Statistical Analysis Plan for Natesto™

Protocol #: NAT-2016-01

A 150-DAY, PROSPECTIVE, PHASE 4, OPEN-LABEL STUDY, EVALUATING PATIENT SATISFACTION AND SYMPTOM IMPROVEMENT WHEN TREATING MALE HYPOGONADISM WITH TESTOSTERONE NASAL GEL (Natesto™) (MY-T STUDY)

Investigational Product: Testosterone nasal gel 4.5% w/w (Natesto™)

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A 150-DAY, PROSPECTIVE, PHASE 4, OPEN-LABEL STUDY, EVALUATING PATIENT SATISFACTION AND SYMPTOM IMPROVEMENT WHEN TREATING MALE HYPOGONADISM WITH TESTOSTERONE NASAL GEL (Natesto™) (MY-T STUDY)

Approval Sheet

This Statistical Analysis Plan (SAP) and accompanying Table Mock-Up (TMU) document has been reviewed and approved by the following personnel:

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1.0 INTRODUCTION

This document provides a detailed description of the statistical methods and procedures to be implemented during the analysis of Acerus Pharmaceutical Corporation protocol # NAT-2016-01. The proposed methods and approaches to the data analysis should be viewed as flexible if the data suggest and warrant deviations from this plan. However, any deviations from this analysis plan must be substantiated by sound statistical rationale and documented in the final clinical study report.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of the study is to measure patient satisfaction with testosterone replacement therapy before (for non-naïve patients), during and after treatment with Natesto™.

2.2 Secondary Objectives

The secondary objectives of this study are to evaluate the following:

1. Improvement in hypogonadism symptoms
2. Patient treatment preference versus prior testosterone replacement therapy
3. Frequency of daily dose of Natesto™
4. Safety monitoring

2.3 Exploratory Objectives

Exploratory objectives will include analysis of the rate of change of the primary or secondary efficacy measures over the treatment period be that 90 days for patients on Natesto™ BID or 120 days for patients on Natesto™ TID.

3.0 STUDY OVERVIEW

This is a phase 4, multi-centre study consisting of two study periods and a post study follow-up.

90-Day Treatment Period: With potential extension by 30 days for those patients requiring a dose increase, as determined by the treating physician. Participants receiving 122.5mg of Natesto™ (5.5 mg of testosterone) per nostril twice daily may have an increased daily dose adjustment on Day 90, based on their hypogonadism symptoms.

1-Day Study Completion Period: Patient will return to the site for examination, discussion of symptoms with physician and questionnaire completion. Serum testosterone levels will be determined for all patients on Day 90 (BID dose) and on Day 120 for the TID patients.

Post Study Follow-Up: All study patients will be followed up at Day 150 after the Treatment Phase to determine if they have continued using NATESTO and why (or why not?).

Schedule of Procedures

Study Phase	**Treatment Period**						
	Treatment Start	**Efficacy Analysis**				**Post Study Follow Up**	**Early Withdrawal/ Termination**
	Day 0	**Day 30 +/- 3 days**	**Day 60 +/- 3 days**	**End of Study: BID Patients Day 90 +/- 3 days**	**End of Study: TID Patients Day 120 +/- 3 days**	**Day 150 +/- 3 days**	
Visit	**1**	**2**	**3**	**4[a]**	**5[b]**	**6**	
Location/Type	**clinic**	**telephone**	**telephone**	**clinic**	**clinic**	**telephone**	**clinic**
Study Procedures:							
Inclusion/exclusion criteria	x						
Informed consent	x						
Medical history	x			x	x		
Demographics	x						
Physical examination + nasal exam	x			x	x		x
Height and weight	x			x	x		x
Vital signs (HR, BP, RR, and temperature)	x			x	x		x
Serum total testosterone plus safety labs	x[c]			x	x[d]		x
Participant training on NATESTO administration	x						
Provide Study Drug Access Card for NATESTO	x						
Provide Pharmacy Prescription	x			x[g]			
Potential study drug daily dose increase to TID				x			
TSQM	x[e]	x	x	x	x		x
qADAM	x[f]	x	x	x	x		x
Patient Preference + Use	x			x	x		x
Concomitant medications	x	x	x	x	x		x
Assess adverse events	x	x	x	x	x		x
Assess voluntary treatment continuation						x	

