosterone Concentrations:

A formal analysis for the correlation of adverse events with peak serum testosterone levels was not conducted by the Sponsor. During the treatment period, the incidence of TEAEs was greater in the TID group than in the BID dose group. This difference seems to narrow over time. It is also noted that over time the incidence of TEAEs in the BID dose group increased to approach that of the TID combined group. When drug-related TEAEs are analyzed for all periods (Post Text Tables 21.1 and 21.4), the TEAE rate was 24.5% (35/143) for BID dosing and 33.3%(26/78) for TID dosing. In my opinion, there appears to be modest increase with increased exposure to TBS-1, but I cannot say it correlates with peak testosterone concentrations.

There was one death in the development program which was not attributable to TBS-1. Eight patients (2.6%) reported SAEs during the study: 3 patients (2.1%) in the TBS-1 BID group and 5 patients (3.0%) in the Combined TBS-1 TID group. None of the SAEs during the study appear to be related to the study drug. Five SAEs occurred during the Treatment Period, 1 during Safety Extension Period 1(SE1) and 3 during Safety Extension Period 2 (SE2). Each SAE had a single incidence of occurrence and two SAEs occurred in the same patient (010-039: Acute coronary syndrome[Treatment Period]; Rocky Mountain Spotted Fever [SE1]). There were no SAEs reported in the 5 Phase 2 studies in 124 hypogonadal men treated with TBS-1 for 1 to 28 days. There were no SAEs reported in the 3 Phase 1 studies in 45 healthy men treated with TBS-1.

In the Pivotal study, Nine patients (2.9%) discontinued from the study due to a TEAE: 3 patients (2.1%) in the TBS-1 BID group and 6 patients (3.7%) in the Combined TBS-1 TID group. In the Treatment Period there were 4 TID patient discontinuations and 1 BID patient discontinuation. One of this discontinuations in a TID patient was secondary to dysgeusia and nasal odor and one BID patient discontinued secondary to headache and depressed level of consciousness. In SE1, one TID patient discontinued secondary to increased PSA and one BID patient discontinued secondary to the three AEs of nasal discomfort, parosmia and scab and a third BID patient discontinued secondary to hypersensitivity. There were no discontinuations due to AEs reported in the 5 Phase 2 studies in 124 hypogonadal men treated with TBS-1 for 1 to 28 days.

Local adverse events are discussed separately in this review under “*Nasal Route of Administration*”. In the Phase 3 study treatment period, non-local AEs occurring at 2% or greater were: chills, nausea, blood pressure increased, myalgia and pyrexia, each of which reported by 2.6 % TID patients. Headache was reported in 3.8% of TID patients in the treatment period.

In SE1, myalgia and headache in TID patients was reported in 1.4% of patients and pain in extremity was reported in 4.3% of patients. In the Combination dose group, there were no non-local (application site) AEs that occurred at a frequency greater than 1 subject.

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In total, 6 (2.0%) subjects had 7 lipid-related TEAEs (3 [2.1%] subjects in the TBS-1 BID group and 3 [1.8%] subjects in the Combined TBS-1 TID group).

Overall, there was a median increase in triglycerides of 3.3% from baseline to Day 360 (3.3% for both the TBS-1 BID group and the TBS-1 TID group). At Day 90 and Day 180, overall median increases in triglycerides were 12.7% and 3.4%, respectively. In the TBS-1 TID group, three patients had elevations of triglycerides. Patient 016-019 had a baseline triglyceride elevation that increased at Visit 4 and returned to normal on Visits 6 and 9. Patient 044-021 had elevated triglycerides at baseline with lower elevated levels at Visits 4, 6 and 9. Patient 007-043 had normal triglycerides at baseline, increased triglycerides at Visits 4 and 6 and normal triglycerides at Visit 9 (Day180). Changes in serum lipid profile are noted in WARNINGS and PRECAUTION.

There were six patients in the Treatment period with creatine kinase (CK) elevations ≥ 2 times the upper limit of normal (3 BID/TID and 3 TID). An additional patient experienced a similar increase at Day 270. These were generally transient and not accompanied by any cardiovascular symptoms (See Table 63). In all, 17 /74(22.9%) of TID patients experienced an increased CK as noted in the 120 Day Safety Update. Each case of CK increase ≥ 2 -fold was reviewed individually. In the majority of these cases, confounding factors appeared to play a role. In addition, changes in CK were highly variable with large standard deviations. Decreases in CK were also observed. There does not appear to be any signal for clinically relevant CK increase for Natesto.

Currently the vast majority of testosterone administration is achieved by the use of topical testosterone gels. These have the risk of potential skin transfer. Testosterone by injection has the disadvantage of an injection. Transdermal testosterone delivery systems can cause skin irritation. Oral 17- α methyl testosterone has the risk of liver toxicity. Testosterone pellets requires an incision to insert and the pellets can be extruded. Buccal bioadhesive testosterone tablets can have gum-related adverse events. While TBS-1 can have nasal adverse reactions, their frequency and severity, and the overall tolerability of TBS-1 is acceptable. The risk benefit analysis for TBS-1 (Natesto) is, in my opinion, satisfactory pending resolution of labeling discussions with Sponsor. The data provided in the Sponsor's submissions support the directions for use by patients. There are no requirements for a post-market commitment or REMS for this submission.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety data for this NDA is derived from an integrated analysis of the safety across the entire TBS-1 clinical program in men and includes these 9 studies: TBS-1-2011-03, TBS-1-2010-01, Nasobol-01-2009, MAT/05, MAT/04, Nasobol-01-2008, TBS-1-2011-01(healthy men), TBS-1-2011-04 (healthy men) and TBS-1A-2011-01(healthy men). The Sponsor presented a safety analysis for the pivotal study TBS-1-2011-03 alone, as this is the only study that used a multiple dose dispenser in men and had a treatment duration longer than 28 days. The Sponsor also presented safety data from the 5 other TBS-1 studies conducted in hypogonadal men as well as

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safety data from the 3 TBS-1 studies in healthy men. In this part of the Clinical review, these latter 2 groups will be discussed only if they add new safety data or considerations to the analysis of safety in the pivotal study. The discussions in this section will include results from the 120-Day Safety Update.

7.1.2 Categorization of Adverse Events

The adverse events were analyzed in the following categories:

- Deaths
- Other serious adverse events
- Dropouts
- Adverse events associated with dropouts
- Other significant adverse events
- Testosterone concentrations >2500 ng/dL

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

This NDA is supported by a single Phase 3 study. Additional safety data is derived an integrated analysis from studies TBS-1-2010-01, Nasobol-01-2009, MAT/05, MAT/04, Nasobol-01-2008, TBS-1-2011-01(healthy men), TBS-1-2011-04 (healthy men) and TBS-1A-2011-01(healthy men) separated by studies conducted in healthy volunteers and hypogonadal men. No pooling was done due to significant differences in the designs of the studies.

7.2 Adequacy of Safety Assessments

Throughout this Summary of Clinical Safety, the Sponsor's intranasal testosterone gel formulation is referred to as TBS-1 (also referred to as Nasobol[®] and testosterone intranasal gel in some reports and supporting documents). Dose is defined as the number of milligrams of testosterone administered from 2 unit-dose containers (one per nostril), from 2 syringes (one per nostril), or from 2 actuations of the multiple-dose dispenser (one per nostril). The testosterone content of TBS-1 is the percent weight per weight (%w/w) delivered. Doses were administered once daily (QD), BID, or TID.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In total, the NDA contains safety data from 460 men exposed to at least one dose of TBS-1. The safety data is derived from the integrated studies TBS-1-2011-03, TBS-1-2010-01, Nasobol-01-2009, MAT/05, MAT/04, Nasobol-01-2008, TBS-1-2011, TBS-1A-2011-01 and

TBS-1-2011-04. The 120 Day Safety Update to NDA 205,488 was received September 3, 2013. The data in this Update was received and reviewed and provide no new safety signals compared to the data in the original NDA. 382 hypogonadal males are included in the integrated safety data base, and 307 healthy males and 96 females are included in the non-integrated safety data base.

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In Phase 1 integrated studies a total of 12 hypogonadal men were exposed to 11.0 mg TBS-1 and 33 healthy men were exposed to any dose of TBS-1. The 12 hypogonadal men were exposed to one daily dose of TBS-1 for two days. Of the 33 healthy men, 18(55%) with seasonal allergies were exposed to three 24 hour treatment regimens of TBS-1 11.00mg TID. 15/33 (45%) of the healthy men, were exposed to three 24 hour treatment regimens of TBS-1A 4.0%, TBS-1A 8.0% or TBS-1A 4.0% viscous TID.

In the Phase 2 studies in hypogonadal men, TBS-1-2010-01, Nasobol-01-2009, MAT.05, MAT/04 and Nasobol-01-2008, a total of 205 men were exposed to any dose of TBS or Nasobol for periods of 1 day up to 28 days.

In the single Phase 3 study, 306 subjects were treated, with 142 at the TBS-1 dose of 11 mg bid and 164 at the dose of 11 mg tid. In all studies, cumulative exposure to TBS-1 (4.5% concentration) for hypogonadal men was: 430 \geq 1 day, 247 \geq 6 months, 67 \geq 1 year. In the Phase 3 study, 90 patients completed 90 days of BID TBS-1 and 152 patients completed 90 days of TID TBS-1. 86 patients were up-titrated in Study TBS-1-2011-03.

A total of 152 patients completed 90 days of therapy with **TID dosing**. 69 patients and 18 patients completed 180 days and 360 days of therapy with TID dosing, respectively.

Overall 30 healthy men and 306 hypogonadal men were exposed to the to-be-marketed drug in the 4.5% dispenser.

Table 39: TBS-1 Subject Exposure by Population, Formulation (%) and Treatment Duration

Study	Testosterone (%w/w)/ Administration	Design (Washout)/ Dose Regimen ^a	Treatment Duration	Safety Population ^b	
				Healthy Adult Subjects	Hypogonadal Men
TBS-1-2011-03	4.5% Dispenser	Parallel groups 11.0 mg BID 11.0 mg TID	180 days (all) 360 days (subset of 75 patients)	NA	306 142 164
TBS-1-2010-01	4.0% and 4.5% Syringe	Parallel groups 10.0 mg TID 4.0% 13.5 mg BID 4.5% 11.25 mg TID 4.5%	7 days	NA	22 8 7 7
Nasobol-01-2009	3.2% Syringe	Crossover (none) 8.0 mg BID 11.0 mg BID 14.0 mg BID Androderm [®] 5.0 mg/day	7 days per period (28 days total)	NA	57 56 56 54 54

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MAT/05	3.2% Unit-dose dispenser	Parallel groups 7.6 mg BID ^e 7.6 mg BID ^e 7.6 mg TID	14 days	NA	21 7 7 7
MAT/04	3.2% Unit-dose dispenser	Crossover (≥3-day) 7.6 mg 15.2 mg 22.8 mg	1 day per period (3 days total)	NA	8 8 8
Nasobol-01-2008	3.2% Unit-dose dispenser	Parallel-group, 2-period 7.6 mg BID 0700, 1200 7.6 mg QD 0700 7.6 mg BID 0700, 2200 7.6 mg QD 2200	28 days (14 days BID, then 14 days QD)	NA (16 untreated)	16 8 8 8 8
TBS-1-2011-01	4.5% Syringe and Dispenser	Crossover (6-day) 11.0 mg (syringe) 11.0 mg (dispenser)	1 day per treatment arm (2 days total)	12 12 12	NA
TBS-1A-2011-01	TBS-1: 4.0% TBS-1A: 4.0% and 8.0% TBS-1A (viscous): 4.0% Syringe	Crossover (6-day) 10.0 mg TID for all	1 day per treatment arm (4 days total)	15	NA
TBS-1-2011-04	4.5% Dispenser	Crossover (4-day) 11.0 mg TID asymptomatic 11.0 mg TID symptomatic, untreated 11.0 mg TID symptomatic, treated	1 day per treatment arm (3 days total)	18 18 15 17	NA

Source: 1 Table 4, SCS page 18

In Study TBS--2011-03, mean exposure to study drug was 86.1 days for 274 subjects, 175.7 days in an additional 90 days extension period 1 for 245 subjects, and in an additional 180 days extension period for 67 subjects.

The safety follow-up was 90 days for 274 subjects, an additional 90 days in extension period 1 for 245 subjects, and an additional 180 days in extension period 2 for 74 subjects.

Mean exposure to study drug was 86.1 days during the Treatment Period, 175.7 days during Safety Extension Period 1, and 346.0 days during Safety Extension Period 2. The exposure to study drug was similar for each treatment group.

Table 40: Summary of Study Medication Exposure-Safety Population-Treatment Period

Characteristic Category/Statistic	TBS-1 BID (N=143)	TBS-1 BID/TID (N=85)	TBS-1 TID (N=78)	Combined TBS-1 TID (N=163)	Total (N=306)
Treatment Period					
Exposure (days) [1]					
n	143	85	78	163	306
Mean (SD)	84.9 (20.68)	89.8 (5.97)	84.4 (19.70)	87.2 (14.50)	86.1 (17.67)
Exposure Category – n (%)					
1 – 30 days	12 (8.4)	0 (0.0)	4 (5.1)	4 (2.5)	16 (5.2)
31 – 60 days	2 (1.4)	1 (1.2)	4 (5.1)	5 (3.1)	7 (2.3)
61 – 90 days	56 (39.2)	43 (50.6)	30 (38.5)	73 (44.8)	129 (42.2)
>90 days	73 (51.0)	41 (48.2)	40 (51.3)	81 (49.7)	154 (50.3)
1. Exposure = date of last dose of the Treatment Period (Day 90) – date of first dose + 1. BID = twice daily; SD = standard deviation; TID = three times daily.					

Source: Table 43, CSR TBS-1-2011-3, Page 117

Table 41: Summary of Study Medication Exposure-Safety Population-Safety Extension Periods TBS-1-2011-03

Characteristic Category/Statistic	TBS-1 BID	TBS-1 TID	Total
Safety Extension Period 1			
Exposure (days) [1]			
n	120	152	272
Mean (SD)	175.5 (18.64)	175.9 (17.01)	175.7 (17.72)
Exposure Category – n (%)			
≤90 days	0 (0.0)	0 (0.0)	0 (0.0)
90 – 120 days	4 (3.3)	6 (3.9)	10 (3.7)
121 – 150 days	6 (5.0)	6 (3.9)	12 (4.4)
151-180 days	59 (49.2)	68 (44.7)	127 (46.7)
>180 days	51 (42.5)	72 (47.4)	123 (45.2)
Safety Extension Period 2			
Exposure (days) [2]			
n	34	40	74
Mean (SD)	345.5 (40.96)	350.5 (36.33)	348.2 (38.34)
Exposure Category – n (%)			
≤180 days	0 (0.0)	0 (0.0)	0 (0.0)
181 – 210 days	1 (2.9)	1 (2.5)	2 (2.7)
211 – 240 days	1 (2.9)	1 (2.5)	2 (2.7)
241 – 270 days	1 (2.9)	0 (0.0)	1 (1.4)
271 – 300 days	1 (2.9)	0 (0.0)	1 (1.4)
301 – 330 days	0 (0.0)	1 (2.5)	1 (1.4)
331 – 360 days	22 (64.7)	24 (60.0)	46 (62.2)
>360 days	8 (23.5)	13 (32.5)	21 (28.4)
1. Exposure = date of last dose of Safety Extension Period 1 – date of first dose + 1. 2. Exposure = date of last dose of Safety Extension Period 2 – date of first dose + 1. BID = twice daily; SD = standard deviation; TID = three times daily.			

Source: Table 44, CSR TBS-1-2011-03, Page 118

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Reviewer's Comment: The overall exposure to Natesto and the doses used are appropriate to evaluate the product safety in my opinion. The adverse event profile of testosterone products is well known and since Natesto provides testosterone levels generally in the low-normal range, it is unlikely that the testosterone-related profile of AEs in this NDA will require a large number of subjects, in my opinion. The major safety issue will be local adverse events at the administrative site. Since the product was used either tid or bid, the number of exposures to these excipients is adequate to assess nasal toxicity, in my opinion.

Section 6.1.2 contains a discussion of the demographics of population studied in TBS-1-2011-03

7.2.2 Explorations for Dose Response

The dosing regimens selected were based on modeling and simulations using data from earlier clinical studies of a 4.5% T gel to provide steady state C_{max} T values that would not exceed 2500 ng/dL in any subject, would not exceed 1800 mg/dL in more than 5 % of subjects, and would not exceed 1500 ng/dL in more than 15 % of subjects. Dosing regimens selected were expected to provide steady state C_{avg} values within the range of 300-1050 ng/dL for at least 75 % of subjects (with a lower bound for the 95 % confidence interval about the proportion being no lower than 65 %).

Comparison of the serum testosterone PK of TBS-1 between Study TBS-1-2010-01 and Study Nasobol-01-2009 demonstrated that intranasal testosterone absorption was limited by gel volume, which led to the formulation of a more concentrated, lower volume gel for TBS-1.

Study MAT/05 demonstrated that TID dosing compared to BID dosing was more likely to generate maximum concentration (C_{max}) values >1500 ng/dL

The safety results observed in the Phase 3 study with administration of TBS-1 for up to 1 year for both BID and TID regimens were generally consistent between the two dosing regimens. The only safety difference was in the incidence of PSA increases reported as TEAEs for the TID regimen, which was perhaps slightly higher.

Reviewer's Comment: Explorations for dose response and dose safety have been performed and are appropriate.

7.2.3 Special Animal and/or In Vitro Testing

No special animal and/or *in vitro* testing was performed.

7.2.4 Routine Clinical Testing

Routine clinical testing is shown in the Schedule of Procedures for Study TBS-1-2011-03 within the Study Summary in this review and was appropriate. The safety assessments included: collection of clinical AEs, clinical laboratory measurements (hematology, chemistry, urinalysis, lipid parameters, PSA), vital signs, physical examination (including digital rectal exam [DRE]), ECG, International Prostate Symptom Score (IPSS-1), Profile of Mood States questionnaire, bone density measurements, and lean body and body fat content assessments via DEXA. These are appropriate.

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7.2.5 Metabolic, Clearance, and Interaction Workup

The following information is available from the approved AndroGel® 1.6% (NDA 22-309) label and was submitted in this NDA application in support of testosterone metabolism, clearance and drug interactions:

There is considerable variation in the half-life of testosterone as reported in the literature, ranging from 10-100 minutes. About 90% of a dose of testosterone given intramuscularly is excreted in the urine as glucuronic acid and sulfuric acid conjugates of testosterone and its metabolites. About 6% of a dose is excreted in the feces, mostly in the unconjugated form. Inactivation of testosterone occurs primarily in the liver.

Testosterone is metabolized to various 17-keto steroids through two different pathways. The major metabolites of testosterone are estradiol (E2) and dihydrotestosterone (DHT).

Additionally, testosterone is primarily cleared by metabolic processes in the liver, skin, genital, and other tissues. This metabolism includes conversion to the active metabolite DHT by 5 α -reductases in the skin and liver and to E2 by aromatase complexes (CYP19) found in the liver, fat, and testes.

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

It is not anticipated that there will be any differences in the excretion of testosterone when it is delivered intranasally as TBS-1 4.5%.

The interaction between TBS-1 and oxymetazoline, a sympathomimetic decongestant, was assessed, but drug interactions with other nasally administered classes of drug, and other drugs were not. The following drug interactions are based on testosterone class labeling:

- Insulin: Changes in insulin sensitivity or glycemic control may occur in patients treated with androgens. In diabetic patients, the metabolic may decrease blood glucose and, therefore, insulin requirements.
- Corticosteroids: The current use of testosterone with ACTH or corticosteroids may result in increased fluid retention and should be monitored cautiously, particularly in patients with cardiac, renal or hepatic disease.
- Oral Anticoagulants: Changes in anticoagulant activity may be seen with androgens. More frequent monitoring of INR and prothrombin time is recommended in patients taking anticoagulants, especially at the initiation and termination of androgen therapy

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7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The following table and text provides a cursory overview of adverse events reported in the current AndroGel 1.6% label. This serves as an example of testosterone-related AEs, albeit for a transdermal formulation. No cross-product comparisons can be made based on this information.

Table 3 (from the AndroGel 1.62% PI): Adverse Reactions Reported in >2% of Patients in the 182-Day, Double-Blind Period of AndroGel 1.62% Clinical Trial

Number (%) of Patients	Number (%) of Patients	
	AndroGel 1.62 % N=234	Placebo N= 40
PSA increased*	26 (11.1%)	0%
Emotional lability**	6 (2.6%)	0%
Hypertension	5 (2.1%)	0%
Hematocrit or hemoglobin increased	5 (2.1%)	0%
Contact dermatitis***	5 (2.1%)	0%

***PSA increased** includes: PSA values that met pre-specified criteria for abnormal PSA values (an average change from baseline > 0.75 ng/mL and/or an average PSA value >4.0 ng/mL based on two measurements) as well as those reported as adverse events.

****Emotional lability** includes: mood swings, affective disorder, impatience, anger, and aggression.

*****Contact dermatitis** includes: 4 patients with dermatitis at non-application sites.

Other adverse reactions occurring in less than or equal to 2% of AndroGel 1.62%-treated patients and more frequently than placebo included: frequent urination, and hyperlipidemia.

In the open-label period of the study (N=191), the most commonly reported adverse reaction (experienced by greater than 2% of patients) was increased PSA (n=13; 6.2%) and sinusitis. Other adverse reactions reported by less than or equal to 2% of patients included increased hemoglobin or hematocrit, hypertension, acne, libido decreased, insomnia, and benign prostatic hypertrophy.

During the 182-day, double-blind period of the clinical trial, 25 AndroGel 1.62%-treated patients (10.7%) discontinued treatment because of adverse reactions. These adverse reactions included 17 patients with PSA increased and 1 report each of: hematocrit increased, blood pressure increased, frequent urination, diarrhea, fatigue, pituitary tumor, dizziness, skin erythema and skin nodule (same patient – neither at application site), vasovagal syncope, and diabetes mellitus.

During the 182-day, open-label period, 9 patients discontinued treatment because of adverse reactions. These adverse reactions included 6 reports of PSA increased, 2 of hematocrit increased, and 1 each of triglycerides increased and prostate cancer.

Reviewer's Comment: While a direct comparison for this drug and events associated with its class cannot be performed secondary to changes in coding dictionaries and terminology updates, with respect to testosterone-related adverse events of interest (e. g. emotional from lability, urinary symptoms, prostate exam abnormal, abnormal laboratory testing), the TBS-1 4.5% AE profile is consistent with similar approved drugs in its class. No new signals or patterns were observed related to non-application site events.

7.3 Major Safety Results

During the study, a total of 196 (64.1%) subjects reported a treatment-emergent adverse event (TEAE): 90 (63.4%) subjects in the TBS-1 BID group and 106 (64.6%) subjects in the Combined (BID/TID) TBS-1 TID group. In total, 43 (30.3%) subjects in the TBS-1 BID group and 67 (40.9%) subjects in the Combined TBS-1 TID group had a TEAE that was considered by

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the Investigator to be at least possibly related to the study drug. The majority of TEAEs and drug-related TEAEs were mild in severity. There were 115 (37.6%) subjects with mild TEAEs and 80 (26.1%) subjects with mild drug-related TEAEs. A total of 67 (21.9%) subjects had moderate TEAEs and 29 (9.5%) subjects had moderate drug-related TEAEs. Only 14 (4.6%) subjects had TEAEs that were severe and only 1 (0.3%) subject (Subject 021-014 in the TBS-1 TID group) had a severe drug-related TEAE of myalgia. The subject's dose was not changed, and he recovered with concomitant medication.

Eight (2.6%) subjects reported SAEs during the study: 3 (2.1%) subjects in the TBS-1 BID group and 5 (3.0%) subjects in the Combined TBS-1 TID group of which 3 were TID-only patients (1.8%). None of the SAEs during the study were considered by the Investigator to be related to the study drug .

Nine (2.9%) subjects discontinued from the study due to a TEAE: 3 (2.1%) subjects in the TBS-1 BID group and 6 (3.7%) subjects in the Combined TBS-1 TID group. 5 of the subjects who discontinued from the Combined TBS-1-TID group were TID-only subjects (3.1% discontinuation due to AE rate). Seven (2.3%) subjects discontinued from the study due to a drug-related TEAE: 3 (2.1%) subjects in the TBS-1 BID group and 4 (2.4%) subjects in the Combined TBS-1 TID group.

Summary safety data for **TBS-1 TID-only** patients may be found in Tables 69 and 70 of this review.

One subject in the TBS-1 TID group (Subject 004-008) died during the Treatment Period as a result of internal injuries due to a motorcycle accident; the Investigator considered this SAE as definitely unrelated to the study drug.

In addition, 1 subject (Subject 001-036) reported 2 SAEs (anterior superior ramus fracture and sacral fracture) during the screening period. The subject did not participate further and is not included in the Safety Population.

Table 42: Overview of Adverse Events-Safety Population TBS-1-2011-03-Treatment Period

Adverse Event Category	TBS-1 BID (N=143) n (%)	TBS-1 BID/TID (N=85) n (%)	TBS-1 TID (N=78) n (%)	Total (N=306) n (%)
Subjects with any TEAE	66 (46.2)	40 (47.1)	46 (59.0)	152 (49.7)
Maximum severity of TEAE				
Mild	46 (32.2)	26 (30.6)	32 (41.0)	104 (34.0)
Moderate	19 (13.3)	13 (15.3)	10 (12.8)	42 (13.7)
Severe	1 (0.7)	1 (1.2)	4 (5.1)	6 (2.0)
Subjects with any drug-related TEAE [1]	35 (24.5)	30 (35.3)	26 (33.3)	91 (29.7)
Maximum severity of drug-related TEAE [1]				
Mild	27 (18.9)	25 (29.4)	18 (23.1)	70 (22.9)
Moderate	8 (5.6)	5 (5.9)	7 (9.0)	20 (6.5)
Severe	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.3)
Subjects with any SAE	2 (1.4)	1 (1.2)	2 (2.6)	5 (1.6)
Subjects with any treatment-emergent SAE	2 (1.4)	1 (1.2)	2 (2.6)	5 (1.6)
Subjects with any drug-related SAE [1]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with any AE leading to death	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.3)
Subjects with TEAE leading to discontinuation	3 (2.1)	1 (1.2)	4 (5.1)	8 (2.6)
Subjects with drug-related TEAE leading to discontinuation [1]	3 (2.1)	1 (1.2)	2 (2.6)	6 (2.0)
Note: Treatment-emergent adverse events were those adverse events having a start date on or after the first dose of study medication, or occurring prior to the first dose and worsening in severity during the Treatment Period. 1. Drug-related includes possible, probable, and definitely related. For the SAE for Subject 010-039, the causality is missing, but the Principal Investigator believes it to be highly unlikely that the study drug was a proximate cause of the exacerbation of the subject's coronary atherosclerosis and anginal symptoms. AE = adverse event; BID = twice daily; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TID = three times daily.				

Source: Table 46, TBS-1-2011-03 CSR, Page 122

Overall, in Safety Extension Period 1, the proportion of subjects with TEAEs, and with drug-related TEAEs in particular, decreased during Safety Extension Period 1 as compared to the Treatment Period. A total of 101 (37.1%) subjects reported a TEAE in Safety Extension Period 1: 42 (35.0%) subjects in the TBS-1 BID group and 59 (38.8%) subjects in the TBS-1 TID group. In total, 44 (16.2%) subjects had a TEAE that was considered by the Investigator to be at least possibly related to study drug: 21 (17.5%) subjects in the TBS-1 BID group and 23 (15.1%) subjects in the TBS-1 TID group. There were 7 (2.6%) subjects with severe TEAEs during Safety Extension Period 1. No subject had a severe drug-related TEAE during Safety Extension Period 1. The majority of TEAEs during Safety Extension Period 1 were also mild in severity. One (0.4%) subject reported an SAE during Safety Extension Period 1. That subject, #010-039 (TBS-1 BID/TID group), had Rocky Mountain spotted fever during the TID regimen, which the Investigator considered definitely unrelated to study drug. No

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other subjects had an SAE during Safety Extension Period 1. Also, fewer subjects discontinued from the study due to a TEAE during Safety Extension Period 1 than during the Treatment Period. Two (0.7%) subjects had TEAEs during Safety Extension Period 1 that led to study discontinuation: 1 (0.8%) subject in the TBS-1 BID group and 1 (0.7%) subject in the TBS-1 TID group. The Investigator considered both of these TEAEs to be related to study drug.

Table 43: Overview of Adverse Events-Safety Population TBS-1-2011-03-Safety Extension Period 1

Adverse Event Category	TBS-1 BID (N=120) n (%)	TBS-1 TID (N=152) n (%)	Total (N=272) n (%)
Subjects with any TEAE	42 (35.0)	59 (38.8)	101 (37.1)
Maximum severity of TEAE			
Mild	30 (25.0)	37 (24.3)	67 (24.6)
Moderate	11 (9.2)	16 (10.5)	27 (9.9)
Severe	1 (0.8)	6 (3.9)	7 (2.6)
Subjects with any drug-related TEAE [1]	21 (17.5)	23 (15.1)	44 (16.2)
Maximum severity of drug-related TEAE [1]			
Mild	17 (14.2)	17 (11.2)	34 (12.5)
Moderate	4 (3.3)	6 (3.9)	10 (3.7)
Severe	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with any SAE	0 (0.0)	1 (0.7)	1 (0.4)
Subjects with any treatment-emergent SAE	0 (0.0)	1 (0.7)	1 (0.4)
Subjects with any drug-related SAE [1]	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with any AE leading to death	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with TEAE leading to discontinuation	1 (0.8)	1 (0.7)	2 (0.7)
Subjects with drug-related TEAE leading to discontinuation [1]	1 (0.8)	1 (0.7)	2 (0.7)
Note: All adverse events that started during Safety Extension Period 1 were considered TEAEs. 1. Drug-related includes possible, probable, and definitely related. AE = adverse event; BID = twice daily; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TID = three times daily.			

Source: Table 47, CSR TBS-1-2011-03, Page 123

The proportion of subjects with drug-related TEAEs was lower during Safety Extension Period 2 than during either the Treatment Period or during Safety Extension Period 1. The percentage of subjects with any TEAE (drug-related or not) in this period was comparable to the Treatment Period, and higher than in Safety Extension Period 1. A total of 39 (52.7%) subjects reported a TEAE in Safety Extension Period 2: 17 (50.0%) subjects in the TBS-1 BID group and 22 (55.0%) subjects in the TBS-1 TID group. In total, 11 (14.9%) subjects had a TEAE that was considered by the Investigator to be at least possibly related to study drug: 5 (14.7%) subjects in the TBS-1 BID group and 6 (15.0%) subjects in the TBS-1 TID group. There were 2 (2.7%) subjects with severe TEAEs during Safety Extension Period 2. No subject had a drug-related severe TEAE during Safety Extension Period 2. The majority of TEAEs during Safety Extension Period 2 were mild or moderate in severity.

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Three (4.1%) subjects reported SAEs during Safety Extension Period 2:

- TBS-1 BID group (1 subject): Subject 025-023 had angina pectoris, which the Investigator classified as definitely unrelated to study drug. This SAE resulted in interruption of study drug.
- TBS-1 BID/TID group (2 subjects): Subject 022-012 reported pneumonia while on TBS-1 TID, and no action was taken with the study drug in response to the event.
- Subject 029-005 reported gastroesophageal reflux disease while on TBS-1 TID, which resulted in interruption of study drug.

