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A Comparison of Side Effects in Hypogonadal Men Treated with Natesto® versus Testosterone Injections: A Phase IV, Prospective, Randomized, Non-Blinded, Multi-Institutional Study

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Table of Contents

1.BACKGROUND 6
1.1 Study Disease 6
1.2 Study Interventions 6
1.3 Study Rationale 6
2. HYPOTHESIS 7
2.1 Alternate hypothesis 7
2.2 Null Hypothesis 7
3. OBJECTIVES 7
3.1 Primary Efficacy Objective 7
3.2 Secondary Efficacy Objective 7
4. STUDY DESIGN 7
4.1 Accrual goal 7
4.2 Duration of Study Participation 8
5 STUDY ENTRY, ENROLLMENT AND WITHDRAWAL 8
5.1 Study Entry 8
5.2 Enrollment Procedure 8
5.3 Cancellation Guidelines 8
6. SUBJECT SELECTION/ELIGIBILITY CRITERIA 9
6.1 Inclusion (Eligibility) Criteria 9
6.2 Exclusion (Eligibility) Criteria 9
6.3 Study Population 10
7. STUDY DESIGN, CLINICAL, RADIOLOGICAL, LABORATORY AND SURGICAL EVALUATIONS 11
7.1 Study Design 11
7.2 Screening Evaluations and Procedures 11
7.3 Pre-Treatment Procedures and Evaluations 11
7.4 Follow-Up Procedures and Evaluations: 11
7.5 Reimbursement 11
8. ADVERSE EVENTS 11
8.1 Expected Adverse Events 12
8.2 Serious Adverse Events 12
9. DATA AND SAFETY MONITORING PLAN 12
10. STATISTICAL CONSIDERATIONS 12
10.1 Primary Study Endpoints 12
10.2 Endpoint definitions 13
10.3 Sample size, accrual and study duration 13
10.4 Statistical Analysis and Power calculation 13
11. INVESTIGATORS RESPONSIBLITIES 13
11.1 Investigator Responsibility/Performance 13
11.3 Confidentiality 13

11.4 Informed Consent and Permission to Use Protected Health Information 14
11.5 Source Documentation and Investigator Files 14
11.6 Recording and Processing of Data 15
11.7 Non-Protocol Research 15
11.8 Ethics 15
11.9 Essential Documents for the conduct of a clinical trial 15
12. STUDY CALENDAR 16
13 REFERENCES 17

Investigator's Statement

This clinical trial shall be conducted in compliance with the protocol, as referenced herein, and all applicable local, national, and international regulatory requirements to include, but not be limited to:

- International Conference on Harmonization (ICH) Guidelines on Good Clinical Practice (GCP)
- Ethical principles that have their origins in the Declaration of Helsinki
- Food and Drug Administration (FDA) Code of Federal Regulation (CFR):
  - Title 21CFR Part 50 and 45 CFR Part 46, Protection of Human Patients
  - Title 21CFR Part 54, Financial Disclosure by Clinical Investigators
  - Title 21CFR Part 56, Institutional Review Boards
  - Title 45 CFR Parts 160, 162, and 164, Health Insurance Portability and Accountability Act (HIPAA)

As the Principal Investigator, I understand that my signature on the protocol constitutes my agreement and understanding of PI responsibilities to conduct the clinical trial in accordance to the protocol and applicable regulations. Furthermore, it constitutes my understanding and agreement that any changes initiated by myself, without prior agreement in writing from the Sponsor, shall be defined as a deviation from the protocol, and shall be formally documented as such.

I understand that my signature constitutes agreement and understanding of acceptance of the defined responsibilities of a Sponsor-Investigator as defined by the protocol, applicable FDA Regulations, and/or business contracts, but does not in any capacity relieve me of my responsibilities as the Sponsor-Investigator. Additionally, my signature constitutes my understanding and agreement that any changes to the protocol shall be implemented timely with my review and approval prior to implementation.

