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ASSESS THE EFFICACY OF FUROSAP®, A TESTOSTERONE BOOSTER SUPPLEMENT, IN HUMAN VOLUNTEERS: AN ADD-ON STUDY

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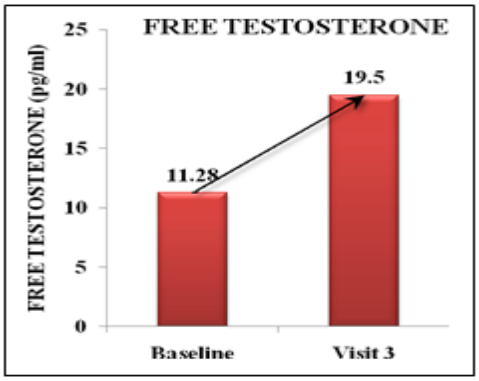
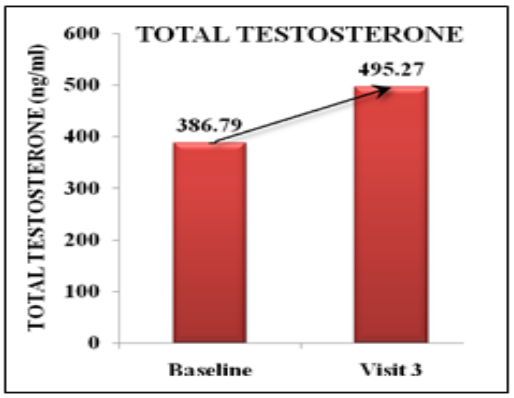
ABSTRACTS

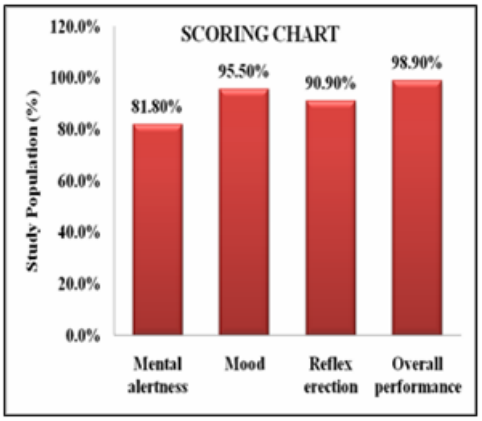
Frequency of sexual intercourse: A significant increase in frequency of sexual intercourse was observed in the study population after 12 weeks of complete treatment. **38.71% increase in the frequency of sexual intercourse was observed. Free testosterone levels:** 88.6% of study population showed significant increase in free testosterone levels. On completion of the **treatment,** 72.87% increase in free testosterone levels was observed in the patients.



Total testosterone levels: On the other hand, total testosterone levels increased significantly up to 28.04% in the study population. These positive effects were seen in 85.02% of the study population. **Sperm profile:** The sperm profile was greatly improved in the enrolled testosterone deficient patients. The sperm count was increased up to 34.82% in the study population. The sperm motility was also observed to be improved in 17.46% of study population. Whereas, abnormal sperm morphology was efficiently decreased up to 18.81% in the study population.



Scoring chart: It was also observed that various parameters of scoring chart showed improvements till the completion of the treatment. 81.8% of study population showed improvement in mental alertness, 95.5% of study population showed improvement in mood, 90.9% of study.



population showed improvement in reflex erection and 98.9% study population showed great improvement in overall performance till the completion of the treatment.

Safety conclusions

On completion of the study, following safety conclusions were made:

i. No significant change in the liver function tests (serum SGOT, SGPT & ALP activities) was observed.
ii. No significant change in BUN level was observed.
iii. No significant change in the hematological parameters was observed on completion of the treatment.