Both of the latter two SAEs were not considered by the Investigator to be related to the study drug, and the subjects continued in the study.

No subjects had TEAEs during Safety Extension Period 2 that led to study discontinuation. For more information on the SAEs during Safety Extension Period 2,

Table 44: Overview of Adverse Events: Safety Population TBS-1-2011-03-Safety Extension Period 2

Adverse Event Category	TBS-1 BID (N=34) n (%)	TBS-1 TID (N=40) n (%)	Total (N=74) n (%)
Subjects with any TEAE	17 (50.0)	22 (55.0)	39 (52.7)
Maximum severity of TEAE			
Mild	7 (20.6)	11 (27.5)	18 (24.3)
Moderate	10 (29.4)	9 (22.5)	19 (25.7)
Severe	0 (0.0)	2 (5.0)	2 (2.7)
Subjects with any drug-related TEAE [1]	5 (14.7)	6 (15.0)	11 (14.9)
Maximum severity of drug-related TEAE [1]			
Mild	3 (8.8)	5 (12.5)	8 (10.8)
Moderate	2 (5.9)	1 (2.5)	3 (4.1)
Severe	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with any SAE	1 (2.9)	2 (5.0)	3 (4.1)
Subjects with any treatment-emergent SAE	1 (2.9)	2 (5.0)	3 (4.1)
Subjects with any drug-related SAE [1]	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with any AE leading to death	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with TEAE leading to discontinuation	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with drug-related TEAE leading to discontinuation [1]	0 (0.0)	0 (0.0)	0 (0.0)
Note: All adverse events that started during Safety Extension Period 2 were considered TEAEs.			
1. Drug-related includes possible, probable, and definitely related.			

AE = adverse event; BID = twice daily; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TID=three time daily.

Source: Table 48, CSR TBS-1-2011-03, Page 125

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7.3.1 Deaths

Subject 004-008: Internal injuries due to motorcycle accident, motorcycle accident

Subject 004-008, a 58 year-old Caucasian male with hypogonadism was randomized to 5.5 mg 4.5% TBS-1 given three times daily on (b) (6). On Study Day 36 (b) (6), the subject was involved in a motorcycle accident and experienced internal injuries. On the same date, the subject expired due to internal injuries from the accident. The last dose of study medication was taken on Study Day 36 (b) (6). The subject's medical history includes impotence, hemorrhoids, colonoscopy, low testosterone, arthritis in bilateral feet joints, decreased vibratory perception of the lower extremities, absence of Achilles reflex, and seasonal allergies. Concomitant medication includes naproxen.

Reviewer's Comment: This event, in my opinion, is unrelated to the study drug.

7.3.2 Nonfatal Serious Adverse Events

Subject 001-036: Ischium and Pubic Fractures

This 28 year old male sustained ischium and pubis fractures on the right without extension into the acetabulum and an extraperitoneal hematoma on the right with bladder displacement from right to left. This event occurred prior to randomization and after screening. This subject is not included in the safety population.

Subject 025-023: Intermittent cardiac chest pain

Subject is a 70 year-old Caucasian male with hypogonadism and a history of myocardial infarction (1998). He was randomized to 5.5 mg 4.5% TBS-1 given two times daily on (b) (6). On Study Day 222 (b) (6), while swimming, the subject experienced abrupt moderate retrosternal left-sided chest pain radiating to the neck with tightness, pressure, and shortness of breath, lasting for five minutes. On Study Day 223 (b) (6), the subject developed mild chest pressure and bilateral leg pain. On Study Day 227 (b) (6), the subject presented to the emergency department with complaints of headache, anxiety, and pain in right leg and was admitted to the hospital. The chest pain had subsided at the time of admission. An extensive evaluation including ECG, CT of the head, laboratory, and echocardiogram were negative for an acute process. Myocardial perfusion imaging revealed normal myocardial perfusion. It was the opinion of the cardiology consult that the chest pain was suspicious for angina. The patient recovered from the acute event and was discharged on Study day 230 (b) (6). The study medication was interrupted on Study Day 227 (b) (6) and resumed on Study Day 231 (b) (6). The subject's medical history includes erectile dysfunction, umbilical hernia with repair, hypertension, type 2 diabetes mellitus, and hyperlipidemia. Concomitant medications include tadalafil, lisinopril, clonidine, metformin, multivitamin, hydrochlorothiazide, and telmisartan.

Reviewer's Comment: It is unlikely that this event was related to the study drug.

Subject 047-003: Broken Hip

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Subject is a 77 year-old Caucasian male with hypogonadism who was randomized to 5.5 mg 4.5% TBS-1 given two times daily on (b) (6). On Study Day 76 (b) (6), the subject was admitted to the hospital for evaluation and treatment of a broken hip. Treatment of the event included unspecified surgery, rehabilitation, calcium with vitamin D, and hydrocodone/acetaminophen. No action was taken with study drug in response to the event. The subject continued in the study. On Study Day 76 (b) (6), the subject recovered from the event of broken hip. On Study Day 86 (b) (6), the subject was discharged from the hospital. The subject's medical history includes cough, hearing loss, decreased breathing in lungs, seizures, back pain, and virus.

Reviewer's Comment: In my opinion, this event is unrelated to the study drug.

Subject 047-022: Fall at work, torn ligaments in knee due to falling at work

The subject is a 32 year-old Caucasian male with history of left-sided torn anterior cruciate ligament (ACL) surgery, knee pain from torn ACL, and left knee pain. He was randomized to 5.5 mg 4.5% TBS-1 given two times daily on (b) (6). On Study Day 107 (b) (6), the patient experienced a fall at work and torn ligaments in his knee due to the fall. On Study Day 107 (b) (6), the patient recovered from the event of fall at work. On Study Day 116 (b) (6), the patient was admitted to the hospital for surgical repair of the torn ligaments in his knee (side not stated). The study medication was interrupted on Study Day 116 (b) (6) and resumed on Study Day 119 (b) (6). The patient recovered from the event of torn ligaments in knee due to falling at work and was discharged from the hospital on Study Day 117 (b) (6). The patient's medical history also includes laparoscopic banding surgery, hyperlipidemia, depression, anxiety, seasonal allergies, and obesity. Concomitant medications include fish oil, rosuvastatin, lamotrigine, and sertraline.

Reviewer's Comment: This event is unrelated to the study drug, in my opinion.

Subject 010-039: Acute Coronary Syndrome

Subject is a 68 year-old Caucasian male with hypogonadism, who was randomized to 5.5 mg 4.5% TBS-1 given two times daily on (b) (6). On Study Day 37 (b) (6), the subject presented to the emergency department with complaints of left sided chest pressure, jaw discomfort, shortness of breath, and periodic dizziness. Patient was admitted for the treatment of an acute coronary syndrome. A nephrology consult was obtained due to elevated creatinine (creatinine at baseline was 1.15 ng/dL and on Day 27 it was 1.6 ng/dL) and a diagnosis of stage III to stage IV chronic kidney disease was made (creatinine on Day 37 was 2.4 ng/dL). Troponin I was reported as "normal." On Study Day 38 (b) (6), the subject underwent cardiac catheterization which revealed 90% stenosis of the right posterior descending coronary artery (RPD), 80% calcified stenosis of the mid right coronary artery (RCA), 40% non-obstructive disease in the left anterior descending coronary artery, and 30% non-obstructive disease in the mid left coronary artery. Coronary angioplasty was performed with stenting in the RPD and mid RCA. On Study Day 38 (b) (6), the subject recovered from the event of acute coronary syndrome and was discharged from the hospital on Study Day 39 (b) (6). The study medication was interrupted on Study Day 37 (b) (6) and resumed on Study Day 39 (b) (6). The subject's medical history includes neurosyphilis (multiple episodes), degenerative joint disease of the back and hips, hyperlipidemia, fasciitis, gynecomastia, erythrocytosis,

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arteriovenous malformation, small testicles, boggy prostate, slight aortic aneurysm, high blood pressure, herniated disc, post-traumatic stress disorder, anxiety, depression, and allergy to codeine (causes upset stomach). Concomitant medications include tizanidine, whey protein, duloxetine, hydrochlorothiazide, metoprolol, hydroxyzine pamoate, hydrocodone/acetaminophen, folic acid, Methyldrene, ginkgo biloba, vitamin B-12, potassium, omega-3, calcium, niacin, vitamin C, vitamin E, and multivitamin. His creatine on 18 October 2012 was 2.3 ng/dL. Originally this event was classified by the investigator as possibly related to the study drug, but upon re-assessment SAE was assessed by the same Investigator as highly unlikely to be a proximate cause of the exacerbation of the patient's coronary atherosclerosis and anginal symptoms and kidney disease.

Reviewer's Comment: It is unlikely that 37 days of TBS-1 therapy was the cause of either the acute coronary syndrome or the renal function changes noted. Coronary angiography revealed that the patient had pre-existing triple vessel coronary atherosclerosis.

Subject 010-039: Rocky Mountain Spotted Fever

This is the same subject as in the previously described SAE above. On Study Day 50, the subject's dose of study medication was increased to three times daily. On Study Day 143 ((b) (6)), the subject presented to the hospital with complaints of a one-week history of fever, chills, diffuse maculopapular rash, arthralgia and myalgias, dry cough, nausea, vomiting, abdominal pain, and loss of appetite with 10 pound weight loss. Upon review of systems, the subject noticed tenderness and swelling of his right forearm after working out and over the course of the next few days, a maculopapular rash erupted on his forearm and spread to his left arm, palms, trunk, lower extremities, and lower face. Additional symptoms associated with the rash included night sweats, generalized weakness, neck pain, and headache. He was diagnosed with Rocky Mountain spotted fever. The subject recovered from the event and was discharged from the hospital on Day 148. His creatine on Day 148 was 1.3 ng/dL. The study medication was interrupted on Study Day 143 ((b) (6)) and was resumed on Study Day 148 ((b) (6)).

Reviewer's Comment: This SAE was not related to the study drug, in my opinion.

Subject 022-012: Pneumonia

The subject is a 68 year-old Caucasian male with hypogonadism and was randomized to 5.5 mg 4.5% TBS-1 given two times daily on (b) (6). On Study Day 52 ((b) (6)), the patient's dose was increased to three times daily. On Study Day 324 ((b) (6)), the patient underwent upper and lower endoscopy for evaluation of recent weight loss and difficulty with bowel movements and urination, and received midazolam and fentanyl during the procedure. Later that same day, the patient experienced uncontrollable vomiting, nausea, headache, general malaise, lethargy, confusion, and fever of 102°F and presented to the emergency department for evaluation. A computed tomography (CT) scan of the chest revealed new areas of focal consolidation in the posterior lung bases, peripheral interstitial fibrosis with areas of consolidation in posterior lung bases, and honeycombing noted in the upper and lower lobes with a few stable small nodules. CT scan of the abdomen revealed mild mural thickening of the descending and rectosigmoid colon. The patient remained in the emergency room until Day 326. On Day 326, pulmonology consult reported that the patient's bibasilar lung infiltrates were most

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likely secondary pneumonia and given the patient's panendoscopy, the patient may have developed aspiration pneumonia. He was treated with appropriate anti microbial therapy. No action was taken with the study drug in response to the event. The patient continued in the study. The patient's medical history includes peripheral artery disease, femoral bypass, cholecystectomy, and inflamed gallbladder. Concomitant medication includes aspirin.

Reviewer's Comment: In light of the pulmonary consultative evaluation is it unlikely the study drug played any role in the causation of this SAE.

Subject 029-005: Gastroesophageal Reflux.

The subject is a 79 year-old Caucasian male with hypogonadism who was randomized to 5.5 mg 4.5% TBS-1 given two times daily on (b) (6). On Study Day 45 (b) (6), the subject's dosing was increased to three times daily. On Study Day 350 (b) (6), the subject presented to the hospital with complaints of non-cardiac chest pain (initially attributed as indigestion), panting, and shortness of breath and was admitted to the hospital for evaluation and treatment of gastroesophageal reflux disease. On Study Day 351 (b) (6), cardiac angiogram revealed evidence of aneurysmal dilatation of aorta and coronary system with 40% stenosis to the proximal circumflex. Features were consistent with nonobstructive coronary artery disease and atypical chest pain, suggestive of underlying gastro-intestinal etiology due to nonocclusive disease. Treatment of the event included omeprazole. Treatment recommendation included esophagogastroduodenoscopy; however, the procedure was not performed. The study medication was interrupted on Study Day 350 (b) (6) and resumed on Study Day 351 (b) (6). The subject recovered from the event on Study Day 351 (b) (6). The subject's medical history includes bilateral cataracts with removal, hypertension, hyperlipidemia, intermittent cough, erectile dysfunction, appendicitis with appendectomy, and cholelithiasis with cholecystectomy. Concomitant medications include clonidine, aspirin, gemfibrozil, enalapril, atenolol, Maxzide, simvastatin, and triamterene.

Reviewer's Comment: Testosterone therapy is not usually associated with upper tract GI symptoms other than nausea. A negative rechallenge is noted.

Subject 004-008: Internal injuries due to motorcycle accident, motorcycle accident

These SAEs led to death. See Death Narrative.

Subject 008-002:

The subject is a 53 year-old Black male with hypogonadism who was randomized to 5.5 mg 4.5% TBS-1 given three times daily on (b) (6). On Study Day 05 (b) (6), the subject experienced headache, chills, fatigue, and abdominal pain after morning dose of TBS-1 at 0700. On the same date, the study medication was interrupted by the subject and never restarted due to the event of abdominal pain. On Study Day 10 (b) (6), the subject presented to the emergency department with complaints of continued headache and abdominal pain with nausea. He admitted to the hospital and on Study Day 11 (b) (6), a computed tomography (CT) scan of the abdomen and pelvis revealed a large cystic mass in the upper abdomen, measuring 10.7 x 8.7 x 10.6 cm in size, located medial to the margin of the left lobe of the liver and along the anterior margin of the traversing distal aspect of the

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stomach. On the same date, the subject underwent CT guided needle drain placement and drainage of the abdominal cystic mass yielding 350 ml of red fluid. Cytology of the drained fluid revealed fibrinous and inflammatory debris and no malignant cells. Future treatment plan included possible removal of the mass. On Study Day 13 (██████████^{(b) (6)}), CT scan of the abdomen revealed a smaller cystic mass, measuring 6.9 x 4.8 cm in size, and presence of a drainage catheter. The subject recovered from the event of abdominal pain on Study Day 15 (██████████^{(b) (6)}). On the next day, the subject was discharged from the hospital. The subject was discontinued from the study on Study Day 26 (██████████^{(b) (6)}). On ██████████^{(b) (6)}, CT scan of the abdomen and pelvis revealed smaller area of fluid collection in the upper abdomen when compared to the prior CT scan, stable appearing right adrenal adenoma, and diverticulosis. On the same date, the subject recovered with sequelae (fluid collection in upper abdomen) from the event of abdominal mass. The subject's medical history includes hyperopia, diabetes type 2, hypertension, hypercholesterolemia, eyebrow dandruff, bilateral hand osteoarthritis, back pain, ruptured lumbar disc, leg cramps, circumcision, penile yeast infection, and bilateral knee crepitus. Concomitant medication includes cyclobenzaprine.

Reviewer's Comment: In my opinion, the study drug not related to these SAEs of abdominal mass and abdominal pain.

Reviewer's Overall SAE analysis: I concur with the Sponsor's analysis that none of the SAEs are related to the study drug

7.3.3 Dropouts and/or Discontinuations

Subject 011-007: Nasal discomfort, alteration of sense of smell, crusting of nasal passage.

This 65 year-old Caucasian male with hypogonadism was randomized to 5.5 mg 4.5% TBS-1 given two times daily on 19-Dec-2011. On Study Day 13 (31-Dec-2011), the subject experienced nasal discomfort. A few days later, on Study Day 16 (03-Jan-2012), the subject developed an alteration of sense of smell and crusting of the nasal passage. No treatment was given for the events. The study medication was withdrawn due to the events. The last dose of study medication was taken on Study Day 121 (17-Apr-2012). On the same day, the subject discontinued from the trial due to the event of nasal discomfort, alteration of sense of smell, and crusting of the nasal passage. The subject recovered from the events on 24-Apr-2012. The subject's medical history includes seasonal allergies and asthma (mild and intermittent).

Reviewer's Comment: In light of the positive dechallenge, the nasal symptoms appear to be related to the TBS-1 drug product.

Subject 012-008: Cloudy sensorium, headaches

This 66 year-old Caucasian male with hypogonadism was randomized to 5.5 mg 4.5% TBS-1 given two times daily on 26-Mar-2012. From Study Day 25 (19-Apr-2012) to Study Day 41 (05-May-2012), the subject experienced moderate headaches and cloudy sensorium. Treatment of the events included Excedrin. No action was taken with the study medication. On Study Day 53 (17-May-2012), the subject experienced a recurrence of headaches and a cloudy sensorium. Treatment of the event of headaches included continued Excedrin, naproxen, and

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tramadol. The study medication was withdrawn due to the events. On Study Day 60 (24-May-2012), the last dose of study medication was administered and the subject was discontinued from the trial due to the events of headaches and a cloudy sensorium. The subject recovered from the events on 01-Jun-2012.

Reviewers Comment: In light of the positive dechallenge and occurrence twice while on study medication, the events of clouded sensorium and headaches could be related to study medication.

Subject 043-004: Allergic reaction – face swelling to unknown allergen – possibly food; allergic reaction – hives, swollen lips to unknown allergen – possibly food; allergic reaction – swollen and numb lips and tongue to unknown allergen – possibly food

This 50 year-old Caucasian male with hypogonadism was randomized to 5.5 mg 4.5% TBS-1 given two times daily on 14-Mar-2012. From Study Day 93 (14-June-2012) to Study Day 94 (15-June-2012), the subject experienced an allergic reaction (face swelling) to unknown allergen. From Study Day 95 (16-Jun-2012) to Study Day 96 (17-June-2012), the subject experienced another two-day episode of an allergic reaction (hives, swollen lips). On Study Day 101 (22-June-2012), the subject experienced a two-day episode of an allergic reaction (swollen and numb lips and tongue) to unknown allergen and recovered on Study Day 102 (23-Jun-2012). Treatment of the events included fexofenadine and diphenhydramine. The study medication was withdrawn due to the events. On Study Day 102 (23-June-2012), the last dose of study medication was administered. The subject discontinued from the trial due to the events allergic reaction to unknown allergy on Study Day 122 (13-July-2012). The subject's medical history includes nose fracture, snoring, tonsillectomy, uvulectomy and seasonal allergies.

Reviewer's Comments: These allergic events are possibly related to the study drug in my opinion, although the information is not sufficient to draw a final conclusion. It is notable that the patient had a history of nose fracture and should not have been enrolled. n

Subject 008-003: Bitter taste after dosing, nasal odor after dosing

This 65 year-old Caucasian male with hypogonadism was randomized to 5.5 mg 4.5% TBS-1 given three times daily on 12-Jan-2012. After each dose of study medication starting with the first dose, the subject experienced a bitter taste and a nasal odor. No treatment was given for the event. The study medication was withdrawn due to the events. The last dose of study medication was administered on Study Day 90 (10-Apr-2012). On the same day, the subject recovered from the events and discontinued from the trial due to the events of bitter taste and nasal odor after dosing.

Reviewers Comment: The events of bitter taste and nasal odor are related to the study drug, in my opinion.

Subject 011-016: Elevated PSA

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This 55 year-old Caucasian male with hypogonadism and a total baseline prostate specific antigen (PSA) of 0.50 ug/mL (Normal Range [NR] 0.01 – 4.00 ug/mL) was randomized to 5.5 mg 4.5% TBS-1 given three times daily on 06-Mar-2012. On Study Day 84 (28-May 2012), laboratory results revealed a total PSA of 0.72 ug/mL. On Study Day 176 (28-Aug-2012), laboratory results revealed an elevated total PSA of 2.08 ug/mL, and on Study Day 183 (04-Sep-2012), a total PSA of 2.23 ug/mL. Unspecified other treatment was given for the event. The study medication was withdrawn due to the event. The last dose of study medication was administered on Study Day 184 (05-Sep-2012). The subject recovered from the event and discontinued from the trial due to the event of elevated PSA on Study Day 197 (18-Sep-2012) with a total PSA of 1.62 ug/mL. The subject's medical does not include any past significant urologic conditions.

Reviewer's Comment: Testosterone replacement has been associated with increases of PSA. This event does not generate a new safety concern, in my opinion.

Subject 021-014: Petechiae

This 39 year-old Caucasian male with hypogonadism was randomized to 5.5 mg 4.5% TBS-1 given three times daily on 27-Mar-2012. From Study Day 23 (18-Apr-2012) to Study Day 24 (19-Apr-2012), the subject experienced severe myalgia, moderate generalized joint pain, moderate fever, and moderate chills. Treatment of the events of myalgia and fever included acetaminophen. On Study Day 25 (20-Apr-2012), the subject developed petechiae and tingling and burning sensation in hands and feet bilaterally. No treatment was given for the event of petechiae. The study medication was withdrawn due to the event of petechiae. The last dose of study medication was administered on Study Day 25 (20-Apr-2012). The subject's platelet counts were 213 million/L on 22 November 2011, 203 million/L on 20 December 2011, 268 million/L on 26 March 2012, and 254 million/L on 25 April 2012. The subject recovered from the events of burning sensation and tingling in hands and feet bilaterally on Study Day 27 (22-Apr-2012). The subject discontinued from the trial due to the event of petechiae on Study Day 30 (25-Apr-2012). The subject recovered from the event of moderate petechiae on 09-May-2012. From 10-May-2012 to 20-May-2012, the petechiae were considered mild in severity. The subject's medical history includes esophageal stricture (multiple episodes) and dilatation (multiple episodes), high cholesterol, hemorrhoids, intermittent heartburn, Klinefelter's syndrome, wears glasses, and allergy to bananas and amoxicillin. Concomitant medications include simvastatin, sucralfate, omeprazole, and Pramosone.

Reviewers Comment: These events could possibly be related to the study drug, in my opinion. While causality is unclear, it would be reasonable to mention this event in labeling.

Reviewer's Overall Discontinuation Analysis: Two subjects discontinued secondary to local tolerability: 1. nasal odor with bitter taste and 2. nasal discomfort, alteration of sense of smell,

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crusting of nasal passage. These events point out that nasal adverse reactions leading to discontinuation is a possibility in a small percentage of patients. The low incidence and general mild severity of these events does not raise a safety concern. The one patient with an elevation of PSA that was greater than 4.0 ng/dL and greater than two times baseline is an expected adverse event with testosterone replacement. The low incidence of this event as a cause for discontinuation does not raise a significant safety concern. There were two incidences of allergic reactions. In neither allergy case is causality with Natesto clear. One is suggestive of angioedema and the other a possible systemic reaction which included petechiae, myalgia, joint pain, fever and chills. The pathophysiology of the second case remains speculative. Nonetheless, it would be reasonable to mention these cases in labeling.

7.3.4 Significant Adverse Events

In the opinion of this reviewer, the significant adverse events observed in these trials are: 1) Increased in the PSA secondary to testosterone use. These increases appeared to occur in a dose dependent manner with the incidence in the TID dose group of 12/78 (15.4%) compared to the BID dose group of 3/143 (2.1%). PSA elevations in most cases reversed with cessation of TBS-1 therapy, with either a return to either Baseline or at least to a level below 4 ng/mL. 2) An increase in hematocrit $\geq 54\%$ was observed in 2/78 (2.6%) TID group patients and 3/143 (2.1%) BID patients. Seven patients were identified with a hematocrit $\geq 54\%$ (Table 60 of this review). There were 3 in the BID dose group, 2 in the BID/TID dose group and 2 in the TID dose group. The Study Day these elevations were Days 180 (4), 270, 30, and 90 (one patient had elevations on Day 180 and 270). Polycythemia is a known testosterone related adverse reactions and is prominently noted in labeling. 3) Blood pressure increased was noted in 0/143 (0.0%) of BID dose patients and in 2/78 (2.6%) of TID dose group patients. Blood pressure increased was not noted in 120 BID dose patients or in the 152 TID dose patients in Safety period 1 and in no patient in Safety Period 2. There is no clear signal of hypertension or increased BP with Natesto.

7.3.5 Submission Specific Primary Safety Concerns

The discussion below will cover what are termed “Adverse Event of Interest” in the TBS-1-2011-03 complete study report (CSR).

7.3.5.1 Nasal Local Tolerance Events

The most common system organ class of TEAEs during all periods was “Respiratory, thoracic, and mediastinal disorders”: 24.2%, 13.6% and 18.9% for Day 90, 180 and 360 respectively. The most frequently reported TEAEs from this system organ class during all periods of the study were the events that can be attributed to and expected for the intranasal route of administration. For the TBS-1 BID group, such events were: rhinorrhea and nasal discomfort (7% each); and nasopharyngitis and epistaxis (6.3% each). Similarly, for the Combined TBS-1 TID group during all periods of the study, these events were rhinorrhea (8.5%) and epistaxis (6.7%). In the TID dose group for all study periods, the incidence of TEAEs was 25 (32.1%) in this SOC. At Day 90, 180 and 360 the incidences for TID subjects were 26.9%, 9.8% and 17.5% respectively. The majority of these events were mild in severity and did not require treatment. No increase in the proportion of the local tolerance events with treatment duration was observed during the study.

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Reviewer's Comment: As part of an analysis of local tolerance effects, I includes some additional AE terms from the "Nervous system disorders" SOC that could potentially be related to local tolerance of Natesto. Specifically, I added the term "headache" as a potential local tolerance AE. While acknowledging that not all reported headaches are likely to be Natesto-related, I included "headache" in the table below. Also, I included the terms, parosmia, dysgeusia (also added to the table below) and anosmia because I consider these to be related to local tolerance.

Table 45: Summary of Nasal(Local Tolerance) Treatment-Emergent Adverse Safety Population-All Periods

System Organ Class Preferred Term	TBS-1 BID (N=142) n (%)	Combined TBS-1 TID (N=164) n (%)	Total (N=306) n (%)
Nervous system disorders			
Parosmia	7 (4.9)	9 (5.5)	16 (5.2)
Headache	4 (2.8)	7 (4.3)	11(3.6)
Anosmia	0 (0.0)	1 (0.6)	1 (0.3)
Dysgeusia	2 (1.4)	5 (3.0)	7 (2.3)
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea	10 (7.0)	14 (8.5)	24 (7.8)
Epistaxis	9 (6.3)	11 (6.7)	20 (6.5)
Nasal discomfort	10 (7.0)	8 (4.9)	18 (5.9)
Nasal dryness	7 (4.9)	6 (3.7)	13 (4.2)
Nasal congestion	5 (3.5)	7 (4.3)	12 (3.9)
Nasal mucosal disorder	6 (4.2)	1 (0.6)	7 (2.3)
Rhinalgia	2 (1.4)	2 (1.2)	4 (1.3)
Nasal odor	2 (1.4)	1 (0.6)	3 (1.0)
Nasal septum disorder	2 (1.4)	1 (0.6)	3 (1.0)
Increased viscosity of nasal secretion	1 (0.7)	1 (0.6)	2 (0.7)
Nasal obstruction	1 (0.7)	1 (0.6)	2 (0.7)
Intranasal paraesthesia	0 (0.0)	1 (0.6)	1 (0.3)
Nasal discharge discoloration	1 (0.7)	0 (0.0)	1 (0.3)
Nasal edema	1 (0.7)	0 (0.0)	1 (0.3)
Nasal septum ulceration	0 (0.0)	1 (0.6)	1 (0.3)
Nasal ulcer	1 (0.7)	0 (0.0)	1 (0.3)
<p>Note: Subjects who were uptitrated to TID at Day 45 are included in the TBS-1 TID treatment group. Treatment-emergent adverse events during the Treatment Period were those adverse events having a start date on or after the first dose of study medication, or occurring prior to the first dose and worsening in severity during the Treatment Period. All adverse events that began during Safety Extension Period 1 and Safety Extension Period 2 were considered TEAEs. BID = twice daily; TEAE = treatment-emergent adverse event; TID = three times daily. Source: Table 50, CSR TBS-1-2011-03, page 129 and Table 20.4 page 958</p>			

Table 46: Summary of Nasal (Local Tolerance) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term-Safety Population-Treatment Period

System Organ Class Preferred Term	TBS-1 BID (N=143) n (%)	TBS-1 BID/TID (N=85) n (%)	TBS-1 TID (N=78) n (%)	Total (N=306) n (%)
Nervous system disorders				
Parosmia	7 (4.9)	3 (3.5)	2 (2.6)	12 (3.9)
Headache	4 (2.8)	7 (4.3)	3 (3.8)	14 (3.6)
Dysgeusia	1 (0.7)	1 (1.2)	2 (2.6)	4 (1.3)
Anosmia	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.3)
Respiratory, thoracic and mediastinal disorders				
Rhinorrhea	8 (5.6)	8 (9.4)	3 (3.8)	19 (6.2)
Epistaxis	6 (4.2)	5 (5.9)	3 (3.8)	14 (4.6)
Nasal discomfort	6 (4.2)	2 (2.4)	3 (3.8)	11 (3.6)
Nasal dryness	6 (4.2)	1 (1.2)	2 (2.6)	9 (2.9)
Nasal congestion	5 (3.5)	3 (3.5)	2 (2.6)	10 (3.3)
Nasal mucosal disorder	4 (2.8)	0 (0.0)	0 (0.0)	4 (1.3)
Rhinalgia	1 (0.7)	1 (1.2)	1 (1.3)	3 (1.0)
Nasal odour	2 (1.4)	0 (0.0)	1 (1.3)	3 (1.0)
Nasal septum disorder	1 (0.7)	0 (0.0)	1 (1.3)	2 (0.7)
Increased viscosity of nasal secretion	0 (0.0)	1 (1.2)	0 (0.0)	1 (0.3)
Nasal obstruction	1 (0.7)	0 (0.0)	1 (1.3)	2 (0.7)
Nasal edema	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)
Nasal ulcer	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)
Note: Treatment-emergent adverse events were defined as those adverse events having a start date on or after the first dose of study medication, or occurring prior to the first dose and worsening in severity during the Treatment Period. BID = twice daily; TID = three times daily.				

Source: Table 51, CSR TBS-1-2011-03, Page 130, CSR Table 20.1, and text page 142.

Reviewer's Comment: Significant nasal AEs such as septal ulceration and nasal ulcer were infrequent. Headache is reported at an incidence rate of $\leq 4.3\%$ in all treatment groups. None of the headaches were reported as severe or serious. Changes in sense of smell, taste are noted and are expected. Rhinorrhea was not uncommon.

7.3.5.2 Allergic Rhinitis and Local Tolerance Events

Overall, 59 subjects in the Phase 3 study reported a medical history of either allergic rhinitis or seasonal allergies/hay fever, and 49 subjects indicated allergies as an ongoing condition. The incidence of allergic symptoms and/or allergy exacerbations reported as an adverse event in this group of subjects during the study was low, even though the study period covered at least one to two allergy seasons. Of the 59 subjects with this medical history, only 3 (5.1%) subjects reported exacerbations of allergic rhinitis.