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INVESTIGATOR'S AGREEMENT

I confirm that I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practices, and the applicable federal, state, and local laws, rules, and regulations relating to the conduct of the protocol.

I have read and understand the information in the Instructions for Use (and/or other such pertinent safety information) regarding the risks and potential benefits.

I agree to inform all those who assist/collaborate with me in the conduct of this study of their responsibilities and obligations.

Once the protocol has been reviewed and approved by the Institutional Review Board (IRB) I understand that any change(s) made during the course of the study must also (first) be approved by the IRB prior to implementation, except when such modification is made to remove any immediate hazard(s) to the subject(s).

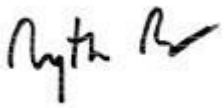
I certify that I, and the study staff responsible, have received the requisite training to conduct this research protocol.

I agree to maintain adequate and accurate records in accordance with the University of Miami policies, federal, state and local laws and regulations.

I agree to maintain the confidentiality of all information received and/or developed in connection with this protocol.

Ranjith Ramasamy

Print Name of Physician



Physician's Signature

02/17/2020
Date

1.BACKGROUND

1.1 Study Disease

Administration of exogenous testosterone as efficacious treatment for male hypogonadism has been part of medical practice for more than 50 years. Testosterone has both anabolic and androgenic properties serving as the primary male hormone promoting development of male reproductive tissues such as the prostate and testis. Several androgen replacement modalities are FDA approved and commercially available or are under clinical investigation. Options for testosterone replacement include intramuscular injection of testosterone esters, subcutaneous implants, transdermal patches, oral tablets and capsules, buccal and sublingual forms, topical gel formulations of testosterone and 5α-dihydrotestosterone (DHT), and intranasal gels, currently marketed as name brand Natesto®.

Testosterone can activate androgen receptors in its native form or it can be converted to 5α-dihydrotestosterone (DHT) by the enzyme 5α reductase before binding to the androgen receptor. Once bound, the receptor-hormone complex moves into the cell nucleus inducing cell specific gene expression profiles, therefore promoting protein synthesis and growth/differentiation of tissues that are sensitive to its action.[1]

Hypogonadism, or low testosterone (Low T), is defined by a deficiency in producing normal amounts of testosterone due to a failure of the testicles (primary hypogonadism), pituitary gland (secondary hypogonadism). Hypogonadism is accompanied by symptoms, such as decreased libido, depression and/or lack of energy. Low T affects more than 10% of men worldwide, with higher incidence in the elderly.[2] It typically occurs in association with aging, chronic disease, physical trauma, chemotherapy and other modifiable risk factors such as obesity and diabetes.[1] Testosterone deficiency has been associated with less muscle mass[4], lower bone mineral density[5], anemia[6], diminished energy and sexual dysfunction.[8,9]

1.2 Study Interventions

Testosterone replacement therapy (TRT) is becoming more widely available and has seen a greater than three-fold increase in use in men 40 years and older.[10] Current delivery systems of TRT include transdermal gels and patches[11], intranasal gels (currently marketed as Natesto®)[12], injection therapy[13], and long acting subcutaneous pellets.[14] TRT has been shown to improve bone mineral density, and sexual function with some studies suggesting improvement in energy, vitality, and depression symptoms.[9]

Advantages of testosterone nasal gel (Natesto®) over other TRT options includes ease of administration, relatively low dose exposure, and no risk of secondary transference. Natesto®, administered, using a multiple-dose dispenser, as three daily doses (5.5 mg per nostril, 11.0 mg single dose restores normal serum total testosterone (≥300 ng/dL, ≤1050 ng/dL) levels in most hypogonadal men after 90 days of use. More recently, it was found that 90.9% of men on Natesto® 11mg TID achieved normal testosterone levels (≥300 ng/dL) after 6 months of use).[12]

Natesto® is a short-acting formulation of testosterone delivered intranasally to men diagnosed with low T. This has the potential to avoid side effects related to TRT that are commonly seen with other delivery methods, namely polycythemia, acne, male-pattern hair loss, azoospermia and hyperestrogenemia. Daily topical applications present a risk of transfer of testosterone to partners and family members which is minimized with Natesto® since it is dispensed with a device high into the nostril and thereby does not come in contact with the hands, and further, the formulation is designed not to be absorbed through the skin (contains no lower alcohols or permeation enhancers).