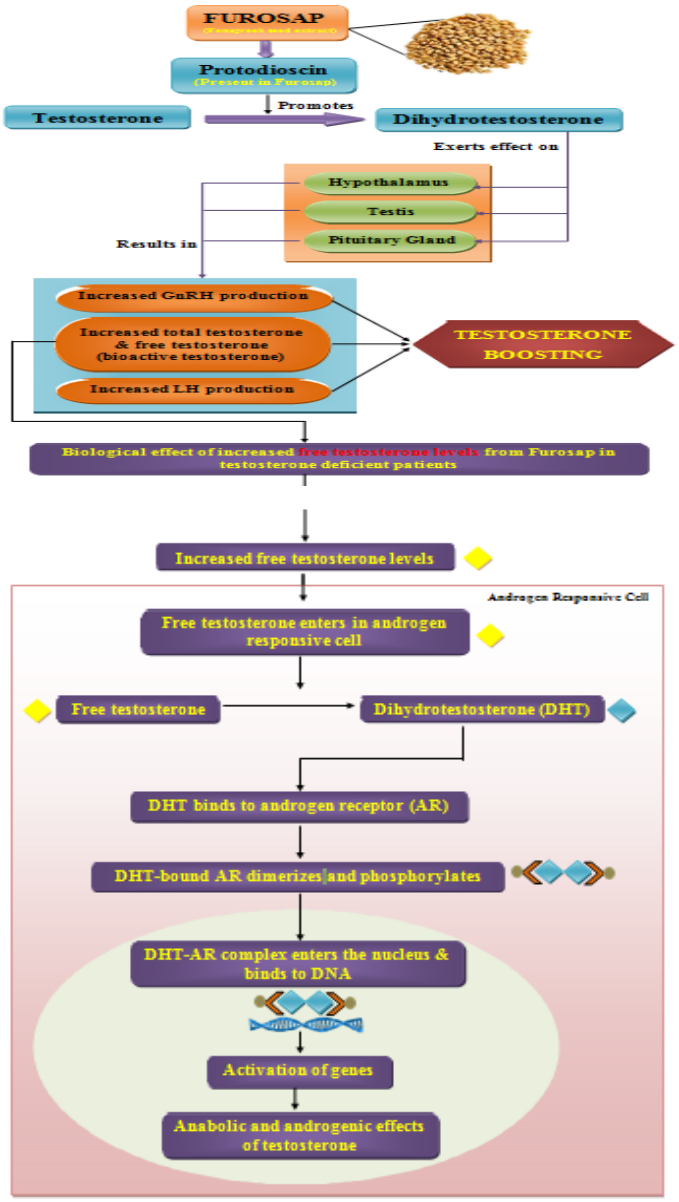
- **Ethical conduct of the study**

The study was performed in compliance and accordance with ICH guidelines for Good Clinical Practices (GCP), including the archiving of essential documents as per International

Ethical Standards guaranteed by the Declaration of Helsinki and its subsequent amendments. Patient confidentiality was maintained throughout the study.

