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STATISTICAL REVIEW(S)



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STATISTICAL REVIEW AND EVALUATION Clinical Studies

NDA/Supporting Doc. #: 205488 / 001

Drug Name: 4.5% TBS-1 [testosterone (17 beta-Hydroxy-4androst-3-on) nasal gel]

Indication(s): Treatment of adult male hypogonadism

Applicant: Trimel BioPharma SRL

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1. EXECUTIVE SUMMARY

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 (17 beta-Hydroxy-4androgen-3-on)] for the treatment of adult male hypogonadism based on the proportion of men who achieved total serum testosterone levels within the normal range. The primary efficacy outcome, the proportion of men with normal total serum testosterone levels was within the pre-specified success criteria for the TID regimen. The men who received the twice a day (BID) dosage regimen or the BID up-titrated to TID dosage regimen (b) (4) for proportions of men with normal total serum testosterone levels.

The evidence is based on achieving total serum testosterone levels within the normal range after 90 days of treatment in at least 75% of men with the lower bound of the 95% confidence interval for the estimate of the proportion of men achieving the total serum testosterone levels within the normal range no less than 65%. The normal range of total serum testosterone level is defined as ≥ 300 ng/dL and ≤ 1050 ng/dL. In addition, only those men who were randomized to the BID dosage regimen had their dosage up-titrated to the TID regimen if their testosterone levels were not in the normal range after 30 days of treatment.

TBS-1 increased the total serum testosterone level to within normal range in 90.4% of men taking TBS-1 three times a day (95% C.I. of 83.7% to 97.2%). For the other two dose regimen groups, TBS-1 increased the total serum testosterone level to within normal range in (b) (4)% of men taking TBS-1 twice daily (b) (4) and in (b) (4)% of men taking TBS-1 twice a day and then changed to three times a day (b) (4). Although the TBS-1 TID group result met the success criteria, only 78 subjects were in this group, which is less than what the Division has required, at least 100 subjects, for a robust point estimate.

2. INTRODUCTION

2.1 Overview

This submission consists of one open-label, randomized, multicenter, parallel-group study to evaluate the efficacy and safety of 4.5% TBS-1 intranasal testosterone gel (5.5 mg per actuation of testosterone (17 beta-Hydroxy-4androgen-3-on)] for the treatment of adult male hypogonadism. Table 2.1 presents a brief study summary.

Brief Summary of Clinical Study for 4.5% TBS-1

Study Number (Country / #) Dates of Study Conduct	Subject Population	Treatment	ITT ¹ Population	Design ²
TBS-1-2011-03 (United States / 39) Sept 2011 to March 2013	Men with clinically verified hypogonadism (total serum testosterone levels <300 ng/dL)	4.5% TBS-1 (5.5 mg) BID 4.5% TBS-1 (5.5 mg) TID Total	228 78 306	OL, R, PG, MC, 360 days

Source: Statistical Reviewer's listing.

¹ ITT = Intent to Treat, received investigational product

² OL = Open-label, R = Randomized, PG = Parallel Group, MC = Multicenter

The proposed indication is:

Intranasal 4.5% TBS-1 gel is indicated for the treatment of adult male hypogonadism.

The proposed dose of 4.5% TBS-1 testosterone gel is 5.5 mg per nostril either two or three times daily.

Testosterone replacement is used to treat the symptoms of hypogonadism and according to the Applicant:

Testosterone ... is an endogenous androgen necessary for normal male growth and development. Through nuclear receptors located throughout the body, testosterone influences the transcription of genes involved in statural growth, protein anabolism, bone remodeling, immune modulation, hematopoiesis, and lipid metabolism. Via conversion to dihydrotestosterone (DHT), testosterone also maintains adult male secondary sex characteristics. Deficiency leads to male hypogonadism with a clinical presentation determined by the age of onset and the duration and severity of deficit. In adults, symptoms vary widely, ranging from depression and cognitive decline to infertility and osteopenia.