Table 47: Listing of Subjects with Medical History of Allergic Rhinitis and/or Seasonal Allergies/Hay Fever Who Experienced Exacerbations- Randomized Population-All Periods

Treatment Subject	TEAE	Period	Adverse Event Verbatim Term (Severity)	Related to Study Drug [1]	Resulted in Discontinuation
TBS-1 BID					
004-035	yes	T	Rhinitis (mild) [2]	yes	no
024-009	yes	T	Worsening seasonal allergy (mild)	no	no*
TBS-1 TID					
001-021	no	P	Acute sinusitis (mild) [2]	no	no*
003-001	yes	SE1	Worsening of allergic rhinitis (mild)	no	no*
022-002	yes	SE2	Worsening seasonal rhinitis (mild)	no	no*
<p>*Took concomitant medication. Note: Treatment-emergent adverse events during the Treatment Period were those adverse events having a start date on or after the first dose of study medication, or occurring prior to the first dose and worsening in severity during the Treatment Period. All adverse events that began during Safety Extension Period 1 and Safety Extension Period 2 were considered TEAEs. 1. Drug-related includes possible, probable, and definitely related. 2. Etiology not specified. Period: P = Pre-treatment; SE1 = Safety Extension Period 1; SE2 = Safety Extension Period 2; T = Treatment Period. BID = twice daily; TEAE = treatment-emergent adverse event; TID = three times daily. Sources: Table 54, CSR TBS-1-2011-03, Page 133</p>					

A total of 19 (32.2%) subjects in this group reported the following nasal adverse events (without allergic etiology specified): parosmia, epistaxis, nasal discomfort, nasal congestion, and/or rhinorrhea. The majority of these events were mild in intensity and did not require intervention. The incidence of these nasal adverse events in this subset of subjects was as follows: parosmia (10.2%), epistaxis (10.2%), nasal discomfort (8.5%), nasal congestion (5.1%), and rhinorrhea (6.8%). The Sponsor observes that the incidence of these nasal adverse events in this subset of subjects was either slightly higher or comparable to the full study Safety Population (i.e., the incidence of epistaxis in the full study Safety Population was 6.5%, nasal discomfort 5.9%, nasal congestion 3.9%, and rhinorrhea 7.8%). Parosmia was the only event with a noticeably higher incidence than in the general Safety Population (5.2%). However, parosmia is a symptom that is often associated with allergic rhinitis in general; therefore, a higher incidence of this condition can be expected in the group of subjects with seasonal allergies.

Table 48: Listing of Subjects with Medical History of Allergic Rhinitis and/or Seasonal Allergies/Hay Fever Who Experienced Local Tolerance Events-Randomized Population-All Periods

Treatment Subject	TEAE	Period	Adverse Event Preferred Term (Severity)	Related to Study Drug [1]	Resulted in Discontinuation
TBS-1 BID					
011-009	yes	T	Parosmia (mild)	no	no
043-007	yes	T	Epistaxis (mild)	yes	no
047-035	yes	T	Epistaxis (mild)	yes	no
	yes	T	Nasal discomfort (mild)	yes	no
010-046	yes	T-SE1	Rhinorrhea (mild)	yes	no
	yes	SE1	Rhinorrhea (moderate)	yes	no
011-007	yes	T-SE1	Nasal discomfort (mild)	yes	yes
	yes	T-SE1	Parosmia (mild)	yes	yes
022-008	yes	SE1	Nasal discomfort (mild)	yes	no
022-042	yes	SE1	Epistaxis (mild)	no	no
029-014	yes	SE1	Rhinorrhea (mild)	yes	no
TBS-1 TID					
004-008	yes	T	Nasal congestion (mild)	yes	no
007-017	yes	T	Nasal discomfort (mild)	yes	no
048-011	yes	T	Epistaxis (mild)	no	no
021-020	yes	T	Epistaxis (mild)	yes	no
	yes	T-SE1	Epistaxis (mild)	yes	no
048-013	yes	T	Nasal congestion (moderate)	yes	no
	yes	T	Parosmia (mild)	no	no
	yes	T-SE1	Rhinorrhea (mild)	no	no
052-015	yes	T	Nasal congestion (mild)	yes	no
	yes	T-SE1	Parosmia (mild)	yes	no
052-027	yes	T-SE1	Rhinorrhea (mild)	yes	no
010-045	yes	SE1	Parosmia (mild)	no	no
011-008	yes	SE1-SE2	Nasal discomfort (mild)	yes	no
003-001	yes	SE2	Parosmia (mild)	yes	no
029-003	yes	SE2	Epistaxis (mild)	yes	no
	yes	SE2	Epistaxis (mild)	yes	no*
<p>*Took concomitant medication.</p> <p>Note: Treatment-emergent adverse events during the Treatment Period were those adverse events having a start date on or after the first dose of study medication, or occurring prior to the first dose and worsening in severity during the Treatment Period. All adverse events that began during Safety Extension Period 1 and Safety Extension Period 2 were considered TEAEs.</p> <p>1. Drug-related includes possible, probable, and definitely related.</p> <p>Period: SE1 = Safety Extension Period 1; SE2 = Safety Extension Period 2; T = Treatment Period.</p> <p>BID = twice daily; TEAE = treatment-emergent adverse event; TID = three times daily.</p> <p>Sources: Table 55, CSR TBS-1-2011-03, Page 134</p>					

7.3.5.3 Lipid Abnormalities

The effect of testosterone replacement on lipid parameters is not entirely clear. Beneficial and detrimental effects have been purported. The reviewer evaluated data from this NDA to assess for signals.

Table 49: Listing of Subjects with Lipid Abnormalities Considered to Be Treatment Emergent Adverse Events-Safety Population-All Periods

Dose Group Subject	Period	Adverse Event Preferred Term (Severity)	Related to Study Drug [1]	Visit: Other Values	Lipid Value Abnormal	Action/ Outcome
TBS-1 BID						
004-001	T	Hypertriglyceridaemia (moderate)	yes	Visit 1- <u>231</u> Visit 4- <u>605</u> Unscheduled- <u>529</u>	(normal range: 50-150 mg/dL)	Dose not changed/ Not recovered/ Not resolved
011-026	T	Hypercholesterolaemia (mild)	yes	Visit 4- <u>226</u> Visit 1-185 Visit 6-187 Visit 9-181	(normal range: 100-200 mg/dL)	Dose not changed/ Concomitant medication/ Not recovered/ Not resolved
		LDL		Visit 1-110 Visit 4- <u>141</u> Visit 6-112 Visit 9-112	LDL-C (normal range: 50-130 mg/dL)	
052-024	SE1	Hypertriglyceridaemia (mild)	no	Visit 1- <u>155</u> Visit 1.1-105 Visit 4-94 Visit 6-97 Early Termination- <u>254</u> Unsched- <u>142</u>	(normal range: 50-150 mg/dL)	Dose not changed/ Not recovered/ Not resolved Early Termination Not for this AE
Combined TBS-1 TID						
016-019	T	Blood triglycerides increased (mild)	no	Visit 1- <u>283</u> Visit 4- <u>1042</u> Visit 6- 71 Visit 9-73	(normal range: 50-150 mg/dL)	Dose not changed/ Concomitant medication/ Recovered/ Resolved

Combined TBS-1 TID (CONTINUATION of Table 51)						
044-021	T	Hyperlipidaemia (moderate)	yes	Visit 1- <u>241</u> Visit 4-195 Visit 6-186 Visit 9-183	(normal range: 100-200 mg/dL) LDL-C 166 mg/dL H (normal range: 50-130 mg/dL)	Dose not changed/ Concomitant medication/ Not recovered/ Not resolved
007-043	T- SE1	Blood triglycerides increased (mild)	no	Visit 1-128 Visit 4- <u>200</u> Visit 6- <u>349</u> Visit 9-90	(normal range: 50-150 mg/dL)	Dose not changed/ Recovered/ Resolved
		HDL decreased (mild)	No	Visit 6- <u>28</u> Visit 1-36 Visit 9-38	(normal range: 35-60 mg/dL)	Dose not changed/ Recovered/ Resolved

SE1=Safety Extension Period 1: T=Treatment Period

Source: Table 56, CSR TBS-1-2011-03, Page 136

In total, 6 (2.0%) subjects had 7 lipid-related TEAEs (3 [2.1%] subjects in the TBS-1 BID group and 3 [1.8%] subjects in the Combined TBS-1 TID group). Three of these 7 lipid-related TEAEs were considered by the Investigator to be related to the study medication. The majority of these events were mild in intensity and no increase in incidence with treatment duration was observed. None of the subjects with lipid-related TEAEs discontinued from the study.

Reviewer's Comment: In the TBS-1 TID group, three patients had elevations of triglycerides. Patient 016-019 had a baseline triglyceride elevation that increased by Visit 4 and returned to normal on Visits 6 and 9. Patient 044-021 had elevated triglycerides at baseline with lower elevated levels at Visits 4, 6 and 9. Patient 007-043 had normal triglycerides at baseline, increased triglycerides at Visits 4 and 6 and normal triglycerides at Visit 9 (Day180). In the BID dose group, only patient 004-001 appears to have a triglyceride elevation that could be related to TBS-1 and this patient had a

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triglyceride elevation at baseline. There is insufficient evidence to conclude a relationship between Natesto and lipid abnormalities. Natesto labeling will be consistent with the class labeling for this issue.

In the 120 Day Safety Update, four additional lipid profile abnormalities were noted in SE2. Patients 011-015, 022-017 and 044-011 (all were TID patients) had LDL-C levels above the upper limit of normal and patient 044-010 had a LDL-C level below normal.

Table 50: Serum LDL (mg/dL) Values Above the Normal Limit in Period 2 Patients BBS-1-2011-03

Patient/Dose	Visit 1	V-4	V-6	V-9	V-12	V-15
011-015 (BID/TID)	121	110	112	120	120	142
022-017 (BID/TID)	Cannot Calculate	Cannot Calculate	140	Cannot Calculate	116	146
044-011 (BID/TID)	193	Cannot Calculate	Cannot Calculate	154	Cannot Calculate	175

Source: Listing 17.3 page 1594, 120 Day Safety Update TBS-1-2011-03

Reviewer's Comment: I can only count patient 011-015 as having a documented LDL elevation, and even in that patient the increase is relatively modest. This additional information does not appreciably alter the TBS-1 safety profile, in my opinion.

7.3.5.4 Prostate Specific Antigen

A total of 6 (3.79%) subjects from the Combined TBS-1 TID group, 3 (2.1%) from the BID dose group and 4 (5.1%) from the TID group in the treatment period had a TEAE of increased PSA. "Increased PSA" was not based upon any clinical parameters, but rather on increases from baseline > 1.4 ng/mL or any value > 4 ng/mL. In Safety Extension Period 1, 4.2% of BID dose patients and 2.9% of TID patients had a TEAE of increased PSA. In Safety Extension Period 2, there was one patient with a TEAE of PSA increased. The elevation of PSA values above the ULN was reported in 5 cases; the remainder of the events were due to elevation of PSA by >1.4 ng/mL. Only 2 subjects were discontinued from the study due to this adverse event (Subject 001-049 and Subject 011-016), per the Investigator's decision. Both subject's PSA values were monitored after TBS-1 discontinuation. A relatively rapid decrease in PSA values was reported for both subjects after TBS-1 discontinuation, with a resolution of the adverse event within an average of 60 days. One subject (Subject 028-005) interrupted TBS-1 administration for 2 weeks after the increase in PSA and then was re-challenged. His PSA initially increased from 0.65 ng/mL at baseline to 3.15 ng/mL at Visit 6, but returned to the baseline value after de-challenge. All of the subject's post-re-challenge PSA measurements were at baseline level, and the subject successfully completed the study (Safety Extension Period 2).

Table 51: Listing of Subjects with Increased PSA Considered to be Treatment-Emergent Adverse Events Safety Population All Periods

Patient Dose in Treatment Period	Period	Adverse Event Preferred Term (Severity)	Related to Study Drug [1]	Visit	PSA Value (Normal Range: 0.01-4 ng/mL)	Action/ Outcome
Combined TBS-1 TID						
003-013 TID	T	PSA Increased (mild)	yes	Visit 1 Visit 6 (Day 90 - 91) Unscheduled visit Visit 9 (Day 180)	1.65 ng/mL 2.67 ng/mL 2.45 ng/mL 2.35 ng/mL	Dose not changed/ Not recovered/ Not resolved
003-022 TID	T	PSA Increased (mild)	yes	Visit 1.1 Visit 6 (Day 90 - 91) Early termination Day 104 visit [2]	1.88 ng/mL 4.33 ng/mL H 7.41 ng/mL H	Dose not changed/ Concomitant medication/ Unknown
008-003 TID	T	PSA Increased (moderate)	no	Visit 1 Early termination Day 43 visit [2]	2.39 ng/mL 5.11 ng/mL H	Dose not changed/ Concomitant medication/ Not recovered/ Not resolved
047-013 BID/TID	T	PSA Increased (mild)	no	Visit 1 Early termination Day 43 visit [2]	2.77 ng/mL 4.81 ng/mL H	Dose not changed/ Recovered/ Resolved
001-049 Discontinued for PSA Increased BID/TID	T-SE1	PSA Increased (mild)	yes	Visit 1 Visit 6 (Day 90 - 91) Unscheduled visit Day 96 Early termination Day 103	1.44 ng/mL 4.24 ng/mL H 3.98 ng/mL 3.10 ng/mL	Drug withdrawn Recovered/ Resolved
052-038 BID/TID	T-SE1	PSA Increased (mild)	yes	Visit 1 Visit 6 (Day 90 - 91) Visit 9 (Day 180)	3.34 ng/mL 4.28 ng/mL H 3.58 ng/mL	Dose not changed/ Recovered/ Resolved
010-005 BID Treat TID SE1	SE1	PSA Increased (mild)	yes	Visit 1 Visit 6 (Day 90 - 91) Visit 9 (Day 180)	3.68 ng/mL 2.93 ng/mL 3.95 ng/mL	Dose not changed/ Not recovered/ Not resolved

Combined TBS-1 TID (Table 52 Continued)						
028-005 BID/TID	SE1	PSA Increased (mild)	yes	Visit 1.1 Visit 6 (Day 90 - 91) Visit 9 (Day 180) Visit 12 (Day 270) Visit 15 (Day 360)	0.65 ng/mL 3.15 ng/mL 0.74 ng/mL 0.74 ng/mL 0.72 ng/mL	Drug interrupted/ Recovered/ Resolved

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052-015 BID/TID	SE1	PSA Increased (moderate)	yes	Visit 1.1 Visit 6 (Day 90 - 91) Visit 9 (Day 180)	1.91 ng/mL 2.64 ng/mL 3.42 ng/mL	Dose not changed/ Not recovered/ Not resolved
011-016 Discontinued for PSA Increased TID	SE1- SE2	PSA Increased (mild)	yes	Visit 1 Visit 6 (Day 90 - 91) Visit 9 (Day 180) Unscheduled visit Day 187 Early termination visit Day 201	0.50 ng/mL 0.72 ng/mL 2.08 ng/mL 2.23 ng/mL 1.62 ng/mL	Drug withdrawn/ Recovered/ Resolved
<p>Note: Treatment-emergent adverse events (TEAEs) during the Treatment Period were those adverse events having a start date on or after the first dose of study medication, or occurring prior to the first dose and worsening in severity during the Treatment Period. All adverse events that began during Safety Extension Period 1 and Safety Extension Period 2 were considered TEAEs.</p> <p>1. Drug-related includes possible, probable, and definitely related.</p> <p>2. Subject's early termination was not due to PSA adverse event.</p> <p>Period: SE1 = Safety Extension Period 1; SE2 = Safety Extension Period 2; T = Treatment Period.</p> <p>BID = twice daily; H = high; PSA = prostate specific antigen; TID = three times daily.</p> <p>Source: Table 57, CSR TBS-1-2011-03, page 139</p>						

Reviewer's Comment: Testosterone can cause PSA elevations. Subject 028-005 shows a positive dechallenge and rechallenge consistent with this effect. There no incident cases of prostate cancer in the treatment and safety extension groups. The incidence of PSA elevations in this study does not raise new safety concerns.

7.3.5.5 Prostate Enlargement

There were 2 (1.4%) subjects in the TBS-1 BID group with a TEAE of prostatomegaly without PSA elevations, as follows:

- Subject 015-021 had prostatomegaly at Day 90 of unknown duration, that was considered by the Investigator to be mild in severity and possibly related to study drug. The subject did not have any PSA abnormalities during the study. He did not have any related medical history reported, and his baseline DRE was normal.
- Subject 052-030 had prostatomegaly that was considered by the Investigator to be moderate in severity and definitely related to study drug. The event began on Day 85 and resolved on Day 175. The subject did not have any PSA abnormalities during the study. He did not have any related medical history reported, and his baseline DRE was normal.

Reviewer's Comment: There is insufficient information to draw conclusions about these two cases. We have not been given information that the same investigator did the rectal exams on these patients. The annotated study book for the protocol does not contain diagrams or ask for specific details of the prostatic exam which could include prostate height, width and length. Rectal exams without standardization may not be a reliable reproducible method of assessing prostatic size. PSA changes may be a more reliable

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indicator of prostate size increase but can be confounded by other factors such as inflammation or lower urinary tract procedure.

Subject 003-022 had a TEAE of benign prostatic hyperplasia reported at Day 113, after he withdrew his study consent on Day 108. At the early termination visit (Day 108), the subject's DRE results were normal, but his PSA was increased to 7.41 ng/mL. He was referred to the urologist for a consultation. The urology consult revealed enlarged prostate, and antibiotic (doxycycline) was prescribed to treat this condition. Since the prostate enlargement on physical exam was considered to be likely due to inflammatory causes, the Investigator assessed this event as not related to study drug. This patient is also listed with increased PSA as a TEAE.

Reviewer's Comment: It is not clear whether the patient had prostate enlargement, but he clearly had an increase in serum PSA, which could be a result of prostate inflammation. As is shown in this case, the investigator's rectal was not in agreement with the urology consult rectal result. Nonetheless, this event raises no new safety concerns.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The table below provides an overview of adverse events for the safety population during all periods of the study. During the study, a total of 196 (64.1%) subjects reported a treatment-emergent adverse event (TEAE): 90 (63.4%) subjects in the TBS-1 BID group, 106 (64.6%) subjects in the Combined TBS-1 TID group and 55 (70.5%) in the TID group. There were 14 (4.6%) subjects with TEAEs that were severe, and only 2 (0.6%) subjects in whom severe drug-related TEAE were reported. The majority of TEAEs and drug-related TEAEs were mild in severity. 1 (0.3%) subject had a severe drug-related TEAE of myalgia (he recovered with concomitant medication [discussed in SAEs] and another had a moderate event (transient prolonged QT [discussed in ECG results]) considered by investigator to be possibly related to the study drug.

For a summary of adverse events in **TID-only** patients the reader is referred to Table 70 of this review. For an overall summary of the TID safety experience, the reader is referred to Tables 69, 73 and 74 of this review.

Eight (2.6%) subjects reported SAEs during the study: 3 (2.1%) subjects in the TBS-1 BID group, 5 (3.0%) subjects in the Combined TBS-1 TID group and 2 (1.2%) in the TID group. None of the SAEs during the study were considered by the Investigator to be related to the study drug. Nine (2.9%) subjects discontinued from the study due to a TEAE: 3 (2.1%) subjects in the TBS-1 BID group, 6 (3.7%) subjects in the Combined TBS-1 TID group and 5 (3.0) in the TID group. Seven (2.3%) subjects discontinued from the study due to a drug-related TEAE: 3 (2.1%) subjects in the TBS-1 BID group and 4 (2.4%) subjects in the Combined TBS-1 TID group.

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One subject in the TBS-1 TID group died during the Treatment Period as a result of internal injuries due to a motorcycle accident.

Table 52: Summary of Treatment-Emergent Adverse Events ($\geq 2\%$ of Subjects in Any Treatment Group) by Organ System Class and Preferred Term-Safety Population-All Periods

System Organ Class Preferred Term	TBS-1 BID (N=142) n (%)	Combined TBS-1 TID (N=164) n (%)	Total (N=306) n (%)
Subjects with any TEAE	90 (63.4)	106 (64.6)	196 (64.1)
Gastrointestinal disorders	8 (5.6)	17 (10.4)	25 (8.2)
Nausea	1 (0.7)	5 (3.0)	6 (2.0)
Vomiting	3 (2.1)	2 (1.2)	5 (1.6)
General disorders and administration site conditions	3 (2.1)	13 (7.9)	16 (5.2)
Pyrexia	0 (0.0)	4 (2.4)	4 (1.3)
Infections and infestations	33 (23.2)	44 (26.8)	77 (25.2)
Nasopharyngitis	9 (6.3)	16 (9.8)	25 (8.2)
Upper respiratory tract infection	6 (4.2)	7 (4.3)	13 (4.2)
Bronchitis	3 (2.1)	5 (3.0)	8 (2.6)
Tooth abscess	0 (0.0)	4 (2.4)	4 (1.3)
Injury, poisoning and procedural complications	10 (7.0)	16 (9.8)	26 (8.5)
Excoriation	3 (2.1)	2 (1.2)	5 (1.6)
Investigations	8 (5.6)	30 (18.3)	38 (12.4)
PSA increased	0 (0.0)	10 (6.1)	10 (3.3)
Blood CPK increased	2 (1.4)	4 (2.4)	6 (2.0)
Musculoskeletal and connective tissue disorders	17 (12.0)	21 (12.8)	38 (12.4)
Back pain	4 (2.8)	5 (3.0)	9 (2.9)
Pain in extremity	3 (2.1)	5 (3.0)	8 (2.6)
Arthralgia	3 (2.1)	4 (2.4)	7 (2.3)
Nervous system disorders	16 (11.3)	26 (15.9)	42 (13.7)
Parosmia	7 (4.9)	9 (5.5)	16 (5.2)
Headache	4 (2.8)	7 (4.3)	11 (3.6)
Dysgeusia	2 (1.4)	5 (3.0)	7 (2.3)

Note: Subjects who were uptitrated to TID at Day 45 are included in the TBS-1 TID treatment group. Treatment-emergent adverse events during the Treatment Period were those adverse events having a start date on or after the first dose of study medication, or occurring prior to the first dose and worsening in severity during the Treatment Period. All adverse events that began during Safety Extension Period 1 and Safety Extension Period 2 were considered TEAEs.
 BID = twice daily; CPK = creatine phosphokinase; PSA = prostate specific antigen;

TEAE = treatment-emergent adverse event; TID = three times daily.

Source: Table 49, CSR TBS-1-2011-03, page 127:

During the Treatment Period, 152 (49.7%) subjects reported a TEAE: 66 (46.2%) subjects in the TBS-1 BID group, 40 (47.1%) subjects in the TBS-1 BID/TID group, and 46 (59.0%) subjects in the TBS-1 TID group. The majority of TEAEs and drug-related TEAEs were mild in severity.

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Five (1.6%) subjects reported a total of 7 SAEs during the Treatment Period: 2 (1.4%) subjects in the TBS-1 BID group, 1 (1.2%) subject in the TBS-1 BID/TID group during the BID regimen, and 2 (2.6%) subjects in the TBS-1 TID group. Eight (2.6%) subjects discontinued during the Treatment Period due to a TEAE: 3 (2.1%) subjects in the TBS-1 BID group, 1 (1.2%) subject in the TBS-1 BID/TID group, and 4 (5.1%) subjects in the TBS-1 TID group. Six (2.0%) subjects discontinued due to a drug-related TEAE: 3 (2.1%) subjects in the TBS-1 BID group, 1 (1.2%) subject in the TBS-1 BID/TID group, and 2 (2.6%) subjects in the TBS-1 TID group.

Reviewer's Comment: Events of deep vein thrombosis/phlebitis, pulmonary embolism, thrombosis or phlebitis were not reported in TBS-1-2011-03(CSR Table 20.4, page 958).

Table 53 Summary of Treatment-Emergent Adverse Events ($\geq 2\%$ of Subjects in Any Treatment Group) by System Organ Class and Preferred Term-Safety Population Treatment Period

System Organ Class Preferred Term	TBS-1 BID (N=143) n (%)	TBS-1 BID/TID (N=85) n (%)	TBS-1 TID (N=78) n (%)	Total (N=306) n (%)
Subjects with any TEAE	66 (46.2)	40 (47.1)	46 (59.0)	152 (49.7)
Gastrointestinal disorders	3 (2.1)	3 (3.5)	4 (5.1)	10 (3.3)
Nausea	1 (0.7)	1 (1.2)	2 (2.6)	4 (1.3)
Retching	0 (0.0)	2 (2.4)	0 (0.0)	2 (0.7)
General disorders and administration site conditions	1 (0.7)	5 (5.9)	3 (3.8)	9 (2.9)
Chills	0 (0.0)	1 (1.2)	2 (2.6)	3 (1.0)
Pyrexia	0 (0.0)	1 (1.2)	2 (2.6)	3 (1.0)
Infections and infestations	15 (10.5)	9 (10.6)	15 (19.2)	39 (12.7)
Nasopharyngitis	4 (2.8)	4 (4.7)	3 (3.8)	11 (3.6)
Bronchitis	2 (1.4)	0 (0.0)	3 (3.8)	5 (1.6)
Tooth abscess	0 (0.0)	1 (1.2)	3 (3.8)	4 (1.3)
Upper respiratory tract infection	1 (0.7)	0 (0.0)	3 (3.8)	4 (1.3)
Sinusitis	0 (0.0)	0 (0.0)	3 (3.8)	3 (1.0)
Injury, poisoning and procedural complications	6 (4.2)	2 (2.4)	5 (6.4)	13 (4.2)
Muscle strain	1 (0.7)	0 (0.0)	2 (2.6)	3 (1.0)
Investigations	3 (2.1)	9 (10.6)	12 (15.4)	24 (7.8)
PSA increased	0 (0.0)	2 (2.4)	4 (5.1)	6 (2.0)
Blood CPK increased	1 (0.7)	2 (2.4)	2 (2.6)	5 (1.6)
Blood pressure increased	0 (0.0)	1 (1.2)	2 (2.6)	3 (1.0)

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Blood thyroid stimulating hormone increased	1 (0.7)	0 (0.0)	2 (2.6)	3 (1.0)
Weight increased	0 (0.0)	2 (2.4)	0 (0.0)	2 (0.7)
Musculoskeletal and connective tissue disorders	12 (8.4)	6 (7.1)	7 (9.0)	25 (8.2)
Back pain	4 (2.8)	1 (1.2)	2 (2.6)	7 (2.3)
Arthralgia	1 (0.7)	1 (1.2)	2 (2.6)	4 (1.3)
Myalgia	0 (0.0)	0 (0.0)	2 (2.6)	2 (0.7)
<p>Note: Treatment-emergent adverse events were those adverse events having a start date on or after the first dose of study medication, or occurring prior to the first dose and worsening in severity during the Treatment Period. BID = twice daily; CPK = creatine phosphokinase; PSA = prostate specific antigen; T Source: Table 59, CSR TBS-1-2011-03, Page 142 TEAE = treatment-emergent adverse event; TID = three times daily.</p>				

During Safety Extension Period 1. Overall, the proportion of subjects with TEAEs, and with drug-related TEAEs in particular, decreased during Safety Extension Period 1 as compared to the Treatment Period. A total of 101 (37.1%) subjects reported a TEAE in in Safety Extension Period 1: 42 (35.0%) in the TBS-1 BID group and 59 (38.8%) in the TBS-1 TID group. There were 7 (2.6%) subjects with TEAEs during Safety Extension Period 1 that were severe. The majority of TEAEs during Safety Extension Period 1 were also mild in severity. One (0.4%) subject reported an SAE during Safety Extension Period 1. Subject 010-039 (TBS-1 BID/TID group) had Rocky Mountain spotted fever during the TID regimen. No other subjects had an SAE during Safety Extension Period 1. Also, fewer subjects discontinued from the study due to a TEAE during Safety Extension Period 1 than during the Treatment Period. Two (0.7%) subjects had TEAEs during Safety Extension Period 1 that led to study discontinuation: 1 (0.8%) subject in the TBS-1 BID group and 1 (0.7%) subject in the TBS-1 TID group. The Investigator considered both of these TEAEs to be related to study drug.

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Table 54: Summary of Treatment-Emergent Adverse Events ($\geq 2\%$ of Subjects in any Treatment Group) by System Organ Class and Preferred Term-Safety Population-Safety Extension Period 1

System Organ Class Preferred Term	TBS-1 BID (N=120) n (%)	TBS-1 TID (N=152) n (%)	Total (N=272) n (%)
Subjects with any TEAE	42 (35.0)	59 (38.8)	101 (37.1)
Infections and infestations	11 (9.2)	18 (11.8)	29 (10.7)
Nasopharyngitis	2 (1.7)	5 (3.3)	7 (2.6)
Upper respiratory tract infection	3 (2.5)	3 (2.0)	6 (2.2)
Bronchitis	1 (0.8)	3 (2.0)	4 (1.5)
Investigations	5 (4.2)	7 (4.6)	12 (4.4)
PSA increased	0 (0.0)	4 (2.6)	4 (1.5)
Musculoskeletal and connective tissue disorders	4 (3.3)	7 (4.6)	11 (4.0)
Pain in extremity	0 (0.0)	3 (2.0)	3 (1.1)
Nervous system disorders	1 (0.8)	10 (6.6)	11 (4.0)
Headache	0 (0.0)	3 (2.0)	3 (1.1)
Parosmia	0 (0.0)	3 (2.0)	3 (1.1)
Respiratory, thoracic and mediastinal disorders	18 (15.0)	19 (12.5)	37 (13.6)
Epistaxis	3 (2.5)	4 (2.6)	7 (2.6)
Nasal discomfort	5 (4.2)	2 (1.3)	7 (2.6)
Nasal dryness	2 (1.7)	3 (2.0)	5 (1.8)
Rhinorrhoea	3 (2.5)	2 (1.3)	5 (1.8)
Skin and subcutaneous tissue disorders	5 (4.2)	7 (4.6)	12 (4.4)
Scab	3 (2.5)	2 (1.3)	5 (1.8)

Note: All adverse events that started during Safety Extension Period 1 were considered TEAEs. BID = twice daily; PSA = prostate specific antigen; TEAE = treatment-emergent adverse event; TID = three times daily.

Source: Table 60, CSR TBS-1-2011-03, Page 144

The proportion of subjects with drug-related TEAEs was lower during Safety Extension Period 2 than during either the Treatment Period or Safety Extension Period 1. The percentage of subjects with any TEAE in this period was comparable to the Treatment Period, and higher than in Safety Extension Period 1. A total of 39 (52.7%) subjects reported a TEAE in Safety Extension Period 2: 17 (50.0%) subjects in the TBS-1 BID and 22 (55.0%) subjects in the TBS-1 TID group. There were 2 (2.7%) subjects with TEAEs during Safety Extension Period 2 that were severe. The majority of TEAEs during Safety Extension Period 2 were mild in severity. In the 120 Day Safety Update, the Sponsor states that the overall number of study drug related TEAEs increased from 10 (13.5%) to 11 (14.9%) at the completion of Safety Extension Period 2. The total of all TEAEs in SE2 was 39/74 (52.7%) with 9/16 (50.0%) TID patients experiencing a TEAE.