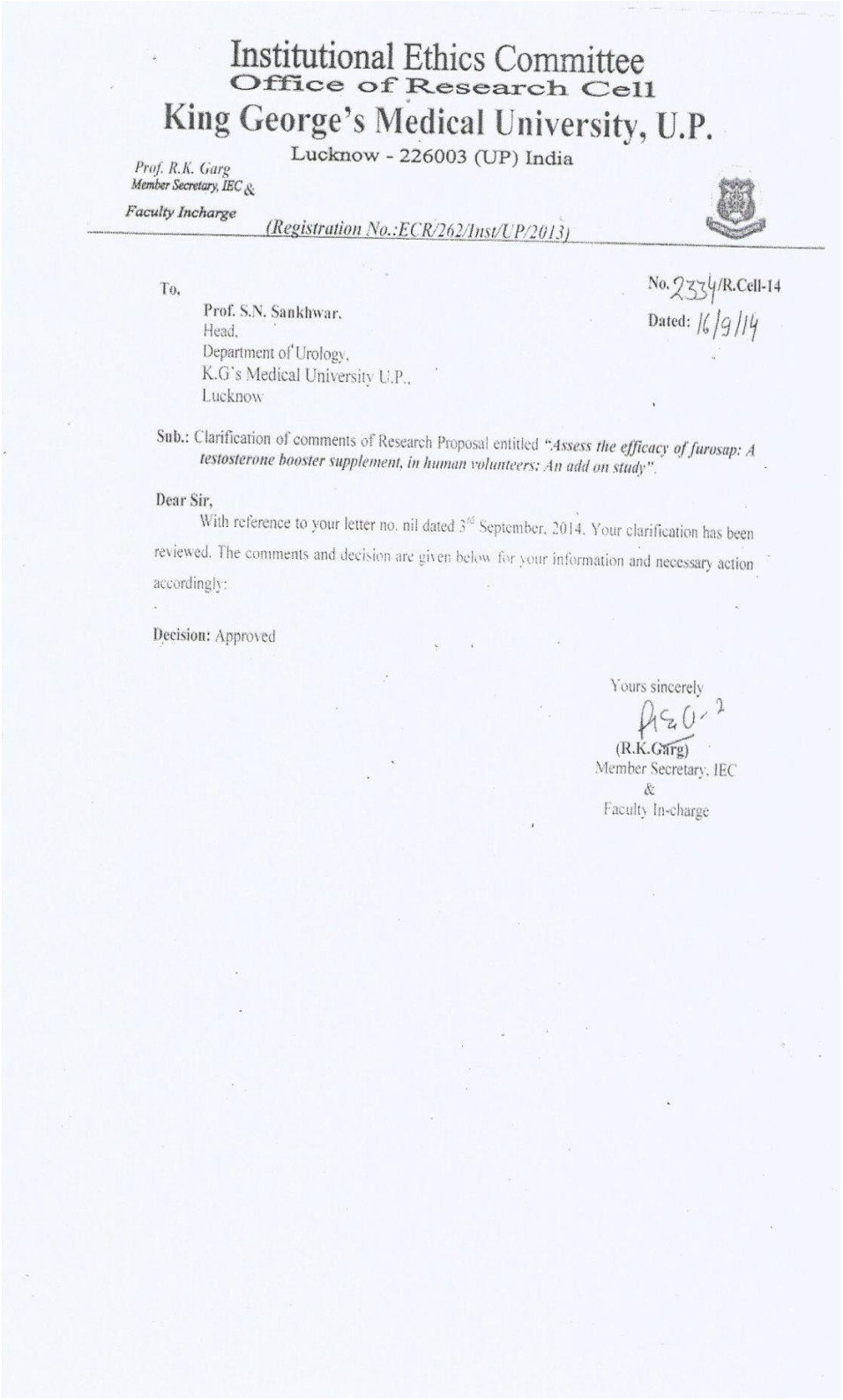
- **Patient information and consent**

All subjects for the study were provided a consent form and provided sufficient information for subjects to make an informed decision about their participation in this study. This consent form was submitted with the protocol for review and approval by IEC for the study. The formal consent of the subjects was obtained before the subject is submitted to any study procedure using the IEC-approved consent form. Consent form was signed by the subject or legally accepted representative and the investigator- designated research professional obtained the consent.



1. INSTITUTIONAL ETHICS COMMITTEE (IEC) APPROVAL

The present study was duly approved by ethics committee named as Institutional Ethics Committee situated at King George's Medical University, Lucknow.



Institutional Ethics Committee
Office of Research Cell
King George's Medical University, U.P.
Lucknow - 226003 (UP) India

Prof. R.K. Garg
Member Secretary, IEC &
Faculty Incharge

(Registration No.:ECR/262/Inst/UP/2013)

No. 2334/R.Cell-14
Dated: 16/9/14

To,
Prof. S.N. Sankhwar,
Head,
Department of Urology,
K.G's Medical University U.P.,
Lucknow

Sub.: Clarification of comments of Research Proposal entitled *"Assess the efficacy of furosap: A testosterone booster supplement, in human volunteers: An add on study"*.

