

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205488Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Memo

| | |
|--|--|
| Date | May 27, 2014 |
| From | Mark S. Hirsch, M.D. |
| Subject | Cross-Discipline Team Leader Memo |
| NDA/BLA # | 205488 |
| Applicant | Trimel Biopharma SRL |
| Date of Submission | August 29, 2013 |
| PDUFA Goal Date | May 28, 2014 |
| Proprietary Name / Established (USAN) names | Natesto testosterone nasal gel 4.5% |
| Dosage forms / Strength | 5.5 mg testosterone in 122.5 mg of gel in each nostril (11 mg testosterone) three times daily |
| Proposed Indication(s) | Replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone |
| Recommended: | <i>Approval</i> |

1. Executive Summary

1.1 Brief Summary and Recommendation

NATESTO (testosterone) nasal gel is intended for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone. The active ingredient in NATESTO is testosterone. NATESTO also contains castor oil, oleoyl polyoxylglycerides and colloidal silicon dioxide. NATESTO is administered via intranasal application using a metered-dose pump. One pump delivers 5.5 mg of testosterone in 122.5 mg of gel. The recommended dose is one pump in each nostril (total 11 mg of testosterone) administered three times daily.

Multiple preparations of testosterone have been approved by the Agency for replacement therapy in hypogonadal men. Each preparation has its own advantages and disadvantages. NATESTO would be an option for testosterone replacement; its benefit over the currently approved T products is the intranasal route that avoids some of the drawbacks of other testosterone formulations (e.g., potential risk of interpersonal transfer with topical gels, need for intramuscular injections with parenterals, etc).

The efficacy and safety of NATESTO is supported in large part by a single, open-label, “pivotal”, Phase 3 study conducted in 306 hypogonadal men (Study TBS-1-2011-03). The study consisted of 4 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 up-titration to TID on Day 45 for subjects in the BID group;

- A 90-day, open-label, Safety Extension Period (Safety Extension Period 1 [SE1]) for all study subjects; and
- An additional 180-day, open-label, Safety Extension Period (Safety Extension Period 2 [SE2]) for remaining subjects.

Prior to deciding on the 4.5% concentration and the 11 mg dosage strength, different strengths, different concentrations, and different dose regimens were tested during the Phase 1 and 2 studies of intranasal testosterone gel.

The single Phase 3 study was intended primarily to demonstrate the benefit of a BID (b) (4) regimen, but it also included a stand-alone, randomized, TID fixed-dose arm. The efficacy results did not reach the pre-determined success threshold for the BID (b) (4) regimen; however, efficacy was shown for the TID-only, fixed-dose regimen. A total of 66 of 73 TID-only subjects (90.4%) had an average total testosterone concentration within the normal range at the end of the Treatment Period. The 95% CI bounds for that point estimate were 83.7% and 97.2%. The 90% responder rate for the TID-only group exceeded the pre-determined threshold of 75% and the 95% CI lower bound of 83% exceeded the required lower bound of 65%. Results of secondary efficacy endpoints correlated with the primary endpoints.

In regard to safety, the adverse reactions associated with intranasal testosterone gel were consistent with adverse reactions associated with all testosterone replacement therapies, except for nasal adverse reactions.

The most commonly reported adverse reactions in the Treatment Period of the Phase 3 study of NATESTO were: serum prostate specific antigen (PSA) increased (5.1%), nasal discomfort (3.8%), nasopharyngitis (3.8%), upper respiratory tract infection (URI) (3.8%), sinusitis (3.8%), bronchitis (3.8%) and nasal scab (3.8%). PSA increased was considered an adverse reaction by meeting one of two pre-specified criteria: (1) increase from baseline serum PSA greater than 1.4 ug/L, or (2) serum PSA greater than 4.0 ug/L. Adverse reactions reported by >2% but <3% of patients included: blood pressure increased, dysgeusia, nasal dryness, nasal congestion, and cough.

Among the 78 patients who received NATESTO three times daily in the 90-day Treatment Period, a total of 69 patients received NATESTO three times daily in the first 90-day safety extension period. Among these 69 patients, the most common adverse reactions were: Nasopharyngitis (8.7%), rhinorrhea (7.2%), PSA increased (5.8%), parosmia (5.8%), nasal discomfort (5.8%), and nasal scab (5.8%).

Finally, a total of 18 patients received Natesto three times daily in all three treatment periods, including the 90-day clinical study, the first 90-day extension period (SE1), and the second 180-day extension period (SE2). Among these 18 TID-only patients, the following adverse reactions were reported in more than one patient each: nasopharyngitis, parosmia, PSA increased, nasal discomfort, nasal scab and hypertension. The following adverse reactions were reported in one patient each: nausea, nasal excoriation, thyroid stimulating hormone increased, decreased appetite, myalgia, anosmia, testicular atrophy, epistaxis, nasal septum disorder, nasal discomfort, and rhinorrhea.

The reported nasal adverse reactions were generally mild to moderate in severity and resolved spontaneously prior to study completion. In addition, monthly otorhinolaryngologic

examinations by a specialist did not reveal any severe or serious gross changes in Phase 3 study participants. The safety results from the larger group of 306 subjects who enrolled in the Phase 3 study and received either BID-only or the BID/TID regimen were consistent with safety results from the smaller TID-only dose group.

The only other Clinical information of note is the potential for interactions with other nasally administered drugs or in the setting of allergic rhinitis (seasonal allergies). In order to address the potential effect of allergic rhinitis on absorption of intranasal testosterone, as well as the potential effect of a symptomimetic decongestant (oxymetazoline) on the absorption of intranasal testosterone in men with allergic rhinitis who are using NATESTO, the Sponsor conducted a randomized, crossover study (TBS-1-2011-04) conducted in healthy men who suffer from seasonal allergic rhinitis. Subjects received NATESTO when they were asymptomatic, symptomatic and untreated, and symptomatic and treated with oxymetazoline nasal spray. The symptomatic state was induced by exposure to *Dactylis glomerata* pollen in an environmental challenge chamber (ECC). The testosterone exposure was approximately 21% higher for subjects in the asymptomatic state than for subjects in the symptomatic and untreated state, as well as for subjects in the symptomatic and treated state. The difference in baseline-corrected testosterone exposure 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 NATESTO. This information has been translated to labeling, including a Warning that the effects of nasally administered drugs other than the sympathomimetic decongestants have not been studied; thus, concomitant use of NATESTO with these drug groups is not recommended

I recommend that this application be **Approved**.