a. All patients are required to complete Visit 4
b. Only patients assigned to NATESTO TID are required to complete Visit 5
c. Naïve patients will require confirmation of hypogonadism by serum testosterone within the last 6 months
d. Only patients who continued on TID
e. TSQM to be completed by non-naïve patients only
f. qADAM to be completed by all patients
g. Patients who are assigned to NATESTO TID will be provided with a new Pharmacy Prescription increasing their dosage to TID

4.0 SAMPLE SIZE

A sample size of approximately 100 participants will be selected to provide a sufficient number of participants for the analysis. Since this is an observational study, no formal sample size calculation will be performed. Interim analysis and sample size re-estimation may be performed after results are acquired from 50 and 75 patients.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Efficacy Endpoints

Primary efficacy is the self-reported patient satisfaction with treatment assessed by the Treatment Satisfaction Questionnaire for Medication (TSQM), a validated, 9-item instrument with domains for Effectiveness, Convenience and Global Satisfaction.

The primary efficacy endpoints are:

- change in satisfaction for each TSQM domain from Visit 1 (Day 0) to Visit 4 (Day 90) for non-naïve BID patients
- change in satisfaction for each TSQM domain from Visit 1 (Day 0) to Visit 5 (Day 120) for non-naïve TID patients

5.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- change in satisfaction for each TSQM domain from Visit 2 (Day 30) to Visit 4 (Day 90) for naïve BID patients
- change in satisfaction for each TSQM domain from Visit 2 (Day 30) to Visit 5 (Day 120) for naïve TID patients

- change in total qADAM score from Visit 1 (Day 0) to Visit 4 (Day 90) for non-naïve BID patients
- change in total qADAM score from Visit 1 (Day 0) to Visit 5 (Day 120) for non-naïve TID patients
- change in total qADAM score from Visit 1 (Day 0) to Visit 4 (Day 90) for naïve BID patients
- change in total qADAM score from Visit 1 (Day 0) to Visit 5 (Day 120) for naïve TID patients
- change in total qADAM score from Visit 1 (Day 0) to Visit 5 (Day 120) for non-naïve ALL patients
- change in total qADAM score from Visit 1 (Day 0) to Visit 5 (Day 120) for naïve ALL patients
- change in total qADAM score from Visit 1 (Day 0) to Visit 5 (Day 120) for non-naïve and naïve ALL patients

- patient preference of therapy as measured by Part A of the Treatment Preference and Use Questionnaire at Visit 1 (Day 0) for the following groups of patients:
  - non-naïve and naive ALL
  - non-naïve ALL
  - naïve ALL
  - non-naïve BID
  - naïve BID
  - non-naïve TID
  - naïve TID
- patient preference of therapy as measured by Part B of the Treatment Preference and Use Questionnaire for the following groups of non-naïve patients:
  - BID at Visit 4 (Day 90)
  - TID at Visit 4 (Day 90)
  - TID at Visit 5 (Day 120)
- patient preference of therapy as measured by Part C of the Treatment Preference and Use Questionnaire for the following groups of naïve patients:
  - BID at Visit 4 (Day 90)
  - TID at Visit 4 (Day 90)
  - TID at Visit 5 (Day 120)
- Natesto™ dosing frequency by hypogonadism treatment status (naïve/non-naïve) assigned at Visit 4 (Day 90)

5.3 Safety Endpoints

Safety endpoints will include:

