CLINICAL STUDY PROTOCOL

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™)

Protocol Number: NAT-2016-01

Sponsor:

Acerus Pharmaceuticals Corporation
2486 Dunwin Drive
Mississauga
ON L5L 1J9
Canada

Telephone: 1-905-817-8191
Facsimile: 1-905-569-1809

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SIGNATURE PAGE

STUDY TITLE: 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).

We, the undersigned, have read this report and confirm to the best of our knowledge that it accurately describes the conduct of the study.

Signature	Date
Nathan Bryson, PhD Vice President, Scientific Affairs Acerus Pharmaceuticals Corporation	13 Feb 2018
Matthew Gronski, PhD Senior Manager, Clinical Affairs Acerus Pharmaceuticals Corporation	13 FEB 2018
Richard Casey, MD FRCS(C) Medical Monitor CMX Research Inc.	13 Feb 2018

SYNOPSIS

TITLE: 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)

PROTOCOL NUMBER: NAT-2016-01

INVESTIGATIONAL PRODUCT: Testosterone Nasal Gel 4.5% w/w (Natesto™)

PHASE: 4

INDICATION: Adult male hypogonadism (primary and secondary)

OBJECTIVES:

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.

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

- Improvement in hypogonadism symptoms;
- Patient treatment preference versus prior testosterone replacement therapy;
- Frequency of daily dose of NATESTO;
- Safety monitoring.

POPULATION:

The population for this study is adult men 18-65 years of age inclusive, with primary or secondary hypogonadism, with historical documented total serum testosterone concentration of ≤300 ng/dL / ≤10.4nmol/L and the ability to provide informed consent. Eligible subjects include treatment-naïve, hypogonadal patients with a documented confirmation of hypogonadism, as well as patients previously treated with an alternate **topical** testosterone replacement therapy (TRT) for at least three months prior to selection.

Participants currently receiving topical testosterone replacement therapy will be required to discontinue their current testosterone treatment before initiating treatment with NATESTO.

Study Duration
The approximate total duration of study participation for participants completing the study will be up to 150 days (~21 weeks).

This is a Phase 4, multicenter study consisting of two study periods as follows:

- A 90-day **Treatment Period, extended to 120-days for those subjects requiring a dose increase,** during which participants will receive 122.5 mg of NATESTO (5.5mg testosterone) per nostril twice daily (BID) for 90 days. At Day 90, the treating physician will assess the patient's hypogonadism symptoms, review patient's completed questionnaires and based on the Canadian Men's Health Foundation Multidisciplinary Guidelines as endorsed by both the Canadian Urological Association and the Canadian Society of Endocrinology and Metabolism[1], decide if continuation at a higher dose frequency of three-times daily (TID) is required for efficacy. For TID patients, there will be a 30-day Treatment Extension during which participants whose symptoms were not adequately treated on a BID dose, will receive 122.5 mg of NATESTO TID (5.5mg testosterone) per nostril. At Day 120, the TID patient will return to the site for examination, discussion of symptoms with the physician and questionnaire completion. All patients will have their blood testosterone levels assessed at Day 90 and only TID patients at Day 120.
- **Post-study follow-up:** All study patients will be requested to follow up at Day 150 to confirm whether they continued therapy with NATESTO.

Patient Screening

Patient selection will come as a result of a doctor's visit for routine controls, prescription renewal and by pre-selection by the physician from among hypogonadal patients currently

receiving topical testosterone replacement therapies (TRT) and willing to participate in a clinical trial with NATESTO, or as a result of an initial consultation for naïve patients.

Eligible patients will receive information about NATESTO and the Informed Consent Form (ICF), and can contact the site to clarify any questions before deciding to participate in the trial.

At Visit 1, patients who agree to participate in the study will come to the site. They will provide written informed consent and undergo a complete physical examination, including a nasal examination, and medical history collection. Blood pressure, heart rate, weight, and height measurements (from which body mass index [BMI] will be determined) will also be performed. Blood will be drawn at a local lab for safety assessment. However, if these values have already been documented in their patient file from the preceding 6 months, then those values will be entered into the eCRF. Previous treatment for hypogonadism (drug and nondrug; daily dose) will be recorded, as well as other concomitant treatment with drug or nondrug therapies. Study questionnaires Treatment Satisfaction Questionnaire for Medication (TSQM) and quantitative Androgen Deficiency in the Aging Male (qADAM) will be reviewed and subjects will be given instructions for proper completion of the instruments. All patients will complete qADAM, and non-naïve patients will complete the TQSM. Patients will also complete Part A of the Patient Preference and Use Questionnaire. Patients will be provided with a prescription for a 90-day supply of the study medication, NATESTO, and a Study Drug Access Card that will be used for payment purposes at the patient's preferred pharmacy.

Non-naïve participants will be instructed to stop their current topical treatment at least one day and no more than 7 days prior to initiation of treatment with NATESTO. Patients should not take both medications simultaneously.

Treatment Period

The open-label Treatment Period will consist of a maximum of 5 study visits: 2 visits will be done via telephone by the Study Coordinator (Visit 2, Day 30; and Visit 3, Day 60) and one clinic visit (Visit 4, Day 90), and a last clinic visit for patients who were placed on a TID dose (Visit 5, Day 120).

At Visit 2 (Day 30) and Visit 3 (Day 60), participants will be required to complete questionnaires (TSQM and qADAM) by telephone with the Study Coordinator, and will also be asked about any concurrent medications or AEs.

At Visit 4 (Day 90), the patient will return to the site. Any unreported adverse events will be recorded. Patients will undergo a basic physical examination including a nasal examination. Blood pressure, heart rate, weight, and height measurements (from which body mass index [BMI] will be determined) will be recorded. Hypogonadism symptoms will be assessed by the Investigator making reference to the qADAM questionnaire results, and the patient will complete the TSQM.

At Visit 4 (Day 90), if in the physician's judgment the patient is adequately treated with twice daily (BID) NATESTO, the physician will decide whether the patient a.) should return to their previous therapy; b.) remain on NATESTO; or c.) consider a new treatment option. The physician will provide the patient with a prescription for the treatment chosen. The BID patients will have a blood draw taken at a local laboratory for safety assessment and to assess their testosterone level. This will constitute the **END OF TREATMENT for BID subjects**. These adequately controlled patients will complete Part B (for Non-naïve) or Part C (for Naïve) of the Patient Preference and Use Questionnaire.

At Visit 4 (Day 90), if the physician's judgement is that the twice daily (BID) dose of NATESTO was not adequate to treat the patient's symptoms and believes that the patient will benefit from a higher dose, then a prescription will be given to the patient for three times daily (TID) NATESTO. The Study Drug Access Card will be used for payment purposes at the patient's preferred pharmacy. These patients moving to TID will have a blood draw taken at a local laboratory to assess safety as well as their testosterone level. The patient will schedule Visit 5 (Day 120) at this time.

At Visit 5 (Day 120 for TID patients only), any unreported adverse events will be recorded. Patients will undergo a basic physical examination including a nasal examination. Blood pressure, heart rate, weight, and height measurements (from which body mass index [BMI] will be determined) will be recorded. The patients will have a blood draw taken at a local laboratory for safety assessment and to assess their testosterone level. In addition to TSQM and qADAM questionnaires, subjects will also complete Part B (for Non-naïve) or Part C (for Naïve) of the Patient Preference and Use Questionnaire. The physician will decide whether the patient a.) should return to their previous therapy; b.) remain on NATESTO; or c.) consider a new treatment option. The physician will provide the patient with a prescription for the treatment chosen.

Post-study Follow-Up

At Visit 6 (Day 150), all study patients will be asked by telephone whether they are still taking NATESTO and why (or why not).

See Appendix A, Schedule of Procedures, page 57.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

Study Drug:	Testosterone nasal gel 4.5% w/w (Natesto$^{TM)}$
Pharmaceutical form:	Gel for intranasal administration
Content:	Active ingredient: testosterone
	Excipients: silicon dioxide, castor oil, and oleoyl polyoxylglycerides
Mode of administration:	Intranasal
Storage conditions:	Controlled Room Temperature (15-30ºC)

NATESTO is administered intranasally by the participant. A multiple-dose dispenser will be used for gel deposition into the nasal cavity. The dispenser is a finger-actuated, non-pressurized dispensing system designed to deliver 122.5mg of NATESTO (5.5mg testosterone) per actuation. The key components of the multiple-dose dispenser include a cap, barrel, pump, and actuator, which are composed of polypropylene, and a piston, which is composed of polyethylene.

The dispenser capacity is 11g which provides for 30 doses (60 actuations; 1 dose = one actuation per nostril) of NATESTO after priming, sufficient for 15 days with twice-daily (BID) administration. For BID administration, NATESTO should be applied in the morning and in the evening (preferably at the same time each day) for a total daily testosterone dose of 22 mg/day of testosterone. For the subset of patients that continue on TID, NATESTO will be administered in the morning, in the afternoon and in the evening (approximately 6-8 hours apart), preferably at the same time each day, for a total daily testosterone dose of 33 mg/day of testosterone.

EFFICACY VARIABLES:

Primary efficacy is the self-reported patient satisfaction with treatment that will be assessed by the Treatment Satisfaction Questionnaire for Medication (TSQM), a validated, 9-item instrument with domains for Effectiveness, Convenience and Global Satisfaction. The change in satisfaction will be determined by the difference in values at Visit 4 (Day 90) relative to Visit 1 for adequately controlled BID patients; and values at Visit 5 (Day 120) relative to Visit 1 for patients up-titrated to TID.

Secondary efficacy variables are:

- For naïve patients the same efficacy assessment as stated above will be extended to being relative to Visit 2 – naïve patients cannot be assessed relative to Visit 1 as they will not have been taking any medication.
- Improvement in hypogonadism symptoms as measured by quantitative Androgen Deficiency in Aging Males (qADAM) questionnaire: patient-reported outcome measure to evaluate symptoms of hypogonadism: a 10-item hypogonadism symptom severity instrument.
- Patient preference of therapy as measured by the Treatment Preference questionnaire.
- NATESTO dosing frequency.

Exploratory analyses will include analysis of the monthly change of the primary or secondary efficacy global and domain measures over the treatment period. Patient's responses from the post-study follow-up will be tabulated.

SAFETY VARIABLES:

Safety assessments will include adverse events, vital signs (blood pressure, heart rate, and temperature), physical examination parameters and total testosterone measurements (if required), hematocrit, lipid profile (total cholesterol, LDL, HDL and triglycerides), hemoglobin, and liver function tests (liver enzyme levels).

STATISTICAL ANALYSES:

The intent-to-treat (ITT) population will consist of all participants who receive study drug and have a valid post-dose efficacy measurement. The safety population will consist of all participants who receive at least one dose of study drug. The primary and secondary efficacy analyses will be based on the ITT population and the safety analyses will be based on the safety population.

Adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities. A general summary of the adverse events and serious adverse events for each treatment group will be presented by the overall number of adverse events, the severity, and the relationship to study drug. The incidence of adverse events will be summarized by system organ class, preferred term, and treatment group. Vital signs will also be summarized by visit and by treatment group along with the change from baseline. Other safety measurements will be summarized and listed if deemed necessary.

Sample Size Determination

A sample size of approximately 100 participants will be selected to provide a sufficient number of participants for the analysis. No more than 25 naïve patients will be allowed in the study. 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.

SITES: Approximately 10 sites in Canada.