1.2 Sources of Clinical Data

1.2.1 Clinical Trial Data

There have been 9 clinical trials of intranasal testosterone gel, including:

- the single, randomized, open-label, Phase 3 study TBS-1-2011-03 (with 90-day Treatment Period, 90-Day Safety Extension 1 Period, and 180-Day Safety Extension 2 Period) (n=306)
- six (6) Phase 2, pharmacokinetic, dose and concentration-ranging studies in hypogonadal men, (n= 124) and
- two (2) Phase 1, pharmacokinetic and tolerability studies in normal healthy volunteers, including Study TBS-1-2011-04, a special drug and disease interaction study in healthy men with a history of allergic rhinitis. (n=30)

2. Background

2.1 DESCRIPTION OF PRODUCT

NATESTO contains testosterone, castor oil, oleoyl polyoxylglycerides and colloidal silicon dioxide. NATESTO is formulated as a slightly yellow gel containing 4.5% testosterone. It is supplied in a metered-dose pump containing 11 gm of gel dispensed as 60 metered pump

actuations. One pump delivers 5.5 mg of testosterone in 122.5 mg of gel. The pump is capable of performing 60 actuations after 10 priming actuations. The daily dose is two pump actuations three times daily.

Aveed is intended for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.

2.2 REGULATORY HISTORY

On October 18, 2004, a pre-IND Meeting was held with Sponsor.

On March 22, 2006, a Type C Guidance Meeting was held with Sponsor.

On March 23, 2010, an Advice/Information Request (AD/IR) letter was conveyed to Sponsor.

On March 14, 2011, an End-of-Phase 2 (EOP2) meeting was held with Sponsor.

On October 31, 2011, September 24, 2012 and March 3, 2013, Advice/Information Request (AD/IR) letters were conveyed to Sponsor.

The key FDA:Sponsor interactions are summarized below:

- Sponsor proposed a single, open-label, “pivotal”, Phase 3 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 overall treated for ≥ 6 months and at least 50 patients overall treated for at least ≥ 1 year. Sponsor was cautioned that lacking a placebo control, it would not be possible to determine the independent effect of intranasal TBS-1 on clinical efficacy endpoints. Incorporation of a placebo arm was strongly recommended (October 31, 2011).
- Because the product is associated with a rapid rise and fall in serum testosterone after each dose, the Division requested supportive evidence to the usual PK-based efficacy endpoints. Time within normal range (TWNRR) would be incorporated into the analysis of efficacy and clinical efficacy should support 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 (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 to initiate NATESTO therapy with 11 mg T two times daily (BID) dosing, (b) (4). However, the Division's analysis of (b) (4) dose regimen. This concern was conveyed to the Sponsor on October 9, 2013.
 - Subsequently, the Sponsor submitted a major Clinical amendment on January 13, 2014 with a new proposal (and accompanying data summaries) to administer NATESTO as an 11 mg 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 was re-set to May 28, 2014. Therefore, the primary efficacy and safety analyses for this NDA are based on the 11 mg T TID-only regimen.

2.3 PRIMARY MEDICAL REVIEWER'S RECOMMENDATION FOR APPROVABILITY

The primary Clinical reviewer, Roger Wiederhorn, stated in his final review dated May 20, 2014:

*“Recommendation on Regulatory Action: It is recommended that NDA 205488 be **APPROVED**. 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 included 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.

In regard to safety, the medical officer concluded:

- *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%).*
- *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.*

CDTL Comment: I concur with Dr. Wiederhorn’s overall recommendation and conclusions.

3. CMC/Device

In their final review #1, dated December 16, 2013, the ONDQA review team (Hitesh Shroff) concluded that the NDA is not recommended for Approval until:

- 1) CMC labeling issues are satisfactorily resolved , and
- 2) the Office of Compliance issues an overall Acceptable recommendation for the facilities involved.

However, the December 16, 2013, CMC review does state:

- *“...this NDA has provided sufficient CMC information to assure the identity, strength, purity and quality of the drug product.”*
- A 24-month expiration dating period was granted.
- There are no novel excipients used in the formulation. All are USP/NF compliant.
- The microbiological testing information was reviewed by Bryan Riley, PhD of OPS/NDMS, on May 1, 2013, and the microbial testing specification was found to be acceptable. Dr. Riley concluded that the NDA submission may be approved from the standpoint of product quality microbiology.
- The Environmental Assessment review was conducted by Mr. Raanan Bloom on September 10, 2013, who concluded that the application qualifies for a categorical exclusion.

On May 22, 2014, Hitesh Shroff and Moo Jhong Rhee of ONDQA completed a final memo stating: 1) On May 21, 2014, the Office of Compliance issued an “Acceptable” recommendation for the facilities involved in this NDA, and 2) On May 11, 2014 and May 21, 2014, the labeling submitted by Sponsor was satisfactory from the ONDQA perspective, and 3) The drug product specification is adequate from the ONDQ perspective. Therefore, the final recommendation from ONDA is for approval of this application.

4. Nonclinical Pharmacology/Toxicology

In her final review, dated January 14, 2014, the Pharmacology/Toxicology reviewer (Lynnda Reid) concluded that “*Nonclinical data support the Approval of TBS-1 for the treatment of male hypogonadism.*”

Dr. Reid noted that in vivo local tolerance studies were conducted in rats and rabbits to support the new route of administration of testosterone. The 3-month, repeat-dose, toxicity study in rabbits exposed the animals to TBS-1 through the nasal mucosa, the same route as proposed for hypogonadal men. Administration of TBS-1 intranasally for three months at doses up to 6-fold the recommended human dose was not associated with any local or systemic toxicity in the organs examined (nasal turbinates, brain, testes, heart, kidneys, and lungs). The formulation was found to be non-irritating in this study.

Dr. Reid further noted that local tolerance studies using an ex vivo model and the nasal route of administration in rats demonstrated that testosterone in combination with the excipients of the gel (castor oil, oleoyl polyoxylglycerides and colloidal silicon dioxide) was non-irritating.

5. Clinical Pharmacology/Biopharmaceutics

In their final review, dated April 30, 2014, the Clinical Pharmacology review team (Chongwoo Yu, Jiang Liu, Yaning Wang, and Myong Jin Kim) stated the following Recommendation:

“The overall Clinical Pharmacology information submitted to support this NDA is acceptable and NATESTO is recommended for approval from the Clinical Pharmacology standpoint.”