Hypogonadism is classified as primary (due to decreased production of androgens in the testes) or secondary (due to dysfunction of the hypothalamic-pituitary-gonadal axis) ... (Source: *Clinical Study Report TBS-1-2011-03, section 7, page 35*).

The study is designed to demonstrate the efficacy of 4.5% TBS-1 for the treatment of adult male hypogonadism.

2.2 Data Sources

The application was submitted electronically. The submitted SAS data sets were complete and well documented. The following review items are located in the CDER Electronic Document Room as described below:

- The complete study report is located at <\\Cdsub1\evsprod\NDA205488\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hypogonadism\5352-stud-rep-uncontr\tbs-1-2011-03> and responses to information requests are located at <\\Cdsub1\evsprod\NDA205488\0007> and <\\Cdsub1\evsprod\NDA205488\0010> under submissions dates 4-29-2013 (eCTD Sequence Number 0000), 8-16-2013 (eCTD Sequence Number 0007), and 10-4-2013 (eCTD Sequence Number 0010), respectively.
- Raw and derived data sets used for analysis and the data set define files are located at <\\Cdsub1\evsprod\NDA205488\0000\m5\datasets\tbs-1-2011-03> under submission date 4-29-2013 (eCTD Sequence Number 0000)

3. STATISTICAL EVALUATION

This section describes the study design, data and analysis quality, evaluation of efficacy, and study results.

3.1 Data and Analysis Quality

The submitted datasets were well documented and easily accessible. The derived efficacy datasets used for the primary efficacy analysis can be created from the raw datasets. I was able to reproduce the primary efficacy results as presented in the study report from the derived efficacy dataset based on frequency of events. The final statistical analysis plan was submitted prior to unblinding and there were no changes to the pre-specified primary analyses as presented in the protocol.

The protocol did not specifically state that the efficacy results would be presented by any treatment group category or which group was the basis for determining efficacy. The clinical review team determined that efficacy results should be presented by the following TBS-1 groups: BID (stayed on this regimen for entire study), BID-to-TID (started out as BID but up-titrated to TID after day 30), TID (stayed on this regimen for entire study), and BID plus BID-to-TID (b) (4).

The protocol definition of the intent to treat (ITT) population was more of a modified ITT population, that is, all subjects who received randomized study drug and had at least one valid post-baseline efficacy measurement. This reviewer conducted a sensitivity analysis in the ITT population, that is, in all randomized subjects who received at least one dose of study drug to assess the impact of dropouts on the efficacy results.

3.2 Evaluation of Efficacy

The Applicant has submitted one clinical study (TBS-1-2011-003) designed to demonstrate the efficacy and safety of 4.5% TBS-1 intranasal testosterone gel for the treatment of adult male hypogonadism. This review will focus on the primary endpoint of proportion of men who achieve a normal total serum testosterone level. The test product will be called TBS-1 for the remainder of the review.

3.2.1 Study TBS-1-2011-03 Design and Endpoints

Study TBS-1-2011-003 was an open-label, randomized, two-group, multicenter, Phase 3 study. Eligible subjects were adult men 18 to 80 years of age with a diagnosis of hypogonadism who had two fasting morning serum total testosterone levels <300 ng/dL at screening.

The screening period was 3 to 7 weeks in duration which included a 2- to 4-week medication washout for subjects currently receiving testosterone therapy. On the first day (baseline) of the 90-day open-label treatment period, eligible subjects were randomized in a 3:1 ratio to either:

- 5.5 mg per nostril of TBS-1 twice daily (BID) for a total daily dose of 22 mg/day

- 5.5 mg per nostril of TBS-1 three times daily (TID) for a total daily dose of 33 mg/day.

About 280 subjects were planned to be randomly assigned as follows: 210 to TBS-1 BID and 70 to TBS-1 TID.