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Three (4.1%) subjects reported SAEs during Safety Extension Period 2:

- TBS-1 BID group (1 subject): Subject 025-023 had angina pectoris which the Investigator judged to be “definitely not related” to study drug, although this SAE resulted in interruption of study drug.

- TBS-1 BID/TID group (2 subjects):

 - Subject 022-012 reported aspiration pneumonia while on TBS-1 TID.

 - Subject 029-005 reported gastroesophageal reflux disease while on TBS-1 TID.

Both of these SAEs were not considered related to the study drug, and the subjects continued in the study.

No subject had TEAEs during Safety Extension Period 2 that led to study discontinuation.

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Table 55: Summary of Treatment -Emergent Adverse Events ($\geq 2\%$ of Subjects in Any Treatment Group) by System Organ Class and Preferred Term-Safety Population-Safety Extension Period 2

System Organ Class Preferred Term	TBS-1 BID (N=34) n (%)	TBS-1 TID (N=40) n (%)	Total (N=7) n (%)
Subjects with any TEAE	17 (50.0)	22 (55.0)	39 (52.7)
Blood and lymphatic system disorders	0 (0.0)	1 (2.5)	1 (1.4)
Pancytopenia	0 (0.0)	1 (2.5)	1 (1.4)
Cardiac disorders	1 (2.9)	0 (0.0)	1 (1.4)
Angina pectoris	1 (2.9)	0 (0.0)	1 (1.4)
Bundle branch block left	1 (2.9)	0 (0.0)	1 (1.4)
Ear and labyrinth disorders	2 (5.9)	0 (0.0)	2 (2.7)
Cerumen impaction	1 (2.9)	0 (0.0)	1 (1.4)
Tinnitus	1 (2.9)	0 (0.0)	1 (1.4)
Eye disorders	0 (0.0)	1 (2.5)	1 (1.4)
Cataract	0 (0.0)	1 (2.5)	1 (1.4)
Gastrointestinal disorders	0 (0.0)	5 (12.5)	5 (6.8)
Colitis	0 (0.0)	1 (2.5)	1 (1.4)
Colonic polyp	0 (0.0)	1 (2.5)	1 (1.4)
Diarrhoea	0 (0.0)	1 (2.5)	1 (1.4)
Dry mouth	0 (0.0)	1 (2.5)	1 (1.4)
Dyspepsia	0 (0.0)	1 (2.5)	1 (1.4)
Gastritis	0 (0.0)	1 (2.5)	1 (1.4)
Gastroesophageal reflux disease	0 (0.0)	1 (2.5)	1 (1.4)
Inguinal hernia	0 (0.0)	1 (2.5)	1 (1.4)
Nausea	0 (0.0)	1 (2.5)	1 (1.4)
Vomiting	0 (0.0)	1 (2.5)	1 (1.4)
General disorders and administration site conditions	1 (2.9)	2 (5.0)	3 (4.1)
Non-cardiac chest pain	0 (0.0)	1 (2.5)	1 (1.4)
Oedema peripheral	1 (2.9)	0 (0.0)	1 (1.4)
Pyrexia	0 (0.0)	1 (2.5)	1 (1.4)
Hepatobiliary disorders	0 (0.0)	1 (2.5)	1 (1.4)
Dilatation intrahepatic duct acquired	0 (0.0)	1 (2.5)	1 (1.4)
Hepatomegaly	0 (0.0)	1 (2.5)	1 (1.4)
Hepatosplenomegaly	0 (0.0)	1 (2.5)	1 (1.4)
Infections and infestations	8 (23.5)	10 (25.0)	18 (24.3)
Nasopharyngitis	3 (8.8)	5 (12.5)	8 (10.8)
Upper respiratory tract infection	2 (5.9)	1 (2.5)	3 (4.1)
Gastroenteritis viral	1 (2.9)	1 (2.5)	2 (2.7)
Urinary tract infection	0 (0.0)	2 (5.0)	2 (2.7)
Bronchitis	0 (0.0)	1 (2.5)	1 (1.4)
Cellulitis	1 (2.9)	0 (0.0)	1 (1.4)
Herpes simplex	0 (0.0)	1 (2.5)	1 (1.4)
HIV infection	0 (0.0)	1 (2.5)	1 (1.4)
Onychomycosis	0 (0.0)	1 (2.5)	1 (1.4)
Otitis externa	1 (2.9)	0 (0.0)	1 (1.4)
Infections and infestations (continued)			
Pneumonia	0 (0.0)	1 (2.5)	1 (1.4)
Scrotal abscess	1 (2.9)	0 (0.0)	1 (1.4)

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Varicella	1 (2.9)	0 (0.0)	1 (1.4)
Viral infection	0 (0.0)	1 (2.5)	1 (1.4)
Injury, poisoning and procedural complications	1 (2.9)	3 (7.5)	4 (5.4)
Contusion	0 (0.0)	1 (2.5)	1 (1.4)
Excoriation	1 (2.9)	0 (0.0)	1 (1.4)
Fall	0 (0.0)	1 (2.5)	1 (1.4)
Foreign body	0 (0.0)	1 (2.5)	1 (1.4)
Meniscus lesion	0 (0.0)	1 (2.5)	1 (1.4)
Tooth fracture	1 (2.9)	0 (0.0)	1 (1.4)
Investigations	2 (5.9)	4 (10.0)	6 (8.1)
Blood glucose increased	0 (0.0)	1 (2.5)	1 (1.4)
Blood prolactin increased	1 (2.9)	0 (0.0)	1 (1.4)
Blood urea increased	0 (0.0)	1 (2.5)	1 (1.4)
Blood uric acid increased	0 (0.0)	1 (2.5)	1 (1.4)
Electrocardiogram QT prolonged	0 (0.0)	1 (2.5)	1 (1.4)
GGT increased	0 (0.0)	1 (2.5)	1 (1.4)
Liver function test abnormal	0 (0.0)	1 (2.5)	1 (1.4)
Urine leukocyte esterase positive	1 (2.9)	0 (0.0)	1 (1.4)
Weight decreased	0 (0.0)	1 (2.5)	1 (1.4)
Musculoskeletal and connective tissue disorders	2 (5.9)	2 (5.0)	4 (5.4)
Pain in extremity	1 (2.9)	1 (2.5)	2 (2.7)
Bursitis	0 (0.0)	1 (2.5)	1 (1.4)
Musculoskeletal pain	1 (2.9)	0 (0.0)	1 (1.4)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (2.9)	2 (5.0)	3 (4.1)
Basal cell carcinoma	1 (2.9)	1 (2.5)	2 (2.7)
Malignant melanoma	0 (0.0)	1 (2.5)	1 (1.4)
Nervous system disorders	4 (11.8)	2 (5.0)	6 (8.1)
Headache	2 (5.9)	1 (2.5)	3 (4.1)
Parosmia	1 (2.9)	1 (2.5)	2 (2.7)
Lacunar infarction	0 (0.0)	1 (2.5)	1 (1.4)
Lethargy	0 (0.0)	1 (2.5)	1 (1.4)
Migraine	1 (2.9)	0 (0.0)	1 (1.4)
Psychiatric disorders	1 (2.9)	1 (2.5)	2 (2.7)
Anxiety	1 (2.9)	0 (0.0)	1 (1.4)
Confusional state	0 (0.0)	1 (2.5)	1 (1.4)
Renal and urinary disorders	1 (2.9)	2 (5.0)	3 (4.1)
Nephrolithiasis	1 (2.9)	0 (0.0)	1 (1.4)
Renal cyst	0 (0.0)	1 (2.5)	1 (1.4)
Urine flow decreased	0 (0.0)	1 (2.5)	1 (1.4)
Reproductive system and breast disorders	0 (0.0)	2 (5.0)	2 (2.7)
Balanitis	0 (0.0)	1 (2.5)	1 (1.4)
Testicular atrophy	0 (0.0)	1 (2.5)	1 (1.4)
Respiratory, thoracic and mediastinal disorders	6 (17.6)	8 (20.0)	14 (18.9)
Epistaxis	1 (2.9)	3 (7.5)	4 (5.4)
Nasal congestion	1 (2.9)	2 (5.0)	3 (4.1)

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Asthma	1 (2.9)	0 (0.0)	1 (1.4)
Cough	1 (2.9)	0 (0.0)	1 (1.4)
Idiopathic pulmonary fibrosis	0 (0.0)	1 (2.5)	1 (1.4)
Nasal discomfort	1 (2.9)	0 (0.0)	1 (1.4)
Nasal dryness	0 (0.0)	1 (2.5)	1 (1.4)
Rhinalgia	1 (2.9)	0 (0.0)	1 (1.4)
Rhinitis seasonal	0 (0.0)	1 (2.5)	1 (1.4)
Rhinorrhoea	1 (2.9)	0 (0.0)	1 (1.4)
Sneezing	0 (0.0)	1 (2.5)	1 (1.4)
Skin and subcutaneous tissue disorders	2 (5.9)	2 (5.0)	4 (5.4)
Scab	2 (5.9)	2 (5.0)	4 (5.4)
Skin fissures	2 (5.9)	0 (0.0)	2 (2.7)
Night sweats	1 (2.9)	0 (0.0)	1 (1.4)
Vascular disorders	0 (0.0)	1 (2.5)	1 (1.4)
Hypertension	0 (0.0)	1 (2.5)	1 (1.4)
Note: All adverse events that started during Safety Extension Period 2 were considered TEAEs. BID = twice daily; GGT = gamma-glutamyltransferase; TEAE = treatment-emergent adverse event; TID = three times daily. Source: Table 61, CSR TBS-1-2011-03, Pages 145-147 Reflects 120 Day Safety Update			

The most frequently reported TEAEs in each treatment group *during all periods of the study* were the following: TBS-1 BID group: rhinorrhea and nasal discomfort (7% each), and nasopharyngitis and epistaxis (6.3% each); Combined TBS-1 TID group: nasopharyngitis (9.8%), rhinorrhea (8.5%), epistaxis (6.7%), PSA increase 6.1%. The most frequently reported drug-related TEAEs in each treatment group during all periods of the the study were: TBS-1 BID group: rhinorrhea, nasal discomfort, and scab (5.6% each); and nasal dryness and parosmia (4.2% each); Combined TBS-1 TID group: rhinorrhea (6.7%), epistaxis (6.1%); and PSA increased and scab (4.9% each). In all groups (total) nasopharyngitis, epistaxis and upper respiratory infection occurred at the rate of 4.1% in each group. In the treatment period, in TID patients, the most frequently the most frequently reported AEs $\geq 3\%$ were: nasopharyngitis 3.8%, bronchitis 3.8%, tooth abcess 3.8%, upper respiratory infection 3.8% and PSA increased 5.1%. In the TID group in SE2, the most frequently reported AEs $\geq 3\%$ were scab 3.0%, epistaxis 7.5% and nasopharyngitis 5.0%.

Reviewer's Comment: Adverse event terms in the "Respiratory, thoracic and mediastinal Disorders" SOC were the most commonly reported events. These reflect "local site" reactions. It is noted that during the treatment phase, the only AE terms reported unfrt "Infections and Infestations" were rhinitis in 1 subject (0.7 %) of the BID dose group and 1subject (1.2%) of the BID/TID dose group and no subjects in the TID dose group. Nasal vestibulitis occurred in 1subject (1.3%) in the TID dose group patient and in no subject in the other groups. In all periods, nasopharyngitis was reported in 9 subjects (6.3%) of the BID dose group and 16 subjects (9.8%) of the combined BID/TID and 3.8% of the TID group. Pneumonia was reported in no subjects in the BID dose group and in 3 subjects (1.8%) of the combined BID/TID and TID dose group. Pneumonia is not believed to be related to Natesto in these cases. Sinusitis was reported in no subject in the BID dose group and 3 subjects (1.8%)in the combined BID/TID and TID group. Bronchitis was reported in 3 subjects (2.1 %) in the BID dose group and 5 subjects

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(3.0%) in the combined BID/TID and and 3.8% of subjects in the TID group. These incidences are small, as are the differences in incidences between dose groups. The absence of a control group makes assessments of causality for individual events and individual event erms difficult.

Within Safety Period 2, the only drug-related TEAES reported in the 40 TID subjects were: prolonged QT interval in 1 subject (1.4%), parosmia in 1 subject (1.4%), epistaxis in 3 subjects (7.3%) and scab in 2 subjects (5.0%).

Reviewer's Comments: These results do not generate any new safety concerns.

7.4.2 Laboratory Findings

An overall mean reduction in high-density lipoprotein cholesterol (HDL-C) of 2.4% was observed from baseline to Day 360 (0.3% reduction for the TBS-1 BID group and 4.0% reduction for the TBS-1 TID group). At Day 90 and Day 180, overall mean reductions in HDL-C from baseline were 1.5% and 2.9%, respectively.

There was a small overall mean increase in low-density lipoprotein cholesterol (LDL-C) from baseline to Day 360 of 0.8% (2.6% increase for the TBS-1 BID group and 0.7% reduction for the TBS-1 TID group). At Day 90, there was an overall mean reduction in LDL-C of 7.7% from baseline. At Day 180, the overall mean reduction in LDL-C was 0.2%.

Similarly, there was a small overall mean increase in total cholesterol from baseline to Day 360 of 0.2% (3.8% increase for the TBS-1 BID group and 2.7% reduction for the TBS-1 TID group). At Day 90 and Day 180, there were slight overall mean reductions in total cholesterol from baseline of 2.3% and 0.9%, respectively.

Overall, there was a median increase in triglycerides of 3.3% from baseline to Day 360 (3.3% increase for both the TBS-1 BID group and the TBS-1 TID group). At Day 90 and Day 180, overall median increases in triglycerides were 12.7% and 3.4%, respectively. For further discussion of this specific parameter, the reader is referred to **Section 7.3.5.3**

The mean baseline hematocrit value was 44.8%. At Day 90, there was a small decrease in hematocrit to 44.1% that might be attributable to PK blood draws. At Day 180 and Day 360, the mean hematocrit values were 45.6% and 45.3%, respectively. A slight increase in hematocrit values observed on 180 and 360 days of treatment may reflect a known effect of testosterone replacement therapy. Hematocrit values did not exceed the ULN during the treatment in the vast majority of subjects.

Table 56: Summary of Hemoglobin, Hematocrit, Platelets- Study TBS-1-2011-03- Treatment Period

Parameter Visit Variable	TBS-1 BID (N=143)	Combined TBS-1 TID (N=163)	TBS-1 TID (N=78)
Hematocrit (%)			
Baseline – n	142	163	78
Mean (SD)	44.8 (3.45)	44.8 (3.51)	45.1(3.60)
Day 30 – n [1]	131	--	
Mean (SD)	43.0 (3.53)	--	43.7(4.18)
Day 30 Change Mean (SD)	-1.9 (2.90)	--	-1.4 (2.75)
Day 90 – n [1]	119	148	69
Mean (SD)	43.5 (3.79)	44.6 (3.97)	44.6(3.78)
Day 90 Change Mean (SD)	-1.4 (3.26)	-0.2 (3.12)	-0.4(3.27)
Hemoglobin (g/dL)			
Baseline – n	142	163	78
Mean (SD)	15.13 (1.150)	15.12 (1.171)	15.23(1.16)
Day 30 – n [1]	131	--	72
Mean (SD)	14.27 (1.140)	--	14.47(1.35)
Day 30 Change Mean (SD)	-0.89 (0.835)	--	-0.74(0.83)
Day 90 – n [1]	119	148	78
Mean (SD)	14.29 (1.237)	14.58 (1.217)	14.56 (1.14)
Day 90 Change Mean (SD)	-0.86 (1.003)	-0.53 (0.966)	-0.64 (0.97)
Platelets (10⁹/L)			
Baseline – n	140	163	78
Mean (SD)	222.7(51.57)	219.8(55.19)	225.3(59.88)
Day 30 – n [1]	128	-----	71
Mean (SD)	220.1(48.47)	-	230.4(58.42)
Day 30 Change Mean (SD)	-2.4(34.47)	-	2.1 (24.07)
Day 90 – n [1]	115	145	68
Mean (SD)	219.9 (50.79)	220.6(56.63)	230.6(62.63)
Day 90 Change Mean (SD)	-1.9	-2.2	0.1

Sources: Table 67 CSR TBS-1-2011-03 and Table 27.1

A total of 8 subjects had hematocrit values $\geq 54\%$ during the study (after baseline/screening): 3 (2.1%) subjects in the TBS-1 BID group and 5 (3.0%) subjects in the Combined TBS-1 TID group (2 [1.2%] in the TID group). Red blood cell (RBC) count abnormalities were experienced by 5 subjects during the study (after baseline/screening): 2 (1.4%) subjects in the TBS-1 BID group and 3 (1.8%) subjects in the Combined TBS-1 TID group. All hematocrit, hemoglobin, or RBC values

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above the normal range were borderline and not clinically significant. The increases in hematocrit and RBCs did not exceed the pre-determined clinical significant post-treatment values of 58% for hematocrit and $6.27 \times 10^{12}/L$ for RBCs. No subjects discontinued the study due to hematology abnormalities.

Although the pre-determined clinical significant limit for hematocrit was $\geq 58\%$, the reviewer analyzed the hematocrit results using a lower cut-point ($\geq 54\%$) and this analysis is shown in the table below.

Table 57: Subject with Any Post-Baseline Hematocrit $\geq 54\%$ in All Periods of TBS-1-2011-03.

Subject Number	TBS-1 doses	Hematocrit (%)					
		Baseline	Day 30	Day 90	Day 180	Day 270	Day 360
001-023	T, SE1, SE2-BID	51	47	50	54	56	55
011-026	T, SE1-BID	51	54	51	51	-	-
001-054	T, SE1-BID	51	46	45	46	-	-
011-020	T, SE1-TID	48	51	55	52	-	-
001-032	T, SE1-TID	52	53	53	57	-	-
016-022	T-BID/TID, SE1-TID	48	48	53	57	-	-
001-031	T-BID/TID, SE1-TID	50	49	50	58	-	-

Treatment Period=T, Safety Extensions=SE1, SE2 Doses=BID or TID

Source: Reviewer's JMP analysis of ADMH data set.

All of these 7 subjects had baseline hematocrits above the average for their respective treatment groups. Subject 001-032 had a medical history of polycythemia (2010) which antedates his study participation. None of these subjects had a total serum testosterone ≥ 1500 ng/dL at any time during their study participation. In one subject (Subject 001-054), the hematocrit was elevated at baseline and was elevated but lower at all post-baseline timepoint. In two subjects (#011-026 and #011-020), the hematocrit elevation was followed by value(s) below 54% while the patient was continuing to receive TBS-1.

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In the 120 Day Safety Update, it was reported that 1 subject in SE2 (#044-008), had a MCH value above the upper limit of normal (43.4 pg at Visit 15). At the same visit, the patient's hematocrit was 45.

The were no additional reports of hematocrit > 54%.

Reviewer's Comment: In the Natesto NDA, a small number of subjects had hematocrits $\geq 54\%$, with several values occurring at single time points that later returned to baselinel. In a few subjects, the hematocrit elevation persisted. RBC production and thus, hematocrit elevation, is a known effect of testosterone replacement therapy. Polycythemia may occur. These results do not generate a new safety concern. Labeling for this issue for Natesto will be consistent with the class.

Mean PSA values for the Safety Population overall demonstrated increases of 0.10 ng/mL after 3 months of treatment at Day 90, 0.06 ng/mL at Day 180, and 0.14 ng/mL at Day 360.

Mean PSA values for the TBS-1 BID group demonstrated increases of 0.06 ng/mL after 3 months of treatment at Day 90, 0.01 ng/mL at Day 180, and 0.06 ng/mL at Day 360.

Mean PSA values for the Combined TBS-1 TID group demonstrated increases of 0.13 ng/mL after 3 months of treatment at Day 90, 0.09 ng/mL at Day 180, and 0.21 ng/mL at Day 360. For the TID group, mean PSA values for the Combined TBS-1 TID group demonstrated increases of 0.60 ng/mL after 3 months of treatment at Day 90, 0.09 ng/mL at Day 180, and 0.27 ng/mL at Day 360.

These small increases in PSA values are consistent with PSA increases reported with other testosterone replacement therapies and they do not exceed the average increases in PSA reported after initiation of testosterone replacement therapy (0.3 ng/mL in young men, and 0.44 ng/mL in older men over 3-6 monthsd), as reported in literature cited by Sponsor and specified in An Endocrine Society Clinical Practice Guideline (J Clin Endocrinol Metab. 2010; 95:2536-2559).

The numbers and percentages of subjects with clinically significant changes in PSA were low, and no differences among the treatment groups were observed.

Reviewer's Comment: PSA elevation is a known phenomenon during testosterone replacement therapy. These results do not generate a new safety concern that would require anything other than class labeling. Also see Discussion Section 7.3.5.4

Only 2 subjects discontinued study drug due to a clinically significant laboratory abnormality (both had increased/elevated PSA levels). The criteria used to define increase of PSA as a TEAE were 1) increase from baseline PSA of >1.4 ng/mL during study 2) any PSA >4.0 ng/mL during the study. Both of these subjects had rises of PSA >1.4 ng/mL. One of these occurred in SE1 and the other in SE2. For additional details of these two events, see Table 54.

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This reviewer also analyzed routine laboratory results, including electrolytes and liver tests.

Table 58 provides a summary of liver test abnormalities.

Table 58: Summary of Liver Test Abnormalities -Treatment Period-TBS-1-2011-03

Parameter Abnormality (for any post-dose measure)	TBS-1 BID (N=143) n (%)	Combined TBS-1 TID (N=163) n (%)	Total (N=306) n (%)
Total bilirubin			
N'	141	162	303
<LLN	0 (0.0)	0 (0.0)	0 (0.0)
>ULN	11 (7.8)	8 (4.9)	19 (6.3)
Albumin			
N'	141	162	303
<LLN	0 (0.0)	1 (0.6)	1 (0.3)
>ULN	0 (0.0)	0 (0.0)	0 (0.0)
AST			
N'	141	162	303
<LLN	0 (0.0)	0 (0.0)	0 (0.0)
>ULN	28 (19.9)	29 (17.9)	57 (18.8)
ALT			
N'	141	162	303
<LLN	0 (0.0)	0 (0.0)	0 (0.0)
>ULN	26 (18.4)	37 (22.8)	63 (20.8)
Alkaline phosphatase			
N'	141	162	303
<LLN	5 (3.5)	4 (2.5)	9 (3.0)
>ULN	4 (2.8)	11 (6.8)	15 (5.0)
Gamma glutamyl transferase			
N'	141	162	303
<LLN	1 (0.7)	1 (0.6)	2 (0.7)
>ULN	21 (14.9)	31 (19.1)	52 (17.2)
% = n/N', where N' is the total number of subjects with a valid post-baseline clinical laboratory measurement during the Treatment Period. The worst value for each subject is summarized. ALT = alanine aminotransferase; AST = aspartate aminotransferase; BID = twice daily; LLN = lower limit of normal; TID = three times daily; ULN = upper limit of normal.			

Source: Post-text table 29.3

There were only 2 patients at Day 90 who had single AST elevations approximately ≥ 2 times the upper limit of normal (104 U/L and 189 U/L) and a single patient at Day 270 with an AST of 270 U/L. With regard to ALT there was one patient with normal baseline value and an elevated ALT at Day 90 (99 U/L). An additional patient with a baseline ALT of 57 U/L had at Day 90 an ALT of 93 U/L. At Day 180, one subject had an ALT of 90 U/L and at Day 360 one subject had an ALT of 112 U/L. None of these subjects had multiple values ≥ 2 times the upper limit of normal. With respect to GGT, there was only one patient with a normal baseline who had a Day 90 GGT ≥ 2 times the upper limit of normal (162 U/L). There were no patients in either safety extension period who GGT ≥ 2 times the upper limit of normal. These patients were either BID/TID or TID dose groups.

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In their inspections of the clinical and analytical portions of Study TBS-1-2011-03, the Division of Bioequivalence and GLP compliance (in their December 20, 1013 memorandum) raised a concern in regard to **Subject 051-114**. On Day 90, this subject had an ALT of 93 U/L, an AST of 189 U/L, a GGT of 185 U/L, and a CK of 7070 U/L. The patient’s baseline CK and GGT were elevated and the baseline AST and ALT were normal. It is noted that alkaline phosphatase and bilirubin were with normal limits for Visits 1-9. The subject’s treatment period dose was BID up-titrated to TID and the SE1 dose was TID. The patient did not participate in SE2. The subjects’ ALT and AST elevations were isolated values that that were followed by normal values by Day 180.

Reviewer’s Comment: This case and the inspection result do not generate either a safety or testing methodology concern in my opinion. The patient’s elevated CK value is addressed below.

Five additional subjects were identified in the 120-Day Safety Update as having liver test abnormalities. These subjects are shown individually in the table below. **Subject 044-008** had a bilirubin value slightly above the upper limit of normal with no other liver test abnormalities, **Subjects 022-008** and **044-011** had AST values just above the upper limit of normal, **Subject 003-025** (not shown in table) had a GGT value below the lower limit of normal, and finally, **Subject 023-024** had an isolated GGT level above the upper limit of normal.

Table 59: Subjects with Abnormally High Liver Tests - SE2 TBS-1-2011-03

Subject (Dose)	Liver Function Parameter	Visit 1	1.1	4	6	9	12	15
044-008(BID)	Bilirubin g/dL	0.96	-	1.27H	0.91	1.08	0.87	1.15H
022-008 (BID)	AST U/L	34	-	29	28	26	32	47H
044-011 (BID-29TID)	AST U/L	29	-	26	22	26	25	35H
023-024(BID)	GGT	22	19	26	22	27	27	67H

Source: Listing 17.4, 120 Day Safety Update, page 1762. H=high

Reviewer’s Comment: The overall liver tests results do not raise a new safety concern for an adverse effect of Natesto on liver tests.

This reviewer also conducted an analysis of serum creatinine kinase (CK) results, based upon several individual subjects with high CK concentrations.

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The mean changes from baseline for creatinine kinase (CK) were highly variable with very large standard deviations. For TID-only Natesto subjects, the mean increase from baseline to Day 180 (N=69) was 149.2 U/L (SD 100.11). There was an insufficient number of subjects (n=18) who completed the second safety extension (SE2) to allow for useful analysis of the CK data, based on the measure's high variability. Of note, 37% of the overall 306 patients in the treatment period experienced an increase of the CK to greater than the upper limit of normal (ULN). A number of subjects also experienced reductions from baseline in CK and many remained unchanged. In Safety Extension Period 1 (SE1), 28/120 (23.9%) of BID patients and 34/152 (23.1%) of combined BID/TID and TID patients experienced an increase of CK to greater than the upper limit of normal (ULN). In Safety Extension Period 2, 7/33 (21.2%) of BID patients and 10/39 (25.6%) of TID patients experienced an increase of the CK to greater than the upper limit of normal (ULN).

Reviewer's Comment: Despite the finding of a percentage of subjects in whom CK increased to above the normal range, there appears to be such variability in changes in CK values, in my opinion, as to make the findings impossible to interpret. In addition, there were no clinical symptoms associated with any of these changes.

When analyzed based on changes in individual subjects, there were seven (7) subjects who experienced a CK level ≥ 3 times the ULN during the study while having a baseline value within normal limits. There are presented below:

Table 60: Patients with Creatine Kinase ≥ 3 Times the Upper Limit of Normal Study TBS-1-2011-03 All Periods

Subject	Dose	Baseline CK U/L	Day 30	Day 90	Day 180	Day 270	Day 360
004-025	TID	97	194	59	114	-	-
				717 Day119 114 Day 128			
018-012	TID	150	105	167	86	2809	
						469 Day276	88
029-003	BID/TID	48	66	2356	51	41	78
051-014	BID/TID	199	549	7070	273	-	-
		Day-12-385					
016-016	BID	157	659	252	134	-	-
047-022	BID	163	108	972	-	-	-
043-007	BID	194	319	732	158	-	-

Source: Reviewer's JMP analysis.

Reviewer's Comment: In 5 of the 7 cases, elevations of CK spontaneously resolved. In addition, the majority of cases in Table 63 are confounded by variables that can increase CK, as follows:

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- *Subject 029-003: This patient has chronic back muscle spasms. He suffered a fall in the bathtub on Day 138 resulting in shoulder pain. He had a syncopal episode on Day 187. It is possible he had other falls or injuries not reported. From Day 180 to Day 360, Natesto was continued and the CK increase resolved (negative re-challenge).*
- *Subject 051-014: This subject had a Day-14 pre-baseline CK of 385. He experienced back spasms on Day 118. He takes simvastatin for hyperlipidemia which can cause muscle pain and increases in CK. From Day 90 until Day 180, Natesto was continued and the CK increases was resolving (negative re-challenge).*
- *Subject 016-016: This patient has a history of back pain. His CK increase was resolving from Day to Day 180 while using Natesto (negative re-challenge).*
- *Subject 043-007: This patient has a herniated nucleus pulposus. His CK increase was resolving from Day 90 to Day 180 while using Natesto (negative re-challenge).*
- *Subject 047-022: This obese patient suffered a fall on Day 107 resulting in torn knee ligaments. He also has fibromyalgia for which he takes duloxetine.*
- *Subject 018-012: This patient suffered from a toothache throughout the study. His CK increase was resolving from Day 276 until Day 360 while using Natesto (negative re-challenge).*
- *Subject 004-025: This patient was diagnosed as subclinically hypothyroid on Day 120 and had a tension headache on Day 129. He had a history of migraines and chronic low back pain.*

In no case was CK elevation a stated reason for study discontinuation. In the 120 Day Safety Update, 1 additional subject (044-011), experienced a CK value above the normal limit. The overall number of patient with a CK abnormality decreased from 16/74 (22.2%) to 17/74 (12.5%) at the completion of SE2. None of the patients with a increase of CK greater than 3 times ULN was reported to experience a cardiac adverse event.

Reviewer's Comment: CK appears to be a highly variable test in the study population. None of the individual outlier cases reveal a drug-related safety signal. This analysis does not reveal a safety finding that might necessitate new labeling, in my opinion

The reviewer also identified a significant mean reduction from baseline in serum cortisol. An analysis of this finding was conducted.

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Table 61: Serum Cortisol Treatment Period Study TBS-1-2011-03

	TBS-1 BID N=143	TBS-1 BID/TID N=85	TBS-1 TID N=76	Combined TBS-1 TID N=163
Baseline n (Week -3)	122	85	69	151
Serum Cortisol ug/dL (SD)	12.3 (4.6)	12.5 (4.2)	12.0 (4.2)	12.3 (4.2)
Day 90				
Serum Cortisol ug/dL (SD)	4.8 (4.3)	5.1 (4.3)	3.9 (3.4)	4.5 (4.0)

Source: CSR TBS-1-2022-03 Table 30.1

In the (b) (4) subjects in Protocol TBS-1-2011-03, the mean (SD) cortisol concentrations at baseline and at Day 90 in the population were 12.3 (4.4) mcg/dL and 4.6 (4.1) mcg/dL, respectively. For the TID group the reader is referred to the table above. The lower limit of detection of the cortisol assay was 0.3 mcg/dL. In Study TBS-1-2011-03, at total of 39% and 43% of subjects in the overall (n=306) and TID (n=76) populations respectively, had serum cortisol concentrations below the lower limit of normal.