1.3. Study Rationale:

Testosterone Cypionate injections are the most common form of TRT in the USA[17]. Testosterone Cypionate has many reported side effects, the most common being polycythemia, gynecomastia, hair loss, acne, decreased spermatogenesis, and testicular atrophy. In a multicenter retrospective study, it has been shown that the prevalence of polycythemia in men on testosterone replacement (injections) was 11.2%[16]. Uniquely, the incidence of polycythemia in patients using Natesto® is 1.3%.[15] In this study, we will compare hematocrit changes caused by treatment with f Testosterone Cypionate and Natesto® in a parallel arm, randomized study. To date, there have been no direct head-to-haed comparisons of these formulations.

Treatment was well tolerated, adverse events 2.1% (b.i.d.) and 3.7% (t.i.d.)

2. HYPOTHESIS

We hypothesize that the short-acting pharmacokinetics of Natesto® more closely resembles the natural pulsatility of testosterone and therefore can avoid side effects traditionally seen in long-acting, exogenous testosterone formulations.

2.1 Alternate hypothesis

The prevalence of side effects in subjects receiving 1 cc (200mg) every 2 weeks IM Testosterone Cypionate is greater than in the subjects receiving 11mg TID Natesto®.

2.2 Null Hypothesis

The prevalence of side effects in subjects receiving 1 cc (200mg) every 2 weeks IM Testosterone Cypionate the same as in the subjects receiving 11mg TID Natesto®.

3. OBJECTIVES

3.1 Primary Efficacy Objective

Primary outcome will be changes in Hematocrit (Hct) from baseline to 4 months.

3.2 Secondary Efficacy Objective

Secondary objectives will be changes in Testosterone (T), Estrogen (E), FSH, LH, 17-hydroxyprogesterone (17-OHP), Dihydrotestosterone (DHT), testicular volume, PSA, and SF-15 and IIEF-15 questionnaires from baseline to 4 months.

4. STUDY DESIGN

4.1 Accrual goal

A total of 200 subjects (estimate 10% dropout rate with 90 men in each arm) with low testosterone (<300ng/dL) on 2 morning measurements meeting the eligibility criteria will be recruited from the Department of Urology clinic.

4.2 Duration of Study Participation

Total study duration will be 4 months (120 days) and subjects will be provided enough testosterone to last until their next visit. Subjects will receive Natesto® 11mg TID or Testosterone Cypionate 200mg IM injections once every 2 weeks.

5. STUDY ENTRY, ENROLLMENT AND WITHDRAWAL

5.1 Study Entry

Study entry, as used in this protocol, will be defined as a subject signing informed consent. Study enrollment, as used in this protocol, will be defined as the investigator's confirmation of the subject's eligibility by signing an eligibility checklist. As per University of Miami policy, each study participant, including participants who have screened failed, who sign an informed consent form, should be entered into the study database.

5.2 Enrollment Procedure

Completed and signed protocol-specific eligibility checklist;

All pages of the original signed informed consent forms (ICFs), including HIPAA Form B;
Relevant source documents or medical records such as: subject medical history and physical exam, admission or discharge notes, diagnostic reports, pathologic confirmation of diagnosis, and relevant subject-specific written communication.

Documentation from the Investigator that he/she has determined the subject meets eligibility criteria.

