Version 1.0
Date: Feb 26, 2019

IRB# 20190906

Randomized Control Trial of Long Acting Subcutaneous Testosterone Pellets for Hypogonadism: Testopel ® vs. Generic Testosterone Pellets.

PRINCIPAL INVESTIGATOR

Ranjith Ramasamy, M.D
Assistant Professor
Department of Urology
1120 N.W. 14th St #1560
Miami, Florida 33136
Phone: 305-243-4562
Email: Ramasamy@miami.edu

SUB-INVESTIGATOR

Libert Ramos, DNP, MSN/Ed, APRN
Department of Urology
1120 N.W. 14th st #1560
Miami, Florida 33136
Phone: 305-243-4562
Email: Libert.Ramos@miami.edu

STUDY COORDINATOR:

Manuel Molina, MD
305-243-4873
Clinical research Coordinator
Email: m.molina.leyba@miami.edu

NCT#

NCT04523480

SPONSOR:

Empower Pharmacy
Houston, TX

Version 1.0
Date: Feb 26, 2019

UHealth
UNIVERSITY OF MIAMI HEALTH SYSTEM

UNIVERSITY OF MIAMI
MILLER SCHOOL of MEDICINE

IRB# 20190906

Randomized Control Trial of Long Acting Subcutaneous Testosterone Pellets for Hypogonadism: Testopel ® vs. Generic Testosterone Pellets.

PRINCIPAL INVESTIGATOR

Ranjith Ramasamy, M.D
Assistant Professor
Department of Urology
1120 N.W. 14th St #1560
Miami, Florida 33136
Phone: 305-243-4562
Email: Ramasamy@miami.edu

SUB-INVESTIGATOR

Libert Ramos, DNP, MSN/Ed, APRN
Department of Urology
1120 N.W. 14th st #1560
Miami, Florida 33136
Phone: 305-243-4562
Email: Libert.Ramos@miami.edu

STUDY COORDINATOR:

Manuel Molina, MD
305-243-4873
Clinical research Coordinator
Email: m.molina.leyba@miami.edu

SPONSOR:

Empower Pharmacy
Houston, TX

Table of Contents

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.

UHealth
UNIVERSITY OF MIAMI HEALTH SYSTEM

UNIVERSITY OF MIAMI
MILLER SCHOOL
of MEDICINE

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).

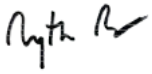
I certify that I, and the study staff responsible, have received the requisite training to conduct this research protocol.

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

March 1st, 2019

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 is an anabolic steroid and the primary male sex hormone promoting development of male reproductive tissues such as prostate and testis. Several androgen replacement modalities are FDA approved and commercially available or are under clinical investigation. These include intramuscular injection of testosterone esters, subcutaneous implants, transdermal patches, oral tablets and capsules, buccal and sublingual dosage forms, implantable T microspheres, and topical gel formulations of testosterone and 5α-dihydrotestosterone (DHT).

It can activate androgen receptors in its unchanged form or it can be converted to 5α-dihydrotestosterone (DHT) by the enzyme 5 α reductase before binding to the androgen receptor. Once bound, the receptor-hormone complex moves into the cell nucleus altering specific gene sequences on the cellular DNA and modifying its transcription, therefore promoting protein synthesis and thus growth of tissues that are sensible to its action.[1]

Hypogonadism, or low testosterone (Low T), is the deficiency in producing testosterone by the testes. Low T affects more than 10% of men worldwide, with high incidence in the elderly (Haring, et al., 2010). It occurs in association with aging, chronic disease, or other modifiable risk factors such as obesity and diabetes.[1] Testosterone deficiencies have been shown to associated with less muscle mass[3], lower bone mineral density[4], lower hematocrit and hemoglobin concentrations[5], smaller prostate glands[6], and diminished energy and sexual function than normal men.[7,8]