By JMP analysis using AVAL data set, this reviewer identified 112 patients with serum cortisols below 3 ug/dL at a time other than baseline (Day 90 was the only other timepoint where serum cortisol was measured). 4 patients had cortisol levels of <1.0 (ug/dL) at Day 90. Despite these low levels of cortisol, we did not identify any clinical adverse events to support evidence of adrenal insufficiency in an individual subject in the submissions.

Therefore, the Sponsor was asked in an April 7, 2012, Information Request to provide their assesment of this laboratory test abnormality. In their response, dated April 11, 2014, the Sponsor provided the following explanation:

- Cortisol concentrations for samples taken in Study TBS-1-2011-03 were analyzed by MedPace Reference Laboratories (MRL), Cincinnati, OH, using an electroluminescence immune-assay method. MRL's SOP LG0IM-22 is provided.
- Per protocol instructions, screening (baseline) samples for cortisol were taken in the *morning* at the typical peak of diurnal cortisol rhythm. Samples for cortisol testing on Day 90 were collected before the first *evening* dose of the study drug, i.e. at 20:45, at or near nadir. The Sponsor has attached this listing of the sample collection times for cortisol testing for all treatment groups.
- Sponsor observes that Nadir cortisol levels can be quite low. In published reports (Gavrilla et al., 2002), observed cortisol nadir levels were 2 - 40% (mean 24.9%) of the 24-hour mean daytime concentration. The Sponsor further explains, thus, it is not unexpected to see lower mean cortisol levels at Day 90 versus screening as the sample times were not identical.

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- This difference, in the Sponsor's opinion, does not indicate hypocortisolemia.

Reviewer's Comment: The peak cortisol levels at Screening (Visit 1) and the nadir levels at Day 90 (Visit 6) do not allow for useful comparisons as there is a marked difference due to diurnal variation and wide intra-subject variability of serum cortisol concentrations based upon the medical literature. Based on the Sponsor's explanation, the change-from-baseline in cortisol concentrations do not indicate a safety concern.

The numbers and percentages of subjects with clinically significant urinalysis abnormalities were low, and no differences among the treatment groups were observed.

7.4.3 Vital Signs

Hypertension was reported as a clinical TEAE in 2 (1.4%) of the 142 BID dose patients and in 3 (1.8%) of the (N=164) Combined TBS-1 dose patients. The mean change in systolic blood pressure noted at Day 90 were actually reductions (-0.4 mm Hg for the 143 BID dose patients and -0.7 mm Hg for the 78 TID dose patients and -0.6 mm Hg for the 163 combined dose patients). By Day 180 the mean change in systolic blood pressure showed further reduction (-2.7 mm Hg mm Hg for the 107 BID dose patients and -3.1 mm Hg for the 132 TID dose patients). The Day 360 results in a small number of study completers showed further decreases in blood pressure. The diastolic blood pressures also decreased modestly during the study. The greatest diastolic BP decrease was -4.6 mm Hg in the 38 TID dose group patients at Day 270. At Day 180, for the 152 TID dose patients the diastolic blood pressure decrease was -2.3 mm Hg. There were no significant heart rate trends during the study. In Sponsor's March 7, 2014, submission in support of the TID-only dose regimen, the group mean baseline systolic blood pressure (N=69) was 131.8 mmHg (SD 12.9) for SE1 and at Day 180 the group mean systolic blood pressure was 128.0 mmHg (n=69, SD11.2). At Day 360 the group mean systolic blood pressure for the TID dose group was 127.3 (n=17, SD14.8). A net change in blood pressure for the 17 patient completing SE2 was -1.6 mmHg. For diastolic blood pressure in TID-only patients the baseline was 80.6 (n=69, SD 8.2). At Day 180, the group mean diastolic blood pressure was 78.0 (n=61, SD 8.8). At Day 360, the group mean diastolic blood pressure for the TID dose group was 79.3 (n=17, SD11.2).

Reviewer's Comment: The blood pressure results do not point to vital signs safety concern, in my opinion. The few clinical AE reports of hypertension are difficult to interpret.

7.4.3.1 Digital Rectal Exam

Two (0.7%) subjects had clinically significant prostate abnormalities identified via DRE at screening. Subject 010-035 had a small prostate and Subject 052-002 had an enlarged prostate that was normal for his age. These two subjects did not develop any new related abnormalities during the study.

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7. 4.3.2 *Otorhinolaryngological(ENT) Examination and Nasal Endoscopy*

Nasal endoscopy was performed at Screening. Further evaluations of nasal symptoms and findings were performed via monthly ENT examinations.

At Week -2, endoscopy results were normal for 68.4% of subjects and abnormal for 31.6% of subjects (29.6% abnormal but not clinically significant; 1.6% abnormal, clinically significant, but not non-exclusionary [1 subject with a posterior deviated septum, 1 subject with nasal polyps, 1 subject with an anterior deviated septum and crusting in the right nostril, 1 subject with an anterior deviated septum and inflamed turbinates, and 1 subject with an anterior deviated septum]; and 0.3% abnormal, clinically significant and exclusionary [1 subject with acute sinusitis at Week -2; however, the subject was treated with antibiotics, the acute sinusitis resolved prior to randomization, and the subject was subsequently randomized and completed the study]). The most frequent abnormal Screening endoscopy findings were anterior deviated septum (56 [18.4%] subjects), "Other" (33 [10.9%] subjects), and crusting in left nostril (11 [3.6] subjects).

At Day 1 (baseline), the majority of subjects (97.4%) had no ENT symptoms. Of those few who reported ENT symptoms at baseline, events included excessive nasal dryness, unexpected nasal bleeding, and progressive nasal obstruction (1 [0.3%] subject each), altered sense of smell (2 [0.7%] subjects), and Other symptom - not specified (5 [1.6%] subjects). The majority of subjects (98.7%) had no ENT examination findings at baseline. In those few with findings, otorhinolaryngological examination at baseline showed large amounts of nasal crusting (1 [0.3%] subject), dried or fresh nasal blood (2 [0.7%] subjects), and Other finding - not specified (2 [0.7%] subjects).

After the first dose of TBS-1, the general purpose of the ongoing monthly basic ENT examination was to determine if there had been any symptoms and findings related to the nose that were caused by either the study drug or the multiple-dose dispenser. A standard list of symptoms to report treatment-related findings was used for these purposes. Other nasal symptoms were also reported, if necessary. At Day 90, 89.0% of subjects had no ENT symptoms. The most common ENT symptom reported was "Other symptom - not specified" (18 [6.6%] subjects). Among treatment-related symptoms, altered sense of smell (7 [2.6%] subjects) was the most frequently reported. A total of 97.4% of subjects had no ENT examination findings, and the only findings were "Other findings - not specified" (7 [2.6%] subjects).

Otorhinolaryngological examination results were similar for the Safety Extension Periods. At Day 180, 92.6% of subjects did not report symptoms and 96.3% of subjects had no ENT examination findings. At Day 360, 93.9% of subjects had no ENT symptoms. Otorhinolaryngological symptoms in the few that reported symptoms were excessive nasal dryness, unexpected nasal bleeding, progressive nasal pain, and altered sense of smell (1 [1.5%] subject each). "Other symptom - not specified" (1 [1.5%] subject) was also reported. There were no ENT examination findings for any subject at Day 360.

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.

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Furthermore, no abnormal ENT examination findings were identified in any subject who completed 360 days of treatment.

7.4.4 Electrocardiograms (ECGs)

There were no changes in 12-lead ECG results that would suggest an association with the study medication, and no clinically meaningful differences among the treatment groups. The QT interval duration decreased overall during the study. There were two reports of QT prolongation:

Subject 003-022 (in the Treatment Period (TID dose group) had the TEAE of ECG prolonged QT. The patient is 61 years old and had history of hypertension, type 2 diabetes mellitus and hyperlipemia. His baseline QT interval was 430 milliseconds and baseline ECG was normal. This patient's concomitant medications included aspirin, azithromycin, tadalafil, Crestor, folic acid, glipizide, giquatusin ac, Januvia, Ketorolac drops, krill oil omega, and metformin. At Visit 6 (Day 90-91[22 May 2012]), his ECG was abnormal with sinus rhythm, prolonged QT interval (468 milliseconds), left axis deviation and non-specific inferior T wave changes. The patient had been on 4 day course of azithromycin from April 4, 2012, to May 5, 2012. An ECG at approximately Day 106 indicated a QT interval of 468 milliseconds. On 7 June 2012 (Day 108), the subject withdrew from the study. The 180 day ECG result was LOCF of the Day 108 result.

Reviewer's Comment: Azithromycin can prolong the QT interval. There is extensive tissue uptake of this drug accounting for its prolonged terminal half-life to 68 hours. Azithromycin may have been responsible for the modest QT prolongation noted. The patient's voluntary withdrawal from the study further confound any ability to assess causality for Natesto. There is insufficient evidence to attribute the QT prolongation in this patient to Natesto, in my opinion.

Subject 022-017 in the TID group was noted to have QT prolongation during the Safety Extension Period 2 between the dates of February 16, 2013 and March 11, 2013. This additional patient was noted in the 120 Day Safety Update. This 46 year-old patient had baseline ECG that was read as normal with a QT interval of 410 ms. His ECG on Day 90-91 was abnormal qualified as "Not Clinically Significant" with a QT interval of 466 ms. On approximately Day 166, the ECG indicated a QT interval of 410 ms while patient continued to use Natesto. The QT interval on Day 270 was also 410 ms. Day 360 (6 March 2013) his ECG was sinus bradycardia QTc prolongation (500 ms). On 11 March 2013, the ECG was "clinically significant long QT (486ms)." By 19 March 2013, the QT interval was 446ms. The patient has a medical of inflamed knee, hypercholesterolemia and heart burn. His medications include aspirin, hydroxylcodone, loratidine, naproxen, simvastatin, vitamin D3, and zantac. During the study, the patient took multivitamins and fish oil supplements only.

Reviewer's Comment: In light of the fact that the patients QT interval became elevated and returned to normal while he was using Natesto and then became abnormal again, it is my opinion that some other process was occurring not related to Natesto. There insufficient evidence to conclude a relation of Natesto to this patient's ECG abnormality.

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7.4.5 Special Safety Studies/Clinical Trials

Aside from a drug interaction study with the sympathomimetic decongestant oxymatazoline (described in detail in previous sections of this review), there were no special safety studies conducted for this NDA.

7.4.6 Immunogenicity

One patient in the BID dose group had what appeared to be an angioedema-type hypersensitivity reaction during the Treatment Period and one other patient may have had a possible allergic reaction. These cases are described individually below. In addition, two patients in the BID dose group had a seasonal allergy adverse event during the two safety periods. No immune phenomena were reported in the TID and combined BID/TID dose groups.

Subject 043-004: Allergic reaction – face swelling to unknown allergen – possibly food; allergic reaction – hives, swollen lips to unknown allergen – possibly food; allergic reaction – swollen and numb lips and tongue to unknown allergen – possibly food

This 50 year-old Caucasian male with hypogonadism was randomized to 5.5 mg 4.5% TBS-1 given two times daily on 14-Mar-2012. From Study Day 93 (14-Jun-2012) to Study Day 94 (15-Jun-2012), the subject experienced an allergic reaction (face swelling) to unknown allergen. From Study Day 95 (16-Jun-2012) to Study Day 96 (17-Jun-2012), the subject experienced another two-day episode of an allergic reaction (hives, swollen lips). On Study Day 101 (22-Jun-2012), the subject experienced a two-day episode of an allergic reaction (swollen and numb lips and tongue) to unknown allergen and recovered on Study Day 102 (23-Jun-2012). Treatment of the events included fexofenadine and diphenhydramine. The study medication was withdrawn due to the events. On Study Day 102 (23-Jun-2012), the last dose of study medication was administered. The subject discontinued from the trial due to the events allergic reaction to unknown allergy on Study Day 122 (13-Jul-2012). The subject's medical history includes nose fracture, snoring, tonsillectomy, uvulectomy and seasonal allergies. Concomitant medications include clobetasol propionate (a topical corticosteroid), glucosamine and multivitamin.

Reviewer's Comment: This is the allergic reaction reported by the Sponsor as an SAE (medically significant). It is of interest that then patient had a history of nose fracture, making him ineligible for the trial. In addition, the patient was taking a topical corticosteroid concomitantly, implying a possible allergic background condition. It is not possible to determine causality between this event an Natesto. Nonetheless, it would be prudent to mention this event in labeling.

Subject 021-014: Petechiae

This 39 year-old Caucasian male with hypogonadism was randomized to 5.5 mg 4.5% TBS-1 given three times daily on 27-Mar-2012. From Study Day 23 (18-Apr-2012) to

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Study Day 24 (19-Apr-2012), the subject experienced severe myalgia, moderate generalized joint pain, moderate fever, and moderate chills. Treatment of the events of myalgia and fever included acetaminophen. On Study Day 25 (20-Apr-2012), the subject developed petechiae and tingling and burning sensation in hands and feet bilaterally. No treatment was given for the event of petechiae. The study medication was withdrawn due to the event of petechiae. The last dose of study medication was administered on Study Day 25 (20-Apr-2012). The subject's platelet counts were 213 million/L on 22 November 2011, 203 million/L on 20 December 2011, 268 million/L on 26 March 2012, and 254 million/L on 25 April 2012. The subject recovered from the events of burning sensation and tingling in hands and feet bilaterally on Study Day 27 (22-Apr-2012). The subject discontinued from the trial due to the event of petechiae on Study Day 30 (25-Apr-2012). The subject recovered from the event of moderate petechiae on 09-May-2012. From 10-May-2012 to 20-May-2012, the petechiae were considered mild in severity. The subject's medical history includes esophageal stricture (multiple episodes) and dilatation (multiple episodes), high cholesterol, hemorrhoids, intermittent heartburn, Klinefelter's syndrome, wears glasses, and allergy to bananas and amoxicillin. Concomitant medications include simvastatin, sucralfate, omeprazole, and Pramosone.

Reviewer's Comment: This reaction was not counted as an allergic reaction. The patient was taking multiple medications and is allergic to foods (bananas) and drugs (amoxicillin). While this event could possibly be an allergic reaction, there are other possible etiologies. There is not enough evidence to conclude a definite immunologic etiology or relationship to Natesto. Nonetheless, it may be still be prudent to mention this event in labeling.

7.5 Other Safety Explorations

Below are tables illustrating study medication exposures.

Table 62: Study Medication Exposure: TBS-1-2011-03 Treatment Period

Characteristic Category/Statistic	TBS-1 BID (N=143)	TBS-1 BID/TID (N=85)	TBS-1 TID (N=78)	Combined TBS-1 TID (N=163)	Total (N=306)
Treatment Period					
Exposure (days) [1]					
n	143	85	78	163	306
Mean (SD)	84.9 (20.68)	89.8 (5.97)	84.4 (19.70)	87.2 (14.50)	86.1 (17.67)
Exposure Category – n (%)					
1 – 30 days	12 (8.4)	0 (0.0)	4 (5.1)	4 (2.5)	16 (5.2)
31 – 60 days	2 (1.4)	1 (1.2)	4 (5.1)	5 (3.1)	7 (2.3)
61 – 90 days	56 (39.2)	43 (50.6)	30 (38.5)	73 (44.8)	129 (42.2)
>90 days	73 (51.0)	41 (48.2)	40 (51.3)	81 (49.7)	154 (50.3)
1. Exposure = date of last dose of the Treatment Period (Day 90) – date of first dose + 1. BID = twice daily; SD = standard deviation; TID = three times daily.					

Source: Post-text Table 5.1

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Table 63: Study Medication Exposure-Safety Extension Periods TBS-1-2011-03

Characteristic Category/Statistic	TBS-1 BID	TBS-1 TID	Total
Safety Extension Period 1			
Exposure (days) [1]			
n	120	152	272
Mean (SD)	175.5 (18.64)	175.9 (17.01)	175.7 (17.72)
Exposure Category – n (%)			
≤90 days	0 (0.0)	0 (0.0)	0 (0.0)
90 – 120 days	4 (3.3)	6 (3.9)	10 (3.7)
121 – 150 days	6 (5.0)	6 (3.9)	12 (4.4)
151-180 days	59 (49.2)	68 (44.7)	127 (46.7)
>180 days	51 (42.5)	72 (47.4)	123 (45.2)
Safety Extension Period 2			
Exposure (days) [2]			
n	34	40	74
Mean (SD)	345.5 (40.96)	350.5 (36.33)	348.2 (38.34)
Exposure Category – n (%)			
≤180 days	0 (0.0)	0 (0.0)	0 (0.0)
181 – 210 days	1 (2.9)	1 (2.5)	2 (2.7)
211 – 240 days	1 (2.9)	1 (2.5)	2 (2.7)
241 – 270 days	1 (2.9)	0 (0.0)	1 (1.4)
271 – 300 days	1 (2.9)	0 (0.0)	1 (1.4)
301 – 330 days	0 (0.0)	1 (2.5)	1 (1.4)
331 – 360 days	22 (64.7)	24 (60.0)	46 (62.2)
>360 days	8 (23.5)	13 (32.5)	21 (28.4)
1. Exposure = date of last dose of Safety Extension Period 1 – date of first dose + 1. 2. Exposure = date of last dose of Safety Extension Period 2 – date of first dose + 1. BID = twice daily; SD = standard deviation; TID = three times daily.			

Sources: Post-text Tables 5.2-5.3

Reviewer's Comment: Duration of exposure was comparable between the BID and TID dose groups.

7.5.1 Dose Dependency for Adverse Events

Table 64: Dose Dependency For Any Adverse Event Study TBS-1-2011-03

Subjects with Any TEAE	TBS-1 BID	TBS-1 BID/TID	TBS-1 TID	Combined TBS-1 TID	Total
Treatment Period	N=143	N=85	N=78	N=163	N=306
	66 (46.2%)	40 (47.1%)	46 (59.%)	86 (52.7%)	152 (49.7%)
All Periods	N=142	-	-	N=164	N=306
	90 (63.4%)			164 (64.6%)	196 (64.1%)

Sources: TBS-1-2011-03 Post Text Tables 20.1 and 20.4

During the Treatment Period the incidence of TEAEs is modestly greater in the TID group than in the BID dose group. This small difference is not observed when the dose groups are analyzed

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for TEAEs over all study periods. When drug related TEAEs are analyzed for all periods (Post Text Tables 21.1 and 21.4), the TEAE rate was 24.5% (35/143) for BID dosing and 33.3%(26/78) for TID dosing, a modest difference. Combined BID/TID incidence of TEAEs was 35.3% (30/85). The incidence of TEAEs for all time periods increased modestly over the treatment period.

7.5.2 Time Dependency for Adverse Events

The first table below shows the incidence of various categories of AE and lab abnormality by dose during the first 90 days of the study (the Treatment Period). The second table below shows AEs by dose in SE1 and the third table for SE2.

Table 65: Adverse Events for the Treatment Period by Dose TBS-1-2011-03

Adverse Event Category	BID TBS-1 Treatment Period N=143	BID/TID, TID Treatment Period N=85, 78, respectively
	Mean Exposure=84.9 Days	Mean Exposure 87.2 Days
	n(%)	n (%)BID/TID / n(%) TID
Deaths	0	1 (1.2%) / none
Serious Adverse Events	5 (3.4%)	4 (4.7%)/ none
Discontinuations Due to TEAE	3(2.1%)	none / 3 (3.8%)
TEAEs	66 (46.3%)	40 (47.1%) / 46 (59.0%)
PSA increased	3 (2.1%)	9 (10.6 %) / 12 (12.9 %)
Hematocrit \geq 54%	3 (2.1%)	2 (2.4 %) / 2 (2.5 %)

Source: Table 46, page 122 TBS-1-2011-03 and Table 60 of this review and review text relating to PSA levels.

Table 66: Adverse Events Safety Extension 1 TBS-1-2011-03

Adverse Event Category	TBS-1 BID N=120	TTS-1 TID N=152
	n (%)	n(%)
Deaths	0	0
Serious Adverse Events	0	1 (0.7)
Discontinuations Due to TEAE	1 (0.8)	1 (0.7)
TEAEs	42 (35.0)	59 (38.8)

Source: Table 47, TBS-1-2011-03 CSR, page 123

Reviewer's Comment: The incidence of AEs in Safety Extension 1 is modestly lower than during the treatment period. It is noted that 12/78 TID patients experienced a PSA increase and 2 discontinued due to PSA increase in the Treatment Period, while in SE1,

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these events were less frequently reported: 4/152 TID patients experienced a PSA increase and none discontinued.

Table 67: Adverse Events Safety Extension 2 TBS-1-2011-03

Adverse Event Category	TBS-1 BID N=34	TTS-1 TID N=40
	n (%)	n(%)
Deaths	0	0
Serious Adverse Events	1 (2.9)	2 (5.0)
Discontinuations Due to TEAE	0	0
TEAEs	17 (50.0)	22 (55.0)

Source: Table 48, TBS-1-2011-03 CSR, page 125

The percentage of subjects with any TEAE in this period was comparable to the Treatment Period, and higher than in Safety Extension Period 1. In this study period there were no PSA elevation reported.

Reviewer's Comment The number of subjects in SE2 is small, making it difficult to draw conclusions.

Reviewer' Comment: It is not quite clear whether the incidence of TEAEs cumulatively increases over time. When drug related TEAES are analyzed, the incidence of TEAEs in the TID dose group is modestly greater than the BID dose group. Notable differences are noted in prostate specific antigen increased. This is a known adverse event associated with testosterone administration.

Seven patients were identified with a hematocrit $\geq 54\%$ (Table 60 of this review), although at least in three of these cases, hematocrit came back down while subject continued Natesto. It is not possible to draw a conclusion concerning dose relatedness of this effect with Natesto. While the number of increased matocrit $\geq 54\%$ was slightly higher in the SE1 and SE2 periods compared to the Treatment Period, it is not clear whether this event increases over time.

7.5.3 Drug-Demographic Interactions

Study TBS-1-2011-03 was conducted entirely at US centers and patients with a BMI up to 35 kg/m² were included as agreed at the End of Phase 2 Meeting. Age, race, ethnicity, and BMI of the population enrolled in the Phase 3 study were representative of the general population of U.S. men with hypogonadism

No formal subgroup analyses were conducted based on intrinsic factors. Review of the Phase 3 study results for TEAEs and other safety parameters did not reveal any apparent intrinsic factor subgroup differences in safety associated with TBS-1 treatment for up to 1 year.

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In the Phase 3 study, subjects with history of allergic rhinitis were not excluded, nor was upper respiratory infection a specific exclusion criterion. Active allergies, however, was a specific exclusion criterion. In addition, a special extrinsic factor drug interaction study (Study TBS-1-2011-04) was conducted in men with seasonal allergic rhinitis in asymptomatic, symptomatic untreated, and symptomatic treated states (treated with oxymetazoline, a vasoconstricting nasal decongestant) . In addition, patients with asymptomatic seasonal allergic rhinitis were allowed to enroll in the Phase 3 study (see Study TBS-1-2011-03).

No formal subgroup analyses of the Phase 3 safety data were conducted based on extrinsic factors; however, review of the Phase 3 study results for TEAEs and other safety parameters did not reveal any apparent extrinsic factor subgroup differences in safety associated with TBS-1 treatment for up to 1 year.

7.5.4 Drug-Disease Interactions

Study TBS-1-2011-04 was conducted to evaluate whether intranasal application of testosterone is a reliable route of administration during naturally occurring nasal inflammation, such as allergic rhinitis in untreated subjects and in subjects treated with a commonly used decongestant (oxymetazoline). The testosterone exposure as determined by serum AUC_{0-24h} , was 21% lower the symptomatic state as compared to the asymptomatic state suggesting that active allergic rhinitis may result in decreased drug absorption. The AUC differences between symptomatic untreated and symptomatic treated (with the decongestant oxymetazoline) subjects were not significant. The Sponsor notes that statistically significant differences in the pre-dose testosterone levels were seen between the asymptomatic state and the symptomatic states, suggesting that different study conditions may have impacted the subject's testosterone levels. The Sponsor states this may be explained by the earlier wake-up time for subjects in both symptomatic treatment arms compared to the asymptomatic state to accommodate the EEC allergen challenge.

Reviewer's Comment: Based upon the considerations the Sponsor has raised, it is possible that the 21% AUC difference between symptomatic and non-symptomatic allergic rhinitis subjects is overstated. This finding, nonetheless will be described in the drug label. There is no indication of a drug-drug interaction between TBS-1 and oxymetazoline.

7.5.5 Drug-Drug Interactions

See **Section 7.5.4.**

Reviewer's Comment: The results of the oxymetazoline DDI study will be included in labeling, along with a statement that no other classes of intranasally administered drugs have been studied; therefore their concomitant use with Natesto is not recommended.

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7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

At the current time, I am not aware of any evidence of the carcinogenicity of TBS-1.

Clinical AEs reported under the SOC “Neoplasms benign, malignant and unspecified” were reported in 3/142 (2.1%) of of TBS-1 BID patients and 6/164 (3.7%) Combined TBS-1 TID (BID/TID and TID) subjects in study TBS-1-2011-03. Of the total of 9 patients in this category, 3 reported basal cell carcinoma, 2 reported malignant melanoma, 1 patient had a lung neoplasm, 1 patient had a melanotic nevus and 1 patient had a squamous cell carcinoma of the skin. The remainder of subjects had benign lesions, including one case each of adrenal adenoma, breast fibroma, hemangioma and lipoma. There was no case of prostate cancer.

The 120 DAY SAFETY UPDATE REPORT lists one case of basal cell carcinoma in each treatment group and one case of malignant melanoma in the TBS-1 TID treatment group.

Reviewer’s comment: The absence of a placebo arm and the different cell types and low incidence of neoplasia in the average age group for the study subjects make interpretation of these clinical AEs difficult. Nonetheless, these data do not suggest a safety concern in my opinion.

7.6.2 Human Reproduction and Pregnancy Data

TBS-1 is not intended for use by, and should not be used by pregnant or lactating women. The clinical safety data is related only to the treatment of hypogonadal males and therefore, safety information is not available, nor applicable, for use in pregnancy and lactation. It is not known how much testosterone transfers into human milk. Exposure of the fetus to androgens may result in varying degrees of virilization.

7.6.3 Pediatrics and Assessment of Effects on Growth

The safety and efficacy of TBS-1 in males <18 years old has not been established. Improper use may result in premature closure of the epiphyses.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No cases of overdose with TBS-1 have been reported in clinical trials. There is 1 report of acute overdosage by injection of testosterone enanthate: testosterone concentrations of up to 11,400 ng/dL were implicated in a cerebrovascular accident.

Treatment of overdosage would consist of discontinuation of TBS-1, together with appropriate

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symptomatic and supportive care. Data from Phase 2 studies shows that the elimination half life for a single dose of TBS-1 (22.8 mg QD) is 10.5 hours (SD 5.43) [Table 9 SCS current submission.

TBS-1 contains testosterone, a Schedule III controlled substance as defined by the Anabolic Steroids Control Act. Anabolic steroids, such as testosterone, are abused. Abuse has been associated with adverse physical and psychological effects. No information on testosterone withdrawal or rebound is available from the TBS-1 development program.

7.7 Additional Submissions

7.7.1 January 7, 2014: Major Clinical Amendment

On January 7, 2014, the Sponsor submitted a Clinical amendment requesting approval of a new dosing regimen, TID dosing-only. Therefore, the review was shifted to focus on assessment for approval of the 11 mg TID dosage of TBS-1. The efficacy and safety data from the pivotal Phase 3 study TBS-1-2011-03 provide the basis for this amendment and have been reviewed. The ITT sample size of 73 patients and relatively “tight” confidence intervals allow the success rate to be estimated with adequate precision, in my opinion. The safety cohort of more than 300 subjects who received at least one dose of the study drug and had at least one post baseline safety measurement is an adequate number. 245 hypogonadal patients completed 180 days of treatment and 152 of these men were treated with the 11 mg TID dose. 67 hypogonadal men completed 365 days of treatment of which 37 were treated with the 11 mg TID dose. The incidence of AEs is discussed in the analysis of safety. Sponsor states that the overall incidence of AEs, local tolerability and severity is similar between the BID and TID dose groups when TID and BID/TID are combined. Clinical AEs are at most, modestly increased when the 78 TID only patients are separately analyzed, in my opinion.

There did not appear to be any significant chemistry, hematologic or adverse endocrine issues that were dose related; however, there was an indication of dose-relatedness for increases in serum PSA. There were no significant dose related vital signs differences.

Reviewer’s Comment: It appears reasonable and appropriate to approve the amended dosing regimen for TBS-1.

7.7.2 March 7, 2014 Information Request Clinical

In response to several Clinical questions conveyed to Sponsor concerning their major Clinical amendment of January 2014, the Sponsor provided the following responses in a submission dated March 7, 2014:

- 1. Sponsor was asked to provide justification for a total of 37 men who received one year of treatment with the proposed dose of TBS-1 of 11 mg TID.**

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{Roger Wiederhorn MD }

{NDA 205488 }

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The Sponsor based their response on an exposure-response concept, whereby dosing of testosterone into the normal range, without outliers is generally safe with known safety risks. They stated:

The Cavg exposure levels produced by TBS-1 TID therapy are similar to the lower range of currently approved testosterone replacement therapies (TRT). Cavg was within the normal range and no subject had a Cavg >1050 ng/dl (upper limit of normal range) on TID treatments during the Treatment Period (see Table 68 below). No unexpected, new treatment emergent adverse events (TEAE) were observed in any treatment group when compared to other currently approved testosterone replacement products. TEAE rates are similar to other approved TRT according to the Sponsor.

Table 68: Selected Mean Serum Total Testosterone Concentrations by Treatment and Time Point at Day 30 and Day 90 Treatment Period TBS-1-2011-03

	BID ng/dl (% CV)	BID/TID ng/dl (% CV)	TID ng/dl (% CV)
Day 30			
N	131	85	73
Predose	296.9 (78)	232.0 (52)	325.7 (50)
9.75h post-dose	336.5 (53)	238.9 (32)	283.8 (37)
24.0h post-dose	242.0 (66)	211.2 (56)	311.7 (59)
Cavg	402.6 (41)	301.3 (23)	414.8 (27)
Cmax	1040.0 (41)	743.8 (41)	912.7 (37)
Day 90			
N	122	82	69
Predose	293.1 (95)	282.8 (46)	355.7 (66)
9.75h post-dose	314.8 (52)	246.8 (45)	290.3 (45)
24.0h post-dose	253.0 (70)	260.6 (48)	278.0 (40)
Cavg	375.3 (34)	358.3 (28)	420.9 (28)
Cmax	1045.7 (45)	843.3 (42)	1043.9 (36)
Constructed using data in CSR TBS-1-2011-03 Tables 9.1.1-9.1.4			

Source: Table 1 of March 7, 2014, information request.

The Sponsor also noted that a sufficient number of hypogonadal men were enrolled such that a sufficient number made it through the study to assess local tolerability. They stated:

A total of 274 patients entered SE1 at Day 90; 250 patients (>90%) completed no less than a total of 151 days of dosing. At total of 75 patients entered SE2 at with 67 (89.3%) completing no less than 331 days. 40 subjects entered the 180 day Safety Extension as part of either BID/TID or TID(Combined BID/TID) dosing regimen and 34 subjects entered on BID dosing. The number of subjects completing at least 331 days of the 1 year study duration was 30 on BID and 37 on Combined TID. Mean exposure days to TBS-1 were similar for BID, BID/TID and TID dosing.