Serum total testosterone level was measured as the 24-hour average concentration (C_{avg}) at baseline, prior to first study drug dose, and on days 30 and 90 during the site visit. Training on drug administration, including maintaining a daily diary documenting drug dose administration, was provided to subjects. Subjects randomized to the BID group with a serum total testosterone level (PK profile or C_{avg}) < 300 ng/dL at day 30 were to have their daily dose increased to TID on day 45 and maintained this dose for the rest of the study.

Study drug was dispensed in amounts exceeding the amount needed for the period of time between visits. Subjects were instructed to return all unused study drug at the next visit. Compliance was evaluated by weighing the study drug dispensers and reviewing the daily diary at each visit. During the treatment period, if compliance was not between 80% and 120%, the subject was counseled about the importance of compliance to the regimen.

The open-label 90-day treatment period, which was used to determine efficacy, was followed by a safety extension period where treatment was continued until day 360.

Primary Efficacy Endpoint

The primary study objective is to demonstrate the efficacy of TBS-1 based on 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) at day 90 in at least 75% of treated subjects.

The primary efficacy variable is the percentage of subjects with a serum total testosterone C_{avg} value within the normal range on day 90, with success being defined as at least 75% of treated subjects are within the specified normal serum testosterone concentration range and with the lower bound of 95% confidence interval (CI) not less than 65%.

Supportive Secondary Efficacy Endpoints

The following secondary endpoints were selected by the clinical reviewer for assessment in order to provide supportive evidence of efficacy. Dual-energy X-ray absorptiometry (DEXA) scans to evaluate body composition (lean body mass (kg), fat mass (kg), and percent fat) and bone mineral density (BMD g/cm^2) of the lumbar spine and hip were performed at baseline in qualified subjects. Follow-up DEXA scans were obtained at Day 180 and Day 360 during the safety extension portion of the study.

3.2.2 Statistical Methodologies

The protocol-specified primary efficacy population is the intent-to-treat (ITT) population, defined as all subjects who received randomized study drug and had at least one valid post-baseline efficacy measurement. This reviewer does not agree with this definition of the ITT population because it does not include all randomized subjects who took at least one dose of study drug. A sensitivity analysis using this definition of the ITT population was conducted to assess the impact of dropouts on the efficacy results. Missing day 90 data was imputed using LOCF of either the last value during the treatment period or the baseline value if not post-baseline data was available.

Primary Efficacy Endpoint

The number and percentage of subjects who reach a serum total testosterone C_{avg} value in the normal range at day 90 was summarized descriptively and the CI was approximated by a binomial distribution. If day 90 data is missing, then the last value during the treatment period, using last value carried forward (LOCF), was used.

Results are presented by the following treatment regimen groups (see Section 3.1 for details): BID (stayed on this regimen for entire study), BID-to-TID (started out as BID but up-titrated to TID after day 30), TID (stayed on this regimen for entire study), and BID plus BID-to-TID ((b) (4)). Primary efficacy analyses are also presented by two body mass index (BMI) categories [< 30 kg/m^2 and ≥ 30 kg/m^2] to assess if efficacy is different in those subjects who are heavy.

Supportive Secondary Endpoints

The supportive secondary efficacy endpoints of lumbar spine BMD, left femur BMD, lean body mass, fat mass, and percent fat are descriptively summarized by the mean change from baseline at each time point (180 and 360

days) and its associated 95% confidence interval based on a t-test. Only those subjects who had both baseline and post-baseline values are included in these analyses.

Additional Analysis of Clinical Interest

Compliance is an additional descriptive analysis that is of clinical interest in evaluating efficacy and is reported as the number and percentage of subjects that fall within the following three compliance ranges: less than 80%; 80% to 120%, inclusive; and greater than 120%. Compliance was evaluated by weighing the study drug dispensers and reviewing the daily diary at each visit.

Sample Size

According to the Applicant, because this was an observational study, no formal sample size calculation was performed. A sample size of approximately 280 subjects (210 in the TBS-1 BID group and 70 in the TBS-1 TID group) was selected to provide a sufficient number of subjects to determine the efficacy and safety of TBS-1.