- adverse events recorded during the study
- clinical laboratory measurements at Visit 1 (Day 0), Visit 4 (Day 90) , Visit 5 (Day 120) and Early Termination
- vitals sign measurements at Visit 1 (Day 0), Visit 4 (Day 90), Visit 5 (Day 120) and Early Termination
- physical examination at Visit 1 (Day 0), Visit 4 (Day 90), Visit 5 (Day 120), and Early Termination

5.4 Exploratory Endpoints

Exploratory endpoints will include:

- change in satisfaction for each TSQM domain from Visit 1 (Day 0) to Visit 5 (Day 120) for non-naïve ALL patients
- change in satisfaction for each TSQM domain from Visit 2 (Day 30) to Visit 5 (Day 120) for naïve ALL patients

6.0 ANALYSIS POPULATION AND ANALYSIS SUBSETS

6.1 All Participants Population

The All Participants population includes all patients who signed the informed consent form and were entered into the MY-T study web-based application. Study enrollment and patient disposition will be reported using the All Participants population.

6.2 BID Intent-to-Treat (ITT) Population

The BID ITT population includes all patients who received at least one dose of study drug, are part of the BID treatment group and have a valid post-dose efficacy measurement at Visit 2 (Day 30) or Visit 3 (Day 60) or Visit 4 (Day 90). Data will be analysed using the BID ITT population as per the Table Mock-Up (TMU) document.

6.3 TID Intent-to-Treat (ITT) Population

The TID ITT population includes all patients who received at least one dose of study drug, are part of the TID treatment group and have a valid post-dose efficacy measurement at Visit 2 (Day 30) or Visit 3 (Day 60) or Visit 4 (Day 90) or Visit 5 (Day 120). Data will be analysed using the TID ITT population as per the Table Mock-Up (TMU) document.

6.4 Intent-to-Treat (ITT) Population

The ITT population includes all patients who are included in either the BID ITT or TID ITT population. Data will be analysed using the ITT population as per the Table Mock-Up (TMU) document.

6.5 Safety Population

The Safety population includes all patients who received at least one dose of the study drug. All safety data including adverse events, physical examination parameters, vital signs, total testosterone and laboratory data will be analysed using the Safety population.

6.6 BID Per-Protocol (PP) Population

The BID PP population includes all BID ITT patients who completed the 90-day (Visit 4) Treatment Period without any major protocol deviations. Data will be analysed using the BID PP population as per the Table Mock-Up (TMU) document.

6.7 TID Per-Protocol (PP) Population

The TID PP population includes all TID ITT patients who completed the 120-day (Visit 5) Treatment Period without any major protocol deviations. Data will be analysed using the TID PP population as per the Table Mock-Up (TMU) document.

6.8 Per-Protocol (PP) Population

The PP population includes all patients who are included in either the BID PP or TID PP population. Data will be analysed using the PP population as per the Table Mock-Up (TMU) document.

7.0 DATA CONVENTIONS

7.1 Definitions

Visit 1 (Day 0) is defined as the day in which the patient provides informed consent and starts the study. All study days are determined relative to Visit 1 (Day 0).

End of treatment is defined as the day on which the last dose of treatment is taken. This date was not collected for this study.

End of study is defined as the last day on which data were collected from the patient. Using the Early Termination Visit eCRF, it is the date of early termination. Using the Visit 6 - Post Study Follow-Up (Day 150) eCRF, it is the post study follow-up date. Otherwise, it is the date of last contact, if the patient was lost to follow-up, or the date of death, if the patient died.

Baseline serum testosterone values will be defined as those values recorded on Visit 1 (Day 0). Naive patients were asked for 2 measurements (average used in analysis) and non-naive patients were asked for 1 measurement at Baseline (Visit 1/Day 0).

Serum Testosterone will be reported in (nmol/L). If value is reported in (ng/dL) then value will be multiplied by 0.0347 to convert to (nmol/L).

Testosterone collected in (pmol/L) will be considered Free Testosterone and will not be used in any analyses.