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Reviewer's Comment: The reviewer agrees that 67 patients in SEI 2 and the 250 patients in SE1 are adequate for safety assessment, especially in light of normal range testosterone exposure. Nonetheless, labeling will describe the limited long-term exposure and long-term safety data.

The aggregate numbers of adverse events for each period of TBS-1-2011-03 are considered below:

The Sponsor also pointed out lack of evidence that clinical AEs increase with time with Natesto.

Table 69: Comparison of Treatment Related Events by Study Periods and Dose

	BID	BID/TID	TID	Total
Treatment Period				
	N=142	N=86	N=78	N=306
Drug Related AEn (%)	34.5 (24.5)	30 (35.3)	26 (33.3)	91 (29.7)
Any TEAE	66 (46.2)	40 (47.1)	46 (59.0)	152 (49.7)
Safety Extension Period 1				
	N=120	N=83	N=69	N=272
Drug Related AEn (%)	21 (17.5)	13 (15.7)	10 (14.5)	44 (16.2)
Any TEAE	42 (35.0)	26 (31.3)	33 (47.8)	101 (37.1)
Safety Extension Period 2				
	N=34	N=22	N=18	N=74
Drug Related AEn (%)	4 (14.7)	4 (18.2)	2 (11.1)	11 (14.9)
Any TEAE	17 (50.0)	13 (59.1)	9 (50.0)	39 (52.7)

Source: Table 2 of [March 7, 2014](#), information request

Reviewer's Comment: This product achieves low-normal total serum testosterone levels. The risks of testosterone replacement are fairly well documented. There was similar exposure days and similar PK values between the dose groups. The absence of a control arm confounds the ability to conclusively determine a drug related AE from a TEAE. TEAEs are modestly higher in frequency the TID dose group..

2. Clarify which patients are included in the “TBS-1 BID” and “TBS-1 TID” groups in Table 2.

The tables supplied by Sponsor defined the dose groups as follows:

- BID subjects as randomized and completed the study on BID regimen.
- BID/TID subjects as randomized to BID, up-titrated to TID and completed on TID regimen
- TID subjects as randomized to and completed the study on TID regimen
- Combined TID as any patient who completed the study on TID. This includes BID/TID and TID patients.

Table 70: Treatment Emergent Adverse Events in Which TID Dose Group Incidence Exceed The BID Dose Group by >= 2% Safety Population All Periods TBS-1-2011-03

TEAE Preferred Term	BID (N=142) n(%)	BID/TID (N=86) n (%)	TID (N=78) n (%)
Nausea	1 (0.7)	2 (2.3)	3 (2.8)
Pyrexia	0 (0.0)	2 (2.3)	2 (2.6)
Chills	0 (0.0)	1 (1.2)	2 (2.6)
Nasopharyngitis	9 (6.3)	8 (9.3)	8 (10.3)
Upper Respiratory Tract Infection	6 (4.2)	1 (1.2)	6 (7.7)
Sinusitis	0 (0.0)	0 (0.0)	3 (3.8)
Tooth Abscess	0 (0.0)	0 (1.2)	3 (3.8)
Procedural Pain	0 (0.0)	0 (0.0)	3 (3.8)
PSA increased	0 (0.0)	4 (4.7)	6 (7.7)
BP increased	0 (0.0)	1 (1.2)	2 (2.6)
Hyperkalemia	0 (0.0)	0 (0.0)	2 (2.6)
Pain in Extremity	3 (2.1)	1 (1.2)	4 (5.1)
Myalgia	0 (0.0)	0 (0.0)	3 (3.8)
Malignant Melanoma	0 (0.0)	0 (0.0)	2 (2.6)
Headache	4 (2.8)	3 (3.5)	4 (5.1)
Dysgeusia	2 (1.4)	2 (2.3)	3 (3.8)

Source: Table 3 of March 7, 2014, information request

Reviewer's Comment: Tooth abscess and malignant melanoma are unlikely TEAEs for testosterone. Sinusitis, procedural pain, dysgeusia, nasopharyngitis, upper respiratory tract infection and headache could reflect the intranasal route of administration. PSA increases is known to be an effect of testosterone replacement. Whether blood pressure increased, myalgia, pain in extremity and pyrexia reflects an effect of testosterone is unknown. With respect to hyperkalemia, one patient was actually TID dose group and one patient was BID dose group according to ADLB data set. Both patients completed Treatment period and SE1 and did go on to SE2. For BID patient 052-016 the baseline potassium was 6.2 mmol/L and subsequent potassium levels at Day 30, Day 90 and Day 180 were 4.5, 3.9 and 5.8 respectively. For TID patient 052-034, The baseline potassium was 5.6 mmol/L and potassium levels at Day 30, Day 90 and Day 180 were 5.0, 4.6 and 6.3 respectively. With the baseline potassium elevations, it appears the hyperkalemia in these two cases, was probably not related to the study drug. This adverse event analysis does not in my opinion indicate that TID dosing is significantly less safe than BID dosing. Increased PSA and the local AEs of nasopharyngitis and URI symptoms may indicate an effect of the TID dose over the BID dose; however, my overall analysis of local tolerance does not indicate a significant local tolerance difference between TID and BID dosing.

- 3. Clarify whether there are differences in duration of patient exposures between the groups in Table 2 (Table 2 was used to derive Table 65 of this Review) that should be accounted for by analyses using patient-year exposures.**

The Sponsor states that the safety population is composed of 130.9 patient years (PY) at 6 month as recorded in Safety Extension Period 1 and 70.6 PY at 1 year as recorded in Safety Extension Period 2. An increase in dose frequency over the periods did not cause an observable increase in incidence or severity events.

Reviewer's Comment: The number of TID-only completer patients in SE2 is small, making it difficult to confirm long-term safety of the regimen, but the long term safety of testosterone replacement is known and the low normal total serum testosterone levels attained with TBS-1 argue against a concern for this aspect of safety. In addition, 6-month safety data provide good evidence of local tolerability and there did not appear to be an increase in the frequency or severity of AEs from 6 months to 1 year. Overall, the limited long term safety data for TID dosing of TBS-1 is not unacceptable, but will be mentioned in labeling.

- 4. Clarify whether the existing datasets submitted in your NDA are amenable to conducting a new safety analysis focusing on three times per day dosing vs. twice daily dosing. If they are not amenable to such analyses, submit updated datasets.**

The Sponsor states that the existing datasets submitted in Trimel's NDA are amenable to conducting a new safety analysis focusing on three times a day dosing vs. twice daily dosing. Additionally, updated tables to present the safety data for all randomization groups separately were created and were provided in Attachment 1 of this submission.

Reviewer's Comment: The submitted materials did allow a new safety analysis focusing on TID dosing as compared to BID dosing.

- 5. The submission contains general safety and tolerability statements. Include more detailed safety information on three times per day dosing compared to twice daily dosing including tables showing patient disposition, serious adverse events, withdrawal due to adverse events, laboratory and vital sign parameters. If this information is already present in the NDA please direct us to their location.**

The Sponsor provided more detailed safety information on TID dosing, including subject disposition, listing of SAEs, AEs that led to study discontinuation, and other information such as lab values and vital signs. . For example, the first two table below summarizes subject mean exposure and disposition for all periods and all randomization groups separately:

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Table 71: Summary of Mean Exposure and Patient-Year Estimations through Safety Period 1 and Safety Period 2 TBS-1-2011-03

	BID	BID/TID	TID	Combined TID	Total
Treatment plus Safety Period 1					
N	120	83	69	152	272
Mean exposure	175.5	177.3	174.2	175.9	175.7
	57.7	40.3	32.9	73.2	130.9
Safety Period 2					
N	34	22	18	40	74
Mean exposure	345.5	350.1	351.0	350.5	348.2
Patient Years	32.2	21.1	17.3	38.4	70.6
Subjects with any TEAE, All Periods	90 (63.4)	51 (59.3)	55 (70.5)	106 (64.6)	196(64)
Mean total doses determined by multiplication of mean exposure and dosing regimen. BID/TID accounts for 45 days at BID and remaining safety exposure at TID. Combined groups (TID and ALL) estimated using weighted averages of subgroups.					

Source: Table 5, March 7, 2014, Information Request.

Table 72: Summary of Subject Disposition TBS-1-2011-03

	BID n (%)	BID/TID n (%)	TID n (%)	Combined TID n (%)	Total n (%)
Treatment Period					
Entered Treatment Period	142 (100.0)	86 (100.0)	78 (100.0)	164 (100.0)	306 (100.0)
Safety Population	142 (100.0)	86 (100.0)	78 (100.0)	164 (100.0)	306 (100.0)
Safety Extension Period 1					
Entered Safety Extension Period 1	122 (100.0)	83 (100.0)	69 (100.0)	152 (100.0)	274 (100.0)
Safety Population	120 (98.4)	83 (100.0)	69 (100.0)	152 (100.0)	272 (99.3)
Safety Extension Period 2					
Entered Safety Extension Period 2	35 (100.0)	22 (100.0)	18 (100.0)	40 (100.0)	75 (100.0)
Safety Population	34 (97.1)	22 (100.0)	18 (100.0)	40 (100.0)	74 (98.7)

Source: Table 6, March 7, 2014, Information Request

The next table below summarizes SAEs by dose group over the course of the study.

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**Table 73: Listing of Subjects with Serious Adverse Events-Safety Populations-All Periods
TBS-1-2011-03**

Treatment Subject	TEAE	Period	Adverse Event Preferred Term (Treatment Regimen if on >1)	Resulted in Discontinuation
TBS-1 BID				
025-023	yes	SE2	Angina Pectoris	No
047-003	yes	T	Hip Fracture	No
047-022	yes	T	Fall	No
	yes	T	Ligament Rupture	No
TBS-1 BID/TID				
010-039	yes	T	Acute Coronary Syndrome (BID)	No
		SE1	Rocky Mountain Spotted Fever (TID)	No
022-012	yes	SE2	Pneumonia (TID)	No
029-005	yes	SE2	Gastroesophageal Reflux disease (TID)	No
TBS-1 TID				
004-008	yes	T	Internal Injury	Yes
	yes	T	Road Traffic Accident	Yes
008-002	yes	T	Abdominal Mass	No

Source: Table 7, March 7, 2014, Information Request

Eight (2.6%) subjects reported SAEs during the study: 3 (2.1%) subjects in the TBS-1 BID group and 5 (3.0%) subjects in the Combined TBS-1 TID group (3 (3.4%) subjects in the TBS-1 BID/TID group and 2 (2.6%) subjects in the TBS-1 TID group). The incidence of SAEs was comparable across all treatment groups. None of the SAEs during the study were considered by the Investigator to be related to the study drug.

Nine (2.9%) subjects discontinued from the study due to a TEAE: 3 (2.1%) subjects in the TBS-1 BID group and 6 (3.7%) subjects in the Combined TBS-1 TID group (1 [1.1%] subjects from the TBS-1 BID/TID group and 5 (6.4%) subjects from the TBS-1 TID group).

Seven (2.3%) subjects discontinued from the study due to a drug-related TEAE: 3 (2.1%) subjects in the TBS-1 BID group and 4 (2.4%) subjects in the Combined TBS-1 TID group (1 [1.1%] subjects from the TBS-1 BID/TID group and 3 [3.8%] subjects from the TBS-1 TID group).

Out of 7 subjects discontinued due to a drug-related TEAE, 3 subjects were discontinued during the Treatment Period (1 from the TBS-1 BID group and 2 from the TBS-1 TID group), 3 subjects during the Safety Extension Period I (2 from the TBS-1 BID group and 1 from the TBS-1 BID/TID group) and 1 subject during the Safety Extension Period 2 (subject from the TBS-1TID group).

The incidence of TEAEs that led to discontinuation was comparable across all treatment

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groups. None of the adverse events that led to discontinuation occurred at a frequency or severity to suggest a safety concern.

Table 74: Listing of Subjects that Led to Study Drug Discontinuation Safety Population All Periods TBS-1-2011-03

Treatment Subject	TEAE	Period	Adverse Event Preferred Term (Treatment Regimen if on >1)	SAE
TBS-1 BID				
011-007	Yes	T-SE1	Nasal Discomfort	
	Yes	T-SE1	Parosmia	
	Yes	T-SE1	Scab	
012-008	Yes	T	Depressed Level of Consciousness	
	Yes	T	Headache	
043-004	Yes	T-SE1	Hypersensitivity x 3	
TBS-1 BID/TID				
001-049	Yes	T-SE1	PSA increased (TID)	
TBS-1 TID				
004-008	Yes	T	Internal Injury	
	Yes	T	Road Traffic Accident	
008-002	Yes	T	Abdominal Pain	
008-003	Yes	T	Dysgeusia	
	Yes	T	Nasal Odor	
011-016	Yes	SE1-SE2	PSA Increased	
021-014	Yes		Petechiae	

Source: Table 8, March 7 Information Request

In the additional tables designed to demonstrate laboratory data summaries, a significant number of subjects with low serum cortisol levels was noted. That concern was subsequently addressed by Sponsor (see previous sections of this review).

Vital sign data do not indicate any additional safety concerns.

Reviewer's Comment: The review of safety data from the standpoint of TID vs BID dosing does not generate any new safety concerns not noted in the review of the overall NDA submission. There is sufficient information on TID-only to assess the safety of this regimen.

6. The Sponsor was asked to provide individual values for fasting serum total testosterone concentrations during the Safety Extension Periods 1 and 2 (i. e. on Days 180, 270 and 360) as they could not be located in the original submission.

The Sponsor pointed out that these values were already available in CSR Listing 17.8. For convenience, the Sponsor provided descriptive statistics in Tables 38.1 and 38.2 of the March 7, 2014, Information Request.

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Reviewer's Comment: The individual patient serum testosterone were found in Appendix 16.2.8 under Listng 17.8 in the CSR.

The majority of the fasting serum total testosterone concentrations during the study were in the normal range.

Reviewer's comment: The reader is referred to the Clinical Pharmacologist's review for additional data and commentary on the mean fasting serum testosterone concentrations. The reviewer points out that only one subject (047-003) had T levels which were above 2500 ng/dL on Day 180. This subject started taking the prohibited medication anastrozole on Study Day 178 (two days before his Day 180 visit).

- 7. The Sponsor was asked the following: In the summary of subject disposition (Table 4 on Page 67 and Table 5 on Page 69 of the CSR) for Study TBS-1-2011-03, you state that 274 subjects completed the 90-day treatment period and entered the extended safety period 1. However, in your primary efficacy results (Table 11 on Page 80 of the CSR) and pharmacokinetic analyses (Table 19 on Page 89 of the CSR) at Day 90, you only included (b) (4) subjects. Clarify this discrepancy.**

The Sponsor responded: The difference in the number of subjects completing the 90-day treatment period and entered the Safety Extension Period 1 vs. the number of subjects included in the ITT analysis of the primary efficacy results (Table 11 on Page 80 of the CSR) and pharmacokinetic analyses (Table 19 on Page 89 of the CSR) occurred due to the fact that 274 subjects completed the Treatment Period of the study, but only (b) (4) subjects had valid 24-hour serum total testosterone Cavg as Day 90 PK profile was not obtained for (b) (4) of the 274 Treatment Period completers. Subject 047-022 didn't attend Visit 6 on Day 90 (+/- 3 days) as required per protocol. On study Day 107, he had an SAE: fall at work, tom ligaments in knee due to falling at work that involved hospitalization. The subject returned to the clinic for Visit 6 on study Day 119 after being discharged from the hospital; however, 24 h PK blood draws were not done at that time. Nonetheless, the PI allowed the subject to continue into Safety Extension Period 1. The subject was lost to follow up after that and didn't come back for future visits. This subject Day 30 PK results were used as a LOCF and this patient was included in the ITT LOCF primary endpoint analysis as presented in the CSR Table 12 on Page 79.

Reviewer's Comment: This response is acceptable. Overall, the Sponsor's responses to these review questions related to the major amend were acceptable and served to complete the database necessary to adequately review the TID dosing regimen for approva;.

7.7.2 April 11, 2014 Information Request-Cortisol

This information was requested by the FDA and received April 11, 2014. The issue is considered resolved.

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8 Postmarket Experience

TBS-1 is not presently commercially available in any part of the world, and there are no pending applications for foreign registration. The postmarketing experience with testosterone replacement of different formulation is extensive and well known. This material is also discussed in **Section 7.4**.

9 Appendices

9.1 Literature Review/References

9.2 Labeling Recommendations

9.3 Advisory Committee Meeting

9.4 Overview of the Protocol for the Pivotal Study: Phase 3, TBS-1-2011-03

The following is a summary overview of the protocol for the pivotal Phase 3 study TBS-1-2011-03. In addition, subject disposition is provided in overview fashion. The reader is referred to more detailed information and study results in the body of this review.

Title of Study: A 90-Day, Randomized, Dose-Ranging Study, Including Potential Dose Titration, Evaluating the Efficacy and Safety of Intranasal TBS-1 in the Treatment of Male Hypogonadism with Sequential Safety Extension Periods of 90 and 180 Days.

Study Sites: 39 sites in the United States.

Study Period: Up to 58 weeks maximum, for subjects who completed all 4 periods. The number of weeks for individual subjects depended upon whether they were receiving testosterone treatment at screening, which necessitated a 2- to 4-week washout period.

Initiation Date: 23 September 2011

90-day Treatment Period Completion Date: 12 October 2012

Safety Extension Period 1 Completion Date: 09 January 2013

Safety Extension Period 2 Completion Date: 11 March 2013

Study Objectives:

Primary: The primary objective of the study was to determine the efficacy of 4.5% TBS-1 gel, administered as 2 or 3 daily intranasal doses of 5.5 mg per nostril, as demonstrated by an

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increase in the 24-hour average concentration (C_{avg}) of serum total testosterone to the normal range (≥ 300 ng/dL and ≤ 1050 ng/dL) in $\geq 75\%$ of male subjects treated for hypogonadism.

Secondary: The secondary objectives of the study were the following:

- To determine the efficacy of 4.5% TBS-1 gel, administered 2 or 3 times daily at a dose of 5.5 mg per nostril, in achieving the following for serum total testosterone maximum concentration (C_{max}):
 - $C_{max} \leq 1500$ ng/dL in $\geq 85\%$ of subjects,
 - C_{max} 1800 to 2500 ng/dL in $< 5\%$ of subjects, and
 - $C_{max} > 2500$ ng/dL in no subjects;
- To determine the safety and tolerability of TBS-1 after 90, 180, and 360 days of treatment;
- To determine the effect of TBS-1 treatment on body composition (total body mass, lean body mass, fat mass, and percent fat);
- To determine the effect of TBS-1 treatment on bone mineral density (lumbar spine and hip);
- To determine the effect of TBS-1 treatment on mood;
- To determine the effect of TBS-1 treatment on erectile function; and
- To determine the serum concentration and pharmacokinetics of total testosterone, dihydrotestosterone (DHT), and estradiol after TBS-1 administration.

Methodology: The study was designed as a Phase 3, 2-group, multicenter 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 currently receiving testosterone treatment;
- A 90-day randomized, open-label Treatment Period during which subjects received 5.5 mg per nostril of 4.5% TBS-1 twice daily (BID) or 3 times daily (TID) with potential daily dose adjustment on Day 45 for subjects in the BID treatment group as determined by the serum total testosterone pharmacokinetic (PK) profile;
- A 90-day, open-label Safety Extension Period (Safety Extension Period 1) for all study subjects; and
- An additional 180-day, open-label Safety Extension Period (Safety Extension Period 2) for a subset of 75 subjects.

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Treatments: At Visit 3 (Day 1), subjects who met the entry criteria were randomly assigned in a 3:1 ratio to 4.5% TBS-1 BID or 4.5% TBS-1 TID. The first dose was administered at 2100 h at the study site.

Subjects assigned to BID dosing took 5.5 mg per nostril of 4.5% TBS-1 at 2100 h and 0700 h for a total daily dose of 22 mg/day.

Subjects assigned to TID dosing took 5.5 mg per nostril of 4.5% TBS-1 at 2100 h, 0700 h, and 1300 h for a total daily dose of 33 mg/day.

At Visit 4 (Day 30) and Visit 6 (Day 90), subjects brought their TBS-1 medication to the site for administration and performance of the 24-hour post-dose complete PK profiles of serum total testosterone, DHT, and estradiol.

After Visit 4 (Day 30), subjects randomized to the BID group with an estimated serum total testosterone $C_{avg} < 300$ ng/dL were contacted by phone and instructed to increase the daily dose of TBS-1 to TID on Day 45. This daily dose was continued throughout the remainder of the Treatment Period and, as applicable, both Safety Extension Periods. The decision to increase the subject's daily dose to TID was made by the Investigator. The estimation of the serum total testosterone C_{avg} was based on the following titration criteria:

- If the sum of the serum total testosterone level values for PK samples collected at 9.0 hours and 10.33 hours was < 755 ng/dL, then the estimated 24-hour C_{avg} was < 300 ng/dL, and
- If the sum of the serum total testosterone level values for PK samples collected at 9.0 hours and 10.33 hours was ≥ 755 ng/dL, then the estimated 24-hour C_{avg} was ≥ 300 ng/dL.

The approximate total duration of study participation for subjects completing all 4 periods was up to 406 days (~58 weeks). The approximate total duration of study drug exposure for subjects completing all 4 periods was up to 360 days (~51 weeks).

The total duration of study participation for subjects completing all 4 periods was up to 406 days (~58 weeks), depending upon whether they were receiving testosterone treatment at screening, which necessitated a 2- to 4-week washout period.

Duration of Treatment: From 180 days (all subjects) to 360 days (for subjects who participated in Safety Extension Period 2).

Inclusion Criteria

Subjects who met all of the following inclusion criteria were eligible for participation in the study:

1. Male between 18 and 80 years of age, inclusive, with a known history of hypogonadism;

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2. Able to understand and provide signed informed consent;
3. Had 2 fasting morning (0900 h \pm 30 min) serum total testosterone levels <300 ng/dL on week apart. If 1 or the 2 serum total testosterone levels was ≥ 300 ng/dL, the serum testosterone level could be tested once more. After that third testing, if 2 of the 3 levels were < 300 ng/dL, then the subject was study eligible.
4. Body mass index (BMI) between 18.5 kg/m^2 and 35 kg/m^2 , inclusive;
5. Hemoglobin level ≥ 13.0 g/dL;
6. Otorhinolaryngological (ENT) examination, including nasal endoscopy without clinically significant abnormal findings, and
7. Normal prostate for age based on DRE and a serum PSA <4.0 ng/mL.

Exclusion Criteria

Subjects who met any of the following criteria were excluded from participation in the study:

1. In the opinion of the Investigator, significant intercurrent disease of any type, in particular liver, kidney, heart disease, or psychiatric illness;
2. Hyperparathyroidism, uncontrolled diabetes mellitus, hypothyroidism, or hyperthyroidism (TSH should be ≤ 1.5 times the upper limit of normal [ULN]);
2. Alanine transaminase (ALT) or aspartate transaminase (AST) $>2 \times$ ULN; unexplained creatine kinase $>3 \times$ ULN; HbA_{1c} $>7.0\%$ (9.5 mmol/L), or any other laboratory discussion with the medical monitor;
4. Hematocrit $>54\%$ at screening;
5. 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;
6. History of nasal surgery, specifically turbinoplasty, septoplasty, rhinoplasty, "nose job," or sinus surgery;
7. History of nasal fractures within the past 6 months and/or prior nasal fractures that caused a severely deviated anterior nasal septum;
8. Active allergies, such as rhinitis, rhinorrhea, and nasal congestion;
9. Mucosal inflammatory disorders, specifically pemphigus or Sjogren's syndrome;
10. Sinus disease, specifically acute sinusitis, chronic sinusitis, or allergic fungal sinusitis;

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11. History of nasal disorders (e.g., polyposis, recurrent epistaxis [>1 nose bleed per month], abuse of nasal decongestants);
12. History of sleep apnea;
13. Use of any form of intranasal medication delivery, specifically nasal corticosteroids and oxymetazoline-containing nasal sprays (e.g., Dristan® 12-Hour Nasal Spray);
14. History of severe adverse drug reaction or leukopenia;
15. A known hypersensitivity to lidocaine or any materials that may have been used during the study;
16. History of abnormal bleeding tendencies or thrombophlebitis unrelated to venipuncture or intravenous cannulation;
17. 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;
18. Presence of human immunodeficiency virus infection or antibodies;
19. History of asthma and ongoing asthma treatment;
20. History of significant sleeping problems or a shift worker;
21. Smoker of >10 cigarettes (or equivalent) per day;
22. History or current evidence of abuse of alcohol or any drug substance.
23. 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 difficult abstaining from alcohol during the 48 hours prior to the 24-hour blood sampling visits;
24. 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., testosterone enanthate 200 mg/mL] and 2 weeks for products administered orally or topically [oral, patch, gel, or buccal])
25. Current treatment with other androgens (e.g., dehydroepiandrosterone [DHEA]), anabolic steroids, or other sex hormones;
26. Treatment with estrogens, gonadotropin-releasing hormone (GnRH) agonists, or growth hormone within the previous 12 months;
27. Treatment with drugs that interfere with the metabolism of testosterone, such as anastrozole, clomiphene, dutasteride, finasteride, flutamide, ketoconazole, spironolactone, or testolactone;

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28. 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);
29. Poor compliance history or low likelihood of maintaining attendance;
30. Participation in any other research study during the conduct of this study or 30 days prior to the initiation of this study; or
31. Blood donation at any time during this study and within the 12-week period prior to Screening.

Number of Subjects:

Planned: Approximately 280 subjects (210 subjects randomized to the BID treatment group; 70 subjects randomized to the TID treatment group)

Screened: 1126 subjects.

Randomized: 306 subjects (228 subjects randomized to TBS-1 BID; 78 subjects randomized to TBS-1 TID).

Completed 90-day Treatment Period: 274 subjects (205 subjects randomized to TBS-1 BID; 69 subjects randomized to TBS-1 TID).

Discontinued During Treatment Period: 32 subjects (23 subjects randomized to TBS-1 BID; 9 subjects randomized to TBS-1 TID).

Entered Safety Extension Period 1: 274 subjects (122 subjects in TBS-1 BID group; 152 subjects in TBS-1 TID group).

Completed Safety Extension Period 1: 245 subjects (107 subjects in TBS-1 BID group; 138 subjects in TBS-1 TID group).

Discontinued During Safety Extension Period 1: 29 subjects (15 subjects from TBS-1 BID group; 14 subjects from TBS-1 TID group).

Entered Safety Extension Period 2: 75 subjects (35 subjects in TBS-1 BID group; 40 subjects in TBS-1 TID group).

Completed Safety Extension Period 2: 55 subjects (25 subjects in TBS-1 BID group; 30 subjects in TBS-1 TID group)

Discontinued During Safety Extension Period 2: 8 subjects (5 subjects from TBS-1 BID group; 3 subjects from TBS-1 TID group).

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Still Enrolled in Safety Extension Period 2 at Time of NDA Submission: 12 subjects (5 subjects in TBS-1 BID group; 7 subjects in TBS-1 TID group).

Investigational Product and Comparator Information:

TBS-1 was administered intranasally by the subject. A multiple-dose dispenser was used for gel deposition into the nasal cavity. The table below summarizes information related to the study drug.

Table 75: Study Information

Study Drug:	4.5% TBS-1
Pharmaceutical form:	Gel for intranasal administration
Content:	Active ingredient: testosterone Excipients: colloidal silicon dioxide, castor oil, and oleoyl polyoxylglycerides
Mode of administration:	Intranasal
Manufacturer:	(b) (4)
Batch number:	TBS-1 Testosterone Nasal Gel (11.0 mg/dose): Batch No. 2372 and Batch No. 2374
Storage conditions:	Between 15-25°C

Source: (Appendix 16.1.1 and Certificates of Analysis (Appendix 16.1.6) CSR TBS-1 -2011-6 Page 5

Criteria for Evaluation:

Efficacy: The primary efficacy variable was the number and percentage of subjects with a serum total testosterone C_{avg} within the normal range (≥ 300 ng/dL and ≤ 1050 ng/dL) on Day 90.

The key (mandatory) secondary efficacy variables included the following:

- The number and percentage of subjects with a serum total testosterone C_{max} in the following ranges on Day 90:
 - ≤ 1500 ng/dL,
 - ≥ 1800 and ≤ 2500 ng/dL, and
 - > 2500 ng/dL;
- 8. The number and percentage of subjects with a serum total testosterone C_{avg} in the normal range (≥ 300 ng/dL and ≤ 1050 ng/dL) on Day 30;
- 9. The number and percentage of subjects with a serum total testosterone C_{max} in the following ranges on Day 30:
 - a. ≤ 1500 ng/dL,
 - b. ≥ 1800 and ≤ 2500 ng/dL, and
 - c. > 2500 ng/dL;

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10. The complete PK profile (including C_{avg} , the minimum concentration [C_{min}], C_{max} , and time to maximum concentration [T_{max}]) of serum total testosterone on Day 30 and Day 90;
11. The time within the normal range for serum total testosterone based on the PK profile on Day 30 and Day 90;
12. The PK profile of serum estradiol on Day 30 and Day 90;
13. The PK profile of serum DHT on Day 30 and Day 90;
14. The ratio of DHT C_{avg} to total testosterone C_{avg} on Day 30 and Day 90;
15. The International Index of Erectile Function (IIEF) scores at baseline, Day 30, Day 60, and Day 90;
16. The Positive and Negative Affect Schedule (PANAS) scores at baseline, Day 30, Day 60, and Day 90;
17. The change in bone mineral density from baseline to Day 180 and from baseline to Day 360; and
18. 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.

Safety Evaluation

Safety assessments included collection of clinical adverse events, clinical laboratory measurements (chemistry, hematology, liver function tests, fasting lipid profile, urinalysis, prostate specific antigen, and endocrine profile [cortisol]), 12-lead electrocardiogram (ECG) parameters, vital signs (blood pressure, heart rate, temperature, and respiratory rate), physical examination parameters, digital rectal examinations (DREs) of the prostate, and otorhinolaryngological (ENT) examinations.

The schedule of procedures and safety evaluations are provided in the following two pages:

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was distributed to subjects to record date and time of study drug administration.

NAS questionnaires were administered to subjects at Early Termination if subjects terminated on or before Visit 6 (Day 90).

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

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), and performed physical examination (may have been performed on Day 90 or Day 91).

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: 1 hour (at 0300 h), 12 hours (at 0900 h), 18 hours (at 1500 h), and 24 hours (at 2100 h).

Study drug dispensers and daily diaries were only distributed to subjects entering Safety Extension Period 2.

event; BID = twice daily; BP = blood pressure; DEXA = dual-energy X-ray absorptiometry; DHT = dihydrotestosterone; DRE = digital rectal examination; ECG = electrocardiogram; ENT = otolaryngological; HbA1c = glycosylated hemoglobin; HR = heart rate; IIEF = International Index of Erectile Function; PANAS = Positive and Negative Affect Schedule; PK = pharmacokinetics; RR = respiratory rate; TID = three times daily.