3.2.3 Study TBS-1-2011-03 Subject Disposition and Baseline Characteristics

Table 3.1 presents the number of randomized subjects and their disposition for study TBS-1-2011-03. Information is presented by group assignment at randomization (BID or TID group) and group status for the BID group after day 45. A total of 306 subjects were randomized and took study drug at 39 centers in the U.S.: 228 subjects to TBS-1 BID and 78 subjects to TBS-1. Of the 228 subjects who started in the TBS-1 BID group, (b) (4) % were up-titrated to receive TBS-1 TID, leaving (b) (4) subjects in the TBS-1 BID group.

The overall discontinuation rate in the TBS-1 BID group ((b) (4) %) was (b) (4) to the TBS-1 TID group (11.5%). The primary reasons for study discontinuation for both groups were withdrawal of consent (b) (4) % for TBS-1 BID and 5.1% for TBS-1 TID) and other (b) (4) % for TBS-1 BID and 1.3% for TBS-1 TID).

Table 3.1
Study TBS-1-2011-03: Randomization and Disposition of Subjects during the 90-Day Treatment Period

	Group Assignment at Randomization		BID Group Only (After Day 45)	
	TBS-1 BID	TBS-1 TID	TBS-1 BID	TBS-1 BID-to-TID
Number Randomized and Took Study Product (ITT)	228	78	(b) (4)	(b) (4)
Completed n (%)*	(b) (4)	69 (88.5)	(b) (4)	(b) (4)
Discontinued n (%)*	(b) (4)	9 (11.5)	(b) (4)	(b) (4)
Number Who Switched Regimens from BID to TID	(b) (4)	- (-)	(b) (4)	(b) (4)
Number with Post-baseline Data (ITT LOCF)	(b) (4)	73 (93.6)	(b) (4)	(b) (4)
Primary Reason for Discontinuation n (%)*:	(b) (4)		(b) (4)	(b) (4)
Withdrawal of Consent	(b) (4)	4 (5.1)	(b) (4)	(b) (4)
Adverse Event	(b) (4)	4 (5.1)	(b) (4)	(b) (4)
Lost to Follow-up	(b) (4)	0 (0.0)	(b) (4)	(b) (4)
Other	(b) (4)	1 (1.3)	(b) (4)	(b) (4)

Source: Figure 1, page 66 and Table 4, page 67, Study TBS-1-2011-3 report and Statistical Reviewer's listing.

* With respect to number of randomized subjects who took study product.

Both groups were similar in baseline and demographic characteristics. The majority of the subjects were Caucasian (88.2% for TBS-1 BID and 89.7% for TBS-1 TID) and were less than 65 years of age (81.1% for TBS-1 BID and 78.2% for TBS-1 TID). Overall, subjects had a mean age of 54.4 years (54.4 years for both groups), had a mean qualifying fasting serum total testosterone concentration of 200.8 ng/dL (197.6 ng/dL for TBS-1 BID and 210.4 ng/dL for TBS-1 TID), and had a mean duration of hypogonadism prior to screening of 4.6 years (4.5 years for TBS-1 BID and 5.0 years for TBS-1 TID).

There were 17 subjects who had no post-baseline data: 12 subjects in the BID group and 5 subjects in the TID group. For the 12 discontinuations in the BID group, nine were due to withdrawal of consent, two were due to lost to follow-up, and one was due to other reasons. Eleven of these BID subjects discontinued after 30 days or less of treatment and one subject discontinued after 62 days of treatment. For the 5 discontinuations in the TID group, two were due to adverse events, two were due to withdrawal of consent, and one was due to other

reasons. Four of these TID subjects discontinued after 30 days or less of treatment and one subject discontinued after 42 days of treatment.

3.2.4 Study TBS-1-2011-003 Results and Conclusions

Primary Efficacy Endpoint

This reviewer has verified the Applicant's results, presented in Table 3.2, based on the percentage of subjects with serum total testosterone level in the normal range at day 90. The results of a sensitivity analysis using the correct definition of the intent to treat (ITT) population are presented in Table 3.3. The pre-specified criteria for success is that at least 75% of treated subjects are within the specified normal serum testosterone concentration range and with lower bound of 95% confidence interval (CI) not less than 65%.