Hematocrit will be reported in (%). Values will be multiplied by 1 and if the value is less than 1 then the value will be multiplied by 100.

Total Cholesterol will be reported in (mmol/L). If value is reported in (mg/dL) then value will be divided by 38.67 to convert to (mmol/L).

LDL will be reported in (mmol/L). If value is reported in (mg/dL) then value will be divided by 38.67 to convert to (mmol/L).

HDL will be reported in (mmol/L). If value is reported in (mg/dL) then value will be divided by 38.67 to convert to (mmol/L).

Triglycerides will be reported in (mmol/L). If value is reported in (mg/dL) then value will be divided by 88.57 to convert to (mmol/L).

Hemoglobin will be reported in (g/L). If value is reported in (g/dL) then value will be divided by 0.1 to convert to (g/L).

ALT and AST will be reported in (U/L).

Study duration (days) will be defined as the (end of study date – date of informed consent + 1).

The ALL treatment group will be defined as patients who were either naïve or non-naïve.

The BID treatment group will be defined as patients who were either naïve or non-naïve and did not titrate to TID (Visit 5/Day 120).

The TID treatment group will be defined as patients who were either naïve or non-naïve and did titrate up to TID (Visit 5/Day 120).

7.2 Visit Windows

The visit window for all post baseline visits was a $\pm$3 day window relative to the expected nominal time point except for Early Termination visit. For example, Visit 2 is Day 30±3. For the purpose of the statistical analyses data entered at the nominal time points will be used (Visit 1/Day 0, Visit 2/Day 30, Visit 3/Day 60, Visit 4/Day 90, Visit 5/Day 120, Visit 6/Day 150 and Early Termination).

7.3 Missing Data

Dates with missing day will be imputed as the 15th. Dates will both missing day and month will be imputed as July 1st. Date of hypogonadism diagnosis will be imputed.

Missing TSQM domain scores for both the BID and TID treatment groups will be imputed using LOCF (Last Observation Carried Forward). For LOCF to apply there must be at least a Visit 2 domain score available so that the patient had sufficient exposure to give a measurable change. The TSQM domain scores will be calculated based on the LOCF domain. Summaries for paired change from Visit 1/Day 0 will require both TSQM domain scores at Visit 1/Day 0 and Visit 2/Day 30 to be available to be included in output. Summaries for paired change from Visit 2/Day 30 will require the TSQM domain scores at Visit 2/Day 30 to be available to be included in output.

Missing qADAM questions for both the BID and TID treatment groups will be imputed using LOCF (Last Observation Carried Forward). For LOCF to apply there must be at least a Visit 2 question available so that the patient had sufficient exposure to give a measurable change. The total qADAM score will be calculated based on the LOCF items. Summaries for paired change

from Visit 1/Day 0 will require both total qADAM scores at Visit 1/Day 0 and Visit 2/Day 30 to be available to be included in output.

7.4 Early Terminations

Patients who withdraw from the study before Visit 6 (Day 150) are considered "early terminations."

8.0 ANALYSIS STRATEGY

A Table Mock-Up (TMU) document which will illustrate the details of presentation and analysis for data collected in this study will accompany this document. A brief discussion of the presentation, planned inferences, and statistical methods follows below. Data not presented in the TMU document will be provided in listings.

Continuous variables will be summarized descriptively by number of observations, number of missing observations, mean, standard deviation, median, 1st quartile, 3rd quartile, minimum and maximum. Categorical variables will be summarized descriptively as frequency counts and percentages.

A number of p-values may be presented in the reported tables for exploratory purposes. Statistical testing will be performed at the two-sided 0.05 significance level unless otherwise specified in the sections that follow. These p-values will not be adjusted for multiple comparisons.

9.0 EFFICACY ANALYSES

9.1 Primary Efficacy Analyses

The primary efficacy analyses will be performed using the ITT and the respective PP populations.