5.3 Cancellation Guidelines

The following are reasons for withdrawal of subjects from the study:

- A subject does not meet the eligibility criteria; (the subject will be considered a screen failure).
- A subject withdraws consent,
- A subject dies during protocol participation from causes other than the study treatment (not due to adverse events) or
- A study investigator decides the subject should be withdrawn from the study (e.g. subject non-compliance)

Regardless of reason for withdrawal, an intention to treat analysis will be performed.

All subjects who either screen fails, is withdrawn from the study or has completed all visits should be de-enrolled from the research database within 48 hours.

6. SUBJECT SELECTION/ELIGIBILITY CRITERIA

6.1 Inclusion (Eligibility) Criteria

Subjects must meet the following criteria:

1. Voluntarily sign and date the study consent form(s), which have been approved by an Institutional Review Board (IRB). Written consent must be obtained prior to the initiation of any study procedures.

2. Male between 18 and 75 years of age.

3. Documented diagnosis of primary hypogonadism (congenital or acquired) or hypogonadotropic hypogonadism (congenital or acquired).

4. Serum total testosterone < 300 ng/dL on 2 measurements

5. Naïve to androgen replacement or has discontinued current treatment and completed a washout of 4 months following androgen treatment.

6. Men deemed to be candidates for TRT based on the results of a medical history, physical examination, vital signs, laboratory profile and a 12-lead electrocardiogram (ECG).

6.2 Exclusion (Eligibility) Criteria

Subjects meeting any of the following criteria will be excluded from the study:

1. History of significant sensitivity or allergy to androgens, or product excipients.

2. Clinically significant findings in the pre-study examinations including abnormal breast examination requiring follow-up, abnormal ECG.

3. Abnormal prostate digital rectal examination (DRE) with palpable nodule(s)

4. Body mass index (BMI) ≥ 40 kg/m2.

5. Clinically significant abnormal laboratory value, in the opinion of the investigator, in serum chemistry, hematology, or urinalysis including but not limited to:

   a. Baseline hemoglobin > 16 g/dL or HCT 48%

   b. PSA > 4 ng/mL

6. History of seizures or convulsions, including febrile, alcohol or drug withdrawal seizures.

7. History of any clinically significant illness, infection, or surgical procedure within 4 weeks prior to study drug administration.

8. History of stroke or myocardial infarction within the past 5 years.

9. History of, or current or suspected, prostate or breast cancer.

10. History of diagnosed, severe, untreated, obstructive sleep apnea.

11. History of abuse of alcohol or any drug substance in the opinion of the investigator within the previous 2 years.

12. Donation or loss of 550 mL or more blood volume (including plasmapheresis) or receipt of a transfusion of any blood product within 12 weeks prior to the start of treatment.

13. Inadequate venous access for collection of serial blood samples required for pharmacokinetic profiles.

14. Receipt of any subcutaneous testosterone pellets within the last 6 months.

15. Inability to understand and provide written informed consent for the study.

6.3 Study Population

The study will consist of 200 males suffering from low testosterone.

6.4 Setting

Subjects will be identified from those visiting the University of Miami – Department of Urology and the UHealth Fertility Center, and receiving the diagnosis of idiopathic hypogonadism. If they meet the inclusion criteria, the subjects will receive an explanation of the study. Subjects will be informed both verbally and in written form of the study and procedures involved. The PI, Resident, Fellows and/or the study coordinator will obtain a signed/dated Informed Consent Document (ICD) before enrolling each subject. Subsequent visits will take place in the same Clinic. Study data will be safely stored in a RedCap database.

7. STUDY DESIGN, CLINICAL, RADIOLOGICAL, LABORATORY AND SURGICAL EVALUATIONS

7.1 Study Design

This is a Phase IV, multicenter, prospective, randomized, non-blinded clinical study aimed to evaluate the comparison between Natesto® vs Testosterone Cypionate for men with low testosterone. Subjects will be enrolled in the study based on selection criteria designed to represent the general population of hypogonadal men while minimizing risk to study participants. Approximately 180 subjects will be enrolled to meet scientific and regulatory objectives. After meeting the selection criteria, the subjects will be randomly assigned in a 1:1 ratio such that 90 subjects will receive Natesto® and 90 subjects will receive Testosterone Cypionate (200mg) one every two weeks and be followed for 4 months. Subjects may be naive to testosterone treatment or may enroll after stopping current treatment and completing an adequate washout period.