For the results in Table 3.2, the TBS-1 BID [redacted] (b) (4) [redacted] in their combined group. (b) (4) the TBS-1 TID group met the two success criteria with success rate of 90.4% and lower bound of 83.7%. Although the TBS-1 TID group result meets the success criteria, only 78 subjects were in this group, which is less than what the Division has required, at least 100 subjects, for a robust point estimate.

Table 3.2
Study TBS-1-2011-03: Percentage of Subjects with Serum Total Testosterone Level in the Normal Range [≥ 300 ng/dL and ≤ 1050 ng/dL] at Day 90 (Sponsor Definition of ITT Population*, LOCF)

TBS-1 Treatment Group**	n	Normal Level	Percentage (95% CI)
BID group	[redacted]	[redacted]	[redacted] (b) (4)
BID-to-TID group	[redacted]	[redacted]	[redacted]
BID group plus the BID-to-TID group	[redacted]	[redacted]	[redacted]
TID group	73	66	90.4 (83.7, 97.2)

Source: Table 12 on page 81 of Clinical Study Report TBS-1-2011-03, Applicant's submission dated 8-16-2013 (supporting document # 8), and Statistical Reviewer's calculations.

* ITT population are those subjects with a serum total testosterone level at Day 90 or LOCF of Day 30 value if Day 90 value was missing.

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

The sensitivity analysis results in Table 3.3 for the primary efficacy endpoint that used the correct definition of the ITT population. The TBS-1 BID group, BID-to-TID group, and their combination [redacted] (b) (4)

The success rate was: [redacted] (b) (4)

[redacted] (b) (4) in their combined group. (b) (4) the TBS-1 TID group met the two success criteria with success rate of 84.6% and lower bound of 76.6%. These results are similar to those in Table 3.2 above.

Table 3.3
Study TBS-1-2011-03: Percentage of Subjects with Serum Total Testosterone Level in the Normal Range [≥ 300 ng/dL and ≤ 1050 ng/dL] at Day 90 (Reviewer Definition of ITT Population*, LOCF)

Treatment Group**	n	Normal Level	Percentage (95% CI)
BID group	[redacted]	[redacted]	[redacted] (b) (4)
BID to TID group	[redacted]	[redacted]	[redacted]
BID group plus the BID to TID group	[redacted]	[redacted]	[redacted]
TID group	78	66	84.6 (76.6, 92.6)

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

Analyses by body mass index (BMI) categories of $< 30 \text{ kg/m}^2$ and $\geq 30 \text{ kg/m}^2$ are presented in Tables A.1 and A.2 in the Appendix. Efficacy does not appear to be affected by low or high BMI.

Supportive Secondary Efficacy Endpoints

Tables A.3 through A.7 in the Appendix present the results for four supportive secondary endpoints (BMD at both the lumbar spine and left femur and for lean body mass, fat mass, and percent fat) that were deemed clinically relevant by the clinical reviewer. These results were based on those subjects who had both baseline and post-baseline values. Over time, the number of these subjects decreased dramatically. For example, for lumbar spine BMD, there were 102 subjects at day 180 and 21 subjects at day 360. Although no definitive conclusions can be drawn, we can describe what the available data tell us based on the point estimate and its 95% C.I. For each time point (180 days and 360 days), there was no change compared to baseline for each treatment regimen group in BMD at both the lumbar spine and left femur, in lean body mass, in fat mass, and in percent fat.

Additional Clinical Endpoint

One clinical endpoint of interest for exploring the lack of efficacy in the TBS-1 BID and BID-to-TID groups is compliance. Compliance is descriptively reported by the number and percentage of subjects that fall within the following three compliance ranges: less than 80%; 80% to 120%, inclusive; and greater than 120%. A subject is considered to be compliant if they are within the 80% to 120% compliance range. Compliance results are presented in Table 3.4.