SPONSOR: (hereafter referred to as Acerus)

Acerus Pharmaceuticals Corporation
2486 Dunwin Drive
Mississauga
ON L5l 1J9
Canada

Telephone: 1-905-817-8191
Facsimile: 1-905-569-1809

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AUC	Area under the curve
BID	Twice daily
BMI	Body mass index
C_{avg}	Average concentration
CFB	Change from baseline
CI	Confidence interval
C_{max}	Maximum concentration
CRA	Clinical research associate
DHEA	Dehydroepiandrosterone
DHT	Dihydrotestosterone
DIN	Drug Identification Number
DM	Data management
DRE	Digital rectal examination
ECC	Environmental challenge chamber
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
GnRH	Gonadotropin-releasing hormone
h	Hour(s)
ICF	Informed consent form
IRB	Institutional Review Board
ITT	Intent-to-treat
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
N	NumberPDE5 Phosphodiesterase 5
PK	Pharmacokinetic
PP	Per-protocol
PSA	Prostate specific antigen
qADAM	Quantitative Androgen Deficiency in the Aging Male
SAE	Serious adverse event
SD	Standard deviation
SHBG	Sex hormone-binding globulin
TBS-1	NATESTO code used for clinical trials
TID	Three times daily
$t_{1/2}$	Half-life
T_{max}	Time to maximum concentration
TRT	Testosterone replacement therapy
TSQM	Treatment Satisfaction Questionnaire for Medication
TU	Testosterone undecanoate
µL	Microlitre
w/w	Weight by weight

1 INTRODUCTION AND BACKGROUND INFORMATION

NATESTO is a bioadhesive testosterone gel for intranasal application developed by Acerus Pharmaceuticals SRL and approved by Health Canada on January 6, 2016 (DIN 02450550). NATESTO is indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone (hypogonadism). Prior studies have demonstrated that NATESTO restores normal serum total testosterone levels when administered two or three times daily with relatively few side effects. The purpose of this study is to evaluate patient satisfaction with the use of NATESTO, as compared to their satisfaction with previously used topical TRT. The study will consist of a Treatment Period up to 120 days in duration; with a follow-up telephone call 30 days later.

1.1 Background

Testosterone, the active ingredient in NATESTO, 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). Data from different groups have shown that testosterone secretion follows a diurnal pattern with a peak at approximately 0800 h to 0900 h and a nadir between 2000 h and 2100 h.[2-4] It is believed that episodic testosterone secretion is required for the normal operation of the neuroendocrine axis that governs testicular function.[5-7]

Immediately after its chemical isolation and synthesis in 1935, testosterone was introduced into clinical medicine and used for the treatment of hypogonadism. It was initially given by compressing the medication into pellets, which were then administered subcutaneously. In the 1950s, longer-acting intramuscular formulations became the preferred therapeutic modality. Orally effective testosterone undecanoate (TU) was added 20 years later. By the mid1990s, transdermal testosterone patches were introduced into clinical practice. Transdermal testosterone gel, currently the most frequently prescribed preparation, became available in 2000.

Testosterone has a well-established profile with over 50 years of accumulated clinical experience. Numerous placebo-controlled studies have demonstrated that testosterone replacement therapy is efficacious in treating symptoms of

hypogonadism. These studies have been summarized in a number of recent meta-analyses.[8-10] Testosterone has been shown to improve sexual function (both libido and erectile function) in older men. Hypogonadal men treated with testosterone before receiving a phosphodiesterase 5 (PDE5) inhibitor have experienced improvement in the quality of erections.[11-12] In some cases, testosterone has reversed erectile dysfunction in participants who fail to respond to PDE5 inhibitors.[13] Testosterone administered in low doses to men with borderline hypogonadism increases muscle mass and decreases fat mass.[14-15] At higher doses, in men with serum total testosterone less than 12 nmol/L, testosterone has been shown to improve strength.[9-10] In a recent large study (N=322 men over 50 years of age), TU improved sexual function, increased lean body mass, decreased body fat mass, and increased bone mineral density at both the hip and the spine.[16] Another large study (N=237 healthy men between 60 to 80 years of age with total testosterone levels below 13.7 nmol/L) showed that TU decreased body fat and increased muscle mass.[17] Additional data also suggests that testosterone improves cognition and mood and may be useful in treating some participants with Alzheimer's disease.[18-22]

There are well known risks associated with the use of testosterone. Testosterone administration is not recommended in participants with a history of prostate or breast cancer, an unevaluated prostate nodule or induration, hematocrit >54%, severe lower urinary tract symptoms, uncontrolled or poorly controlled congestive heart failure, or a prostate specific antigen (PSA) >4 ng/mL. Testosterone is a teratogen and extensive data is available on its reproductive and developmental effects. As expected for a hormonally active compound, literature demonstrates excess testosterone exposure increases the incidence of prostate, endometrium, breast, and liver tumors.

Despite the variety of current testosterone formulations available for treatment of male hypogonadism, several significant disadvantages remain. Some of the preparations (oral TU and scrotal patches) elevate DHT levels or the DHT:testosterone ratio beyond the normal physiologic range. Long-acting injection formulations result in high initial testosterone levels that can remain supraphysiologic for distinct periods of time, leading to wide fluctuations in systemic androgen levels. These fluctuations are thought to be responsible for the mood lability many men experience during treatment with the injection and TU formulations. Excessive erythrocytosis, especially in older participants, has also been observed with injection preparations. Patches frequently cause skin irritation and allergic contact dermatitis. Gel preparations have caused unintentional exposures in household contacts, which can be significantly detrimental to developing fetuses and young children.[23-27] Buccal formulations frequently cause gum irritation and taste alterations.[28]

In 2002, it was theorized that the intranasal route could provide an alternate method of administration of testosterone. Animal experiments showed that intranasal testosterone was minimally metabolized in the nose and offered

excellent bioavailability.[29-30] Two local tolerance studies in rats and rabbits (study 208040401 and study 208040402) following single- and repeat-dose administrations showed that NATESTO was well tolerated. In another study (study 208040403), NATESTO was classified as a non-irritant using the Hen's Egg Test-Chorioallantoic Membrane evaluation. In a 3-month study conducted in rabbits (study 22712040417), doses of 0.093 mg/kg, 0.550 mg/kg, and 1.867 mg/kg (1, 5, and 10 times the proposed clinical dose of intranasal testosterone gel, respectively) resulted in no abnormal histopathologic changes in the nasal turbinates, brain, testes, heart, kidneys, and lungs. Centrilobular glycogenic vacuolation in the liver was marginally greater in the high dose testosterone group compared to the untreated control.[31]

1.2 Summary of Clinical Studies

Similar to other androgen replacement therapies, the evaluation of the efficacy of NATESTO has been based on pharmacokinetic (PK) studies. NATESTO is referred to as TBS-1 or Nasobol (code for clinical trials) in this section. Clinical experience with NATESTO includes the following 6 completed studies:

- A Phase 1/2, 3-period study (TST-PKP-01-MAT/04) conducted in 8 hypogonadal men evaluating the PK profile after administration of 3 different single doses of 3.8% TBS-1;
- A Phase 2, parallel-group, open-label study (TST-DF-02-MAT/05) conducted in 21 hypogonadal men comparing the PK profile and tolerability of 3 different doses of 3.8% TBS-1;
- A Phase 2, 4-period, parallel-group, open-label study (Nasobol-01-2009) conducted in 57 hypogonadal men comparing the PK profile and tolerability of 3 different doses of 3.2% TBS-1 versus Androderm® 5.0 mg patch; and
- A Phase 2, parallel-group, open-label study (TBS-1-2010-01) conducted in 22 hypogonadal men comparing the PK profile and tolerability of 3 different doses of 4.0% and 4.5% TBS-1.
- A Phase 2, open-label, randomized, cross-over study (TBS-1-2011-04) conducted in 18 health men suffering from seasonal allergic rhinitis. 4.5% TBS-1 11.0 mg TID was administered in 3-treatment states for a 3-period cross-over separated by a 4-day washout period.
- A Phase 3, 90-day, randomized, dose-ranging study (TBS-1-2011-03), including potential dose titration, evaluating the efficacy and safety of intranasal 4.5% TBS-1 in the treatment of male hypogonadism with sequential safety extension periods of 90 and 180 days.

TST-PKP-01-MAT/04

TST-PKP-01-MAT/04 was a Phase 1/2, open-label, 3-period study conducted in 8 hypogonadal men to determine the PK profile of testosterone after varying doses of 3.8% w/w TBS-1. Each participant received single doses of 7.6 mg, 15.2 mg, and 22.8 mg of TBS-1 separated by 24 hour washout periods. Blood samples to determine the PK profile, including the maximum concentration (C_{max}), and half-life ($t_{1/2}$) for serum total testosterone and DHT, were collected just before each dose and at regular time intervals after each dose.

Results from study TST-PKP-01-MAT/04 showed that testosterone was well absorbed after TBS-1 administration. The C_{max} values for total testosterone were all within the normal reference range for healthy young males (739 ng/dL, 925 ng/dL, and 952 ng/dL for the 7.6 mg, 15.2 mg, and 22.8 mg groups, respectively). The time to maximum concentration (T_{max}) was 1 to 2 hours after administration, which is significantly shorter than the T_{max} for gels and patches, indicating a rapid absorption of testosterone from the nasal cavity. The testosterone was cleared from the serum with a $t_{1/2}$ of approximately 10 hours. The concentration of DHT remained low over the observation period. None of the participants experienced a serious adverse event (SAEs). No adverse events were considered to be related to the study drug.

TST-DF-02-MAT/05

TST-DF-02-MAT/05 was a Phase 2, randomized, parallel, open-label study conducted in 21 hypogonadal men to identify the optimum daily dose of 3.8% w/w TBS-1. Each participant in the 3 treatment groups received 7.6 mg of testosterone administered via TBS-1 for 2 weeks. The first treatment group received TBS-1 twice daily (BID) at 0800 h and 1400 h (total daily dose of 15.2 mg); the second treatment group received TBS-1 twice daily (BID) at 0800 h and 2000 h (total daily dose of 15.2 mg); and the third treatment group received TBS-1 three times daily (TID) at 0800 h, 1400 h, and 2000 h (total daily dose of 22.8 mg). Blood samples to determine the PK profile, including the average concentration (C_{avg}) and C_{max} for serum total testosterone and DHT, were collected.

Results from study TST-DF-02-MAT/05 showed that the mean C_{avg} for serum total testosterone remained within the physiologic range in all 3 treatment groups. However, the 95% confidence interval remained entirely within the physiologic range only in the TID treatment group. The C_{max} values exceeded the physiologic range in 3 participants (1 participant from each treatment group) but only for a very brief period of time (minutes). The C_{avg} of DHT did not exceed the upper limit of the physiologic range. In total, 36 adverse events were observed but none were considered drug related. No participant had an SAE.

Nasobol-01-2009

Nasobol-01-2009 was a Phase 2, randomized, 4-group, 4-period, open-label, crossover study conducted in 57 hypogonadal men comparing the efficacy and tolerability of 3 different doses of 3.2% w/w TBS-1 versus Androderm 5.0 mg patch. All participants were administered the 5.0 mg Androderm patch and TBS-1 at doses of 8.0 mg BID, 11.0 mg BID, and 14.0 mg BID. TBS-1 was prepared as 127 µL, 174 µL, and 222 µL for the 8.0 mg, 11.0 mg, and 14.0 mg doses, respectively. Each treatment was given for a 7-day period after which the participants rotated to 1 of the 3 other treatment groups. After 28 days (4 periods), all groups had rotated through each of the 4 treatment groups. Blood samples to determine the PK profile, including the C_{avg} and C_{max} for serum total testosterone and DHT, were collected at the end of each period.