7.2 Screening Evaluations and Procedures

The first visit of the subjects will be for screening and medical evaluation. Subject's medical history will be collected and documented and a physical examination will be performed.

Previous blood test results will be reviewed including a general chemistry panel and Testosterone levels during chart review.

Subjects will sign an informed consent and in case they meet all inclusion criteria (and do not meet any exclusion criteria), they will be recruited to the study.

7.3 Pre-Treatment Procedures and Randomization

The results of all screening evaluations must be within clinically acceptable limits, reviewed and approved by the investigator, prior to the start of treatment. Subjects who meet the inclusion criteria and do not meet any of the exclusion criteria may proceed to randomization. A central randomization scheme of 1:1 will be used. To account for a 10% dropout rate, 200 randomization

codes will be generated. As subjects are enrolled in the study, they will be assigned unique consecutive numbers starting at 001. At least 180 subjects who meet all the entry criteria will be randomized 1:1 such that approximately 90 subjects are assigned to the Natesto® treatment arm and 90 subjects are assigned to the Testosterone Cypionate arm in order to reach statistical power of 81.3% (randomization will be performed by a computer software maintained by the Department of Urology). Subjects enrolled in trial will be instructed to stop any use of androgen replacement therapy for 4 months prior to first treatment session and refrain from using any other testosterone therapy option during the study.

7.4 Treatment procedures

Intranasal testosterone will be administered using a multiple-dose dispenser, as two or three daily doses (5.5 mg per nostril, 11.0 mg single dose) for 4 consecutive months vs. intramuscular testosterone cypionate injections 1 cc (200mg) every 14 days for four months. Teaching session (for men to self medicate) will be conducted at the University of Miami, Professional Art center building unit 309 at the time of enrollment.

7.5 Follow-Up Procedures and Evaluations:

Follow-up visits will be conducted at 4 weeks and 16 weeks and include:

- Taking serum HCT, T, E, FSH, LH, 17-hydroxyprogesterone, DHT and PSA levels along with SF-15 and IIEF-15 questionnaires.

- Reporting and recording adverse events.

7.6 Reimbursement

The subjects prior to enrollment in the trial will be billed to the insurance or self-pay. Once enrolled in the trial, the medications and the visits will be covered as part of the study. Subjects will be provided testosterone study medication, injection or nasal, free of charge. For transportation and parking for the 2 study visits, the subjects will be provided a gift card for $50 at the end of the study.

8. ADVERSE EVENTS

8.1 Expected Adverse Events

In a 90-day clinical study, the most commonly reported adverse reactions to Natesto® were increased prostate specific antigen (PSA), headache, rhinorrhea, epistaxis, nasal discomfort, nasopharyngitis, upper respiratory tract infection (URI), sinusitis, bronchitis and nasal scab.

More common adverse reactions to Testosterone Cypionate include erythrocytosis, urinary retention, acne, reduced sperm production/infertility, and testicular atrophy/failure. Less

common adverse reactions include gynecomastia, adrenergic alopecia, worsening benign prostatic hyperplasia, obstructive sleep apnea or worsening of already existing obstructive sleep apnea, fluid retention, growth of an already existing prostate cancer, and breast cancer.[18]

8.2 Serious Adverse Events

Serious injury or death

Any adverse event and eventual complication must be recorded at any time during the treatments and the follow up visits, and throughout the entire study duration. Subjects will be instructed to alert the study investigator by telephone of any side effects occurring in the period after the treatment and until the study end.