1.2 Study Interventions

Testosterone replacement therapy (TRT) is becoming more widely available and has seen a greater than three-fold increase in use men 40 years and older.[9] Current delivery systems of TRT include transdermal gels and patches[10], injection therapy[11], and long acting subcutaneous pellets.[12] TRT has been shown to improve bone mineral density, prostate volume, energy, and sexual function.[8]

Testosterone pellets is a long-acting formulation of TRT that is delivered subcutaneously to men diagnosed with low T. This method of administration has the potential to avoid side effects related to TRT that are commonly seen with other delivery methods, daily topical applications present a risk of transfer of testosterone to partners and family members as well as a short half-life of injectable and intranasal products. A recent study showed that this medication is well tolerated with very low adverse events and discontinuation rates among patients. [11]

Low Adverse well tolerated, adverse events rates were 2.1% (b.i.d.) and 3.7% (t.i.d.)

1.3 Study Rationale

Current advantages to subcutaneous testosterone pellets include ease of delivery and decreased risk of the medication being transfer upon skin contact to woman or children.[11] Long acting testosterone replacement Implantation of six to ≥10 testosterone pellets (450 to ≥750 mg) increased

total testosterone into the therapeutic range at 1 month post-implantation and sustained therapeutic levels (>300) for 4-6 months. Higher pellet numbers (10-12 pellets) were associated with higher, more consistent, and longer maintenance of testosterone levels within the therapeutic range.

Our hypothesis Pellets provide sustained eugonadal T levels for 3–6 months with not significant difference between Testopel ® and compound subcutaneous testosterone.

2. **HYPOTHESIS**

2.1 Alternate hypothesis

Treatment groups will show a sustainable testosterone value between 300ng/dl and 1000 ng/dl from baseline in patients with low T, to 6 months post-therapy.

2.2 Null Hypothesis

There is no difference between the patient receiving Testopel ® vs Subcutaneous compound testosterone pellets.

3. OBJECTIVES

3.1 Primary Efficacy Objective

Primary outcomes will be changes in Testosterone (T) from baseline, 2 month, 4 month and 6 month.

3.2 Secondary Efficacy Objective

We will evaluate changes in Hematocrit (HCT), Estrogen (E) and PSA from baseline to 2 month, 4 month and 6 months.

4. STUDY DESIGN

4.1 Accrual goal

A total of 120 patients with low testosterone (<300ng/dL) on 2 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 6 months (180 days) and subjects will be provided subcutaneous testosterone one time. Implantation of Testopel ® 750 mg (10 pellets with 75mg pellet) or

compounded subcutaneous testosterone 800mg (8 pellets with 100mg pellet) or compounded subcutaneous testosterone 800mg (4 pellets with 200mg pellets).

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. PATIENT 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 weeks following androgen treatment.

6. Judged to be in good general health as determined by the principal investigator based upon 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) or I-PSS score > 19 points.

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

   b. Hematocrit < 35% or > 50%

   c. 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 investigational product within 4 weeks or within 5 half-lives prior to the start of treatment.

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

6.3 Study Population

The study will consist of 120 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 patients will receive an explanation of the study. Patients 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 prospective, Phase 3, randomized, clinical study aimed to evaluate comparison between Testopel ® vs subcutaneous compounded testosterone 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 120 subjects will be enrolled to meet scientific and regulatory objectives. After meeting the selection criteria, the subjects will be randomly assigned in 1:1:1 ratio such that 40 subjects will receive Testopel, 40 subjects will receive Compounded testosterone pellets (8 pellets with 100mg pellets) once and 40 subjects will receive compounded testosterone pellets (4 pellets with 200mg pellets) once and will be followed for 6 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 patients will be for screening and medical evaluation. Patient's medical co-medication history will be collected and documented and a physical examination will be performed.