All 3 TBS-1 treatment groups showed appreciable increases in serum testosterone levels above Baseline and sizeable increases in area under the curve (AUC) for serum total testosterone with increasing TBS-1 dose. After Day 7 of treatment, the serum total testosterone C_{avg} was within the normal range in 79.6% of participants treated with the Androderm 5.0 mg patch, 52% of participants treated with 14.0 mg TBS-1 BID, 36.5% of participants treated with 11.0 mg TBS-1 BID, and 49.1% of participants treated with 8.0 mg TBS-1 BID. The serum total testosterone C_{max} values tended to be lower and the AUC values tended to be higher following Androderm administration compared to TBS-1 administration. The increase in serum total testosterone values following TBS-1 treatment in the 3 escalating doses was not linear. This finding suggested that the larger gel volumes (174 µL and 222 µL) were too great to be consistently absorbed in the nasal cavity. Serum DHT profiles were similar with all doses of TBS-1 compared to Androderm and all treatment groups had DHT levels within the normal range.

All treatments were well tolerated by participants. No participant had an SAE and no participant discontinued due to an adverse event. In total, 56 adverse events were reported, 22 of which were related to study drug. Two of these adverse events were moderate in severity. Nasal complaints such as dryness, discomfort, congestion, inflammation, and epistaxis reported in the TBS-1 group were transient and mild in intensity.

TBS-1-2010-01

TBS-1-2010-01 was a Phase 2, randomized, parallel-group, open-label study conducted in 22 hypogonadal men comparing the efficacy and tolerability of 4.0% w/w and 4.5% w/w TBS-1 at 3 different doses. Participants were randomized to 1 of the following 3 treatment groups for 7 days:

- Group A: 10.0 mg 4.0% w/w TBS-1 TID (total daily dose of 30.0 mg),
- Group B: 13.5 mg 4.5% w/w TBS-1 BID (total daily dose 27.0 mg), or
- Group C: 11.25 mg 4.5% w/w TBS-1 TID (total daily dose of 33.75 mg).

Blood samples to determine the PK profile, including the C_{avg} and C_{max} for serum total testosterone and DHT, were collected after 7 days of treatment in each group.

Serum total testosterone C_{avg} values within the normal range were achieved in 87% of participants in Group A, 100% of participants in Group B, and 85% of participants in Group C. No participant had a serum total testosterone C_{max} >1800 ng/dL. Serum DHT and estradiol C_{avg} values remained within the normal range in all treatment groups. All 3 TBS-1 doses were well tolerated by participants. No participant had an SAE and no participant discontinued due to an adverse event. In total, there were 8 adverse events, 2 of which were considered drug related. All events were of mild or moderate severity.

TBS-1-2011-04 Study

Study TBS-1-2011-04 was a randomized, crossover study conducted in healthy men who suffer from seasonal allergic rhinitis. Participants received 4.5% w/w TBS-1 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 objectives of the study were (1) to evaluate whether intranasal application of testosterone is a reliable route of administration during naturally occurring nasal inflammation, such as allergic rhinitis; and (2) to investigate the potential interaction of TBS-1 with the common over-the-counter nasal decongestant spray, oxymetazoline (Nasivin®), in the presence of swelling of the nasal mucosa, as it occurs during allergic rhinitis. Drug interaction was assessed from the relative bioavailability of Baseline-corrected serum testosterone concentrations and determination of bioequivalence.

Participants each received TBS-1 11.0 mg TID for 1 day, while in each of the 3 treatment states: the asymptomatic state, the symptomatic and untreated state, and the symptomatic and treated with oxymetazoline state. TBS-1 doses were administered at 0700, 1300, and 2100 hours. Treatment periods were separated by a 4-day washout period.

A reliable increase in serum testosterone was observed in patients with symptomatic allergic rhinitis, however serum total testosterone concentrations were decreased by 21 to 24%. A 2.6% decrease in mean AUC(0-24) and 3.6% decrease in mean C_{max} of total testosterone was observed in males with symptomatic seasonal rhinitis when treated with oxymetazoline 30 minutes prior to TBS-1 compared to when left untreated. Oxymetazoline did not impact the absorption of testosterone when concomitantly administered with TBS-1.

TBS-1-2011-03 Study

Study TBS-1-2011-03 was a Phase 3, open-label, randomized, parallel 2-group, dose-ranging study, including dose-titration, evaluating clinical efficacy, PK, and safety endpoints in hypogonadal men. The study period was up to 58 weeks and included a screening period, and a 90-day treatment period followed by 2 sequential safety extension periods of 90 and 180 days.

Participants were randomized to receive 11.0 mg (5.5 mg per nostril) of 4.5% w/w TBS-1 BID (22.0 mg daily) or TID (33.0 mg daily) with potential daily dose adjustment on Day 45 for patients in the BID treatment group as determined by the titration assessment conducted on Day 30.

Inclusion criteria included men with primary or secondary hypogonadism and a morning serum testosterone level of <300 ng/dL; a normal otorhinolaryngological nasal endoscopy examination; a normal prostate examination; and a serum prostate specific antigen (PSA) ≤4.0 ng/mL. The study was conducted at 39 centers in the US.

The primary objective of this pivotal Phase 3 study was to determine the efficacy of TBS-1, administered as BID or TID intranasal doses of 11.0 mg (5.5 mg per nostril), as demonstrated by an increase in the 24 hour C_{avg} of serum total testosterone to the normal range (≥300 and ≤1050 ng/dL) in ≥75% of male patients treated for hypogonadism.

At Day 90 in the ITT population, 90% (95% CI – 83% - 97%) of patients on the TBS-1 TID regimen and 71% (95% CI = 62% - 79%) of patients on the BID regimen had C_{avg} in the normal total testosterone range.

Number and Percentage of Patients by Serum Total Testosterone C_{avg} Category at Day 90 – ITT Population and Per Protocol Population– Treatment Period

Serum Total Testosterone C_{avg} in Normal Range on Day 90	**ITT Population (N = 303)**	**Per-Protocol Population (N = 237)**
TBS-1 BID	71%	75%
N'	122	102
95% CI for frequency [1]	(62, 79)	(66, 83)
TBS-1 BID/TID	63%	63%
N'	82	68
95% CI for frequency [1]	(53, 74)	(52, 75)
TBS-1 TID	90%	91%
N'	69	67
95% CI for frequency [1]	(83, 97)	(84, 98)
TBS-1 Combined TID	76%	77%

Serum Total Testosterone C_{avg} in Normal Range on Day 90	ITT Population (N = 303)	Per-Protocol Population (N = 237)
N'	151	135
95% CI for frequency [1]	(69, 82)	(70, 84)
Note: N' is the number of participants who had a C_{avg} at Day 90. % = n/N'. 1. The CI for the frequency was approximated by a binomial distribution within each treatment. C_{avg} = average concentration; CI = confidence interval; ITT = Intent-to-Treat;		

All populations (ITT [both based on patients with assessments on Day 90 and on LOCF] and PP Populations) met the primary efficacy endpoint success criterion for the TID regimen. The PP Population met the primary efficacy endpoint success criterion also for the BID regimen. The ITT Population at Day 90, and at Day 90 LOCF, was very close to meeting the primary efficacy endpoint success criterion for the BID regimen, at 71% and 72%, respectively. The requirement that the lower 95% CI be not less than 65% was met. The lower bound of the 95% CI for both TBS-1 treatment groups overall was 68% for the ITT Population and 71% for the PP Population.

In addition, 88.6% of the ITT population had mean testosterone C_{max} at Day 90 below 1500 ng/dL (Supplemental Table 1). Nine (3.3%) subjects had C_{max} between 1800 and 2500 ng/dL. One subject showed a C_{max} >2500 ng/dL (3570 ng/dL); this subject, presumably did not discontinue concomitant finasteride treatment prior to the study as evidenced by increased testosterone AUC and an unusually low DHT/T ratio as a result of the inhibition of 5a-reductase that blocks conversion of testosterone to DHT. No safety concerns were identified for this subject.

Number and Percentage of Subjects with Serum Total Testosterone C_{max} Values in Selected Ranges at Day 90 of the Treatment Period by Treatment and Population

Population	Number, C_{max} Value	TBS-1 BID (n = 141)	TBS-1 TID (n = 162)	Total (N = 303)
ITT	n	122	151	273
	C_{max} ≤1500 ng/dL, n (%)	107 (87.7)	135 (89.4)	242 (88.6)
	C_{max} ≥1800 to ≤2500 ng/dL, n (%)	6 (4.9)	3 (2.0)	9 (3.3)
	C_{max} >2500 ng/dL, n (%)	1 (0.8)	0	1 (0.4)
PP	n	102	135	237
	C_{max} ≤1500 ng/dL, n (%)	91 (89.2)	120 (88.9)	211 (89.0)
	C_{max} ≥1800 to ≤2500 ng/dL, n (%)	5 (4.9)	2 (1.5)	7 (3.0)
	C_{max} >2500 ng/dL, n (%)	0	0	0

1.3 Rationale

Although controversy for specific treatment criteria exists, clinical investigations have shown that testosterone replacement in symptomatic male hypogonadism is generally safe and well tolerated.[28] Testosterone treatment has positive effects on sexual function and, in some cases, can reverse total failures to respond to PDE5

inhibitors.[11-13] Testosterone also increases muscle mass, decreases fat mass, improves strength, increases bone mineral density, and may improve mood and cognition.[16-22]

Injection site reactions, frequent rashes, and medication transference remain significant disadvantages for participants treated with current therapies. Gels and patches provide continuous testosterone exposure with levels in the mid or high physiologic range depending on the dose applied. Injection forms of testosterone cause high levels during the first weeks that then gradually decline. It has been suggested that continuous exposure to testosterone might cause down-regulation of receptors and desensitization of target cells.

NATESTO is applied within a matter of seconds, readily absorbed and rapidly elevates serum testosterone levels during the first 2 hours after application. With a $t_{1/2}$ of approximately 10-100 min, it is quickly cleared from the circulation. Through carefully timed administration of NATESTO, it is expected that the normal physiologic increase that is seen in eugonadal men can be mimicked.[33-35]

As the intranasal route of administration is novel for TRTs, the goal of this study is to investigate self-reported satisfaction with treatment with NATESTO in men with hypogonadism either previously treated with other topical TRTs or naïve to testosterone treatment.

1.4 Risk/Benefit

Participants participating in this study are at risk for the side effects common to all formulations of testosterone. Adverse events for which there is evidence of association with testosterone administration include: erythrocytosis, detection of subclinical prostate cancer, growth of metastatic prostate cancer, worsening of acne, oily skin, and reduced sperm production and fertility. There is also weak evidence of association with testosterone administration for the following uncommon adverse events: gynecomastia, male pattern balding, growth of breast cancer, and induction or worsening of obstructive sleep apnea. Clinical evidence also shows that testosterone supplementation increases prostate volume and PSA levels leading to a higher frequency of prostate biopsies in participants treated with testosterone.[13]

In addition to risks inherent to all testosterone administration, participants receiving NATESTO in prior clinical studies have experienced mild nasal symptoms including rhinorrhea, nasal discomfort, epistaxis and scab. None of these adverse events were indicative of any major nasal tolerability issues.

Potential benefits for participants participating in this study include improvement of the signs and symptoms associated with hypogonadism as outlined above. NATESTO provides a hands-free means of administration, reducing the risks of transference.

2 STUDY OBJECTIVES AND HYPOTHESES

The primary objective of the study is to measure patient satisfaction with testosterone replacement therapy before, during and after treatment with NATESTO.

The secondary objectives of this study to evaluate the following:

- Improvement in hypogonadism symptoms;
- Patient treatment preference versus prior testosterone replacement therapy;
- Frequency of daily dose of NATESTO; and
- Safety monitoring.

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 STUDY DESIGN

3.1 Summary of Study Design

Approximately 100 participants (25 treatment-naïve and 75 previous topical TRT users) will be enrolled at approximately 10 investigative sites in Canada.

- This is a Phase 4, multicenter study consisting of two study periods as follows: a 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;
- A one-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?).