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Source: Table 2, CSR TBS-1-2011-03, page 52

Statistical Methods:

The Randomized Population consisted of all subjects who signed the informed consent form and were assigned a randomization number at Visit 3 (Day 1). The Intent-to-Treat (ITT) Population consisted of all subjects who received randomized study drug and had at least 1 valid post-baseline efficacy measurement. The Safety Population for each period consisted of all subjects who received randomized study drug and had safety measurements in the respective period. The efficacy analyses were performed on the ITT Population and the safety analyses were performed on the Safety Populations. 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 (e.g., noncompliance with the titration scheme). The primary efficacy analysis was performed for both the ITT and Per-Protocol Populations.

The primary efficacy parameter, the C_{avg} of serum total testosterone at Day 90, was calculated from the area under the curve (AUC) using the following formula:

$$C_{avg} = AUC_{0-24h} / 24$$

The AUC curve for both 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. The missing PK data were imputed in the AUC calculation.

The number and percentage of subjects who reached the treatment goal (i.e., serum total testosterone C_{avg} in the normal range) at Day 90 or Early Termination (Day 90 Last Observation Carried Forward [LOCF]) were summarized by treatment group. Ninety-five percent (95%) confidence intervals (CIs) for the frequency were approximated by a binomial distribution within each treatment group.

The primary efficacy analysis was repeated for the serum total testosterone C_{avg} on Day 30. Additionally, for C_{avg} on Day 30, the Total BID treatment group and the TID treatment group were compared using the chi-square test to evaluate the number of subjects with C_{avg} within the

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normal range (≥ 300 ng/dL and ≤ 1050 ng/dL). The odds ratio, 95% confidence interval, and p-value are presented.

The serum total testosterone C_{\max} on Day 30 and Day 90 were summarized by counts and percentages for each treatment group for the following categories: $C_{\max} \leq 1500$ ng/dL, $C_{\max} \geq 1800$ ng/dL and ≤ 2500 ng/dL, and $C_{\max} > 2500$ ng/dL.

The PK profile, including AUC_{0-24h} , C_{avg} , C_{\min} , C_{\max} , and T_{\max} , for serum total testosterone, serum estradiol, and serum DHT were summarized with descriptive statistics, including the arithmetic mean, standard deviation, coefficient of variation (CV%), geometric mean, median, minimum, and maximum by treatment at Day 30 and Day 90. The same descriptive statistics were calculated for serum concentrations at each sampling time by treatment and visit.

The time within normal range (≥ 300 ng/dL and ≤ 1050 ng/dL) for serum total testosterone and the ratio of DHT C_{avg} to total testosterone C_{avg} on Day 30 and Day 90 were summarized with descriptive statistics for each treatment group.

The concentrations of fasting serum total testosterone, DHT, and estradiol were summarized with descriptive statistics at baseline, Day 30, Day 90, Day 90 LOCF, Day 180, Day 180 LOCF, Day 270, Day 360, and Day 360 LOCF. The change from baseline was also summarized.

The change in bone mineral density, total body mass, lean body mass, fat mass, and percent fat were summarized with descriptive statistics at baseline, Day 180, and Day 360, as well as the change from baseline to Day 180 and the change from baseline to Day 360 for each treatment group.

The Day 30 24-hour C_{avg} serum total testosterone values for all subjects in the BID treatment group were assessed for appropriate dose titration (from BID to TID) at Day 45.

The IIEF questionnaire was broken up into 5 domains: erectile function, intercourse satisfaction, orgasmic function, sexual desire, and overall satisfaction. Point values were assigned to each answer in the questionnaire according to the Statistical Analysis Plan. Domain scores were the sum of the points of each question making up the domain.

Positive and Negative Affect Schedule scores were summarized with descriptive statistics for each emotion/feeling as well as the PANAS score by treatment at baseline, Day 30, Day 60, Day 90 and Day 90 LOCF.

All safety analyses were conducted on the Safety Population and were summarized by treatment group and in total. Safety assessments included adverse events, clinical laboratory measurements, DRE of the prostate, 12-lead ECGs, vital sign measurements, basic ENT examination, and physical examination.

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

/s/

A R WIEDERHORN
05/20/2014

MARK S HIRSCH
05/20/2014
I concur.

DIVISION OF PULMONARY, ALLERGY, and RHEUMATOLOGY PRODUCTS
MEDICAL OFFICER CONSULTATION

Date: August 20, 2013
To: Jeannie Roule, RPM, Division of Reproductive and Urologic Products (DRUP)
From: Sofia Chaudhry, MD, Medical Officer
Through: Susan Limb, MD, Medical Team Leader
Through: Badrul Chowdhury, MD, PhD, Division Director
Subject: NDA 205,488

General Information

NDA#: 205,488
Sponsor: Trimel Biopharma
Drug Product: Testosterone nasal gel
Request From: Jeannie Roule, RPM Division of Reproductive and Urologic Products
Date of Request: June 12, 2013
Materials: NDA 205-488 Integrated Summary of Safety, TBS-1-2011-03 and
Reviewed: TBS-1-2011-04 protocols and completed study reports

Executive Summary:

The Division of Reproductive and Urologic Products (DRUP) has requested a Division of Pulmonary Allergy and Rheumatology (DPARP) consult to assist in the review of the nasal safety data and the results of an allergic rhinitis study submitted in support approval of TBS-1, a 4.5% testosterone gel for intranasal administration. The proposed indication for the product is for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. The proposed starting dose is two pump actuations twice daily, [REDACTED] (b) (4) [REDACTED]. Each pump actuation delivers 5.5 mg of testosterone nasal gel (4.5%) to the nasal cavity.

The effect of repeat dose administration on local nasal safety was primarily assessed in the phase 3 study TBS-1-2011-03. This study provides 6 months of repeat dose exposure in 245 subjects and 12 months exposure in 55 subjects. Data from an additional 12 subjects out to one year are still pending at the time of this review. In addition to the adverse event data, this study included monthly ENT examinations, including nasal endoscopy, throughout the study duration.

In addition to the phase 3 study, the sponsor conducted a dedicated study evaluating TBS-1 administration in the setting of symptomatic nasal conditions (allergic rhinitis) in both a treated (oxymetazoline) and untreated state. This study, TBS-1-2011-04, was a randomized 3 way cross over study in 18 male subjects using an environmental chamber challenge (ECC).

Overall, the safety review finds that use of TBS-1 is associated with low rates of nasal irritation. The irritation appears largely minor, and in many cases appears to be self-limited as it did not result in a large number of drug discontinuations. A few AEs of potentially more severe findings are seen (nasal ulceration), but there are no reports of more significant irreversible toxicity (e.g., nasal septal perforation) in the safety database. DPARP recommends including the risk of nasal irritation in the product label.

The allergic rhinitis study demonstrates a 21% decrease in serum testosterone levels, measured by AUC₀₋₂₄, in subjects with active allergic rhinitis symptoms compared to those in an asymptomatic state. There was no effect on drug absorption demonstrated by concomitant use of oxymetazoline. Of note, analyzing the difference in serum testosterone between symptomatic allergic rhinitis and the asymptomatic state is complicated by a difference in pre-dose (pre TBS-1) testosterone levels for the symptomatic treatment periods compared to the asymptomatic treatment period. The discrepancy in pre-dose levels may be attributable to a flaw in study conduct, resulting in inconsistent testosterone sampling times. An exploratory analysis of the testosterone levels adjusted for pre-dose levels still suggests diminished absorption in the symptomatic state, but the validity of the exploratory analysis is uncertain.

Whether results of the trial are reliable and the magnitude of the decrease in testosterone absorption seen in Study TBS-1-2011-04 is clinically significant, DPARP defers to DRUP. If DRUP deems that inclusion of the information in the label is warranted, DPARP recommends general language regarding the potential decrease in testosterone absorption secondary to chronic nasal conditions or changes in nasal anatomy, not just allergic rhinitis.

Drug Product:

TBS-1 will represent the first nasal formulation of testosterone; however there are multiple testosterone preparations approved for topical application to non-genital areas (e.g., axilla, back, shoulders and arms) for the treatment of male hypogonadism.

TBS-1 contains (b)(4) grams of 4.5% testosterone gel as the active ingredient and castor oil, oleoyl polyoxylglycerides, and colloidal silicon dioxide as excipients. Each actuation of the dispenser deposits 5.5 mg of TBS-1 (4.5%) testosterone gel into the nasal cavity. The excipients have not been used in any approved nasal formulation in the U.S; however, they are used in other topical formulations.

The sponsor's formulation is contained in a multiple dose dispenser with an actuator that

(b)(4)

Regulatory History with DPARP

DPARP was previously consulted by DRUP in March 2011 to provide advice on the assessment of local nasal toxicity in the drug development program and to provide comment on the oxymetazoline co-administration study in allergic rhinitis. DPARP was subsequently consulted in January 2013 to assist in the review of the nasal safety data and the results of the allergic rhinitis study included in a pre-NDA package.

In 2011, the Division provided the following advice on the assessment of nasal safety in the phase 3 program and the allergic rhinitis study, the details of which can be found in the consult by Dr. Lydia Gilbert-McClain dated March 31, 2011:

- Plans to conduct monthly ENT evaluations and the patient daily diary are adequate to assess for local toxicity.
- The lack of a placebo arm in the phase 3 study means any nasal toxicity will be attributed to investigational product.
- Exposure of 200 patients for 6 months is reasonable. Data out to one year should be collected in a subset of patients. The sponsor's proposal to follow 50 patients appears small, but may be adequate based on the safety data.
- Given the objective of the study TBS-1-2011-2 to evaluate decreased absorption of testosterone, use of oxymetazoline is reasonable given its vasoconstrictor effects. In addition, the patient population and exclusion criteria seem appropriate.

In 2013, the Division reviewed the nasal safety data from the pivotal phase 3 study and the results of allergic rhinitis study and provided the following assessments. Additional details can be found in the consult by Dr. Sofia Chaudhry dated February 4, 2013:

- Nasal irritation for intranasal testosterone is seen from a review of the phase 3 trial; however, overall rates appear low
- DPARP lacks the clinical expertise to comment on whether the decreases in testosterone absorption in the allergic rhinitis study are clinically relevant. If they are, inclusion in the product labeling would be warranted.
- The NDA submission should include adverse event data tabulated by treatment exposure and the ENT symptoms and examination findings should be presented by dose group in addition to by exposure.
- If 21% decrease in serum testosterone is clinically relevant, this language should be included in Section 2.1 of product label and outline a need for more frequent clinical monitoring of serum testosterone levels in the setting of chronic nasal conditions or changes in nasal anatomy.

Review Strategy

TBS-1 intranasal testosterone gel was evaluated in 9 clinical studies evaluating a total of 475 subjects. The local nasal safety of repeat dose administration was primarily assessed in a randomized, open-label, phase 3 study, TBS-1-2011-03. This review focuses on the nasal safety results from the phase 3 study. Nasal safety data from the additional, smaller TBS-1 trials included in the sponsor's ISS were reviewed, but as the review did not result in a different safety assessment, the results are not presented in this review.

To address use of the product in patients with active nasal conditions, a specific extrinsic factor and drug interaction study, Study TBS-1-2011-04, was conducted to evaluate the

effect of TBS-1 use in patients with active allergic rhinitis, with and without co-administration of oxymetazoline. The results of this study are discussed later in this consult after discussion of the phase 3 nasal safety data.

Phase 3 Study: TBS-1-2011-03

Study Design

Study TBS-1-2011-03 was a randomized, open-label, 2-arm, parallel group trial using the commercial formulation and dispenser in males with primary or secondary hypogonadism. The treatment period of the trial was 90-days in duration with sequential safety extensions for an additional 3 months (6 months total) and 6 months (12 months total). Subjects were enrolled into either BID or TID treatment groups with the option for subjects in the BID treatment group to titrate up to the TID treatment arm at day 45 based on their PK profile. At the time of this review, 12 subjects were still enrolled in Safety Extension 2.

The study included the following four periods:

- a 3 to 7 week screening period.
- a 90-day randomized, open-label, treatment period with subjects receiving 5.5 mg per nostril of 4.5% TBS-1 twice daily or three times daily with a potential daily dose adjustment on Day 45 for subjects in the BID treatment group based on their serum total testosterone PK profile.
- a 90-day open-label safety extension period (Safety Extension 1) for all study subjects
- an additional 180-day open-label safety extension period (Safety Extension 2) for a subset of patients (75 planned).

Full ENT examinations, including nasal endoscopy by an ENT specialist, were conducted at screening and monthly intervals for the duration of the study. The study included specific exclusion criteria for conditions that the applicant felt could significantly affect absorption or use of the dispenser. These exclusion criteria included:

- nasal surgery or fracture within 6 months that caused severely deviated septum
- active allergies
- mucosal inflammatory disorders
- sinus disease
- sleep apnea

As noted above, a specific study was conducted to address use of the product in patients with active nasal conditions. The results of this study are presented following the review of the phase 3 nasal safety data.

Adverse events, including those related to nasal toxicity were assessed throughout the trial and were coded using MedDRA 14.1. Treatment emergent adverse events (TEAEs) were defined as adverse events (AEs) that had a start date on or after the first dose of study drug or occurred prior to the first dose and worsened in severity during the

treatment period. In this trial, TEAEs were summarized in the period in which the AE began (e.g. TEAE that occurred during the Safety Extension 1 were any TEAEs that occurred on or after the 1st day of the Safety Extension 1 through the end of the study or the start of Safety Extension 2 for subjects who continued in the trial).

The safety population for this study consisted of all subjects who received randomized study drug and had safety measurements during the study period. Thus, the safety population for each respective study period may differ from the intent to treat population which was used for efficacy purposes.

The applicant pooled the adverse event data for patients who titrated from the BID to TID treatment regimen at Day 45 into the TID treatment arm in its Integrated Summary of Safety (ISS), but the data from this treatment group were also presented separately in the completed study report (CSR). All datasets were reviewed in this review, however the tables in this review present the BID→TID treatment group separately as it allows for an approximation of an intermediate drug exposure between BID and TID. In addition, this dosage group may reflect real world usage for some patients if [REDACTED] (b) (4)

Extent of Exposure and Subject Disposition

Overall, the size of the safety database is adequate for review. While the number followed to one year is small, the nasal safety findings found during this review are relatively minor and available data are not suggestive of a high frequency of more severe local toxicity.

A total of 306 subjects were randomized in this trial; 228 to the BID treatment arm and 78 to the TID treatment arm. Of these 306 subjects, 274 completed the 90 day treatment period (90% completion) with 86 subjects increasing from BID to TID dosing at Day 45. A total of 245 subjects completed Safety Extension 1 and received 6 months of therapy (90% completion for Safety Extension 1 and 80% completion for combined study periods of Treatment Period + Safety Extension 1). At the time of this review, 55 subjects have completed Safety Extension 2 with an additional 12 subjects (5 in the BID group and 7 in the TID group) still enrolled.

A total of 5 subjects discontinued due to an AE during the initial 90 treatment period, an additional 3 subjects discontinued due to an AE during Safety Extension Period 1, and 1 from Safety Extension Period 2. A review of the line listings for these subjects reveals that 2 of these 9 subjects discontinued due to nasal irritation (PTs: nasal discomfort/parosmia/scab and nasal odor/dysgeusia). Overall, this is a low number of discontinuations related to nasal irritation and events were not severe, which supports the safety findings of nasal irritation but not of more serious local toxicity.

As noted earlier, the Safety Population for this study consisted of all subjects who received study drug and had safety measurements in the respective study period. The Safety Population for the treatment period was 306 subjects, 272 subjects for Safety Extension 1, and 74 subjects for Safety Extension 2. Given the focus on local nasal

safety, the remainder of the review for this trial will focus on data for the Safety Populations.

Local Nasal Safety

Overall, the local nasal safety findings demonstrate that use of intranasal testosterone is associated with local nasal irritation, but the effects appear relatively minor with only a few patients discontinuing treatment due to local nasal irritation. There is no evidence of dose-related increase in toxicity and there were no Serious Adverse Events related to local nasal irritation. There were two AE reports of nasal ulceration from the AE data. While the presence of ulceration is potentially suggestive for more severe local irritation, overall rates were low and this is a clinically monitorable condition. There were no AE reports of irreversible nasal toxicity, including nasal septal perforations.

The safety findings from monthly ENT examinations, which included nasal endoscopy, were supportive of the findings from the AE data. Symptom assessments and examination findings also demonstrated evidence of nasal irritation, albeit at low rates. Again, no events of irreversible toxicity, including nasal septal perforation, are seen from a review of the ENT examination data.

Local Nasal Safety: Adverse Event Data

As summarized above, evidence of local nasal irritation is seen from a review of the adverse event data with no evidence of a dose dependent increase (see Table 1 and Table 2). While overall rates of local nasal AE do initially increase from Day 1 to Day 30, they subsequently decrease and plateau at later time points (Table 2). This may be a reflection of drug discontinuation due to local tolerances issues; however as described earlier reported rates of discontinuation due to nasal irritation were low. While the individual Preferred Terms (PTs) are not presented for Safety Extension 1 and 2, these data supported the conclusions drawn from the Treatment Period (data not shown; refer to the sponsor's ISS Tables 52 and 53 for these data).

Rates of more severe toxicity in the database are also low. There was one nasal ulcer AE and 2 non-specific reports of nasal septum disorder in the Treatment Period (Table 1). Similar conclusions are drawn from review of the individual PTs related to nasal safety in Safety Extension 1 and 2 with one AE each of nasal ulcer and nasal septum disorder in Safety Extension 1 (data not shown). There were no AE reports related to nasal septal perforation during any study period.

Table 1: Local Nasal Adverse Event Data: Treatment Period

System Organ Class Preferred Term	TBS-1 BID (N=143) n (%)	TBS-1 BID/TID (N=85) n (%)	TBS-1 TID (N=78) n (%)
Nervous system disorders			
Parosmia	7 (4.9)	3 (3.5)	2 (2.6)
Anosmia	0 (0.0)	0 (0.0)	1 (1.3)
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea	8 (5.6)	8 (9.4)	3 (3.8)
Epistaxis	6 (4.2)	5 (5.9)	3 (3.8)
Nasal discomfort	6 (4.2)	2 (2.4)	3 (3.8)
Nasal dryness	6 (4.2)	1 (1.2)	2 (2.6)
Nasal congestion	5 (3.5)	3 (3.5)	2 (2.6)
Nasal mucosal disorder	4 (2.8)	0 (0.0)	0 (0.0)
Rhinalgia	1 (0.7)	1 (1.2)	1 (1.3)
Nasal odor	2 (1.4)	0 (0.0)	1 (1.3)
Nasal septum disorder	1 (0.7)	0 (0.0)	1 (1.3)
Increased viscosity of nasal sections	0 (0.0)	1 (1.2)	0 (0.0)
Nasal obstruction	1 (0.7)	0 (0.0)	1 (1.3)
Nasal edema	1 (0.7)	0 (0.0)	0 (0.0)
Nasal ulcer	1 (0.7)	0 (0.0)	0 (0.0)
Source: CSR TBS-1-2011-03 Table 51			

Table 2: Total Number of Local Nasal Adverse Events by Study Period

	TBS-1 BID n (%)	TBS-1 BID/TID n (%)	TBS-1 TID n (%)
Treatment Period			
N	143	85	78
Local nasal AEs ¹	49 (34)	24 (28)	20 (26)
Safety Extension 1			
N	120	--	152

	TBS-1 BID n (%)	TBS-1 BID/TID n (%)	TBS-1 TID n (%)
Local nasal AEs ¹	20 (17)	--	17 (11)
Safety Extension 2			
N	34	--	40
Local nasal AEs ¹	6 (17)	--	7 (18)
Sources: CSR TBS-1-2011-03 modified from Table 51, 52, 53 ¹ Includes all Preferred Terms related to local nasal safety as identified by the sponsor			

ENT Examinations and Nasal Endoscopy

Monthly ENT examinations and nasal endoscopy were conducted throughout the treatment period and the two Safety Extensions. These examinations included an assessment of a standard list of treatment-related nasal symptoms including nasal dryness, crusting, bleeding, pain, obstruction, an alteration in sense of smell and “other”. Nasal endoscopy included an assessment for large amounts of nasal crusting, scar tissue blocking the nose, dried or fresh nasal blood, fissuring of nasal skin, as well as an “other” category. Table 3 presents the ENT symptoms as the total number of symptom reports and examination findings for select study visits. Of note, the percentage of positive reports plus subjects with no findings may not equal 100, as individual subjects may have had more than one symptom or exam finding.

The majority of subjects had no symptoms or examination findings. In general, the most common nasal symptom or exam finding was categorized as “other” (data not shown). In addition, symptoms and exam findings do not increase with dose, nor do they appear to substantially increase with time except for an increase from Day 1 to Day 30 as is seen for the AE data. A review of the individual symptom and examination findings does not alter the safety conclusions (data not shown, refer to the sponsor’s CSR TBS-1-2011-03 Tables 35.1 and 35.2 for these data).

Table 3: ENT Symptoms and Examination Findings

	TBS-1 BID n (%)	TBS-1 BID/TID n (%)	TBS-1 TID n (%)
Day 1			
N	142	85	78
All symptoms	6 (4)	4 (5)	0 (0)
No symptoms	138 (97)	81 (95)	78 (100)
All exam findings	4 (3)	1 (1)	0 (0)

	TBS-1 BID n (%)	TBS-1 BID/TID n (%)	TBS-1 TID n (%)
Day 1			
No exam findings	139 (98)	84 (99)	78 (100)
Day 30			
N	132	85	73
All symptoms	18 (14)	13(15)	8 (11)
No symptoms	116 (88)	73 (86)	65 (89)
All exam findings	8 (6)	2 (2)	4 (5)
No exam findings	124 (94)	83 (98)	69 (95)
Day 90			
N	122	81	69
All symptoms	18 (15)	12 (15)	10 (14)
No symptoms	109 (89)	70 (86)	63 (91)
All exam findings	5 (4)	1 (1)	1 (1)
No exam findings	117 (96)	80 (99)	68 (99)
Day 180			
N	107	--	137
All symptoms	9 (8)	--	18 (13)
No symptoms	100 (94)	--	126 (92)
All exam findings	5 (5)	--	4 (3)
No exam findings	102 (95)	--	133 (97)
Day 270			
N	31	--	38
All symptoms	3(10)	--	9 (23)
No symptoms	29 (94)	--	32 (84)
All exam findings	2 (6)	--	3 (8)
No exam findings	30 (97)	--	36 (95)
Day 360			
N	26	--	31
All symptoms	1 (3.8)	--	3 (10)
No symptoms	25 (96)	--	29 (93)
All exam findings	0 (0)	--	0 (0)
No exam findings	26 (100)	--	31 (100)
Sources: CSR TBS-1-2011-03 Modified from Tables 35.1 and 35.2			

Allergic Rhinitis Study: TBS-1-2011-04

Study Design

This study was a 3-way, randomized, cross-over study to assess the relative bioavailability, safety and tolerability of TBS-1 (4.5%) administered to 18 male subjects with seasonal allergic rhinitis in symptomatic, symptomatic but treated (oxymetazoline),

and asymptomatic states using an environmental challenge chamber (EEC). The study objectives were to evaluate whether intranasal application of testosterone is a reliable route of administration in nasal inflammatory states such as allergic rhinitis, as well as to evaluate the drug-drug interaction with co-administration of oxymetazoline.

Symptomatic allergic rhinitis state was induced by exposure to *Dactylis glomerata* (orchard grass) pollen in an environmental exposure chamber (EEC). To be enrolled in the study, subjects had to have a positive clinical history, positive skin prick test SPT or ID test to *Dactylis glomerata*. In addition to a baseline screening EEC challenge, subjects had a 24 hour baseline testosterone and dihydrotestosterone profile prior to being randomized into one of three treatment sequences. There was a minimum 4-day washout period between dosages/challenges between each treatment period.

Assessment of nasal symptoms was done using the total nasal symptom score (TNSS) which is a composite nasal symptom score frequently used in allergic rhinitis drug development programs. TNSS is scored 0 to 12 and includes assessments of nasal congestion, rhinorrhea, nasal itching and sneezing each scored on a 4 point scale (0 = no symptoms up to 3 = severe symptoms).

For the study, an asymptomatic state was defined by a TNSS score < 3 and congestion score < 2. After exposure allergen exposure, a symptomatic state was defined by achieving a total TNSS score of ≥ 6 with a congestion score ≥ 2 between hour 1 and 2. This was prior to TBS-1 administration in the symptomatic treatment periods. Subjects in the symptomatic but treated arm received 2 sprays per nostril of 0.05% oxymetazoline 30 minutes prior to a 7 am dose of TBS-1 and then again 12 hours after allergen exposure. All subjects in each study period received 3 doses of TBS-1 in the presence of site staff and PK assessments were performed at multiple time points during the subsequent 24-hour time period¹.

While EECs are not typically relied upon for formal efficacy assessments by DPARP, in this situation, the use of the model to approximate clinical allergic rhinitis and evaluate the effect of intranasal oxymetazoline on TBS-1 drug administration is reasonable.

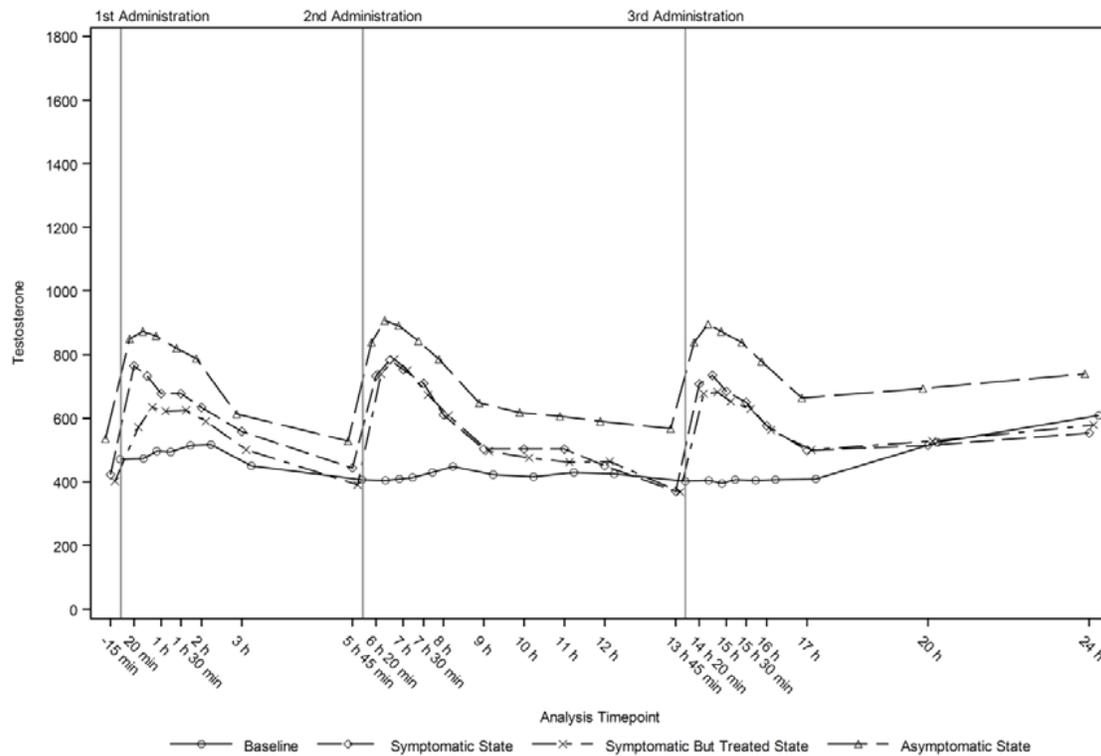
Study Results

The pharmacokinetic results of the study are presented below. Overall, the applicant notes that administration of TBS-1 under all three conditions – asymptomatic, symptomatic, and symptomatic but treated – resulted in an increase in serum testosterone concentrations from baseline. Testosterone levels were similar between the symptomatic and symptomatic but treated state suggesting that use of oxymetazoline, a potent vasoconstrictor, does not alter testosterone exposure. However, the testosterone exposure, as determined by serum AUC_{0-24h} , was 21% lower for the symptomatic state

¹ PK measurements performed at -0.25, 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 after TBS-1 administration.

compared to the asymptomatic state suggesting that active allergic rhinitis may result in decreased drug absorption. A possible explanation includes dilution of the testosterone gel by allergic nasal secretions. Alternatively, nasal mucosal edema post-challenge may have impacted absorption. If the latter were the case, one might expect to see levels increase after use of oxymetazoline, which is a rapid and effective treatment for nasal congestion, but a mitigating effect was not observed. These data are presented in Figure 1 below.

Figure 1: Serum Testosterone (ng/dL)



ial

Source: CSR TBS-1-2011-04 Figure 1

Of note, the sponsor notes that statistically significant differences in the pre-dose testosterone levels were seen between the asymptomatic state and the symptomatic states, suggesting that the different study conditions may have impacted the subject's testosterone levels. Per the sponsor this may be explained by the earlier wake-up time for subjects in both symptomatic treatment arms compared to the asymptomatic state to accommodate the EEC allergen challenge.

Overall, DPARP defers to DMEP on whether the results from the trial are valid and clinically relevant. If DRUP deems that inclusion of the information is warranted, DPARP would recommend inclusion of general language regarding the potential decreased absorption of testosterone secondary to chronic nasal conditions or changes in nasal anatomy, not just allergic rhinitis.

Summary

The nasal safety data in the TBS-1 application is suggestive of the potential for local nasal irritation with use of the product. However, rates of more severe toxicity are low, and there were no reports of irreversible toxicity seen. DPARP recommends inclusion of the risk information in the label.

The allergic rhinitis study demonstrates a 21% decrease in serum testosterone levels, measured by AUC_{0-24} , in subjects with active allergic rhinitis symptoms compared to those in an asymptomatic state. There was no effect on drug absorption demonstrated by concomitant use of oxymetazoline in subjects with active allergic rhinitis symptoms. DPARP defers to DMEP on whether the results from the trial are valid and clinically relevant. If DRUP deems that inclusion of the information is warranted, DPARP would recommend inclusion of general language regarding the potential decreased absorption of testosterone secondary to chronic nasal conditions or changes in nasal anatomy, not just allergic rhinitis.

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/s/

SOFIA S CHAUDHRY
08/20/2013

SUSAN L LIMB
08/21/2013

BADRUL A CHOWDHURY
08/21/2013
I concur

NDA 205-488

Medical Officer's Memorandum: NDA Filing

Date Submitted: April 29, 2013
Date Received: April 29, 2013
Draft Memo Completed June 24, 2013

Drug Product: Testosterone 4.5% intranasal gel (TBS-1)
Dose: 5.5 mg per nostril BID or TID
Sponsor: Trimel Biopharma SRL
Indication: Testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone

I. Summary

Objective:

This review of the submitted data for safety, efficacy, and dosing recommendations is conducted to fulfill the regulatory requirement that a NDA be reviewed to determine its suitability for filing under 21 CFR 314. This memorandum will also serve as a basis for identifying potential review issues discovered during the filing review period to be communicated to sponsor as required by CDER MaPP 6010.x.