The ClinPharm review contained the following additional notable statements:

- The Sponsor originally proposed to initiate NATESTO therapy with 11 mg T two times daily (BID) dosing, (b) (4). However, the Division’s analysis of the primary efficacy data showed that the (b) (4) dosing regimen. This concern was conveyed to the Sponsor on October 9, 2013. Subsequently, the Sponsor submitted a major Clinical amendment on January 13, 2014 containing a new proposal seeking approval of NATESTO as an 11 mg T TID regimen only (b) (4).
- The agreed-upon level of success was achieved only in the TID-only group (n=73). In the TID-only group, in the Intent-to-Treat (ITT) population, on Day 90, using last observation carried forward (LOCF), 66 of 73 subjects had a C_{avg} in the normal range ($300 \leq C_{avg} \leq 1050$ ng/dL). The percentage of responders was 90%, with 95% CI for frequency of response (84, 97). Of the non-responders on Day 90, all were a consequence of C_{avg} below the normal range (<300 ng/dL) and none had a C_{avg} above the normal range (>1050 ng/dL).

- The critical secondary safety endpoint was total T C_{max} within 3 pre-determined ranges on Day 90:
 - < 5% of subjects with a serum total T C_{max} in the range of 1800-2500 ng/dL
 - No subjects with a serum total T C_{max} of > 2500 ng/dL
 - At least 85% of subjects with a serum total T $C_{max} \leq 1500$ ng/dL

Two of the criteria for this mandatory secondary endpoint were met:

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

However, the percentage of subjects with a serum total T $C_{max} \leq 1,500$ ng/dL on Day 90 was 84.1%, marginally less than the pre-specified criterion of at least 85%

- There were no unresolved inspection findings from an Office of Scientific Investigations audit of the clinical and analytical study sites.
- The Sponsor conducted a Phase 1, open label, randomized, 3-way crossover, 3-treatment, 3-period drug-drug interaction study (Study TBS-1-2011-04) in male subjects with seasonal allergic rhinitis (aged 18-45 years) in symptomatic/untreated, symptomatic/treated, or asymptomatic states. The drug treatment was oxymetazoline, a vasoconstrictor decongestant. Total T exposure ($AUC_{[0-24]}$, C_{max} , and C_{avg}) was approximately 21-24% higher in the asymptomatic state compared to the symptomatic state regardless of treatment with oxymetazoline. The difference between the symptomatic untreated and symptomatic treated states was small (approximately 2.6% increases in $AUC_{[0-24]}$), indicating that administration of oxymetazoline did not significantly impact the absorption of T following the administration of NATESTO.

6. Clinical Microbiology

There are no Clinical Microbiology issues for this NDA. From a product quality microbiology standpoint, however, the microbiological testing information was reviewed by Bryan Riley, PhD of OPS/NDMS on May 1, 2013, and the microbial testing specification was found to be acceptable. Dr. Riley concluded that the NDA submission may be approved from the standpoint of product quality microbiology.

7. Clinical/Statistical - Efficacy

7.1 OVERVIEW OF CLINICAL PROGRAM

For efficacy, the NDA is supported by a single, 90-day, Phase 3, randomized, dose-ranging study (Study TBS-1-2011-03), that evaluated the efficacy and safety of Natesto in the treatment of male hypogonadism with sequential safety extension periods of 90 and 180 Days.

The study consisted of 4 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 up-titration to TID on Day 45 for subjects in the BID group;
- A 90-day, open-label, safety extension period (SE1) for all study subjects; and
- An additional 180-day, open-label, safety extension period (SE2) for remaining subjects.

At Visit 4 (Day 30) and Visit 6 (Day 90), 24-hour post-dose complete PK profiles of serum total testosterone, DHT, and estradiol were obtained.

After Visit 4 (Day 30), subjects randomized to the BID group who had 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. The estimation of the serum total testosterone C_{avg} was based on the following criteria:

- If the sum of the serum total testosterone level values for PK samples collected at 1 hour before the 7 am dose and 20 minutes after the 7 am dose 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 1 hour before the 7 am dose and 20 minutes after the 7 am dose was ≥ 755 ng/dL, then the estimated 24-hour C_{avg} was ≥ 300 ng/dL.

In addition to Study TBS-1-2011-03, intranasal testosterone gel was administered in 8 other Phase 1 and Phase 2 clinical studies. All of these had pharmacokinetics (PK) of serum testosterone as their primary endpoint. Five were conducted in hypogonadal men and 3 were conducted in healthy men (including Study TBS-1-2011-04, conducted in healthy men with allergic rhinitis).

The remainder of the efficacy sections will provide data from the Phase 3 study TBS-1-2011-03, with particular emphasis on the to-be-marketed 11 mg three times daily regimen.

7.2 DEMOGRAPHICS

The main diagnostic criteria for inclusion in Study TBS-1-2011-03 were men at least 18 years of age with morning screening serum testosterone concentration < 300 ng/dL.

Critical exclusion criteria included: 1) Hematocrit $> 54\%$ at Screening, 2) History of nasal or sinus surgery, 3) History of nasal fractures within the past 6 months and/or any prior nasal fracture that caused a deviated anterior nasal septum, 4) Active allergies, 5) Mucosal inflammatory disorders, 6) Active sinus disease, 7) History of chronic nasal disorders, 8) History of sleep apnea, 9) Use of any intranasal medication delivery, 10) History of asthma, 11) Serum prostate specific antigen level ≥ 4 ng/mL, 12) Abnormal sized prostate, 13) Serum liver tests exceeding 2 times the upper limit of normal, and 14) Uncontrolled diabetes mellitus.

In brief, the demographics of the study population were as follows:

There were 306 (100.0%) male subjects in total. The majority of subjects were White / Caucasian (89%). The overall mean age of subjects was 54 years. The mean weight at screening was 93 kg, mean height was 177 cm, and mean BMI was 30 kg/m². In total, 72% of subjects had primary hypogonadism and 28% had secondary hypogonadism. The mean duration of hypogonadism prior to screening was 4.6 years. Overall, 27% of subjects required a wash-out from their previous testosterone replacement therapy. The mean qualifying fasting serum total testosterone concentration was 201 ng/dL, mean DHT concentration was 19 ng/dL and mean estradiol concentration was 18 pg/mL.

Demographics were similar between the overall group (n=306) and the 78 subjects randomized to TID-only.

7.3 DISPOSITION OF SUBJECTS

A total of 306 subjects were randomized and took study drug at 39 centers in the U.S. A total of 228 subjects were randomized to the BID dose group and 78 subjects to the TID dose group. Of the 228 subjects who started in the BID dose group, (b) (4) % were up-titrated to TID.