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

Patients 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 will be used. To allow subjects in screening once the target 120 subjects have been enrolled and to account for dropouts, 145 randomization codes will be generated. As subjects are enrolled in the study, they will be assigned unique consecutive numbers starting at 001. At least 120 subjects who meet all the entry criteria will be randomized 1:1:1 such that approximately 40 subjects are assigned to the Testopel treatment arm, approximately 40 subjects are assigned to the Compounded treatment arm (100mg pellets) and 40 subjects are assigned to the Compounded treatment arm (200mg pellets), (Randomization will be performed by a computer software maintained by the Department of Urology). Patients randomized to the treatment group will be instructed to stop any use of androgen replacement therapy for 4 weeks

prior to first treatment session and refrain from using any other testosterone therapy option during the study.

7.4 Treatment procedures

Clean and numb the insertion site with lidocaine at 1%, followed by small incision in the skin, implantation of pellets into subdermal fat layer and sealing the incision with Steri-strip. This is the current standard of care of Testopel insertion and same procedure will be followed with both compounded and commercial pellets.

7.5 Follow-Up Procedures and Evaluations:

Follow-up visits will be conducted at 2, 4. 6 months, these visits shall include:

- Taking serum T, HCT, E, PSA levels.
- Reporting and recording adverse events at every follow-up visit.

7.6 Reimbursement

Once the patient is included into the trial, the sponsor company (Empower pharmacy) will reimburse $75 for participation. Once randomized, the sponsor company (Empower Pharmacy) will provide one time treatment “Testopel or Compounded Testosterone” based on the results of randomization.

8. ADVERSE EVENTS

8.1 Expected Adverse Events

The following adverse reactions have been identified during post-approval use of testosterone replacement therapy, including TESTOPEL®. Including implantation site infection and pellet extrusion, gynecomastia, oligospermia, hirsutism, male pattern of baldness, and acne. Cardiovascular disorders as myocardial infarction, stroke. Fluid and electrolyte disturbances, increased or decreased libido, headache, anxiety, or depression. Metabolic increased serum cholesterol.

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. Patients 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. Ramgopal Satyanarayana 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 T, after 6 months of treatment.

The primary endpoint will be the change in T, post-treatment subjects who achieve an average serum T concentration within the normal range upon completion of 24 weeks of post- treatment.

10.2 Secondary Study Endpoints

The secondary endpoints will be changes in HCT, ESTROGEN and PSA, after 6 months of treatment

10.3 Endpoint definitions

Total testosterone will be expressed in ng/dL, HCT(%), E (pg/ml), and PSA ng/ml Hormone determinations will be done by peripheral venous puncture blood draw.

10.4 Sample size, accrual and study duration

TOTAL SAMPLE SIZE: 120
TOTAL ACCRUAL: 120
ACCURAL DURATION: 12 months
STUDY DURATION: 6 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.

Change in Testosterone, Hematocrit, estrogen and PSA will be analyzed using the ANOVA and MANOVA. A change in < ± 10% will be reject the null hypothesis.

Demographic characteristics such as age and testosterone level will be compared between groups A and B using student's test. Other demographic characteristics, such as medical background and risk factors will be compared between these groups using Fisher's exact test.

10.6 Randomization:

120 patients will be randomized 1:1:1 to Testopel ® vs compound groups with 40 patients in the Testopel ® arm , 40 patients in the compounded pellets arm (100mg) and 40 patients in the compounded pellets arm (200mg) . An online-based randomization tool called Redcap.com will be used. The PI will not have the knowledge of patient's treatment group beforehand. However, the study coordinator will be aware of Testopel vs compound group randomization.

11. INVESTIGATORS RESPONSIBLITIES

11.1 Investigator Responsibility/Performance

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

The investigator should provide the patient 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 patient. Neither the investigator, nor the study staff, should coerce or unduly influence a patient to participate or to continue to participate in a study.