Conclusion:

Review of the clinical sections of the NDA submission failed to identify any deficiencies that would constitute the basis for a Refuse-to File action. In the opinion of this reviewer, the information and data in the submitted application is adequate to permit a substantive Clinical review.

II. Filing Review

Review Method:

This review is based on criteria proposed in FDA guidance for filing, reflecting FDA's interpretation of 21 CFR 314.101 (d)(3);

- Omission or incomplete submission of a required section of the NDA under 21 CFR 314.50.
- Failure to include evidence of effectiveness compatible with statutes and regulations.
- Omission of critical data, information or analyses necessary for evaluation of safety and effectiveness, or failure to provide adequate directions for product use.

Question: Does the submission have omissions or incomplete presentations of required sections as listed in Table 1?

Answer: No. The NDA contains the critical sections in sufficient detail to conduct an adequate review.

Question: Does the submission have the required sections from the Clinical perspective?

Answer: Yes. The following is the checklist for critical Clinical sections of the NDA

<u>Required Sections (21 CFR 314.50)</u>	<u>Archive Copy Location</u>
The proposed text of the labeling	m1\1.14-label\1.14.1.3-draft-label\proposed.doc
A summary of clinical data	m5\5.3-clin-stud-rep\5.3.5-rep-effic-safety
Technical sections	m2 com-tech-doc-sum
Controlled clinical studies including summaries of efficacy, safety, and benefits/risks	m5\5.3-clin-stud-rep\5.3.5-rep-effic-safety-stud 5.3.5.1
Case report forms and tabulations	m5\5.3.5.2 sample-case-rep
Financial certification and disclosure	m1\1.3.4-admin-info\financial-cert

Drug Product:

Testosterone 4.5% intranasal gel (TBS-1) is a bioadhesive testosterone gel for intranasal application proposed for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.

Despite the variety of currently available testosterone replacement therapy formulations, each is associated with formulation-related risks and side effects, such as injection site reactions, skin irritation, unintentional exposures in household contacts, and gum irritation.

Intranasal testosterone gel is proposed as another option for testosterone replacement therapy.

A. Brief Overview of the Clinical Program

Testosterone (T), the active ingredient in Natesto, is an endogenous androgen which, together with dihydrotestosterone (DHT), is responsible for normal growth and development of the male sex organs and the maintenance of secondary male sex characteristics, in addition to playing a role in numerous other normal physiologic and metabolic functions. The normal range for serum total testosterone concentrations in healthy males is approximately 300 to 1050 ng/dL.

In support of this **NDA 205-488**, the sponsor submitted results from a single, uncontrolled, open-label, Phase 3 study (**TBS-1-2011-03**), which involved 306

subjects at 39 U.S. study sites. In this study, 228 subjects were initially randomized to a twice daily (BID) regimen and 78 subjects were randomized to a three times daily (TID) regimen. After 45 days, subjects originally randomized to the BID regimen could either stay on the BID regimen or could be titrated up to the TID regimen based upon their individual serum testosterone concentrations. The randomized treatment period was a total duration of 90 days. Subsequently, subjects could enroll in open-label extension periods of 90 and 180 days. The rest of this memo includes details of the study design, study procedures and study results.

B. Overview of the Phase 3 Study Protocol (TBS-1-2011-03)

Title of Study:

A 90-Day, Randomized, Dose-Ranging Study, Including Potential Dose Titration, Evaluating the Efficacy and Safety of Intranasal TBS-1 in the Treatment of Male Hypogonadism with Sequential Safety Extension Periods of 90 and 180 Days.

Study Period:

Up to 58 weeks maximum for subjects who completed all 4 periods. The number of weeks for individual subjects depended upon whether they were receiving testosterone treatment at screening, which necessitated a 2- to 4-week washout period.

Initiation Date: 23 September 2011

90-day Treatment Period Completion Date: 12 October 2012

Safety Extension Period 1 Completion Date: 09 January 2013

Safety Extension Period 2 Completion Date: 11 March 2013

Study Objectives:

Primary Objective: The primary objective of the study was to determine the efficacy of 4.5% TBS-1 gel, administered as 2 or 3 daily intranasal doses of 5.5 mg per nostril (11 mg per dose), as demonstrated by an increase in the 24-hour average concentration (C_{avg}) of serum total testosterone to the normal range (≥ 300 ng/dL and ≤ 1050 ng/dL) in $\geq 75\%$ of male hypogonadal subjects.

Secondary Objectives: The secondary objectives of the study were the following:

- To determine the efficacy of 4.5% TBS-1 gel, administered 2 or 3 times daily at a dose of 5.5mg per nostril, in achieving the following for serum total testosterone maximum concentration (C_{max}):
 - $C_{max} \leq 1500$ ng/dL in $\geq 85\%$ of subjects,
 - C_{max} 1800 to 2500 ng/dL in $< 5\%$ of subjects, and
 - $C_{max} > 2500$ ng/dL in no subjects;

- To determine the safety and tolerability of TBS-1 after 90, 180, and 360 days of treatment;
- To determine the effect of TBS-1 treatment on body composition (total body mass, lean body mass, fat mass, and percent fat);
- To determine the effect of TBS-1 treatment on bone mineral density (lumbar spine and hip);
- To determine the effect of TBS-1 treatment on mood;
- To determine the effect of TBS-1 treatment on erectile function; and
- To determine the serum concentration and pharmacokinetics of dihydrotestosterone (DHT) and estradiol after TBS-1 administration.

Reviewer's Comment: Despite the Division's strong encouragement to add a concurrent placebo control group and blinding to the protocol, the Sponsor conducted an open-label, uncontrolled study. Thus, the results from all clinical efficacy endpoints are considered exploratory and not appropriate for labeling.

Study Design and Methodology:

The study was designed as a Phase 3, 2-group, multicenter 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 currently receiving testosterone treatment;
- A 90-day randomized, open-label Treatment Period during which subjects received 5.5 mg per nostril of 4.5% TBS-1 twice daily (BID) or 3 times daily (TID) with potential daily dose adjustment on Day 45 for subjects in the BID treatment group as determined by the serum total testosterone pharmacokinetic (PK) profile;
- A 90-day, open-label Safety Extension Period (Safety Extension Period 1) for all study subjects; and
- An additional 180-day, open-label Safety Extension Period (Safety Extension Period 2) for a subset of 75 subjects.

The total duration of study participation for subjects completing all 4 periods was up to 406 days (~58 weeks), depending upon whether they were receiving testosterone treatment at screening, which necessitated a 2- to 4-week washout period.

Duration of Study Treatment:

From 180 days (all subjects) to 360 days (for subjects who participated in Safety Extension Period 2).

Disposition of Subjects:

Randomized: 306 subjects (228 subjects randomized to TBS-1 BID; 78 subjects randomized to TBS-1 TID)

Completed 90-day Treatment Period: 274 subjects (205 subjects randomized to TBS-1 BID; 69 subjects randomized to TBS-1 TID)

Discontinued During Treatment Period: 32 subjects (23 subjects randomized to TBS-1 BID; 9 subjects randomized to TBS-1 TID)

Entered Safety Extension Period 1: 274 subjects (122 subjects in TBS-1 BID group; 152 subjects in TBS-1 TID group)

Completed Safety Extension Period 1: 245 subjects (107 subjects in TBS-1 BID group; 138 subjects in TBS-1 TID group)

Discontinued During Safety Extension Period 1: 29 subjects (15 subjects from TBS-1 BID group; 14 subjects from TBS-1 TID group)

Entered Safety Extension Period 2: 75 subjects (35 subjects in TBS-1 BID group; 40 subjects in TBS-1 TID group)

Completed Safety Extension Period 2: 55 subjects (25 subjects in TBS-1 BID group; 30 subjects in TBS-1 TID group)

Discontinued During Safety Extension Period 2: 8 subjects (5 subjects from TBS-1 BID group; 3 subjects from TBS-1 TID group)

Still Enrolled in Safety Extension Period 2: 12 subjects (5 subjects in TBS-1 BID group; 7 subjects in TBS-1 TID group).

Reviewer's Comment: In order to assess chronic nasal safety, the Division requested safety data for at least 50 subjects treated with TBS-1 for at least 1 year.

Diagnosis and Main Criteria for Inclusion:

The population for this study was adult men 18 to 80 years of age, inclusive, with 2 fasting morning (0900 h \pm 30 min) total serum testosterone levels <300 ng/dL. In subjects with a known history of male hypogonadism, if 1 of the 2 serum total testosterone levels 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. Subjects currently being

treated with testosterone must have undergone 2 to 4 weeks of washout depending on the type of testosterone therapy and the date of their last dose.

Efficacy Assessments:

Primary Efficacy Variable: The primary efficacy variable was the number and percentage of subjects with a serum total testosterone C_{avg} within the normal range (≥ 300 ng/dL and ≤ 1050 ng/dL) on Day 90.

Secondary Efficacy Variables: Secondary efficacy variables included the following:

- The number and percentage of subjects with a serum total testosterone C_{max} in the following ranges on Day 90:
 - ≤ 1500 ng/dL
 - ≥ 1800 and ≤ 2500 ng/dL, and
 - > 2500 ng/dL
- The number and percentage of subjects with a serum total testosterone C_{avg} in the normal range (≥ 300 ng/dL and ≤ 1050 ng/dL) on Day 30;
- The number and percentage of subjects with a serum total testosterone C_{max} in the following ranges on Day 30:
 - ≤ 1500 ng/dL,
 - ≥ 1800 and ≤ 2500 ng/dL, and
 - > 2500 ng/dL;
- The complete PK profile (including C_{avg} , the minimum concentration [C_{min}], C_{max} , and time to maximum concentration [T_{max}]) of serum total testosterone on Day 30 and Day 90;
- The time within the normal range (TWNR) for serum total testosterone based on the PK profile on Day 30 and Day 90;
- The PK profile of serum estradiol on Day 30 and Day 90;
- The PK profile of serum DHT on Day 30 and Day 90;
- The ratio of DHT C_{avg} to total testosterone C_{avg} on Day 30 and Day 90;
- The International Index of Erectile Function (IIEF)) domain 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 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.

Safety Assessments:

Safety assessments included clinical adverse events, clinical laboratory measurements (chemistry, hematology, liver function tests, fasting lipid profile, urinalysis, glycosylated hemoglobin [HbA1c], prostate specific antigen, and endocrine profile), 12-lead electrocardiogram (ECG) parameters, vital signs (blood pressure, heart rate, temperature, and respiratory rate), physical examination parameters, digital rectal examinations (DREs) of the prostate, and otorhinolaryngological (ENT) examinations.

Reviewer's Comment: To assess nasal safety, pre-specified ENT examinations were carried out in this study. These exams were agreed upon in consultation with the Division of Pulmonary, Allergy and Rheumatology Products (DPARP).

C. Preliminary Brief Summary of Efficacy Results:

The primary efficacy variable was the percentage of subjects with a serum total testosterone C_{avg} value within the normal range (≥ 300 ng/dL and ≤ 1050 ng/dL) on Day 90, with success being defined as $\geq 75\%$ of subjects on treatment within the specified normal serum testosterone concentration range and with the lower 95% CI not less than 65%.

The primary efficacy endpoint analysis was performed for the ITT and Per-Protocol Populations.

At Day 90, there were ^{(b) (4)} subjects in the ITT Population with valid 24-hour serum total testosterone C_{avg} , and ^{(b) (4)} subjects were included in the Per-Protocol Population.

Table 1, derived from the Sponsor's analysis in the NDA, shows the proportion of all subjects having serum total testosterone C_{avg} within the normal range on Day 90.

Table 1: Proportion of All Subjects with C_{avg} Within the Normal Range on Day 90

	ITT Population	Per-Protocol Population
Both TBS-1 treatment regimens	73%	76%
N'	(b) (4)	(b) (4)
95% CI for frequency [1]	(b) (4)	(b) (4)
Combined TBS-1 TID (33.0 mg)	(b) (4)	(b) (4)
N'	(b) (4)	(b) (4)
95% CI for frequency [1]	(b) (4)	(b) (4)
TBS-1 BID (22.0 mg)	(b) (4)	(b) (4)
N'	(b) (4)	(b) (4)
95% CI for frequency [1]	(b) (4)	(b) (4)

Note: N' is the number of subjects who had a C_{avg} at Day 90. % = n/N'.
 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; ITT = Intent-to-Treat; TID = three times daily.

Reviewer's Comment: The Sponsor analyzed the primary efficacy endpoint in 3 different populations:

- All subjects (n = (b) (4)),
- All TID subjects, whether randomized to fixed-dose TID or up-titrated from BID to TID (n = 151), and
- Fixed-dose BID subjects (n = (b) (4)).

However, the proposed labeling calls for all subjects to be (b) (4) on

the BID regimen. Therefore, the primary efficacy endpoint should be analyzed in a population that reflects the to-be-marketed (labeled) use.

Therefore:

- (b) (4)
- The C_{max} safety criteria should be analyzed in this same "to-be-marketed" population.

Secondary efficacy endpoint analyses included additional PK and clinical assessments.

A key secondary efficacy PK endpoint was the percentage of subjects with a serum total testosterone C_{max} within the specified ranges on Day 90. This endpoint was analyzed in both the ITT and Per-Protocol Populations. A summary of Day 90 serum total testosterone C_{max} within selected ranges for the analysis populations is presented in Table 2.

Table 2: Proportion of Subjects with Serum Total Testosterone C_{max} Within the Pre-Specified Ranges on Day 90

	Target	ITT Population (N' = (b) (4))	Per-Protocol Population (N' = (b) (4))
Day 90			
$C_{max} \leq 1500$	$\geq 85\%$	242 (89%)	211 (89%)
$1800 \text{ ng/dL} \leq C_{max}$	$\leq 5\%$	9 (3%)	7 (3%)
$C_{max} > 2500$	0	1 (0.4%)	0 (0%)

Note: N' is the number of subjects who had a C_{max} at the specified visit.
% = n/N'. C_{max} = maximum concentration; ITT = Intent-to-Treat.

Reviewer's Comment: The C_{max} endpoint should also be analyzed in the "to-be-marketed" (labeled) population.

A summary of Day 30 serum total testosterone C_{max} within selected ranges for the ITT Population is presented in Table 3.

Table 3: Proportion of Subjects with Serum Total Testosterone C_{max} Within the Pre-Specified Ranges on Day 30

	Target	ITT Population (N' = (b) (4)) n (%)
Day 30		
$C_{max} \leq 1500 \text{ ng/dL}$	$\geq 85\%$	268 (92%)
$1800 \text{ ng/dL} \leq C_{max} \leq 2500$	$\leq 5\%$	4 (1%)
$C_{max} > 2500 \text{ ng/dL}$	0	3 (1%)

Note: N' is the number of subjects who had a C_{max} at the specified visit. % = n/N'. C_{max} = maximum concentration; ITT = Intent-to-Treat.

Table 4 presents mean C_{avg} and C_{max} for serum total testosterone on Day 30 and on Day 90 for 4 different populations (BID alone, combined BID, TID alone, combined TID) for the ITT Population.

Figures 1 and 2 show 24-hour total T concentration-time curves for the "BID" and "TID" populations at Day 30 and Day 90, respectively, for the ITT population.

Table 4: Mean C_{avg} and C_{max} for serum total testosterone on Day 30 and on Day 90 in the ITT population

PK Parameter/Treatment Group	Day 30	Day 90
Mean C_{avg} /TBS-1 BID		(b) (4)
Mean C_{avg} /Combined TBS-1 BID		
Mean C_{avg} /TID	414.8 ng/dL	420.9 ng/dL
Mean C_{avg} /Combined TBS-1 TID		(b) (4)

BID = twice daily; C_{avg} = average concentration; C_{max} = maximum concentration; PK = pharmacokinetic; TID = three times daily.

Figure 1: Plot of Serum Total Testosterone Concentration by Treatment and Time Point at Day 30 - Intent-to-Treat Population

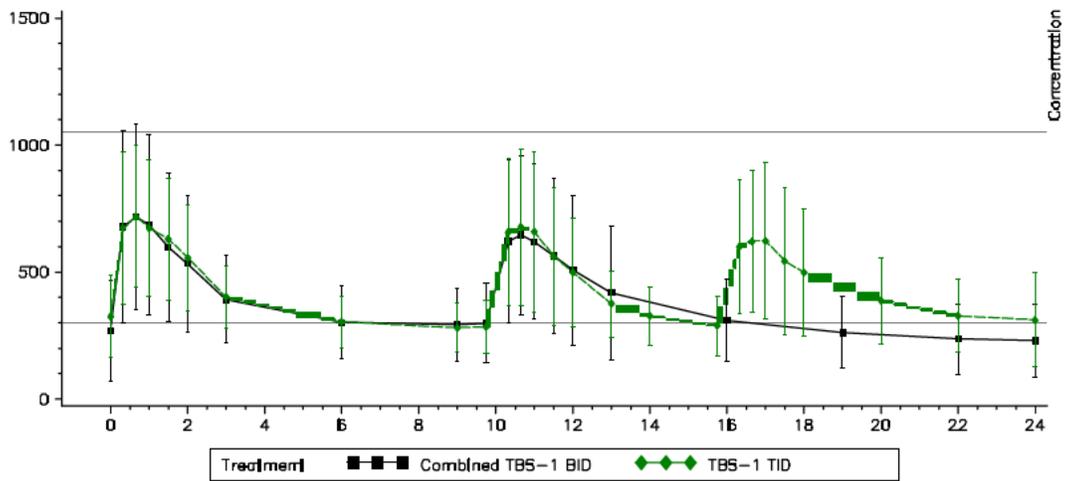
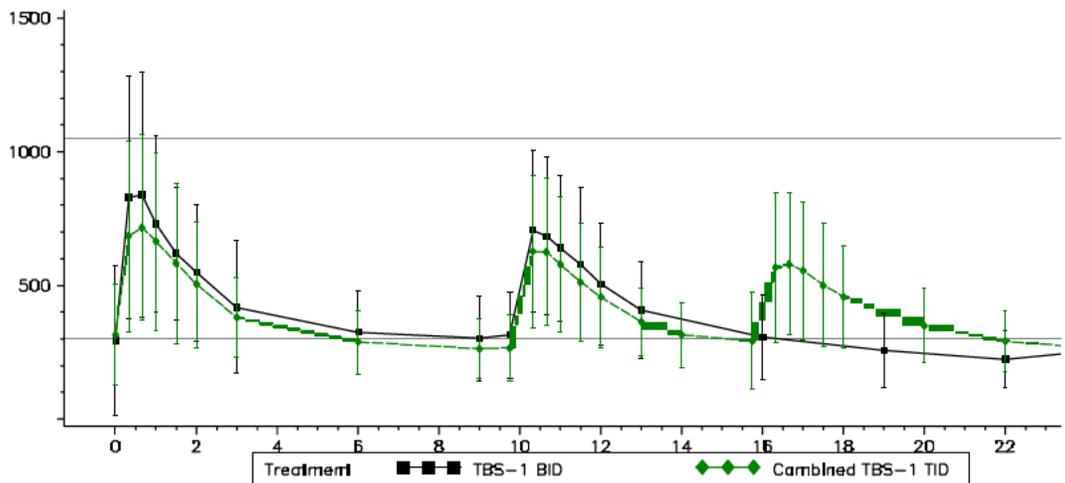


Figure 2: Plot of Serum Total Testosterone Concentration by Treatment and Time Point at Day 90 – Intent-to-Treat Population



Reviewer's Comment: Table 4 and Figure 1 demonstrate that for both the BID and TID populations, the Cavg are generally in the low-normal range as a consequence of the wide peak-to- trough fluctuations associated with TBS-1 therapy.

The following is an overview of the clinical secondary efficacy assessments:

- Statistically significant changes from baseline to Day 90 were observed in all IIEF questionnaire domain scores within all treatment groups. Domains demonstrating a positive change included sexual desire, erectile function, and overall satisfaction.
 - The Sponsor points out that the mean total sexual desire domain score of 6.8 points on Day 90 is comparable to the mean score of 7 points reported for normal healthy males.
 - The Sponsor points out that the mean change in erectile function domain score was a clinically relevant improvement as evidenced by a reduction in mean group severity from moderate at baseline (scores range 11-16) to mild at Day 90 (scores range 17-25).
 - The Sponsor states that changes in IIEF scores from baseline seen with TBS-1 treatment were similar to those achieved with other marketed testosterone replacement therapies.
 - The Sponsor notes that improvement in IIEF domain scores was consistent in all groups, with no statistically significant difference demonstrated for between-group comparisons, suggesting that the treatment was effective for all TBS-1 doses.
- Statistically significant changes from baseline to Day 90 were observed in the Positive Affect Score and Negative Affect Score (PANAS) within all treatment groups.
 - The Sponsor states that Positive Affect Scores increased to the level of normal average males on Day 90. Similar improvement was observed for Negative Affect Scores.
 - The improvement in Positive and Negative Affect Scores was consistent in all groups, with no significant difference demonstrated for between-group comparisons.
- There were no significant changes in bone mineral density (BMD) for any of the treatment groups at either Day 180 or Day 360. However, at Day 360, the Sponsor believes that there was a trend observed toward increasing bone mineral density values from baseline in both total lumbar spine and total hip measurements. The total spine and hip bone mineral density increased from baseline values of 1.118 g/cm² and 1.029 g/cm², respectively, to values of 1.121 g/cm² and 1.033 g/cm², respectively, at Day 360.

- Baseline values for lean body mass, fat mass, and percent fat were 58.9 kg, 30.3 kg, and 32.4%, respectively. The Sponsor states that TBS-1 treatment resulted in positive changes in body composition both at Day 180 and Day 360, with increases in lean body mass and decreases in fat mass and percent fat.

Reviewer's Comment: Although this study was uncontrolled, and all clinical endpoints (e.g., erectile function, libido, body composition, mood) are exploratory, the reported changes-from-baseline in the clinical endpoints appear to reflect an androgenic effect.

D. Brief Summary of Safety Results

The following information, derived from the NDA, provides a preliminary overview of the safety results reported in the NDA.

Safety Exposure:

Overall mean exposure to study drug was 86.1 days during the Treatment Period, 175.7 days during Safety Extension Period 1, and 346.0 days during Safety Extension Period 2. The exposure to study drug was similar for each treatment group.

Treatment-Emergent Adverse Events (TEAEs):

During the study, a total of 195 (63.7%) subjects reported a treatment-emergent adverse event (TEAE): 90 (63.4%) subjects in the TBS-1 BID group and 105 (64.0%) subjects in the Combined TBS-1 TID group.

In total, 44 (31.0%) subjects in the TBS- 1 BID group and 66 (40.2%) subjects in the Combined TBS-1 TID group had a TEAE that was considered by the Investigator to be at least possibly related to the study drug.

The majority of TEAEs and drug-related TEAEs were mild in severity. There were 115 (37.6%) subjects with mild TEAEs, and 81 (26.5%) subjects with mild drug-related TEAEs. There were 14 (4.6%) subjects with TEAEs that were severe, and 1 (0.3%) subject who had a severe drug-related TEAE. The rest of the reported TEAEs and drug-related TEAEs were moderate in severity.

The most common system organ class (SOC) of TEAEs during all periods was respiratory, thoracic, and mediastinal disorders (24.2% for Day 90, 13.6% for Day 180, and 18.9% for Day 360). The most frequently reported TEAEs from this SOC during all periods of the study were the events that can be attributed to the intranasal route of administration. For the TBS-1 BID group, the most frequently reported TEAEs from this SOC during all periods of the study were rhinorrhea and nasal discomfort (7% each), and epistaxis (6.3%). Similarly, for the combined TBS-1 TID group during all periods of the study, such events were rhinorrhea

(8.5%) and epistaxis (6.7%). For the TBS-1 BID group, the most frequently reported drug-related TEAEs from the respiratory, thoracic, and mediastinal disorders SOC during all periods of the study were rhinorrhea, nasal discomfort, and scab (5.6% each). The most frequently reported drug-related TEAEs in this SOC for the combined TBS-1 TID group during all periods of the study were rhinorrhea (6.7%), epistaxis (6.1%), and scab (4.9%). The majority of these events were mild in severity and did not require treatment. No increase in the proportion of the nasal adverse events with treatment duration was observed during the study.

A total of 10 (3.3 %) subjects had a TEAE of increased prostate specific antigen (PSA): 4 subjects in the TBS-1 BID/TID group and 6 subjects in the TBS-1 TID group. Eight of these 10 TEAEs of increased PSA (in the TBS-1 TID group) were considered by the Investigator to be related to the study medication. The majority of these events were mild in severity. The elevation of PSA values above the ULN was reported in 5 cases; the remainder of the events were due to elevation of PSA by >1.4 ng/dL. Only 2 subjects were discontinued from the study due to this adverse event as per Investigator's decision.

Among 49 subjects with an active medical history of either allergic rhinitis or seasonal allergies, 3 (6.1%) subjects reported exacerbations of allergies during the study. An incidence of other nasal adverse events in this group was consistent with the incidence of nasal adverse events reported in the overall Safety population of the study

In total, 6 (2.0%) subjects had 7 lipid-related TEAEs (3 [2.1%] subjects in the TBS-1 BID group and 3 [1.8%] subjects in the Combined TBS-1 TID group). Three of these 7 lipid-related TEAEs were considered by the Investigator to be related to the study medication. The majority of these events were mild in intensity. None of the subjects with lipid-related TEAEs discontinued from the study.

Eight (2.6%) subjects reported SAEs during the study: 3 (2.1%) subjects in the TBS-1 BID group and 5 (3.0%) subjects in the Combined TBS-1 TID group. None of the SAEs during the study were considered by the Investigator to be related to the study drug.

Nine (2.9%) subjects discontinued from the study due to a TEAE: 3 (2.1%) subjects in the TBS-1 BID group and 6 (3.7%) subjects in the Combined TBS-1 TID group. Seven (2.3%) subjects discontinued from the study due to a drug-related TEAE: 3 (2.1%) subjects in the TBS-1 BID group and 4 (2.4%) subjects in the combined TBS-1 TID group.

One subject in the TBS-1 TID group died during the Treatment Period as a result of internal injuries due to a motorcycle accident; the Investigator considered this SAE as definitely unrelated to the study drug.

During the study, there were no clinically meaningful changes in chemistry, hematology, liver function, urinalysis, or endocrine parameters for any of the treatment groups.

An overall mean reduction in high density lipoprotein cholesterol (HDL-C) of 3.2% occurred from baseline to Day 360 (0.3% for the TBS-1 BID group and 5.6% for the TBS-1 TID group). The mean baseline HDL-C value was 45.8 mg/dL. At Day 90, HDL-C showed a slight decrease (44.6 mg/dL). At Day 180 and Day 360, the mean HDL-C value was 43.5 mg/dL and 43.0 mg/dL, respectively.

There was a small overall mean increase in low density lipoprotein cholesterol (LDL-C) from baseline to Day 360 of 1.5% (3.2% for the TBS-1 BID group and 0.2% for the TBS-1 TID group). The mean baseline LDL-C value was 117.1 mg/dL. At Day 90, LDL-C showed a slight decrease (104.0 mg/dL). At Day 180 and Day 360, the mean LDL-C value was 113.2 mg/dL and 118.7 mg/dL, respectively.

Similarly, there was a small overall mean increase in total cholesterol from baseline to Day 360 of 1.0% (mean increase of 4.3% for the TBS-1 BID group and a mean reduction of 1.7% for the TBS-1 TID group). The mean baseline total cholesterol value was 196.0 mg/dL. At Day 90, total cholesterol showed a slight decrease (187.9 mg/dL). At Day 180 and Day 360, the mean total cholesterol values were 190.9 mg/dL and 196.8 mg/dL, respectively.

The mean baseline hematocrit value was 44.8%. At Day 90, it showed a slight decrease (44.1%) that can be attributed to the PK blood draws. At Day 180 and Day 360, the mean hematocrit values were 45.6% and 45.7%, respectively. A slight increase in hematocrit values after 180 and 360 days of treatment was consistent with testosterone replacement therapy. Hematocrit values did not exceed the ULN during the treatment in the vast majority of subjects.

The increases in PSA values were consistent with testosterone replacement therapy.

In conclusion, overall, it appears that intranasal TBS-1 was reasonably well tolerated. The general adverse event profile was consistent with other testosterone replacement products, with the majority of adverse events mild in severity. All nasal adverse events were mild and not indicative of any major nasal tolerability issues. There were no reports of severe ENT examination findings.

The occurrence of adverse events associated with laboratory abnormalities caused by testosterone replacement therapy (i.e., increased PSA, increased hematocrit, and worsened lipid profile abnormalities) was comparable to other marketed testosterone therapies and did not appear to increase with treatment duration.

No adverse events of either secondary exposure or drug product administration issues due to patient mishandling of the study drug were reported.

The majority of the subjects (89%) had total testosterone C_{max} levels of ≤ 1500 ng/dL. No safety concerns were identified for the few subjects with C_{max} values in the range of ≥ 1500 ng/dL and ≤ 2500 ng/dL.

The vast majority of subjects had no abnormal changes in physical examination, DRE, ECG and vital signs 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.

III. Conclusion

From the Clinical perspective, the NDA is fileable.

The Clinical review issues noted at the time of filing (provided in the next section) should be conveyed to Sponsor in the 74-Day letter.

IV. Clinical Review Issues Noted at the Time of Filing

1. Clinical correlation of the 24-hour PK profile is a review issue. There are two or three wide peak-to-trough fluctuations over a 24-hour period and it is not known how this unique PK profile correlates with clinical efficacy or with safety.
 - a. The time-concentration profile shows a considerable duration at low-normal T concentration. Does this finding have implications for clinical efficacy? The efficacy and safety results will be carefully assessed to discern markers of clinical androgenic effects. The Sponsor should also provide an analysis of time within the normal range (TWNRR).
 - b. The time-concentration profile shows two or three rapid rises in serum testosterone over a 24-hour period. Does this finding have implications for clinical safety? If approved, potential safety risks for Natesto may need to be further addressed in a longer-term, larger, post-marketing study due to the small size of the overall NDA safety database
2. 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. All clinical endpoints (e.g., erectile function, libido, body composition, mood) are considered exploratory for purposes of labeling claims.
3. The product is a chronically administered nasal gel. Nasal adverse events were collected and otorhinolaryngologic examinations were conducted during the Phase 3 study. In addition, a special, Phase 1, safety study related to allergic rhinitis was conducted. The results of these nasal safety assessments will be analyzed in consultation with the Division of Pulmonary, Allergy and Rheumatology Products (DPAAP).

4. The accuracy and reliability of the (b) (4) paradigm is a review issue. Specifically, has sufficient evidence been provided that the (b) (4)
[REDACTED]
5. The primary efficacy data should be analyzed in a patient population that reflects the to-be-marketed (labeled) use. (b) (4)
[REDACTED]
The Cmax safety criteria should be analyzed in this same to-be-marketed population.

V. Recommended Regulatory Action

From the Clinical perspective, the NDA should be filed. The Clinical review issues noted at the time of filing (in Section IV above) should be conveyed to Sponsor in the 74-Day Letter.

Harry Handelsman DO, Medical Reviewer
Division of Bone, Reproductive and Urologic Products (DBRUP).

Mark S. Hirsch MD, Medical Team Leader, DBRUP

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

/s/

HARRY HANDELSMAN
06/25/2013

MARK S HIRSCH
06/25/2013
I concur.