The overall discontinuation rate from the 90-Day Treatment Period in the originally randomized BID group (b) (4)

The primary reasons for discontinuation from the 90-Day Treatment Period for both groups were withdrawal of consent ((b) (4) % for BID and 5% for TID) and “Other” ((b) (4) % for BID and 1.3% for TID). A total of 5 subjects discontinued the Treatment Period due to adverse events, 1 in the BID dose group and 4 in the TID-only dose group.

Of the 274 subjects who entered Safety Extension Period 1 (SE1), a total of 29 (10.6%) subjects discontinued during SE1 (15 [12.3%] subjects in the BID group and 14 [9.2%] subjects in the TID group). The primary reason for discontinuation during SE1 was withdrawal of consent (11 [4.0%] subjects). The discontinuation rate during SE1 due to adverse events was low (3 [1.1%] subjects).

Of the 245 subjects who completed SE1, 75 subjects elected to enter SE2 (35 subjects in the BID group and 40 subjects in the TID group). Eight (10.7%) subjects discontinued during SE2 (5 [14.3%] subjects in the BID group and 3 [7.5%] subjects in the TID group). The primary reason for discontinuation during SE2 was withdrawal of consent (6 [8.0%] subjects). Only 1 (1.3%) subject (in the TID group) discontinued during SE2 due to an adverse event. A total of 67 (89.3%) subjects completed SE2 (30 [85.7%] subjects in the TBS-1 BID group and 37 [92.5%] subjects in the TBS-1 TID group).

7.4 EFFICACY FINDINGS

7.4.1 Assessment of Efficacy

The primary endpoint in the Phase 3 study was the percentage of subjects with average serum total testosterone concentrations within the normal range on Day 90. The threshold for success was set as 75% with a lower bound of the 95% CI of 65%.

A key secondary endpoint was serum total T C_{max} within 3 pre-determined ranges on Day 90:

- < 5% of subjects with a serum total T C_{max} in the range of 1800-2500 ng/dL
- No subjects with a serum total T C_{max} of > 2500 ng/dL
- At least 85% of subjects with a serum total T $C_{max} \leq 1500$ ng/dL

In addition, the following secondary endpoints were evaluated:

- Other pharmacokinetic assessments of testosterone, including concentrations below the normal range (<300 ng/dL).
- The number and percentage of subjects with a serum total T C_{avg} in the normal range on Day 30.
- The number and percentage of subjects with a serum total T C_{max} in the “high” ranges on Day 30.
- The complete total T PK profile (including C_{avg} , C_{min} , C_{max} , and T_{max}) on Days 30 and 90.
- The time within the normal range (TWNR) for serum total T on Days 30 and 90.
- The PK profile of serum estradiol on Days 30 and 90.
- The PK profile of serum DHT on Days 30 and 90.
- The ratio of DHT C_{avg} to total testosterone C_{avg} on Days 30 and 90.
- The International Index of Erectile Function (IIEF) scores at baseline, Day30, Day 60, and Day 90.
- The Positive and Negative Affect Schedule (PANAS) scores at baseline, Day 30, Day 60, and Day 90.
- The change in bone mineral density (BMD – from DEXA) from baseline to Days 180 and 360.
- The change in body composition (total body mass, lean body mass, fat mass, and percent fat – from DEXA) from baseline to Day 180 and from baseline to Day 360.

7.4.1.1 Primary Efficacy Analysis

The primary efficacy endpoint in this study was the percentage of responders defined as C_{avg} within the normal range (300 – 1050 ng/dL). To meet the primary efficacy criterion, the point estimate for the pre-determined primary endpoint was set as at least 75% and the lower bound of the two-sided 95% confidence interval was set as not lower than 65%.

Ninety percent (90%) of TID-only patients (66 of 73) had serum total T C_{avg} within the 300 – 1050 ng/dL range. The 95% confidence interval around this point estimate was 84 – 97%. Of the 7 patients who did not meet this criterion, all failed due to $C_{average}$ below 300ng/dL. This result demonstrates that the primary efficacy success criterion was achieved for the TID-only group.

However, the (b) (4) for (b) (4) subjects dosed with BID-only (b) (4)

Table 1 and Figure 1 summarize the mean pharmacokinetic parameters of serum total T on Day 90 for the 69 subjects who had sufficient data on Day 90 to allow for these assessments.

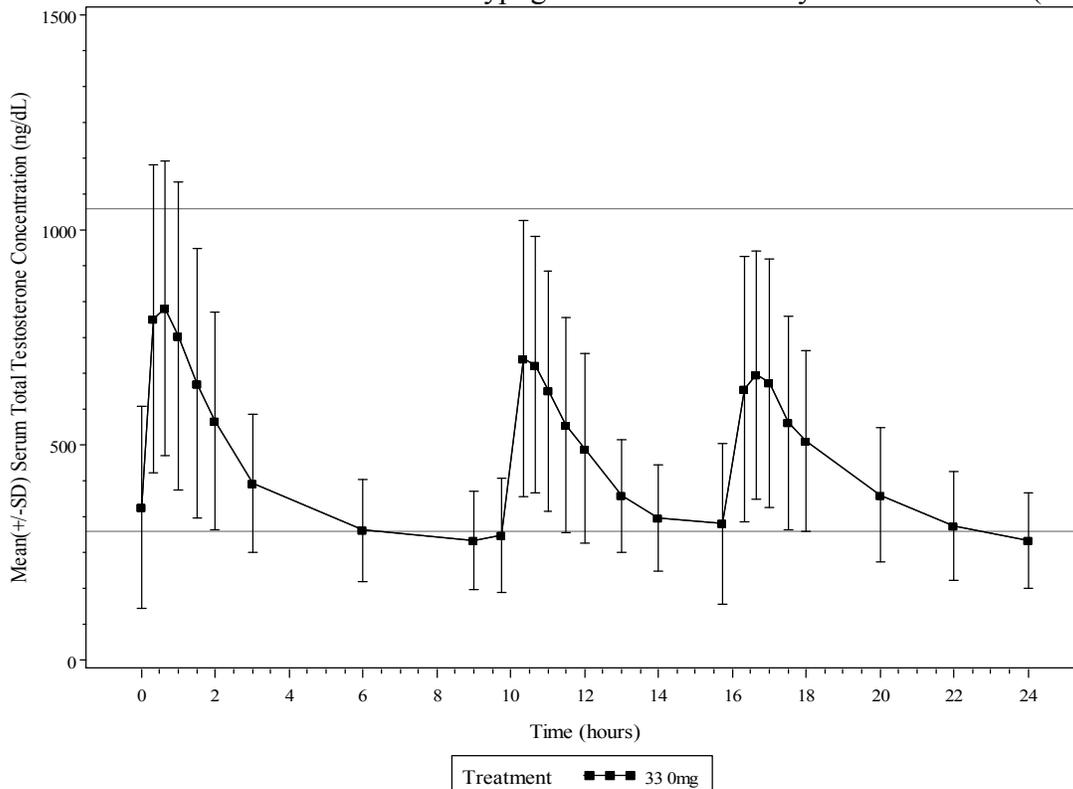
Table 1: Mean (SD) PK Parameters of Serum Total T on Day 90 Following Administration of TID Administration of NATESTO to Hypogonadal Men in Study TBS-1-2011-03