11.3 Confidentiality

The identity of the patients in this study will be treated as confidential. Patients eligible to participate in the study following the pre-treatment visit will be assigned a unique patient code. The results of the study, including any other data, may be published for scientific purposes but will

not give the patients' name or include any identifiable references to them. However, any records or data obtained as a result of the patient 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 patient 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 patient 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 (1st month) Screening	Visit 2 (Week 2)	Visit 3 (Week 6)	Visit 4 (Week 14)	Visit 5 (Week 22)	Visit 6 (Week 24)	Visit 7 (Week 26)
Medical & Urological History	●						●
Physical Examination	●						●
Informed Consent	●						
Randomization		●					
Inclusion & Exclusion Criteria	●						
Blood Analysis (T, E, HCT, PSA)	●		●	●	●	●	
Subcutaneous testosterone therapy in-office insertion (CPT 11980)		●					

- Pellets will be provided by sponsor
- Laboratory visits at LABCORP on Visit 3, 4, 5 and 6 will be covered by the sponsor with a separate account provided by sponsor

13 REFERENCES

1. Corona G, Rastrelli G, Maggi M. Diagnosis and treatment of late-onset hypogonadism: Systematic review and meta-analysis of TRT outcomes. Best Practice & Research Clinical Endocrinology & Metabolism. 2013; 27(4):557-579.

2. Walker WH. Testosterone signaling and the regulation of spermatogenesis. Spermatogenesis. 2011; 1(2): 116-120.

3. Katznelson L, Finkelstein J, Schoenfeld D, Rosenthal D, Anderson E, Klibanski A. Increase in bone density and lean body mass during testosterone administration in men with acquired hypogonadism. The Journal of Clinical Endocrinology & Metabolism. 1996; 81(12):4358-4365.

4. Finkelstein J, Klibanski A, Neer R, et al: Osteoporosis in Men with Idiopathic Hypogonadotropic Hypogonadism. Annals of Internal Medicine. 1987;106(3):354

5. Jockenhovel F, Vogel E, Reinhardt W, Reinwein D: Effects of various modes of androgen substitution therapy on erythropoiesis. Eur J Med Res. 1997; 2: 293-298.

6. Behre H, Bohmeyer J, Nieschlag E. Prostate volume in testosterone-treated and untreated hypogonadal men in comparison to age-matched normal controls. Clinical Endocrinology. 2010; 40(3):341-349.

7. Davidson J, Camargo C, Smith E: Effects of Androgen on Sexual Behavior in Hypogonadal Men. The Journal of Clinical Endocrinology & Metabolism. 1979; 48(6):955-958.

8. Snyder P, Peachey H, Berlin J, et al: Effects of Testosterone Replacement in Hypogonadal Men. Journal of Clinical Endocrinology & Metabolism. 2000; 85(8):2670-2677.

9. Baillargeon J, Urban R, Ottenbacher K, Pierson K, Goodwin J. Trends in Androgen Prescribing in the United States, 2001 to 2011. JAMA Internal Medicine. 2013; 173(15):1465.

10. Koch C, Ullah M, Riche D. Transdermal testosterone replacement therapy in men. Drug Design, Development and Therapy. 2014; 101.

11. Seal L. Testosterone replacement therapy. Medicine. 2009; 37(9):445-449.

12. Amory J, Anawalt B, Blaskovich P, Gilchriest J, Nuwayser E, Matsumoto A. Testosterone Release From a Subcutaneous, Biodegradable Microcapsule Formulation (Viatrel) in Hypogonadal Men. Journal of Andrology. 2002; 23(1):84-91.

13. Rhoden E, Morgentaler A. Risks of Testosterone-Replacement Therapy and Recommendations for Monitoring. New England Journal of Medicine. 2004; 350(5): 482-492.

14. Conners, W., Morgentaler, A., Guidry, M., Westfield, G., Bryson, N., & Goldstein, I. (2016) Preservation of Normal Concentrations of Pituitary Gonadotropins Despite Achievement of Normal Serum Testosterone Levels in Hypogonadal Men Treated with a 4.5% Nasal Testosterone Gel. Poster Presented at American Urological Assoication Annual Meeting.

15. Kim E, McCullough A, Kaminetsky J. Oral enclomiphene citrate raises testosterone and preserves sperm counts in obese hypogonadal men, unlike topical testosterone: restoration instead of replacement. BJU International. 2015; 117(4):677-685.