Patient selection will come as a result of a doctor's visit for routine controls, prescription renewal and by pre-selection by the physician from among hypogonadal patients currently receiving topical testosterone replacement therapies and willing to participate in a clinical trial with NATESTO, or as a result of an initial consultation for naïve patients.

Eligible patients will receive information about NATESTO and the Informed Consent Form. The maximum total duration of study participation for participants completing the study will be 150 days (~21 weeks).

During Treatment Period visits are to occur on the scheduled visit date ± 3 days.

The population for this study is adult men 18-65 years of age inclusive with primary or secondary hypogonadism, with historical documented total serum testosterone concentration of ≤300 ng/dL / 10.4 nmol/L and the ability to provide informed consent. Participants may include naïve hypogonadal patients (up to 25) with a confirmation of hypogonadism diagnosis and non-naïve patients, who have previously been treated with an alternate topical testosterone replacement therapy (TRT) for at least three months prior to screening.

Non-naïve participants will be instructed to stop their current topical treatment at least one day and no more than 7 days prior to initiation of treatment with NATESTO.

Patient Screening

Patient selection will come as a result of a doctor's visit for routine controls, prescription renewal and by pre-selection by the physician from among hypogonadal patients currently receiving topical testosterone replacement therapies and willing to participate in a clinical trial with NATESTO, or as a result of an initial consultation for naïve patients.

At Visit 1, patients who agree to change their current topical TRT to NATESTO will provide written informed consent and undergo a complete physical examination, including a nasal examination, and the patient's medical history will be documented. Blood pressure, heart rate, weight, and height measurements (from which body mass index [BMI] will be calculated) will also be performed. Patients will undergo a blood draw at a local laboratory for assessment of hematocrit, lipid profile (total cholesterol, LDL, HDL and triglycerides), hemoglobin and liver function tests (liver enzyme levels). However if the patient already has these values documented in their patient file from the preceding 6 months, then those values can be entered into the eCRF and a fresh test will not be required. Previous treatment for hypogonadism (drug and nondrug) will be recorded, as well as other concomitant treatment with drug or nondrug therapies.

Study questionnaires (TSQM and qADAM) will be reviewed and all subjects will be given instructions for proper completion of the instruments. Non-naïve patients will complete both questionnaires. All patients will complete Part A of the Patient Preference and Use Questionnaire.

All patients will be instructed to complete TSQM and qADAM questionnaires by telephone, with the Study Coordinator on Day 30 and Day 60; at the same time concomitant drugs and AEs will be queried.

All patients will be trained on the proper administration of NATESTO. They will receive their 90-day prescription for NATESTO and be asked to obtain the drug at the pharmacy within the next three days. Non-naïve participants will be instructed to stop their current topical testosterone therapies at least one day and up to 7 days prior to initiation of treatment with NATESTO.

Patients will be instructed to contact the site to report any adverse events experienced. Patients will schedule their Day 90 visit at Visit 1.

Treatment Period
The open-label Treatment Period will consist of up to 5 site or telephone visits: Visit 1 site visit as study initiation; Visit 2 (Day 30) via telephone with Study Coordinator, Visit 3 (Day 60) via telephone with Study Coordinator, Visit 4 (Day 90) as a site visit and, for patients on NATESTO TID, a Visit 5 (Day 120) as a site visit

Visit 2 and Visit 3

On Day 30 and Day 60 participants will be required to complete questionnaires (TSQM and qADAM) by telephone with the Study Coordinator; at the same time the coordinator will query concurrent medications and any AEs, and verbally confirm the patients are taking their NATESTO as prescribed. At the discretion of the Investigator, participants may be required to complete a site visit if they experience an adverse event that is considered to require a physician assessment.

Visit 4

At Visit 4, Day 90, all patients will return to the site. Hypogonadism symptoms will be assessed by the Investigator with the qADAM questionnaire results being used for reference. If required, BID dose of NATESTO will be increase to TID at the discretion of the physician.

Any previously unreported adverse events and concomitant medications will be recorded. Patients will undergo a basic physical examination including a nasal examination. Blood pressure, heart rate, weight, and height measurements (from which body mass index [BMI] will be determined) will be recorded. In addition to TSQM and qADAM questionnaires, subjects will also complete the Treatment Preference questionnaire. All patients will also be required to provide a blood sample for the total testosterone measurement at the local lab. The blood sample will need to be taken 20 minutes to 2 hours after the morning dose of NATESTO. In addition sufficient blood will be drawn for assessment of hematocrit, lipid profile (total cholesterol, LDL, HDL and triglycerides), hemoglobin, and liver function tests (liver enzyme levels). The BID patients who are adequately controlled will complete Part B (for Non-naïve) or Part C (for Naïve) of the Patient Preference and Use Questionnaire.

The physician will question the patient about their symptoms. If this assessment indicates that symptoms persist and the patient requires additional benefit from a higher dose of testosterone, the physician may ask the patient if he is willing to continue treatment at three times daily (TID) for an additional 30 days and answer questionnaires thereafter. In the affirmative, the patient will receive a prescription for three additional dispensers and treatment with NATESTO will be continued for another 30 days. An appointment will be scheduled for Visit 5 to occur at Day 120 of treatment.

For patients assessed to be adequately controlled on BID this will mark the end of study and the physician will decide whether the patient a.) should return to their previous therapy; b.) remain on NATESTO; or c.) consider a new treatment option. The physician will provide the patient with a prescription for the treatment chosen.

Visit 5.
TID patients will come to the site to complete qADAM, TSQM and Part B (for Non-naïve) or Part C (for Naïve) of the Patient Preference and Use Questionnaire. Any previously unreported adverse events and concomitant medications will be recorded. Patients will undergo a basic physical examination including a nasal examination. Blood pressure, heart rate, weight, and height measurements (from which body mass index [BMI] will be calculated) will be recorded. Patients will also be required to provide a blood sample for the total testosterone measurement at the local lab. The blood sample will need to be taken 20 minutes to 2 hours after the morning dose of NATESTO. In addition sufficient blood will be drawn for assessment of hematocrit, lipid profile (total cholesterol, LDL, HDL and triglycerides), hemoglobin, and liver function tests (liver enzyme levels).

This will mark the end of study for the TID patients and the physician will decide whether the patient a.) should return to their previous therapy; b.) remain on NATESTO; or c.) consider a new treatment option. The physician will provide the patient with a prescription for the treatment chosen.

Patient follow-up.

Visit 6

All study patients will be contacted by phone three months (Day 150 +/- 3 days) after they have concluded the study to confirm whether they continued therapy with NATESTO after completing the study.

A detailed schedule of procedures is provided in Appendix A.

3.2 Study Indication(s)

The indication for this study is the treatment of a deficiency or absence of endogenous testosterone (hypogonadism).

4 STUDY POPULATION

4.1 Inclusion Criteria

Participants who meet all of the following inclusion criteria will be eligible for participation in the study:

1. Hypogonadal male between 18 and 65 years of age, inclusive;
2. Able to understand and provide signed informed consent;
3. Have documented total serum testosterone levels ≤300 ng/dL / 10.4 nmol/L; for non-naïve patients this can be any previous documented value in their medical history; for naïve patients this will be two documented values within the last 6 months;
4. Are currently being treated with any form of a topical testosterone replacement therapy for at least three months, or are treatment-naive.

4.2 Exclusion Criteria

Participants who meet any of the following criteria will be excluded from participation in the study:

1. In the opinion of the Investigator, significant intercurrent disease of any type, in particular liver, kidney, heart disease, stroke, or psychiatric illness;
2. History of pituitary or hypothalamic tumors or history of any malignancy (including breast and prostate cancers) excluding basal cell or squamous cell carcinoma of the skin curatively treated by surgery;
3. Prostatomegaly or history of abnormal PSA levels (>10.0 ng/mL). If PSA is >10 ng/mL, a recent negative biopsy must be documented (within the last 12 months);
4. History of nasal disorders, nasal or sinus surgery, nasal fracture within the previous 6 months or nasal fracture that caused a deviated anterior nasal septum surgery, mucosal inflammatory disorders, specifically Sjogren's syndrome;
5. Use of any form of intranasal medication delivery other than periodic short-term (less than 3 days) use of sympathomimetic decongestants;
6. History of severe adverse drug reactions to testosterone therapies;
7. History or current evidence of abuse of alcohol or any drug substance;
8. Current treatment with other androgens (e.g., dehydroepiandrosterone [DHEA]), anabolic steroids, or other sex hormones;

9. Treatment with estrogens, gonadotropin-releasing hormone (GnRH) agonists, or growth hormone within the previous 12 months;
10. Treatment with drugs that interfere with the metabolism of testosterone, such as anastrozole, clomiphene, dutasteride, finasteride, flutamide, ketoconazole, spironolactone, or testolactone;
11. Poor compliance history;
12. Participation in any other research study during the conduct of this study or 30 days prior to the initiation of this study.
13. Any prior exposure to NATESTO.

5 STUDY PROCEDURES

5.1 Assessment Schedule

See Appendix A, Schedule of Procedures, on page 57.

5.1.1 Patient Screening

Patient selection will come as a result of a doctor's visit for routine controls, prescription renewal and by pre-selection by the physician from among hypogonadal patients currently receiving topical testosterone replacement therapies and willing to participate in a clinical trial with NATESTO, or as a result of an initial consultation for naïve patients.

Naïve patients will require confirmation within the last 6 months of hypogonadism by ensuring that serum testosterone concentrations have been measured in the morning on at least two separate days and that these serum testosterone levels concentrations are below the normal range.

Patients will be informed about the trial and given a copy of the ICF to review.

Visit 1 (Day 0)

The following procedures will be performed at Visit 1:

- Evaluate inclusion/exclusion criteria and confirm patient eligibility;
- Obtain signed informed consent form;
- Register participant in the study using data management (DM) system;
- Record the date of hypogonadism diagnosis;
- Obtain medical, surgical, and family history; including any adverse events in the preceding 30 days;
- Record demographics;
- Record concomitant medications;
- Obtain height and weight, and determine BMI;
- Obtain vital sign measurements (heart rate, blood pressure, and temperature);
- Perform physical examination including a nasal examination;
- For naïve patients document the two serum testosterone values from within the last 6 months.
- Undergo a blood draw at a local laboratory for assessment of hematocrit, lipid profile (total cholesterol, LDL, HDL and triglycerides), hemoglobin, liver function tests (liver enzyme levels). However if the patient already has these values documented

in their patient file from the preceding 6 months, then those values can be entered into the eCRF and a fresh test will not be required.

- Complete qADAM questionnaires (all patients) and TSQM (non-naïve patients only); and complete Patient Preference and Use questionnaire Part A.
- Provide participant with training and instructions for study drug administration and 90-day prescription for NATESTO, along with a Study Drug Access Card;
- Instruct participant to obtain NATESTO from pharmacy within 3 days using their Study Drug Access Card.
- Naïve participants can initiate treatment with NATESTO immediately, but no more than 7 days after Day 0 (Visit 1).
- Non-naïve participants will be instructed to stop their current topical testosterone therapies and wait at least one day, but no more than 7 days prior to initiating treatment with NATESTO;
- Instruct participants that on Day 30 (Visit 2) and Day 60 (Visit 3), they will be contacted by the Study Coordinator via telephone to complete TSQM and qADAM questionnaires and be asked about any adverse events and concomitant medications;
- Instruct participant to contact the site to report any adverse event experienced during the treatment period.
- Schedule Visit 4 (Day 90).