| | Day 90 (N=69 ^b) |
|-----------------------------|-----------------------------|
| C_{max} (ng/dL) | 1044 (378) |
| C_{min} (ng/dL) | 215 (74) |
| C_{avg} (ng/dL) | 421 (116) |
| T_{max} (hr) ^a | 0.65 (0.3, 6.1) |

^a Median (min, max)

^b Number of subjects who had a valid C_{max} on Day 90.

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



7.4.1.2 Secondary Efficacy Analysis

C_{max} was an important secondary efficacy endpoint in TBS-1-2011-03. To meet the C_{max} efficacy criterion, the following criteria must have been met:

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

For the TID-only dosing group, the following criteria of this critical secondary endpoint were met:

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

However, only 84.1% of TID-only subjects had a serum total T $C_{max} \leq 1,500$ ng/dL on Day 90 compared to the pre-specified criteria of at least 85%. *Table 2* presents the number and percentage of subjects in the ITT population on Day 90.

Table 2: Number (Percentage) of Subjects in the ITT Population by Selected Ranges of Serum Total T C_{max} on Day 90 Following TID Administration of NATESTO to Hypogonadal Men in Study TBS-1-2011-03

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

^a The number of subjects who had a C_{max} value on Day 90

CDTL Comment: *In my opinion, the data show that the C_{max} efficacy objective was achieved for the TID-only dosing regimen in Study TBS-1-2011-03.*

In addition to the increase in serum total T concentration, serum concentrations of the known metabolites, dihydrotestosterone and estradiol, were also increased. The increases in serum DHT and E_2 were expected.

- Observed increases in serum DHT concentrations were consistent with dosing with T. In the 69 TID-only subjects with sufficient data on Day 90, the mean DHT C_{avg} , C_{max} and C_{min} were 40 ng/dL, 65 ng/dL, and 26 ng/dL, respectively. The mean DHT T_{max} was 1.45 hrs.
- Observed increases in serum estradiol concentrations were consistent with dosing with T. In the 69 TID-only subjects with sufficient data on Day 90, the mean estradiol C_{avg} , C_{max} and C_{min} were 28 pg/dL, 45 pg/dL, and 19 pg/dL, respectively. The mean DHT T_{max} was 1.57 hrs.
- The concentration versus time profiles for DHT and E_2 generally paralleled the T concentration-time profile. The mean DHT:T ratio (0.09) was comparable to reported DHT: T ratio values for other T replacement products and for normal eugonadal men.

The reader is referred to the original and subsequent medical officer's primary reviews and to the Clinical Pharmacology reviews for additional details, tables and figures for these variables.

In regard to other secondary endpoints:

- Mean change from baseline to Day 90 in the TID-only group in the EF domain score of the IIEF, a validated measure of erectile function, was 6.2 points, a clinically significant improvement and one that far exceeds the expectation from a placebo in men with ED.
- Mean change from baseline to Day 90 in the TID-only group in the overall IIEF score was 14.4 points, including improvements in the Sexual Desire domain that are not usually observed for placebo or for drugs intended to treat ED.
- There were no significant changes from baseline in the Positive and Negative Affects Scores, suggesting no effect of Natesto on mood.
- There were no significant changes from baseline to Day 180 or Day 360 in bone mineral density values either at the lumbar spine or the hip.
- There was a significant positive change from baseline to Day 180 in lean body mass, which was quantitatively similar on Day 360. There were also decreases from baseline in fat mass and percent fat after 180 days of treatment that continued to Day 360.

While it is not possible to draw definitive conclusions from these secondary endpoints without data from a concurrent control group, these data may suggest a clinical androgenic effect.

Statisticians' Conclusion

In their final review dated April 4, 2014, the Biometrics team (Sonia Castillo and Mahboob Sobhan) stated the following conclusion:

“The one submitted study provides evidence demonstrating the efficacy of the three times per day (TID) dosage regimen of 4.5% TBS-1 intranasal testosterone gel (5.5 mg per actuation of testosterone for the treatment of adult male hypogonadism.”

The Biometrics review also had the following notable statements:

- On Day 90, the percentage of subjects with C_{avg} in the normal range (using Sponsor's definition of ITT [n=73]), was 90.4% (95% C.I. 84%, 97%).
- For the other two dose regimens tested (BID-only, and BID changed to TID), the percentages of subjects with C_{avg} within the normal range was (b) (4) % in men taking TBS-1 twice daily ((b) (4)) and (b) (4) % in men taking TBS-1 twice daily who were then up-titrated to three times daily ((b) (4) %).
- In the combined dose group of BID-only + BID changed to TID, the success rate was (b) (4) .
- The Biometrics sensitivity analysis, which used the Biometrics Reviewer's definition of the ITT population (n=78) still supported efficacy in the TID-only dose group

7.4.2 Overall Assessment of Efficacy

The Natesto TID dosing regimen was found to provide adequate replacement of testosterone, while not providing excessive testosterone (as measured by testosterone C_{max}). The TID dosing regimen demonstrated a mean C_{avg} within the normal range and a C_{max} profile that did not exceed the approvability thresholds provided. Thus, the primary and critical secondary efficacy objectives of the Phase 3 study were met for the TID-only dosing regimen, but not for the BID-only regimen nor for a dose-titration regimen of BID to TID.

8. Safety

8.1 SAFETY FINDINGS

Safety Contents

This Original NDA contained safety data from **475 men** exposed to at least one dose of intranasal testosterone gel. A total of **430 hypogonadal men** and **45 healthy volunteers** received intranasal T gel in the 9 clinical studies.