Table 3.4
Study TBS-1-2011-03: Number and Percentage of Subjects within Three Different Compliance Ranges at Day 90
(Sponsor Definition of ITT Population)

TBS-1 Treatment Group	Compliance Range		
	Less than 80%	80% to 120%	Greater than 120%
BID group	(b) (4)		
BID-to-TID group			
BID group plus the BID-to-TID group			
TID group	7 (9.1%)	68 (88.3%)	2 (2.6%)

Source: Table from page 1 of cover letter of sponsor submission dated October 1, 2013, supporting doc number 11 (10-04-2013). From an IR request dated 9-23-2013.

Note that one subject in the ITT population, in the BID group, was not included in the analysis. Compliance could not be calculated as more than one dispenser weight was missing.

About 80% or greater of subjects in each of the four groups listed in the table were compliant. Although compliance was “good” (80% or more of subjects in the 80% to 120% range), not enough men in either the BID group or the BID-to-TID group or their combined group achieved a normal T-level. Given the “good” compliance results, it is not clear why the compliance and efficacy results do not coincide for all groups other than the TBS-1 TID group.

3.3 Evaluation of Safety

For information about the evaluation of safety, refer to the clinical evaluation of safety section.

4. FINDINGS IN SUBGROUP POPULATIONS

No subgroup analyses by gender or geographic region were necessary because all subjects were men and the study was conducted in the United States. There were too few non-Caucasian subjects ($< 12\%$) and too few subjects less than 65 years ($< 22\%$) to conclude if the efficacy endpoint was similar by race or age group. The clinical reviewer did not identify any additional subgroup of interest for statistical review.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

No major statistical issues were identified in this submission. The Applicant adhered to statistical methods for the primary endpoint as specified in the protocol and Statistical Analysis Plan.

There was one clinical issue identified that affected how the efficacy results were to be presented for clinical interpretation. The protocol did not specify how to present the efficacy results based on treatment regimen. The clinical team determined that based on the instructions for use provided in the label, the data should be presented by those subjects who remained on the twice a day (BID) regimen throughout the study, those subjects who started in the BID regimen and then were up-titrated to the three times a day (TID) regimen, all subjects randomized to the BID regimen at baseline (the combination of the always on BID regimen and the BID-to-TID regimen), and those subjects who remained on the TID regimen throughout the study.

5.2 Collective Evidence

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 (17 beta-Hydroxy-4androst-3-on)] for the treatment of adult male hypogonadism based on the proportion of men who achieved total serum testosterone levels within the normal range. The proportion of men with normal total serum testosterone levels was within the pre-specified success criteria for the TID regimen. The men who received the twice a day (BID) dosage regimen or the BID up-titrated to TID dosage regimen (b) (4) for proportions of men with normal total serum testosterone levels.

The evidence is based on achieving total serum testosterone levels within the normal range after 90 days of treatment in at least 75% of men with the lower bound of the 95% confidence interval for the estimate of the proportion of men achieving the total serum testosterone levels within the normal range no less than 65%. The normal range of total serum testosterone level is defined as ≥ 300 ng/dL and ≤ 1050 ng/dL. In addition, those men who were randomized to the BID dosage regimen had their dosage up-titrated to the TID regimen if their testosterone levels were not in the normal range after 30 days of treatment.

TBS-1 increased the total serum testosterone level to within normal range in 90.4% of men taking TBS-1 three times a day (95% C.I. of 83.7% to 97.2%). For the other two dose regimen groups, TBS-1 increased the total serum testosterone level to within normal range in (b) (4) of men taking TBS-1 twice a day and then changed to three times a day (b) (4). Although the TBS-1 TID group result met the success criteria, only 78 subjects were in this group, which is less than what the Division has required, at least 100 subjects, for a robust point estimate.