5.1.2 Treatment Period

Visit 2 (Day 30)

The following procedures will be performed at Visit 2:

- Telephone call by Study Coordinator to complete TSQM and qADAM questionnaires, confirm patient compliance with NATESTO (is the patient taking NATESTO as prescribed) and query concomitant medications and AEs

Visit 3 (Day 60)

The following procedures will be performed at Visit 3:

- Telephone call by Study Coordinator to complete TSQM and qADAM questionnaires, confirm patient compliance with NATESTO (is the patient taking NATESTO as prescribed) and query concomitant medications and AEs.

Visit 4 (Day 90)

All patients will be required to complete Visit 4.

The following procedures will be performed at Visit 4:

- Assess and record adverse events;
- Record concomitant medications;
- Height and Weight
- Obtain vital sign measurements (heart rate, blood pressure, and temperature);
- Perform physical examination including a nasal examination;
- Ask patient to complete TSQM, qADAM; and for those patients adequately controlled on BID complete Part B (for Non-naïve) or Part C (for Naïve) of the Patient Preference and Use Questionnaire;
- Assess patient's hypogonadism symptoms, primarily by questioning the patient about their level of energy (tiredness) and interest in sex life;
- Register participant completion of the study in the DM system, if symptoms are properly managed at BID dose;
- The physician will decide whether the patient a.) should return to their previous therapy; b.) remain on NATESTO; or c.) consider a new treatment option. The physician will provide the patient with a prescription for the treatment chosen.
- Request serum total testosterone measurement at local lab along with blood draw for assessment of hematocrit, lipid profile (total cholesterol, LDL, HDL and triglycerides), hemoglobin, liver function tests (liver enzyme levels).

For patients who do not respond clinically to a BID Dose:

- Provide a 30-day TID drug prescription, if the patient's symptoms are not adequately managed and extend treatment period to Day 120 with NATESTO.
- Instruct patient to increase daily NATESTO dose to TID, if necessary (e.g. patient does not feel better as compared to the start of treatment with NATESTO);
- Instruct participant to contact the site to report any adverse event experience during the treatment period.
- Schedule Day 120 (Visit 5).

Visit 5 (Day 120)

Only patients prescribed NATESTO TID will be required to complete Visit 5.

The following procedures will be performed at Visit 5:

- Assess and record adverse events;
- Record concomitant medications;
- Height and Weight
- Obtain vital sign measurements (heart rate, blood pressure, and temperature);
- Perform physical examination including a nasal examination;
- Ask patient to complete TSQM, qADAM and to complete Part B (for Non-naïve) or Part C (for Naïve) of the Patient Preference and Use Questionnaire.
- Assess patient's hypogonadism symptoms, primarily by questioning the patient about their level of energy (tiredness) and interest in sex life;
- Register participant completion of the study in the DM system;
- The physician will decide whether the patient a.) should return to their previous therapy; b.) remain on NATESTO; or c.) consider a new treatment option. The physician will provide the patient with a prescription for the treatment chosen.
- Request serum total testosterone measurement at local lab along with blood draw for assessment of hematocrit, lipid profile (total cholesterol, LDL, HDL and triglycerides), hemoglobin, liver function tests (liver enzyme levels).

5.1.3 Post Study Follow Up (Day 150).

All patients will be required to complete the Post Study Follow Up.

- Patient will contacted by phone to determine if they have continued on NATESTO (Y/N). If they have discontinued, ask when approximately, and why.

5.1.4 Early Termination Visit

For participants who withdraw from the study prematurely, an Early Termination Visit should if possible be scheduled. See Section 10, Treatment Discontinuation/Participant Withdrawals.

The following procedures will be performed at the Early Termination Visit:

- Assess and record adverse events;
- Record concomitant medications;
- Height and Weight
- Obtain vital signs measurements (heart rate, blood pressure, and temperature);
- Perform physical examination including a nasal examination;
- Instruct participant to restart prior testosterone medication (if applicable);
- Register participant discontinuation from the study in the DM system;
- Request serum total testosterone measurement at local lab along with blood draw for assessment of hematocrit, lipid profile (total cholesterol, LDL, HDL and triglycerides), hemoglobin, liver function tests (liver enzyme levels).

Ask patient to complete TSQM, qADAM and to complete Part B (for Non-naïve) or Part C (for Naïve) of the Patient Preference and Use Questionnaire.

5.2 Study Procedures

5.2.1 Medical, Surgical, and Family History

Medical history information will be collected from all participants during the Visit 1, Day 0. Medical history will include hypogonadism history, family history and details regarding all illnesses and allergies, date(s) of onset, status of current condition, and smoking, drug and alcohol use. Additional information to be collected includes past surgical and medical procedures as well as medications.

5.2.2 Demographics

Demographic information will be collected from all participants during the Visit 1, Day 0. Demographic information will include day, month, and year of birth, race and gender.

5.2.3 Vital Signs

Vital signs will be measured during Visit 1, Day 0, and Visit 4, Day 90 and Visit 5, Day 120 (for TID subjects), and at Early Termination, if applicable. Vital signs will include heart rate, blood pressure, and temperature.

5.2.4 Physical Examination

A physical examination including a nasal examination will be performed during the Visit 1 (Day 0), at Visit 4 (Day 90) and Visit 5 (Day 120) [only for TID] or at Early Termination, if applicable. The physical examination must include general appearance, skin, and specific head and neck, heart, lung, abdomen and extremities.

5.2.5 Height and Weight

Height and weight will be measured during the Visit 1, Day 0 and Visit 4, Day 90 and Visit 5, Day 120 (for TID subjects), and at Early Termination, if applicable. Measurement of weight should be performed with the participant dressed, coat and shoes removed and bladder empty.

5.2.6 Total Testosterone Test

Total Testosterone measurement will be performed for patients who are assessed to be effectively controlled on BID after Visit 4 (Day 90); and for patients on the higher dose frequency (TID) after Visit 5 (Day 120) at the local laboratory. **Blood sample will need to be taken 20 minutes to 2 hours after the morning dose of NATESTO.**

5.2.7 Blood Test

Blood will be drawn at a local laboratory for assessment of hematocrit, lipid profile (total cholesterol, LDL, HDL and triglycerides), hemoglobin and liver function tests (liver enzyme levels) at Visit 1 (all subjects), Visit 4 (all subjects) and Visit 5 (TID subjects). However, if at Visit 1, the patient already has these values documented in their patient file from the preceding 6 months, then those values can be entered into the eCRF and a fresh test will not be required.

6 TREATMENT AND RESTRICTIONS

6.1 Treatment

6.1.1 Treatment Regimen, Dosage, and Duration

All study participants who meet the entry criteria will be assigned to NATESTO twice daily administration (BID). Patients will be provided with a prescription for 90 days of the study medication, NATESTO, and a Study Drug Access Card which will be used for payment purposes. Patients can fill their prescription using the Study Drug Access Card at their preferred pharmacy. The site will contact the patient on Day 4 to record the date of the first dose of NATESTO.

Participants will be instructed to administer 5.5 mg of testosterone (1 actuation) per nostril of NATESTO once in the morning and once in the evening (at least 6 hours apart), preferably at the same time each day for a total daily dose of 22 mg/day of testosterone. Patients should be instructed to completely depress the pump 1 time in each nostril to receive the total dose.

For three times daily (after Visit 4 [Day 90] if symptoms not adequately managed by a BID dose), NATESTO will be administered intranasally once in the morning, once in the afternoon and once in the evening (approximately 6-8 hours apart), preferably at the same time each day for a total daily dose of 33 mg/day of testosterone.

The maximum total duration of study participation for participants will be up to 150 days (~21 weeks).

6.1.2 Treatment Assignment

6.1.2.1 Identification Number

Participant identification numbers will consist of 6 digits. The first 3 digits will be the 3-digit site number assigned to the Investigator and the second 3 digits will be the 3-digit participant number.

The participant identification number will be used to identify the participant throughout the study and will be entered on all documentation. A participant identification number will not be assigned to more than 1 participant. If a participant is not eligible to receive treatment, or if a participant discontinues from the study, the participant identification number cannot be assigned to another participant. At Visit 1, site personnel will register the participant in the EDC system.

At Visit 1 (Day 0), qualified participants who meet all of the inclusion criteria and none of the exclusion criteria will receive a prescription for 90 days of open-label NATESTO along with a Study Drug Access Card. The participant will be instructed to obtain NATESTO from pharmacy within 3 days using their Study Drug Access Card. Non-naïve participants will be instructed to stop their current

topical testosterone therapies at least one day and up to 7 days prior to initiation of treatment with NATESTO. The patient will contact the site by telephone to indicate the date of their first dose. The Investigator, or designee, will enter the participant's first dose record in the EDC system to confirm the start of the study treatment.

6.2 Study Restrictions

6.2.1 Concomitant Medications

Any medications administered during the study must be documented in the EDC system. Participants must not have taken any investigational medication within 30 days prior to screening. Participants cannot participate in any other clinical study involving an investigational agent while participating in this study. Testosterone medications that are part of the participant's regimen at screening will be discontinued for the duration of the study.

Participants undergoing current treatment with other androgens (ie, DHEA), anabolic steroids, other sex hormones, or drugs that interfere with the metabolism of testosterone (i.e., anastrozole, clomiphene, dutasteride, finasteride, flutamide, ketoconazole, spironolactone, and testolactone), will be excluded from the study. Participants treated within the past 12 months prior to Screening with estrogens, GnRH agonists, or growth hormone will also be excluded.

Administration of any other intranasal medication, other than oxymetazoline-containing nasal sprays (e.g., Dristan 12-Hour Nasal Spray) for a short duration (no more than 3 days) is prohibited during the study.

6.2.2 Participant Restrictions

Participants should be instructed not to blow their nose or sniff for 1 hour after intranasal administration of NATESTO.

If a participant with a history of allergic rhinitis develops an exacerbation of rhinitis during the study, continued application of study drug will be permitted, provided the symptoms are mild according to the Investigator's assessment. Mild symptoms require sporadic treatment for control and are generally characterized by normal sleep, no impairment of activities of daily living, and no troublesome symptoms.

Participants with moderate and severe allergic rhinitis symptoms that cause an impairment of sleep and/or activities of daily living and that require daily treatment should be instructed to temporarily discontinue study drug application until symptoms improve. If these symptoms last longer than 72 hours or if longer treatment is required, participants will be evaluated for discontinuation from the study. The same restrictions will apply to participants with rhinitis of viral etiology during the study (i.e. influenza).

6.3 Important Added Safety Considerations

6.3.1 Endocrine and Metabolism

All diabetic patients (Type 1 and Type 2) should be followed carefully and the insulin or oral hypoglycemic dosage adjusted accordingly as testosterone may have a glucose lowering effect. The patient's endocrinologist should be advised of their participation in the My-T trial.

6.3.2 Genitourinary

If a patient presents with progressive difficulty with urination or a change in voiding habits, then PSA and a Digital Rectal Examination should be undertaken and evaluated accordingly.

6.3.3 Hepatic

NATESTO is not known to produce serious hepatic adverse events associated with some orally active androgens. Nonetheless patients should be asked about any signs or symptoms of hepatic dysfunction (e.g. jaundice) and the clinician should also review the results of the blood safety values for liver enzymes. If any indication of serious hepatic adverse effects are suggested, the patient should be discontinued on NATESTO while the cause is evaluated.

6.3.4 Hematologic

Increases in hematocrit, reflective of increases in red blood cell mass, may require discontinuation of NATESTO. The hematocrit value obtained at Day 90 for all patients and Day 120 for TID patients should be compared to the baseline value. If the hematocrit becomes elevated, NATESTO should be stopped until the hematocrit decreases to acceptable levels.

6.3.5 Respiratory

NATESTO may potentiate sleep apnea, particularly for any patients with obesity.

6.3.6 Sexual Function

NATESTO may cause patients to develop gynecomastia, priapism or excessive sexual stimulation, and also oligospermia may occur after prolonged exposure to NATESTO.