<u>BID Treatment Group</u>:
TSQM domain scores at Visit1, Visit 2, Visit 3 and Visit 4 will be summarized and presented descriptively for non-naïve patients. There are three domains which include effectiveness (3 items), convenience (3 items) and global satisfaction (3 items).

TSQM domain change from baseline (Visit 1) scores at Visit 2, Visit 3 and Visit 4 (primary endpoint) will be summarized and presented descriptively for non-naïve patients using 2 different approaches, LOCF and no LOCF. Change from baseline scores will be analysed using a two-sided paired t-test or a non-parametric equivalent if warranted by the data.

<u>TID Treatment Group</u>:

TSQM domain scores at Visit 1, Visit 2, Visit 3, Visit 4 and Visit 5 will be summarized and presented descriptively for non-naïve patients. There are three domains which include effectiveness (3 items), convenience (3 items) and global satisfaction (3 items).

TSQM domain change from baseline (Visit 1) scores at Visit 2, Visit 3, Visit 4 and Visit 5 (primary endpoint) will be summarized and presented descriptively for non-naïve patients using 2 different approaches, LOCF and no LOCF. Change from baseline scores will be analysed using a two-sided paired t-test or a non-parametric equivalent if warranted by the data.

9.2 Secondary Efficacy Analyses

The following secondary efficacy analyses will be performed using the ITT and the respective PP populations where indicated.

BID Treatment Group:
TSQM domain scores at Visit 2, Visit 3 and Visit 4 will be summarized and presented descriptively for naïve patients. There are three domains which include effectiveness (3 items), convenience (3 items) and global satisfaction (3 items). (ITT/PP)

TSQM domain change from baseline (Visit 2) scores at Visit 3 and Visit 4 (secondary endpoint) will be summarized and presented descriptively for naïve patients using 2 different approaches, LOCF and no LOCF. Change from baseline scores will be analysed using a two-sided paired t-test or a non-parametric equivalent if warranted by the data. (ITT/PP)

Total qADAM scores at Visit 1, Visit 2, Visit 3 and Visit 4 will be summarized and presented descriptively for non-naïve patients. (ITT/PP)

Total qADAM change from baseline (Visit 1) scores at Visit 2, Visit 3 and Visit 4 will be summarized and presented descriptively for non-naïve patients using 2 different approaches, LOCF and no LOCF. Change from baseline scores will be analysed using a two-sided paired t-test or a non-parametric equivalent if warranted by the data. (ITT/PP)

Total qADAM scores at Visit 1, Visit 2, Visit 3 and Visit 4 will be summarized and presented descriptively for naïve patients. (ITT/PP)

Total qADAM change from baseline (Visit 1) scores at Visit 2, Visit 3 and Visit 4 will be summarized and presented descriptively for naïve patients using 2 different approaches, LOCF and no LOCF. Change from baseline scores will be analysed using a two-sided paired t-test or a non-parametric equivalent if warranted by the data. (ITT/PP)

Part A questions 5, 6, 7, 8, 9, 10 and 11 of the Patient Preference and Use Questionnaire at Visit 1 will be summarized and presented descriptively/categorically for non-naïve and naïve patients. (ITT)

TID Treatment Group:
TSQM domain scores at Visit 2, Visit 3, Visit 4 and Visit 5 will be summarized and presented descriptively for naïve patients. There are three domains which include effectiveness (3 items), convenience (3 items) and global satisfaction (3 items). (ITT/PP)

TSQM domain change from baseline (Visit 2) scores at Visit 3, Visit 4 and Visit 5 (secondary endpoint) will be summarized and presented descriptively for naïve patients using 2 different approaches, LOCF and no LOCF. Change from baseline scores will be analysed using a two-sided paired t-test or a non-parametric equivalent if warranted by the data. (ITT/PP)