The safety data comes primarily from the single, U.S., pivotal Phase 3 study TBS-1-2011-03 and also from eight other Phase 1 and Phase 2 studies: TBS-1-2010-01, Nasobol-01-2009, MAT/05, MAT/04, Nasobol-01-2008, TBS-1-2011, and TBS-1A-2011-01.

The cumulative exposure to testosterone intranasal gel was 283 patients for at least 90 days, 247 patients for at least 6 months, and 67 patients for at least 1 year.

The overall exposure to the TID-only regimen is 152 hypogonadal men for 90 days, 69 hypogonadal men for 180 days, and 18 hypogonadal men for 360 days.

The 120-Day Safety update was received on September 3, 2013 and provided no new safety signals compared to safety data from the original NDA.

The remainder of this section provides data from the Phase 3 study TBS-1-2011-03.

8.1.1.1 Deaths, Serious Adverse Events, and Discontinuations Due to Adverse Events

Deaths and Serious Adverse Events (SAEs)

One subject died in Study TBS-2-2011-03. Subject 004-008, a 58 year-old Caucasian male with hypogonadism was randomized to the TID dose group. On Study Day 36, the subject was involved in a motorcycle accident and experienced internal injuries. On the same date, the subject died due to internal injuries from the accident. The last dose of study medication was taken on Study Day 36. The Clinical reviewer concluded that the event was unrelated to study drug.

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%). Five SAEs were reported in the 90-Day Treatment Period. None of the SAEs during the study were considered by the Investigator to be related to the study drug .

Of this total, one subject reported an SAE during Safety Extension Period 1 (Rocky Mountain spotted fever, considered unrelated to study medication by the Investigator) and three reported SAEs during Safety Extension Period 2 (gastroesophageal reflux, pneumonia and chest pain, none of which was consider to be related to study medication by the Investigator).

The treatment-emergent SAEs were: chest pain (ruled out for myocardial infarction), broken hip, fall at work (with torn knee ligaments), acute coronary syndrome (in a patient with three-vessel coronary atherosclerosis), Rocky Mountain spotted fever, pneumonia, gastroesophageal reflux, death due to motor cycle accident, and cystic abdominal mass.

Discontinuations due to Adverse Events

Study medication was discontinued due to adverse events in a total of ten (10) patients in the entire Phase 3 study (3.2%). Of that total, 8 patients discontinued due to AEs in the 90-day Treatment Period (2.6%), two (2) patients discontinued due to AEs from Days 91 to 180 in SE1 (0.7%), and no (0) patient discontinued due to AEs from Days 181 to 360 in SE2.

Of the 10 discontinuations due to AEs, 5 were in the TID-only group.

Seven of the 10 discontinuations due to AEs were considered by the Investigator to be at least possibly related to study medication. These included: increased PSA (2 subjects), nasal adverse reaction (2 subjects), allergic-type reaction (2 subjects), and headache (1 subject). Of the two nasal adverse reactions leading to discontinuation, the events were described as: 1) nasal discomfort, altered sense of smell, and nasal crusting, and 2) nasal odor and dysgeusia. Of the two allergic-type reactions, the events were described as: 1) facial swelling and hives, and 2) myalgia, joint pain, fever, chills and petechiae.

8.1.2 Other Adverse Events

Overall Adverse Events

For the Entire Safety Population:

In the 1-year study, a total of 196 of 306 subjects (65% of total) reported a treatment-emergent adverse event (TEAE).

An analysis by dose group shows that 63%, 65%, and 70% of BID, Combined TID (BID/TID), and TID subjects reported a TEAE, respectively.

An analysis by time of report shows that 50%, 37%, and 53% of subjects reported a TEAE in the Treatment Period (Day 1-90), in SE1 (Days 91-180), and in SE2 (Days 181-360), respectively.

An analysis by event severity shows that TEAEs were reported as mild or moderate in severity in 93% of subjects who reported a TEAE (182 of 196 subjects); the majority reported as mild (115 of 182 subjects).

An analysis by treatment-relatedness shows that TEAEs were reported as possibly related to study medication by the Investigator in 110 subjects (31% of total). Only 1 “severe” TEAE was reported as possibly related to treatment: Subject 021-014 with myalgia in the TID dose group.

For the entire study, at all doses, in the entire population (n=306), the following TEAEs were reported by at least 2% of subjects:

Nasopharyngitis (8.2%), parosmia (5.2%), upper respiratory infection (4.2%), headache (3.6%), PSA increased (3.3%), back pain (2.9%), pain in extremity (2.6%), bronchitis (2.6%), dysgeusia (2.3%), arthralgia (2.3%), nausea (2.0%), and CPK increased (2.0%).

For the TID-only Population:

An analysis by time of report shows 59%, 48%, and 50% of TID-only subjects (n=78) reported a TEAE in the Treatment Period (Day 1-90), in SE1 (Days 91-180), and in SE2 (Days 181-360), respectively.

An analysis by treatment-relatedness shows that TEAEs were reported as possibly related to study medication by the Investigator in 33%, 15%, and 11% of TID-only subjects in the Treatment Period (Days 1-90), in SE1 (Days 91-180), and in SE2 (Days 181-360), respectively.

In the 90-Day Treatment Period only, TEAEs and treatment-related TEAEs were reported in 59%, and 33% of TID-only subjects, respectively. Of the treatment-related TEAEs, a total of 18, 7 and 1 event were reported as mild, moderate and severe in severity, respectively.

The following AEs were reported by at least 3% of TID-only subjects (n=78) in the Treatment Period:

PSA increased (5.1%), headache (3.8%), rhinorrhea (3.8%), epistaxis (3.8%), nasal discomfort (3.8%), nasopharyngitis (3.8%), upper respiratory tract infection (3.8%), sinusitis (3.8%), bronchitis (3.8%) and nasal scab (3.8%).

The following AEs were reported by at least 3% of TID-only subjects (n=69) in the SE1 Period:

Nasopharyngitis (8.7%), rhinorrhea (7.2%), PSA increased (5.8%), parosmia (5.8%), nasal discomfort (5.8%), nasal scab (5.8%), upper respiratory tract infection (4.3%), bronchitis (4.3%), procedural pain (4.3%), pain in extremity (4.35%), headache (4.3%) and epistaxis (4.3%).

Among TID-only subjects who participated in SE2 (n=18), the following adverse reactions were reported in more than one patient each: nasopharyngitis, PSA increased, parosmia, nasal discomfort, nasal scab and hypertension.