7 INVESTIGATIONAL PRODUCT

7.1 Clinical Study Material

NATESTO will be provided in multiple-dose dispensers by way of a prescription filled at the patient's preferred pharmacy. Placebo gel multiple-dose dispensers will be provided directly to the Investigator sites, which will only be used for the training of site personnel and participants.

7.2 Pharmaceutical Formulation

The study drug NATESTO, to be used in this trial, was approved on January 6, 2016 by Health Canada. It is provided in a multiple-dose dispenser with each finger-initiated actuation dispensing 122.5 mg of 4.5% w/w testosterone gel. The active ingredient is testosterone. The inactive ingredients are silicon dioxide, castor oil, and oleoyl polyoxylglycerides. Testosterone belongs to the pharmacologic class of androgens. The empirical formula of testosterone is C19H28O2 and its molecular weight is 288.4 Da.

7.3 Labeling and Packaging

A multiple-dose dispenser will be used for gel deposition into the nasal cavity. The dispenser is a finger-actuated dispensing system designed to deliver 122.5 mg of NATESTO (5.5 mg of testosterone) per actuation from a non-pressurized dispenser into the nasal cavity. The dispenser is designed to administer 30 doses (60 actuations; one dose equals one actuation to each nostril) of NATESTO after priming. The key components of the multiple-dose dispenser include a barrel, base, pump, and actuator, which are composed of polypropylene, and a piston, which is composed of polyethylene.

All study drug dispensers will be labeled according to regulatory requirements for marketed products in Canada.

7.4 Dispensing Procedures and Storage Conditions

7.4.1 Dispensing Procedures

Patients will be prescribed a 90 day supply of the study medication, NATESTO, and a Study Drug Access Card for payment purposes. Patients can fill their prescription using the Study Drug Access Card at their preferred pharmacy.

All participants will be trained on proper administration of NATESTO. See Appendix B for priming and drug administration instructions.

7.4.2 Storage Conditions

NATESTO is stored at room temperature (15º to 30°C). It should be kept in a safe place out of the reach and sight of children and pets.

After multiple-dose dispensers are primed, they should be kept with the dust cap securely in place. Gel that remains on the tip of the actuator should be wiped away using a clean, dry swab.

8 EFFICACY ASSESSMENTS

Primary efficacy is the self-reported patient satisfaction with treatment that will be assessed by the TSQM, Treatment Satisfaction Questionnaire for Medication, a validated, 9-item instrument with domains for Effectiveness, Convenience and Global Satisfaction. The change in satisfaction will be determined by the difference in values at Visit 4 (Day 90) relative to Visit 1; and values at Visit 5 (Day 120) relative to Visit 1 for patients up-titrated to TID.

Secondary efficacy variables are:

- For naïve patients the same efficacy assessment as stated above will be extended to being relative to Visit 2 – naïve patients cannot be assessed relative to Visit 1 as they will not have been taking any medication.
- Improvement in hypogonadism symptoms as measured by quantitative Androgen Deficiency in the Ageing Male (qADAM), a 10-item patient-reported outcome measure to evaluate the symptom severity of hypogonadism.
- Patient preference of therapy as measured by the Treatment Preference questionnaire.
- NATESTO dosing frequency assigned at Visit 4.

Exploratory analyses will include analysis of the monthly change of the primary or secondary efficacy measures, including global and domain specific analyses, over the treatment period.

9 SAFETY ASSESSMENTS

Safety assessments will include adverse events, clinical laboratory measurements of serum testosterone levels, vital sign measurements, and physical examination.

9.1 Adverse Events

An adverse event is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All adverse events, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

Adverse events, which include clinical laboratory test variables, will be monitored from the time of informed consent until study participation is complete. Participants should be instructed to report any adverse event that they experience to the Investigator and to contact the site between study visits to report any adverse events experienced. Beginning with Visit 1 (Day 0) Investigators should assess for adverse events at each visit and record the event on the appropriate adverse event eCRF. Adverse events that occur prior to treatment will be recorded as pre-treatment events.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate adverse event on the eCRF.

Any medical condition that is present when a participant is screened or present at Baseline that does not deteriorate should not be reported as an adverse event. However, medical conditions or signs or symptoms present at Baseline that change in severity or seriousness at any time during the study should be reported as an adverse event.

Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at Baseline and significantly worsen will be reported as adverse events. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. All abnormal laboratory values considered clinically significant by the Investigator must be recorded on the adverse event page of the eCRF. Significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant.

The Investigator will rate the severity (intensity) of each adverse event as mild, moderate, or severe, and will also categorize each adverse event as to its potential relationship to study drug using the categories of Definitely Unrelated, Unlikely, Possible, Probable, or Definitely Related.

Assessment of Severity

Severity will be assessed under the following scale:

Mild – An event that is usually transient in nature and generally not interfering with normal activities.

Moderate – An event that is sufficiently discomforting to interfere with normal activities.

Severe – An event that is incapacitating with inability to work or do usual activity or inability to work or perform normal daily activity.

Assessment of Causality

The relationship of an adverse event to the administration of the study drug is to be assessed according to the following definitions:

Definitely Unrelated
Should be reserved for those events which occur prior to administration of study drug (e.g. washout) or for those events which cannot be even remotely related to study participation.

Unlikely
Event with a time to drug intake that makes a relationship improbable (but not impossible). Disease or other drugs provide plausible explanations for the event.

Possible
The suspected adverse event may or may not follow a reasonable temporal sequence from administration of study drug but seems to be the type of reaction that cannot be dismissed as unlikely. The event could have been produced or mimicked by the participant's clinical state or by other modes of therapy concomitantly administered to the participant.

Probable
The suspected adverse event follows a reasonable temporal sequence from administration of study drug, abates upon discontinuation of the medication, and cannot be reasonably unexplained by the known characteristics of the participant's clinical state.

Definitely Related
Should be reserved for those events which have no uncertainty in their relationship to administration of study drug.

The following factors should also be considered:

- The temporal sequence from study drug administration;
    - The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases;
    - Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the participant may have.
- Concomitant medication;
    - The other medications the participant is taking or the treatment the participant receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study drug;
    - Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses; and
    - The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology and PK of the study drug.
    - The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

Suspected Adverse Reaction- Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of investigational new drug safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.

Unexpected Adverse Events- An unexpected adverse event is an adverse event either not previously reported or where the nature, seriousness, severity, or outcome is not consistent with the current Investigator's Brochure. Additionally, unexpected adverse events include those that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but not specifically mentioned as occurring with the particular drug under investigation.

9.2 Serious Adverse Events (SAEs)

An adverse event or suspected adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening adverse event;
    - NOTE: An adverse event or suspected adverse event is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the participant at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires hospitalization or prolongation of existing hospitalization;
    - NOTE: In general, hospitalization for treatment of a pre-existing condition(s) that did not worsen from Baseline is not considered an adverse event and should not be reported as an SAE.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect; or
- An important medical event.
    - NOTE: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

9.3 Serious Adverse Event Reporting-Procedure for Investigators

Initial Reports

All SAEs occurring from the time of informed consent through until Visit 4, Day 90 (BID patients) or Visit 5, Day 120 (TID patients) or the last administration of study drug must be reported to the Sponsor within 24 hours of the knowledge of the occurrence (this refers to any adverse event that meets any of the aforementioned serious criteria). Serious adverse events that the Investigator considers related to study drug occurring after the treatment period will also be reported to the Sponsor.

To report the SAE, the reporter must complete the Serious Adverse Event Report Form. When the form is completed and signed by the Investigator, the form will

be transmitted to Acerus c/o Innomar Strategies Inc., within 24 hours of awareness of the event. Reports are reviewed during normal business hours.

Safety Contact Information: Acerus c/o Innomar Strategies Inc.

Tel: 1-844-850-1642
Facsimile: 1-877-597-6344
e-mail: AcerusPV@innomar-strategies.com

The Investigator is required to submit SAE reports to the Institutional Review Board (IRB) in accordance with local requirements. All Investigators involved in studies using the same investigational product will receive any investigative new drug Safety Reports for onward submission to their local IRB as required.

Follow-Up Reports

The Investigator must continue to follow the participant until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment) or the participant dies. Within 24 hours of receipt of follow-up information, the Investigator must submit a new Serious Adverse Event Report Form stating that this is a follow-up to a previously reported SAE using the same contact details as above. Any supporting documentation (e.g., laboratory test reports, hospital discharge summary, or autopsy reports) may be attached to the Serious Adverse Event Report Form after removal of any identifying participant information (e.g., participant name, or initials).

10 TREATMENT DISCONTINUATION/PARTICIPANT WITHDRAWALS

Participants may be discontinued from the study at any time, at the discretion of the Investigator or request of the patient. The Sponsor or their representative should be notified if a participant is discontinued because of an adverse event or laboratory abnormality. Participants must be followed until the adverse event or laboratory abnormality is resolved.

A participant may be withdrawn for any of the following reasons:

- Participant withdraws consent or requests discontinuation from the study for any reason;
- Sponsor discontinues the study;
- Occurrence of a clinical or laboratory adverse event, either serious or non-serious, at the discretion of the Investigator;
- Need to initiate therapy with an excluded concomitant medication;
- Increase in serum PSA concentration >1.4 ng/mL above Baseline;
- Increase in hematocrit to >54%; or
- Any medical condition or personal circumstance that, in the opinion of the Investigator, exposes the participant to risk by continuing in the study or precludes adherence to the protocol.

Participants who are withdrawn from the study should complete all procedures described for Early Termination (see Section 5.1.4). Every attempt must be made to have the participant return for the Early Termination Visit.

11 STATISTICS

11.1 Analysis Populations

All Participants: This consists of all participants who signed the informed consent form.

Intent-to-Treat (ITT) : Participants who receive at least one dose of study drug and have a valid post-dose efficacy measurement.; this analysis set will serve as the basis for the primary analysis of efficacy.

Safety Population: All participants who received at least one dose of the study drug. This analysis set will be used for all assessments of safety and also some sensitivity analyses with respect to efficacy.

Per-Protocol (PP) Population: This will consist of all ITT participants who complete the 90-day Treatment Period without any major protocol deviations. Selected efficacy analyses may be repeated for the per-protocol population to confirm the robustness of the results for the ITT population.

11.2 Statistical Methods

11.2.1 General Considerations

Analyses (including the primary and secondary) will be performed on the complete study population and stratified by dose level). Further subgrouping may be considered.

The statistical analyses will be reported using validated summary tables, figures, and data listings generated with SAS Version 9.2 or higher.

Data from all assessments, whether scheduled or unscheduled, will be listed by participant and visit.

Continuous variables will be summarized with means, %CV, standard deviations (SDs), medians, minimums and maximums. For change from Baseline (CFB), individual differences of the scheduled post Baseline value to the Baseline value will be summarized. Categorical variables will be summarized by counts and by percentage of participants in corresponding categories. Percentages will be based on the overall N for the analysis set used unless otherwise specified.

11.3 Efficacy

11.3.1 Primary Analysis

The primary objective of this study is to measure patient satisfaction with testosterone replacement therapy before, during and after treatment with NATESTO. Patient satisfaction with treatment will be measured by TSQM (Treatment Satisfaction Questionnaire for Medication) Version 9, a 9 item validated instrument. TSQM domains include – Effectiveness, Convenience, Global Satisfaction. Point values will be assigned to each answer in the questionnaire according to Appendix C.

Domain scores will be the sum of the points of each question making up the domain. The scores for each domain will be summarized with descriptive statistics at Baseline and Day 90, and the change from Baseline at Day 90 for BID patients; similarly at Baseline and Day 120 for TID patients. Mean domain scores at Baseline and Day 90 for BID patients, and Day 120 for TID patients will be compared using ANOVA methods; any missing data points will be assessed using LOCF methodology and other statistical analyses as deemed appropriate.