9. DATA AND SAFETY MONITORING PLAN

The study investigators will report to a surgeon monitor Dr. Sanjay Swain in the department of urology (who is not involved in the study) to ensure data quality and subject safety. The investigators will conduct continuous reviews of the data and subject safety; keeping track of the number of subjects, significant toxicities in accordance with the protocol and observed responses, which will be discussed at research committee meetings. All grade 3-5 adverse events (CTCAE v4.0), regardless of association with the subcutaneous testosterone, will be entered into study database and reviewed at research committee meetings. In addition, all adverse reactions considered "serious", will be entered into the research database and reviewed by the Surgeon monitor on an ongoing basis. If a death occurs within 30 days of subcutaneous testosterone implantation treatment and is determined to be related to the study, the investigators will notify the Department Chair Dr. Dipen Parekh within 1 business day. If an increase in the frequency of grade 3 or 4 adverse events is noted in the study, a report will be submitted to the Department Chair Dr. Dipen Parekh at the time the increased rate is identified. If at any time the principal investigator stops enrollment or stops the study due to safety issues, the Department Chair (Dr. Dipen Parekh) will be notified within 1 business day and a formal letter will be sent to the Department Chair (Dr. Dipen Parekh) to be received within 10 business days. Additionally to reporting to the Department chair, all serious events will also be reported to the supervising IRB in the same timely manner.

10. STATISTICAL CONSIDERATIONS

10.1 Primary Study Endpoints

The primary endpoint will be change in Hematocrit levels after 4 months of treatment.

10.2 Secondary Study Endpoints

The secondary endpoints will be changes in T, E, FSH, LH, 17-hydroxyprogesterone, DHT, testicular volume, PSA levels and SF-15 and IIEF-15 questionnaires after 4 months of treatment.

10.3 Endpoint definitions

Total testosterone will be expressed in ng/dL, HCT(%), E (pg/ml), FSH (mlU/ml), LH (mlU/ml), 17-hydroxyprogesterone (ng/dL), DHT (ng/dl), testicular size (cc), PSA (ng/ml), and SF-15 and IIEF-15 questionnaires. Hormone determinations will be done by peripheral venous puncture blood draw.

10.4 Sample size, accrual and study duration

TOTAL SAMPLE SIZE: 180
TOTAL ACCRUAL: 200
ACCURAL DURATION: 12 months
STUDY DURATION: 4 months

10.5 Statistical Analysis and Power calculation

The average and standard deviation of all relevant variables and baseline characteristics, primary and secondary outcomes will be calculated.

The chi-square test will be used to evaluate difference of prevalence of polycythemia. Changes in testosterone, estrogen, 17-hydroxyprogesterone, DHT, testicular volume, PSA, and SF-15 and IIEF-15 questionnaires will be analyzed using means and standard deviations.

In a multicenter retrospective study, it has been shown that the prevalence of polycythemia in men on testosterone replacement (injections) was 11.2%[16]. Uniquely, the incidence of polycythemia in subjects using Natesto® is 1.3%.[15] In order for a power of at least 80% with an alpha of 0.05 we need to collect 90 subjects in each treatment arm.

10.6 Randomization:

180 subjects will be randomized 1:1 to 90 Natesto® vs 90 subjects in the Testosterone Cypionate injections. An online-based randomization tool called Redcap.com will be used. The PI will not have the knowledge of subject's treatment group beforehand. However, the study coordinator will be aware of the Natesto® vs Testosterone Cypionate injections randomization.

11. INVESTIGATORS RESPONSIBLITIES

11.1 Investigator Responsibility/Performance

The investigator (or a person designated by the investigator) should inform the subject of all pertinent aspects of the study, including the written information.

The investigator should provide the subject ample time and opportunity to inquire about details of the study and to decide whether to participate in the study or not. All questions about the study should be answered to the satisfaction of the subject. Neither the investigator, nor the study staff, should coerce or unduly influence a subject to participate or to continue to participate in a study.