For the entire study, the following AEs were reported by at least 3% of TID-only subjects:

Nasopharyngitis (10.3%), upper respiratory infection (7.7%), PSA increased (7.7%), headache (5.1%), pain in extremity (5.1%), sinusitis (3.8%), dysgeusia (3.8%), myalgia (3.8%), procedural pain (3.8%) and tooth abscess (3.8%).

Adverse Events of Special Interest

In this NDA, the “*adverse events of special interest*” were those related to the local site of administration (nasal adverse reactions) and those related to testosterone replacement therapy itself (e.g., PSA increased, serum lipid abnormalities, increased hematocrit, worsening of benign prostatic hypertrophy symptoms, and mood disorders, among others).

Nasal Adverse Reactions and Otorhinolaryngologic Examinations

Among all subjects (n=306) who received Natesto at any dose in the 90-day clinical study and its 90- and 180-day extension periods, the following nasal adverse reactions were reported: nasopharyngitis (8.2%), rhinorrhea (7.8%), epistaxis (6.5%), nasal discomfort (5.9%), parosmia (5.2%), nasal scab (5.2%), upper respiratory infection (4.2%), nasal dryness (4.2%), and nasal congestion (3.9%).

This list of nasal adverse reactions and their overall frequencies for all dose groups combined is generally in line with the nasal adverse reaction list and reporting frequencies for the TID-only group.

Almost all nasal adverse reactions were reported as mild or moderate in severity. There were no serious adverse events of nasal reactions.

Of the 59 subjects with a history of allergic rhinitis (or “hay fever”), 3 subjects (5.1%) subjects reported exacerbations of their underlying condition. 32% of subjects with a history of allergic rhinitis reported nasal adverse reactions, a frequency similar to that reported in subjects without a background rhinitis condition.

Otorhinolaryngologic examinations were performed by an ENT specialist on all subjects at Screening and every month while on treatment. At Day 90, 89% of subjects had no ENT symptoms. The most common ENT symptom reported was “Other - not specified” (6.6%) Among treatment-related ENT symptoms, altered sense of smell (2.6%) was the most frequently reported. On Day 90, 97% of subjects had no ENT examination findings. On Day 180, 93% of subjects did not report ENT symptoms and 96% of subjects had no ENT examination findings. At Day 360, results were similar.

Adverse Reactions Associated with Testosterone Replacement Therapy

Adverse reactions previously reported for testosterone replacement therapy were reported in subjects using Natesto.

For example, increased PSA (pre-defined as an increase from baseline in serum PSA >1.4 ng/mL or a single PSA level > 4 ng/mL) was reported in 2%, 4%, and 5% of the BID, Combined TID (BID/TID) and TID-only groups, respectively in the Treatment Period. In the SE1, 4% and 3% of BID and TID patients, respectively, had a TEAE of increased PSA. In SE2, one patient had a TEAE of increased PSA.

Two percent of all subjects reported lipid-related TEAEs. No clear pattern of lipid-related events was discerned.

A total of 7 subjects had post-baseline hematocrit values of >54% during the study. All of these subjects had baseline hematocrits above the average for their respective treatment groups. Subject 001-032 had a medical history of polycythemia (2010) which antedated his study participation. In another subject (#001-054), the hematocrit was elevated at baseline and was elevated but lower than baseline at all post-baseline timepoints. In two subjects (#011-026 and #011-020), the hematocrit elevation was followed by hematocrit value(s) below 54% while the patient continued to use study medication. Among all subjects who received Natesto in the entire study, a total of 4 subjects had a hematocrit level > 55%. These 4 patients had baseline hematocrits of 48% and 51%. In no case did hematocrit exceed 58%.

8.1.3 Postmarketing Safety Findings

Natesto is not marketed in countries outside of the U.S., not are there any other known intranasal formulations of testosterone marketed outside the U.S. Therefore, there are currently no known postmarketing safety data for intranasal testosterone gel.

8.1.4 Overall Assessment of Safety Findings

My overall assessment of the safety findings is that Natesto is associated with a small percentage of mild to moderate nasal adverse reactions, including nasopharyngitis, upper respiratory infection symptoms, rhinorrhea, epistaxis, and nasal scabbing. Evidence from otorhinolaryngologic specialty examinations did not reveal findings of concern. In addition to nasal adverse reactions, Natesto is associated with the expected adverse reactions associated with the pharmacological action of testosterone (e.g., increased serum PSA, increased hematocrit, changes in lipid profiles, etc).

9. Advisory Committee Meeting

No Advisory Committee Meeting was held for this application.

10. Pediatrics

The Sponsor requested a full waiver of the requirement to conduct assessments in pediatric patients. The Sponsor stated that studies in pediatric patients are impossible or highly impractical because the disease/condition does not occur in children. The Division agreed with Sponsor that there are too few children with permanent (lifelong) hypogonadism to feasibly conduct clinical studies in the population. Therefore, on November 20, 2013, the Division recommended to the Pediatric Review Committee (PeRC) that the Sponsor's request be granted. The PeRC agreed with a full waiver based on the Sponsor's rationale.

11. Other Relevant Regulatory Issues

Office of Prescription Drug Promotion (OPDP)

A consultation regarding potential promotional issues in labeling was requested from OPDP. Brian Tran represented OPDP at each review team milestone and labeling meeting. All of OPDP's recommendations and suggestions for labeling were incorporated during the labeling negotiation process.

Office of Scientific Investigation (OSI)

Three clinical and one bioanalytical site inspections were conducted by the Office of Scientific Investigation. In their final memo dated March 14, 2014, the OSI team (Gopas Biswas and William Taylor) had the following conclusion:

“After evaluation of the additional responses for the analytical portion of the above inspections, I recommend that the study data are acceptable for further review.”

Other notable statements in the OSI review included the following:

- The Clinical reviewer was advised to carefully assess the liver test and serum creatinine kinase (CK) results for Subject #051-114 ((b) (6)). The liver tests were mildly elevated on Day 90. GGT was also mildly elevated on Day 30. CK was markedly increased on Day 90, as a singular event. The Investigator stated that the CK result was a consequence of very strenuous exercise and the liver test elevations were not clinically significant. The Clinical Reviewer assessed the case and agreed with the Investigator.
- The OCP Reviewer was advised to carefully assess the impact of early (b) (4) (b) (4) is no longer relevant as the to-be-marketing regimen is (b) (4) (TID-only) (b) (4) .