Total qADAM scores at Visit 1, Visit 2, Visit 3, Visit 4 and Visit 5 will be summarized and presented descriptively for non-naïve patients. (ITT/PP)

Total qADAM change from baseline (Visit 1) scores at Visit 2, Visit 3, Visit 4 and Visit 5 will be summarized and presented descriptively for non-naïve patients using 2 different approaches, LOCF and no LOCF. Change from baseline scores will be analysed using a two-sided paired t-test or a non-parametric equivalent if warranted by the data. (ITT/PP)

Total qADAM scores at Visit 1, Visit 2, Visit 3, Visit 4 and Visit 5 will be summarized and presented descriptively for naïve patients. (ITT/PP)

Total qADAM change from baseline (Visit 1) scores at Visit 2, Visit 3, Visit 4 and Visit 5 will be summarized and presented descriptively for naïve patients using 2 different approaches, LOCF and no LOCF. Change from baseline scores will be analysed using a two-sided paired t-test or a non-parametric equivalent if warranted by the data. (ITT/PP)

Part A questions 5, 6, 7, 8, 9, 10 and 11 of the Patient Preference and Use Questionnaire at Visit 1 will be summarized and presented descriptively/categorically for non-naïve and naïve patients. (ITT)

ALL Treatment Group:
Total qADAM scores at Visit 1, Visit 2, Visit 3, Visit 4 and Visit 5 will be summarized and presented descriptively for non-naïve patients. (ITT/PP)

Total qADAM change from baseline (Visit 1) scores at Visit 2, Visit 3, Visit 4 and Visit 5 will be summarized and presented descriptively for non-naïve patients using 2 different approaches, LOCF and no LOCF. Change from baseline scores will be analysed using a two-sided paired t-test or a non-parametric equivalent if warranted by the data. (ITT/PP)

Total qADAM scores at Visit 1, Visit 2, Visit 3, Visit 4 and Visit 5 will be summarized and presented descriptively for naïve patients. (ITT/PP)

Total qADAM change from baseline (Visit 1) scores at Visit 2, Visit 3, Visit 4 and Visit 5 will be summarized and presented descriptively for naïve patients using 2 different approaches, LOCF

and no LOCF. Change from baseline scores will be analysed using a two-sided paired t-test or a non-parametric equivalent if warranted by the data. (ITT/PP)

Total qADAM scores at Visit 1, Visit 2, Visit 3, Visit 4 and Visit 5 will be summarized and presented descriptively for non-naïve and naïve patients combined. (ITT/PP)

Total qADAM change from baseline (Visit 1) scores at Visit 2, Visit 3, Visit 4 and Visit 5 will be summarized and presented descriptively for non-naïve and naïve patients combined using 2 different approaches, LOCF and no LOCF. Change from baseline scores will be analysed using a two-sided paired t-test or a non-parametric equivalent if warranted by the data. (ITT/PP)

Part A questions 5, 6, 7, 8, 9, 10 and 11 of the Patient Preference and Use Questionnaire at Visit 1 will be summarized and presented descriptively/categorically for non-naïve, naïve, and non-naïve and naïve patients combined. (ITT)

Various Treatment Groups:
Part B questions 5, 6, 7, 8, 9 and 12 of the Patient Preference and Use Questionnaire will be summarized and presented descriptively/categorically for non-naïve patients for the following groups and time points:

- BID at Visit 4 (ITT)
- TID at Visit 4 (ITT)
- TID at Visit 5 (ITT)

Part B questions 5, 6, 7, 8 and 11 of the Patient Preference and Use Questionnaire will be summarized and presented descriptively/categorically for naïve patients for the following groups and time points:

- BID at Visit 4 (ITT)
- TID at Visit 4 (ITT)
- TID at Visit 5 (ITT)

Natesto™ dosing frequency (BID/TID) by hypogonadism treatment status (naïve/non-naïve) assigned at Visit 4 will be summarized and presented categorically for non-naïve and naïve patients combined. (ITT/PP)

9.3 Exploratory Analyses

ALL Treatment Group:
TSQM domain scores at Visit 1, Visit 2, Visit 3, Visit 4 and Visit 5 will be summarized and presented descriptively for non-naïve patients. There are three domains which include effectiveness (3 items), convenience (3 items) and global satisfaction (3 items).