5.2 Conclusions and Recommendations

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 (17 beta-Hydroxy-4androst-3-on)] for the treatment of adult male hypogonadism.

6. APPENDIX

Table A.1
Study TBS-1-2011-03: 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 (Sponsor 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	39	33	84.6 (69.5, 94.1)
BMI ≥ 30 kg/m²			
BID group			(b) (4)
BID-to-TID group			
BID group plus the BID-to-TID group			
TID group	34	33	97.1 (84.7, 99.9)

Source: Statistical Reviewer's calculations

* ITT population are those subjects with a serum total testosterone level at Day 90 or LOCF of Day 30 value if Day 90 value was missing.

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

Table A.2
Study TBS-1-2011-03: 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 (Reviewer 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.

Table A.3
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% CI)			
	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.

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

Table A.4
Study TBS-1-2011-03: Summary of Left Femur 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% CI)			
	n	At Day 180	n	At Day 360
BID group	(b) (4)			
BID to TID group				
TID group	57	-0.003 (-0.009, 0.003)	12	0.007 (-0.006, 0.019)

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

* BMD value based on the total BMD value.

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

Table A.5
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% CI)			
	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.

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

Table A.6
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% CI)			
	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.
 BID = twice daily; C_{avg} = average concentration; CI = confidence interval; TID = three times daily

Table A.7
Study TBS-1-2011-03: Summary of Percent Fat (PF) by Treatment and Visit
(All ITT Subjects with Both Baseline and Post-Baseline Values at Each Time Point)

Treatment Group	PF (%) Mean Change from Baseline (95% CI)			
	n	At Day 180	n	At Day 360
BID group	(b) (4)			
BID to TID group				
TID group	54	-0.14 (-0.80, 0.51)	10	-0.17 (-1.48, 1.14)

Source: Statistical Reviewer's listing. 95% confidence interval based on t-test.
 BID = twice daily; C_{avg} = average concentration; CI = confidence interval; TID = three times daily

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/s/

SONIA CASTILLO
04/03/2014

MAHBOOB SOBHAN
04/04/2014

STATISTICS FILING CHECKLIST FOR A NEW NDA

NDA Number: 205488 / Supporting Doc. 001

Applicant: Trimel BioPharma SRL

Stamp Date: 4-29-2013

Drug Name: 4.5% TBS-1 [testosterone (17 beta-Hydroxy-4androst-3-on) nasal gel]

NDA Type: Standard

Indication: Treatment of hypogonadism

The one study submitted for the indication of treatment of hypogonadism is summarized in the table below.

Brief Summary of Clinical Study for 4.5% TBS-1

Study Number (Country / #) Dates of Study Conduct	Subject Population	Treatment	ITT ¹ Population	Design ²
TBS-1-2011-03 (United States / 39) Sept 2011 to Oct 2012	Men with clinically verified hypogonadism (total serum testosterone levels <300 ng/dL)	4.5% TBS-1 (5.5 mg) BID 4.5% TBS-1 (5.5 mg) TID Total	228 78 306	OL, R, PG, MC, 90 days

Source: Statistical Reviewer's listing.

¹ ITT = Intent to Treat, received investigational product

² OL = Open-label, R = Randomized, PG = Parallel Group, MC = Multicenter

On **initial** overview of the NDA application for Refuse-To-File (RTF):

	Content Parameter for RTF	Yes	No	NA	Comments
1A	Paper Submission			X	
1B	Electronic Submission: Indexing and reference links within the electronic submission are sufficient to permit navigation through the submission, including access to reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.		X		All subjects were men; no analyses by racial or geriatric subgroups presented.
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			Program files are not present; SAS can open data sets

THE STATISTICAL SECTION OF THE APPLICATION IS FILEABLE Yes

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses were pre-specified in protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

Requests to the Applicant for the 74-day letter: There are no requests for the 74-day letter.

Requests for information that are not hold issues: At this time, there are no requests for information based on this cursory review of the application.

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/s/

SONIA CASTILLO
06/12/2013