Financial Disclosure

All of the clinical investigators in the United States pivotal Phase 3 Study TBS-1-2011-004 (34 investigators) responded to the request for financial disclosure and none had any relevant financial disclosure information to declare. There were no investigators with a proprietary interest in the product and none with significant equity in the Sponsor as defined in 21 CFR 54.2 (b). No investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(b).

Office of Surveillance and Epidemiology: Division of Medication Error Prevention and Analysis (DMEPA)

For this review cycle, DMEPA provided consultation on the container/carton and Package Insert labeling from the medications errors perspective; as well as on the tradename.

Container/Carton Labeling/PI

In their final review dated September 30, 2013, Denise Baugh and James Schlick stated that improvements were needed to promote the safe use of the product, to mitigate any confusion, and to clarify information. DMEPA provided comments to the Division and to the Sponsor.

All of DMEPA's comments to Sponsor were conveyed directly to Sponsor and these issues were resolved through productive and iterative labeling negotiations. All comments to the Division were discussed amongst the review team at NDA status and labeling meetings and these issues (including use during transient rhinitis episodes, and potential secondary exposure), were resolved to the satisfaction of all on the review team.

Tradename

In a final review dated July 11, 2013, Manizeh Siahpoushan, James Schlick and Carol Holquist stated that the proposed tradename, Natesto, is acceptable from both a promotional and safety perspective. This consult stated that the proprietary name must be re-reviewed within 90 days of the anticipated approval date.

In a final memo dated May 7, 2014, Lisa Khosla stated that DMEPA no longer re-reviews proprietary names within 90 days of approval, unless there is a change in the product characteristics. Since there has been no change to the characteristics of Natesto, the proposed tradename remains acceptable, with no objections from DMEPA.

Office of Medical Policy / Division of Medical Policy Programs (DMPP)

In their final review dated May 14, 2014, Shawna Hutchins, Trung-Hieu (Brian) Tran, Melissa Hulett and LaShawn Griffiths provided recommendations for edits to the proposed Patient Package Insert (PPI) which contained Instructions for Use (IFU). DMPP's recommendations were intended to

- simplify wording and clarify concepts.
- ensure the PPI and IFU are consistent with the Prescribing Information (PI),
- remove unnecessary and redundant information,
- remove promotional language,
- ensure the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Information, and
- ensure the PPI is consistent with approved comparator labeling where applicable.

DMPP's recommendations were conveyed to the Sponsor and all DMPP-related issues in the PPI were resolved through iterative labeling correspondences with Sponsor.

Study Endpoints and Labeling Development Team (SEALD)

A final review by SEALD is pending in regard to compliance with labeling regulations. Any recommendations from SEALD will be incorporated into final labeling.

Office of Compliance

For this review cycle, Office of Compliance issued an Acceptable recommendation in EES on May 21, 2014.

Division of Pulmonary, Allergy and Rheumatology Products (DPARP)

DPARP was asked to assist DBRUP in the review of 1) Natesto nasal safety data, and 2) results of the special allergic rhinitis / drug interaction study.

On August 21, 2013, in their final DPARP consult, Sofia Chaudhry, Susan Limb, and Badrul Chowdhury provided comments on: 1) nasal safety from 245 subjects with 6 months of repeat dose exposure and 55 subjects with 1 year of exposure, and 2) the dedicated study TBS-1-2011-04 evaluating TBS-1 administration in the setting of symptomatic nasal conditions (allergic rhinitis) in both a treated (oxymetazoline) and untreated state.

DPARP had the following conclusions:

- Overall, the safety review finds that use of TBS-1 is associated with low rates of nasal irritation. The irritation appeared largely minor, and in many cases, self-limited. It did not result in a large number of drug discontinuations. A few adverse events of potentially more severe findings were seen (nasal ulceration) but there were no reports of irreversible toxicity. DPARP recommended the inclusion of the risk of nasal irritation in the product label. Labeling to this effect has been included.
- The allergic rhinitis study demonstrated a 21% decrease in serum testosterone levels, as measured by AUC[0-24], in subjects with allergic rhinitis symptoms compared to those in the asymptomatic state. There was no effect on drug absorption demonstrated by concomitant use of oxymetazoline. If DBRUP considered the results of this trial reliable and the magnitude of the decrease clinically significant, DPARP recommended that general language be incorporated in the label regarding the potential decreases in testosterone absorption secondary to allergic rhinitis, but also secondary to chronic nasal conditions or changes in nasal anatomy. Labeling to this effect has been included.

12. Labeling

The Sponsor and FDA worked collaboratively to generate a label that accurately described the efficacy and safety results for Natesto and would allow for safe and effective use of Natesto.

The key aspects of the label include: 1) a Warning concerning nasal adverse reactions (not severe) and limited long-term safety information, 2) a Warning advising against concomitant use with classes of nasally administered products other than sympathomimetic decongestants, 3) a Warning advising against use in patients with background sinus conditions, previous nasal surgery, recent broken nose, etc, and 4) an extensive Dosage and Administration section showing how to properly administer the product. In addition, considerable effort was placed into making the PPI user-friendly and informative.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

I recommend that the NDA be approved at this time.

13.2 Risk Benefit Assessment

Natesto provides total testosterone serum concentrations within the normal range in >90% of subjects when dosed three times daily. The rate of excessive testosterone concentrations with Natesto is quite low. The intranasal dosing regimen is novel and serves to obviate some of the drawbacks associated with other testosterone formulations. The risks of Natesto include the usual androgen-related side effects plus the nasal adverse reactions that were reported in clinical studies. These include nasopharyngitis, rhinorrhea, epistaxis, nasal discomfort, nasal congestion, parosmia, dysgeusia, nasal dryness and nasal scabbing. The vast majority of these events were reported as mild in severity, and less frequently, moderate in severity. The risk of severe nasal adverse reactions appears very low.

Overall, Natesto thrice daily has demonstrated the required level of efficacy in the context of a tolerable safety profile.

The reader is referred to previous sections of this memo, including the Executive Summary, for additional discussion and detail.

13.3 Recommendation for Postmarketing Risk Management Activities

There are no specific recommendations for postmarketing risk management activities.

13.4 Recommendation for other Postmarketing Study Commitments

There are no specific recommendations for postmarketing study commitments

13.5 Recommended Comments to Applicant

There are no recommended comments to the Applicant at this time.

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

/s/

MARK S HIRSCH
05/27/2014

HYLTON V JOFFE
05/27/2014

I agree that Natesto can be approved. See the Division Director Summary Review.