11.3.2 Secondary Analysis

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

- Improvement in hypogonadism symptoms;
- Patient treatment preference versus prior testosterone replacement therapy;
- Frequency of daily dose of NATESTO;

Improvement in hypogonadism symptoms will be measured by the qADAM, a 10 point validated instrument. Point values will be assigned to each answer in the questionnaire according to Appendix D. The scores for each qADAM item will be summarized with descriptive statistics at Baseline and Day 90 (BID)/Day 120 (TID), and the change from Baseline at Day 90 (BID)/Day120 (TID). Patient treatment preference versus prior testosterone replacement therapy will be measured by the Treatment Preference questionnaire. Mean item scores at Baseline and Day 90(BID)/Day 120(TID) for these instruments will be compared using ANOVA methods.

Frequency of daily dosing with NATESTO will be summarized and descriptive statistics provided.

These analyses will be performed using the ITT population.

11.3.3 Exploratory Analysis

Exploratory analyses will include analysis of the rate of change of the primary or secondary efficacy measures over the treatment period, including the eventual extension.

11.4 Safety

Adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). A general summary of the adverse events and SAEs for each treatment group will be presented by the overall number of adverse events, the severity and the relationship to study drug. The incidence of treatment emergent adverse events will be summarized by system organ class and preferred term. The total testosterone laboratory data for both the BID and TID patient populations will be summarized and descriptive statistics provided. Vital signs will also be summarized by visit and by treatment group along with the change from Baseline. The clinical findings in the physical examination will be summarized at each scheduled visit. Other safety measurements will be summarized and/or listed, if necessary.

11.5 Sample Size Determination

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.

12 DATA MANAGEMENT AND RECORD KEEPING

12.1 Data Management

12.1.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the clinical research associate (CRA) during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for.

12.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

12.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All study-site personnel must log into the system using their secure user name and password in order to enter, review, or correct study data. These procedures must comply with the Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

12.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

- Latest version of MedDRA for adverse events and
- World Health Organization Drug Dictionary for concomitant medications.

12.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and deemed complete and correct by an Investigator who signed the protocol.

12.2 Record Keeping

Records of participants, source documents, monitoring visit logs, eCRFs, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, Acerus must be notified in writing and be given the opportunity to further store such records.

13 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator and research institution agree that Acerus, its representatives, regulatory authorities and the IRB will have the right, both during and after the clinical study, to review and inspect pertinent medical records related to the clinical study.

14 QUALITY CONTROL AND QUALITY ASSURANCE

CMX Research Inc., (CMX) as the agent for Acerus for Study Protocol NAT-2016-1, will perform quality control and quality assurance checks for this trial. Before the enrollment of any participant in this study, CMX personnel will review with the Investigator and site personnel the following documents: protocol, Product Monograph, eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs. Site visits will be performed by the CMX CRAs and/or other Acerus representatives. During these visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data is entered by the site, CMX will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators.

By signing the protocol, CMX and Acerus agree to be responsible for implementing and maintaining quality control and quality assurance systems with written standard operating procedures to ensure that studies are conducted and data are generated, documented, and reported in compliance with the protocol and accepted standards of Good Clinical Practice.

15 ETHICS AND GOOD CLINICAL PRACTICE COMPLIANCE

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human participants. Compliance with this standard provides public assurance that the rights, safety, and wellbeing of study participants are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

16 PUBLICATION POLICY

Acerus is responsible for preparing a fully integrated report in cooperation with the Investigators and CMX.

17 STUDY ADMINISTRATIVE INFORMATION

17.1 Protocol Amendments

Any amendments to the study protocol that seem to be appropriate as the study progresses will be communicated to the Investigator by CMX or Acerus. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB and Health Canada as required, unless immediate implementation of the change is necessary for participant safety. In this case, the situation must be documented and reported to the IRB within 5 working days.

17.2 Address List

17.2.1 Sponsor

Matthew Gronski, PhD
Senior Manager, Clinical Affairs
Acerus Pharmaceuticals Corporation
2486 Dunwin Drive
Mississauga
ON L5l 1J9,
Tel: 1-905-817-8191
Fax: 1-905-569-1809

17.2.2 Contract Research Organization

CMX Research Inc.
2 – 416 North Service Road East
Oakville, Ontario, L6H 5R2
Tel: 905-338-1078
Fax: 905-338-0054

17.2.3 Drug Safety

All serious adverse events and abnormal laboratory values associate with the study should be reported within 24 hours of receipt at the Investigator site to:

Acerus Pharmaceuticals Corp.
c/o Innomar Strategies Inc.
3470 Superior Court East Oakville, Ontario L6L 0C4
E-mail: AcerusPV@innomar-strategies.com
Tel: 1-844-850-1642
Fax: 1-877-597-6344

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19 SUPPLEMENT

19.1 Investigator's Agreement

By signing below I agree that:

I have read this protocol and agree to conduct this study in accordance with the design and specific provision of this protocol. I will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by Acerus Pharmaceuticals Corporation to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to Acerus Pharmaceuticals Corporation and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by Acerus Pharmaceuticals Corporation with or without cause, or by me if it becomes necessary to protect the best interests of the study participants.

I agree to conduct this study in full accordance with Health Canada Regulations, Institutional Review Board Regulations, and International Conference on Harmonization Guidelines for Good Clinical Practice.

_____ _____

Investigator's Signature Date

_____

Investigator's Name

APPENDIX A: 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, 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	

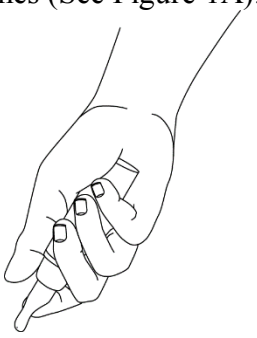
a. All subjects are required to complete Visit 4
b. Only subjects assigned to NATESTO TID are required to complete Visit 5
c. Naïve patients will require confirmation of hypogonadism by serum testosterone within the last 6 months
d. Only patients who continued on TID
e. TSQM to be completed by non-naïve 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

APPENDIX B: DRUG ADMINISTRATION PROCEDURES

PROCEDURE FOR MULTIPLE-DOSE DISPENSER PRIMING (to be performed by the site coordinator prior to the first use only):

Before use of the applicator for the first time, it is necessary to prime the applicator pump.

How to prime the applicator pump:
Hold the applicator over a sink, turn it upside down (invert) and slowly press the pump and release 10 times (See Figure 1A).

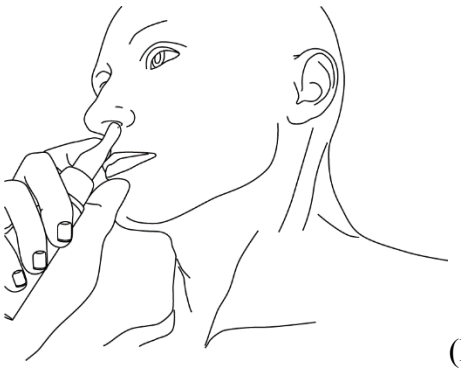


(Figure 1A)

All the gel that comes out when the pump is primed should be rinsed down the sink with warm water.
If there is any gel on the tip of the actuator after priming, wipe the tip with a clean, dry tissue.
If any gel gets on your hands, it is recommended to wash your hands with warm water and soap.

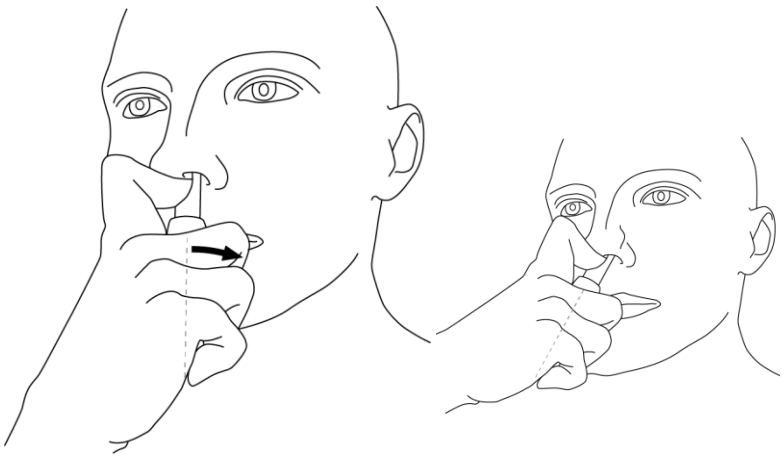
PROCEDURE FOR MULTIPLE-DOSE DISPENSER (Participant Instructions):

Applying the nasal gel with the applicator:
Step 1: Blow your nose.
Step 2: Remove the applicator cap.
Step 3: While looking in the mirror, put your right first (index) finger on the pump of your actuator and slowly slide the tip of the actuator up into your left nostril until your finger on the pump touches the bottom of your nose (See Figure A).



(Figure A)

Step 4: Gently tilt the actuator so that the hole in the tip touches the lateral (side) wall of your nostril. This will make sure that the gel is delivered in the correct place (See Figure B).

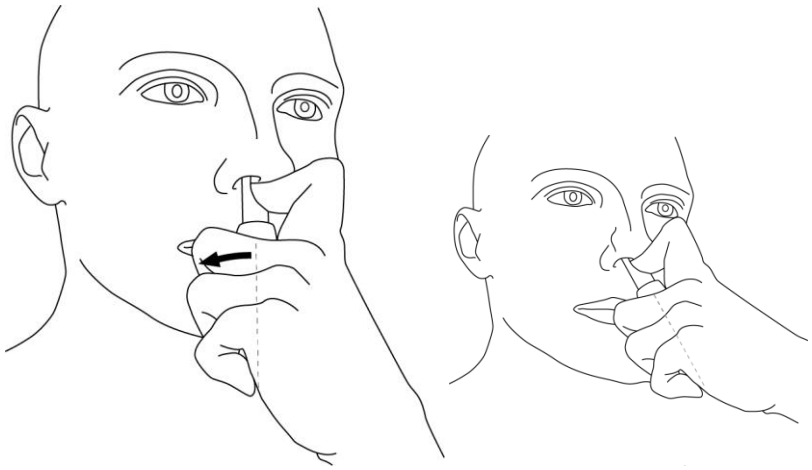


(Figure B)

Step 5: With the actuator in place, slowly push the pump down until it stops and remove the actuator from your nose.
Step 6: While looking in the mirror, put your left first (index) finger on the pump of your actuator and slowly slide the tip of the actuator up into your right nostril until your finger on the pump touches the bottom of your nose (See Figure C).

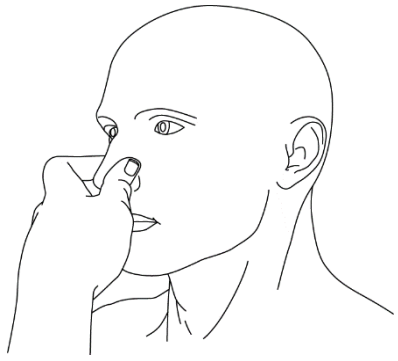
(Figure C)

Step 7: Gently tilt the tip of the actuator so that the hole in the tip touches the lateral (side) wall of your nostril. This will make sure that the gel is delivered in the correct place (See Figure D).



(Figure D)

Step 8: Slowly push down on the pump until it stops and remove the actuator from your nose.
Step 9: Wipe the tip of the actuator with a clean, dry tissue.
Step 10: Replace the cap.
Step 11: Press your nostrils together just below the middle of your nose (bridge) and lightly rub them together (See Figure E).