TSQM domain change from baseline (Visit 1) scores at Visit 2, Visit 3, Visit 4 and Visit 5 will be summarized and presented descriptively for non-naïve patients using 2 different approaches, LOCF and no LOCF. Change from baseline scores will be analysed using a two-sided paired t-test or a non-parametric equivalent if warranted by the data.

TSQM domain scores at Visit 2, Visit 3, Visit 4 and Visit 5 will be summarized and presented descriptively for naïve patients. There are three domains which include effectiveness (3 items), convenience (3 items) and global satisfaction (3 items).

TSQM domain change from baseline (Visit 2) scores at Visit 3, Visit 4 and Visit 5 will be summarized and presented descriptively for naïve patients using 2 different approaches, LOCF and no LOCF. Change from baseline scores will be analysed using a two-sided paired t-test or a non-parametric equivalent if warranted by the data.

10.0 SAFETY ANALYSES

The following safety analyses will be performed using the Safety population.

10.1 Adverse Events

Adverse event data will be tabulated separately for each treatment group (ALL, BID, TID) by system organ class and preferred term. Adverse events will be summarized by presenting counts and percentage of patients (each patient contributes a single count to a category) and the total number of events in each system organ class and in each system organ class/preferred term.

In addition, adverse event data with a possible drug relationship (possible, probable, definitely related) will be tabulated separately for each treatment group (ALL, BID, TID) by system organ class and preferred term. Adverse events will be summarized in a similar manner as above.

As well, adverse event data will be tabulated separately for each treatment group (ALL, BID, TID) by system organ class, preferred term and severity (mild, moderate, severe). Adverse events will be summarized by presenting counts and percentage of patients (each patient contributes a single count to a category) and the total number of events in each system organ class by severity and in each system organ class/preferred term by severity.

The Medical Dictionary for Regulatory Activities (MedDRA™ version 20.1) will be utilized for the coding of adverse events.

All adverse events that occurred on or after the date of informed consent up to 30 days after the end of study date will be summarized.

Serious adverse events will not be tabulated due to the expected small number of events. Narratives will be provided for serious adverse events.

10.2 Laboratory Data

Laboratory data (Hematocrit (%), Total Cholesterol (mmol/L), LDL (mmol/L), HDL (mmol/L), Triglycerides (mmol/L), Hemoglobin (g/L), ALT (U/L), AST (U/L)) at Visit 1, Visit 4, Visit 5

and Early Terminations will be summarized and presented descriptively for the ALL and TID treatment groups.

Laboratory data change from baseline (Visit 1) results at Visit 4, Visit 5 and Early Terminations will be summarized and presented descriptively for the ALL and TID treatment groups. Change from baseline results will be analysed using a two-sided paired t-test or a non-parametric equivalent if warranted by the data.

Laboratory data (Hematocrit (%), Total Cholesterol (mmol/L), LDL (mmol/L), HDL (mmol/L), Triglycerides (mmol/L), Hemoglobin (g/L), ALT (U/L), AST (U/L)) at Visit 1, Visit 4 and Early Terminations will be summarized and presented descriptively for the BID treatment group.

Laboratory data change from baseline (Visit 1) results at Visit 4 and Early Terminations will be summarized and presented descriptively for the BID treatment group. Change from baseline results will be analysed using a two-sided paired t-test or a non-parametric equivalent if warranted by the data.

10.3 Testosterone Data

Testosterone data (nmol/L) at Visit 1, Visit 4, Visit 5 and Early Terminations will be summarized and presented descriptively for the non-naïve TID, naïve TID, non-naïve ALL, naïve ALL and the non-naïve and naïve combined ALL treatment groups.