11.3 Confidentiality

The identity of the subjects in this study will be treated as confidential. subjects eligible to participate in the study following the pre-treatment visit will be assigned a unique subject code. The results of the study, including any other data, may be published for scientific purposes but will not give the subjects' name or include any identifiable references to them. However, any records or data obtained as a result of the subject participation in this study may be inspected by the sponsor, by any relevant governmental agency, by the Hospital Ethics Committee, or by the persons conducting this study, provided that such inspectors are legally obligated to protect any identifiable information from public disclosure, except where disclosure is otherwise required by law or a court of competent jurisdiction. These records will be kept private as permitted by law.

11.4 Informed Consent and Permission to Use Protected Health Information

It is the responsibility of the investigator to obtain written informed consent from each subject participating in this study after adequate explanation, in lay language, of the methods, objectives, anticipated benefits, and potential hazards of the study. The investigator must also explain that the subject is completely free to refuse to enter the study or to discontinue participation at any time (for any reason) and receive alternative conventional therapy as indicated. Prior to study participation, each subject will sign an IRB approved informed consent form and receive a copy of same (and information leaflet, if appropriate).

The investigator or designee **must** explain to the subject before enrollment into the study that for evaluation of study results, the subject's protected health information obtained during the study may be shared with the study sponsor, regulatory agencies, and the IRB. It is the investigator's (or designee's) responsibility to obtain permission to use protected health information per HIPAA from each subject, or if appropriate, the subjects' parent or legal guardian.

11.5 Source Documentation and Investigator Files

The investigator will maintain adequate and accurate records to document the conduct of the study and to ensure that study data can be subsequently verified. These documents will be classified into two separate categories: (1) investigator study file and (2) subject clinical source documents that corroborate data collected on the CRF's. Subject clinical source documents would include hospital/clinic subject records; physician's and nurse's notes; original laboratory, radiology, pathology, and special assessment reports; QOL forms, signed informed consent forms. When the

CRF or any form is used as the source document, this will be clearly stated in the investigator study file.

At a minimum, the following be documented in source documents:

- Medical history/physical condition and diagnosis of the subject before involvement in the study sufficient to verify protocol entry criteria.
- Study number, assigned subject number, and verification that written informed consent was obtained (each recorded in dated and signed notes on the day of entry into the study)
- Progress notes for each subject visit.
- Laboratory test results.
- Condition and response of subject upon completion of or early termination from the study.

11.6 Recording and Processing of Data

Data for this study will be entered into electronic CRFs in research database (a web-based clinical research management application). A CRF is required for every subject who received any study intervention. The investigator will ensure that the CRF's are accurate, complete, legible and timely. Separate source records are required to support all CRF entries. All corrections to study data will be made by drawing a single line through the information to be corrected without obscuring it. All corrections will be initialed, dated, and explained, if necessary. **Do not use "white-out" or obscuring correction tape.**

11.7 Non-Protocol Research

No investigative procedures other than those described in this protocol will be undertaken on the enrolled subjects without the agreement of the IRB.

11.8 Ethics

The investigator agrees to conduct the study in compliance with the protocol, current good clinical practices, and all applicable (local, FDA) regulatory guidelines and standard of ethics

11.9 Essential Documents for the conduct of a clinical trial

Essential documents are those documents with individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced.

The following documents will be on file:

- CV's and license of all investigators.

- IRB documentation/correspondence.
- Documentation of IRB certification.

12. STUDY CALENDAR

Visit #, Time / Activity	Visit 1 (Week 1) Screening/ Enrollment	Visit 2 (Week 4)	Visit 3 (Week 16)
Medical & Urological History	●		
Physical Examination &ECG	●		●
Informed Consent	●		
Inclusion & Exclusion Criteria	●		
Blood Analysis (HCT, E, T, PSA, 17 OHP) and Questionnaires (SF-15 and IIEF-15)	●		●
Dispense medication intranasal T or TC injections	●	●	

- Medications will be provided by sponsor

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