(Figure E)

APPENDIX C: TSQM

TSQM-9

Abbreviated Treatment Satisfaction Questionnaire for Medication

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are taking in this clinical trial. We are interested in your evaluation of the effectiveness, side effects, and convenience of the medication *over the last two to three weeks, or since you last used it*. For each question, please place a single check mark next to the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

3. How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

4. How easy or difficult is it to use the medication in its current form?

☐1 Extremely Difficult
☐2 Very Difficult
☐3 Difficult
☐4 Somewhat Easy
☐5 Easy
☐6 Very Easy
☐7 Extremely Easy

5. How easy or difficult is it to plan when you will use the medication each time?

☐1 Extremely Difficult
☐2 Very Difficult
☐3 Difficult
☐4 Somewhat Easy
☐5 Easy
☐6 Very Easy
☐7 Extremely Easy

6. How convenient or inconvenient is it to take the medication as instructed?

☐1 Extremely Inconvenient
☐2 Very Inconvenient
☐3 Inconvenient
☐4 Somewhat Convenient
☐5 Convenient
☐6 Very Convenient
☐7 Extremely Convenient

7. Overall, how confident are you that taking this medication is a good thing for you?

☐1 Not at All Confident
☐2 A Little Confident
☐3 Somewhat Confident
☐4 Very Confident
☐5 Extremely Confident

8. How certain are you that the good things about your medication outweigh the bad things?

☐1 Not at All Certain
☐2 A Little Certain
☐3 Somewhat Certain
☐4 Very Certain
☐5 Extremely Certain

9. Taking all things into account, how satisfied or dissatisfied are you with this medication?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

APPENDIX D: qADAM

Questions Used as Part of the qADAM Questionnaire

1. How would you rate your libido (sex drive)?
   1(terrible) 2(poor) 3(average) 4(good) 5(excellent)

2. How would you rate your energy level?
   1(terrible) 2(poor) 3(average) 4(good) 5(excellent)

3. How would you rate your strength/endurance?
   1(terrible) 2(poor) 3(average) 4(good) 5(excellent)

4. How would you rate your enjoyment of life?
   1(terrible) 2(poor) 3(average) 4(good) 5(excellent)

5. How would you rate your happiness level?
   1(terrible) 2(poor) 3(average) 4(good) 5(excellent)

6. How strong are your erections?
   (1= extremely weak 5= extremely strong)
   1 2 3 4 5

7. How would you rate your work performance over the past 4 weeks?
   1(terrible) 2(poor) 3(average) 4(good) 5(excellent)

8. How often do you fall asleep after dinner?
   1(never) 2(1-2/week) 3(3-4/week) 4(5-6/week) 5(every night)

9. How would you rate your sports ability over the past 4 weeks?
   1(terrible) 2(poor) 3(average) 4(good) 5(excellent)

10. How much height have you lost?
    1(2" or more) 2(1.5-1.9") 3(1-1.4") 4(0.5-0.9") 5(none-0.4")

APPENDIX E: PATIENT PREFERENCE & USE QUESTIONNAIRE

OVERVIEW

- Patients will undertake the questionnaire as follows:
    - All patients will complete PART A at Visit 1 (Day 0)
    - Patients who were assessed to be controlled on BID will complete PART B if **Non-naïve** and PART C if **Naïve** at Visit 4 (Day 90)
    - Patients who were up-titrated to TID will complete PART B if **Non-naïve** and PART C if **Naïve** at Visit 5 (Day 120)

- The Study Coordinator is to enter the Patient Study Number for the patient on their questionnaire

Part A: ALL PATIENTS at Study Initiation

1. Patient Study Number (**to be entered by Study Coordinator**) _____
2. Age (years) _____
3. City, Province _____
4. Date _____

5. Read the list of symptoms below, indicate if you have experienced each symptom (in the Y/N column) and how important it is for you to treat that symptom.

My low-testosterone symptoms include ….	Do you or did you experience these symptoms? (Y/N)	If yes, please rate how important this symptom was to you. (put an x in the appropriate column)			
		Very Important	Important	Somewhat Important	Not Important at all
Low sex drive					
Difficulty achieving or maintaining an erection					
Increased body fat					
Decreased muscle/strength					
Fatigue (tiredness)/loss of energy					
Decreased physical activity/vitality					
Loss of facial, underarm and/or pubic hair					
Decline in general feeling of well-being					
Depression (feeling unhappy)/depressed mood					
Mood changes/irritability					
Inability to concentrate					
difficulty falling asleep/staying asleep					

6. Of the above symptoms please tell us which is the most important symptom for you : _____

7. Read each statement and indicate how important each of the following considerations are to you when selecting your testosterone treatment.

My Testosterone Therapy (TRT) ……..	If yes, please rate how important this aspect is to you. (put an x in the appropriate column)			
	Very Important	Important	Somewhat Important	Not Important at all
restores my testosterone levels to the normal range				
relieves my symptoms				
has no/few side effects				
Is easy to administer/use				
is affordable				
is recommended by my physician				
is recommended by my friends/family				
should be at the lowest dose of testosterone that provides symptom relief				
minimizes the risk of transference to women and/or children				

8. Were you ever prescribed a testosterone replacement therapy prior to this study?
   - ☐ Yes – Please continue and answer questions 9-13 below.
   - ☐ **No – Please stop here and return the questionnaire to the Study Coordinator**

9. Answer the following questions:

	Family Doctor	Urologist	Endocrinologist	Other Specialist (specify type)	Not Applicable
Which doctor did you see first regarding your symptoms?					
Which doctor first diagnosed your low testosterone condition?					
Which doctor asked you to do a blood test to confirm the diagnosis of low testosterone?					
Which doctor gave your first prescription for testosterone therapy?					
Which doctor now prescribes your testosterone treatment?					

10. Answer Yes or No to the following questions

	YES	NO	Don't Know
Were you asked to undertake a blood test for your testosterone level			
Did you research low testosterone and possible treatment options prior to visiting your physician?			
Did you ask your physician/specialist to prescribe a specific product for low testosterone?			
If yes, did your physician prescribe the specific testosterone product you asked for?			
Did you ever interrupt your testosterone therapy for any reason after you were placed on a therapy?			

11. For your previous testosterone replacement therapy (TRT) list the brand(s) and approximate length of time you used each one

TRT Brand (e.g. Axiron, Androgel, Androderm, Testim)	Length of Time Used (approx.) (put an x in the appropriate column)				
	0-3 months	3-6 months	6-12 months	1-2 years	2+ years

12. If you listed more than one prescription TRT brand above, indicate the reason(s) why you switched from one product to another.

    _____
    _____
    _____

13. If you ever paused or interrupted therapy for a period of time, can you explain why?

    _____
    _____
    _____

Part B: At Study Completion for Non-naïve Patients

1. Patient Study Number (**to be entered by Study Coordinator**) _____
2. Age _____
3. City, Province _____
4. Date _____

5. Are you aware that the testosterone from gels or solutions that are normally applied to the skin (i.e. shoulders, upper arms, etc.) can accidentally get onto and through the skin of women and children, causing undesirable side effects, such as early puberty or masculinization (hair growth, voice changes)?
   - ☐ Yes
   - ☐ No

6. Is being on the lowest effective dose of testosterone important to you?
   - ☐ Yes
   - ☐ No

7. Please indicate if you agree or disagree with the following statements. **(Check one box per line).**

General Statements	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree	Not applicable
NATESTO restores my testosterone levels back to a normal range						
NATESTO relieves my symptoms						
NATESTO has no/few side effects						
NATESTO is easy to administer/use						
NATESTO is the lowest dose of testosterone that will provide symptom relief						
NATESTO cannot be transferred to women and/or children						
NATESTO is affordable						

Use Statements	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree	Not applicable
NATESTO is easier to use than my previous testosterone therapy						
NATESTO is less messy than my previous testosterone therapy						
NATESTO takes less time to use than my previous therapy						
I can take NATESTO at home without visiting my doctor						
The time it takes to use NATESTO is acceptable/convenient						
Symptom Statements	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree	Not applicable
NATESTO alleviates my symptoms better than my previous therapy						
NATESTO increased my sex drive						
NATESTO helps in achieving and/or maintaining an erection						
NATESTO reduced my body fat						
NATESTO increased my muscle/strength						
NATESTO increased my energy level						
NATESTO increased my physical activity level/vitality						
NATESTO reduced my loss of facial, underarm and/or pubic hair						
NATESTO improved my general feeling of well-being						
NATESTO helped me feel less depressed						
NATESTO helped me to feel less irritable						
NATESTO improved my concentration						
NATESTO improved my ability to fall asleep/stay asleep						
Preference Statements	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree	Not applicable
I prefer NATESTO over other testosterone therapies						

8. How much would you be willing to pay out-of-pocket for NATESTO if your health insurance does not cover the full amount or you do not have health insurance? (Select one)

- ☐ Up to $25 per month
- ☐ Up to $50 per month
- ☐ Up to $75 per month
- ☐ Up to $100 per month
- ☐ Up to $150 per month
- ☐ I would not pay anything out-of-pocket for NATESTO

9. If NATESTO cost you exactly the same as the product you were using before joining the study, would you choose to switch to NATESTO?

- ☐ Yes
- ☐ No
- ☐ Undecided

10. What do you like about NATESTO?

_____
_____
_____
_____
_____

11. What do you dislike about NATESTO?

_____
_____
_____
_____
_____

12. Following this study, do you plan to continue taking NATESTO?

- ☐ Yes
- ☐ No
- ☐ Undecided

Part C: At Study Completion for Naïve Patients

1. Patient Study Number (**to be entered by Study Coordinator**) _____
2. Age (years) _____
3. City, Province _____
4. Date _____

5. Are you aware that the testosterone from gels or solutions that are normally applied to the skin (i.e. shoulders, upper arms, etc.) can accidentally get onto and through the skin of women and children, causing undesirable side effects, such as early puberty or masculinization (hair growth, voice changes)?
   - ☐ Yes
   - ☐ No

6. Is being on the lowest effective dose of testosterone important to you?
   - ☐ Yes
   - ☐ No

7. Please indicate if you agree or disagree with the following statements. **(Check one box per line).**

General Statements	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree	Not applicable
NATESTO restores my testosterone levels back to a normal range						
NATESTO relieves my symptoms						
NATESTO has no/few side effects						
NATESTO is easy to administer/use						
NATESTO is the lowest dose of testosterone that will provide symptom relief						
NATESTO cannot be transferred to women and/or children						
NATESTO is affordable						

Use Statements	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree	Not applicable
I can take NATESTO at home without visiting my doctor						
The time it takes to use NATESTO is acceptable/convenient						
Symptom Statements	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree	Not applicable
NATESTO increased my sex drive						
NATESTO helps in achieving and/or maintaining an erection						
NATESTO reduced my body fat						
NATESTO increased my muscle/strength						
NATESTO increased my energy level						
NATESTO increased my physical activity level/vitality						
NATESTO reduced my loss of facial, underarm and/or pubic hair						
NATESTO improved my general feeling of well-being						
NATESTO helped me feel less depressed						
NATESTO helped me to feel less irritable						
NATESTO improved my concentration						
NATESTO improved my ability to fall asleep/stay asleep						

8. How much would you be willing to pay out-of-pocket for NATESTO if your health insurance does not cover the full amount or you do not have health insurance? (Select one)
   - ☐ Up to $25 per month
   - ☐ Up to $50 per month
   - ☐ Up to $75 per month
   - ☐ Up to $100 per month
   - ☐ Up to $150 per month
   - ☐ I would not pay anything out-of-pocket for NATESTO

9. What do you like about NATESTO?

_____
_____
_____
_____
_____

10. What do you dislike about NATESTO?

_____
_____
_____
_____
_____

11. Following this study, do you plan to continue taking NATESTO?
    - ☐ Yes
    - ☐ No
    - ☐ Undecided