Testosterone data change from baseline (Visit 1) results at Visit 4, Visit 5 and Early Terminations will be summarized and presented descriptively for the non-naïve TID, naïve TID, non-naïve ALL, naïve ALL and the non-naïve and naïve combined ALL treatment groups. Change from baseline results will be analysed using a two-sided paired t-test or a non-parametric equivalent if warranted by the data.

Testosterone data (nmol/L) at Visit 1, Visit 4, Visit 5 and Early Terminations will be summarized and presented descriptively for the non-naïve BID and naïve BID treatment groups.

Testosterone data change from baseline (Visit 1) results at Visit 4, Visit 5 and Early Terminations will be summarized and presented descriptively for the non-naïve BID and naïve BID treatment groups. Change from baseline results will be analysed using a two-sided paired t-test or a non-parametric equivalent if warranted by the data.

10.4 Vital Signs

Vital signs (Systolic Blood Pressure (mmHg), Diastolic Blood Pressure (mmHg), Heart Rate (beats/minute), Oral/Tympanic Temperature (Celcuis), BMI (kg/m*m)) at Visit 1, Visit 4 and Early Terminations will be summarized and presented descriptively for the BID treatment group.

Vital signs (Systolic Blood Pressure (mmHg), Diastolic Blood Pressure (mmHg), Heart Rate (beats/minute), Oral/Tympanic Temperature (Celcuis), BMI (kg/m*m)) at Visit 1, Visit 4, Visit 5

and Early Terminations will be summarized and presented descriptively for the ALL and TID treatment groups.

10.5 Physical Examination

Physical examination (General Appearance, Skin, Nose, Head/Neck, Heart, Lungs, Abdomen, Neuromuscular, Extremities, Other) at Visit 1, Visit 4, Visit 5 and Early Terminations will be summarized and presented categorically for the ALL treatment group.

11.0 COMPARABILITY ANALYSES

11.1 Demographic Characteristics

Quantitative and/or categorical summaries will be presented for age, height, weight, bmi, race, patient smoke and patient drink alcohol by overall, naïve and non-naïve patients.

11.2 Disease Characteristics

Quantitative and/or categorical summaries will be presented for hypogonadal treatment status, baseline testosterone, and age of hypogonadism diagnosis by overall, naïve and non-naïve patients.

11.3 Medical/Surgical History

Categorical summaries (% yes) will be presented for each body system by overall, naïve and non-naïve patients.

11.4 Study Duration

Quantitative summaries will be presented for study duration (days) by overall, naïve and non-naïve patients.

11.5 Concomitant Medications

Concomitant medications will be recorded at Day 0 (Visit 1) and reviewed at each subsequent visit until the end of study. All medications taken 30 days prior to Day 0 (Visit 1) and during the study period will be tabulated. Numbers and percentages of overall, naïve and non-naïve patients will be presented for concomitant medication data levels 3 and 5. Medication will be coded using the Anatomical-Therapeutic-Chemical (ATC) classification text from the WHO Drug Dictionary version January 2017.

12.0 RANDOMIZATION AND BLINDING

This was a phase 4 open-label study. Randomization and blinding was not performed.

13.0 INTERIM ANALYSIS

As stated in the protocol an interim analysis and sample size re-estimation may be performed after results are acquired from 50 and 75 patients.

14.0 ANALYSIS PROGRAMS and SOFTWARE

SAS® Version 9.2 or higher will be utilized for all analyses, data listings and figures.

The biostatistician will specify all summary programs for the study in a Table Mock-Up (TMU) document with Sponsor sign-off. The biostatistician will implement these specifications and then validate the output of each summary program. The same biostatistician will create a separate validation program for each summary output and the output from the summary program and the validation program will be compared.

15.0 REFERENCES

Not applicable.