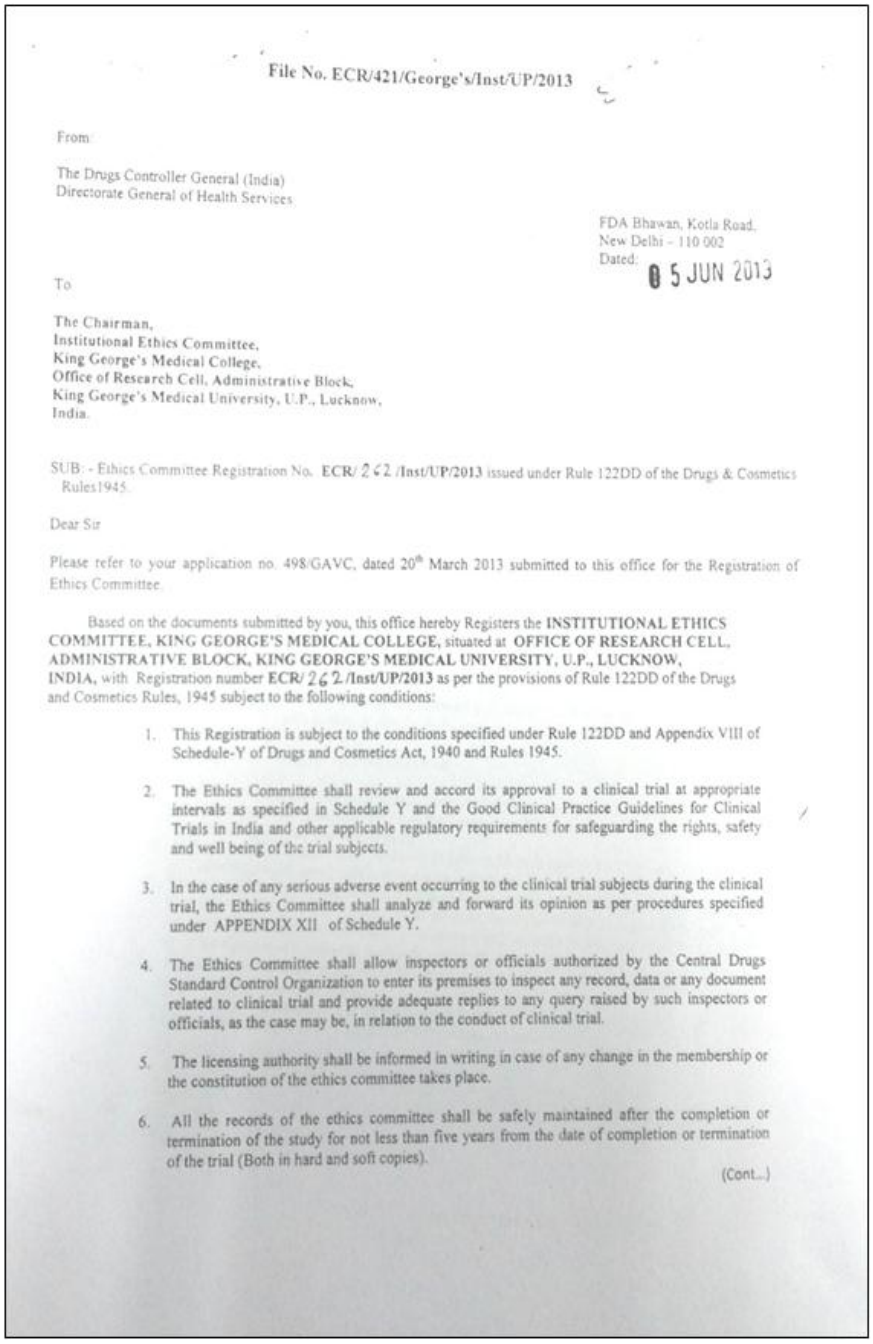
Dear Sir,

With reference to your letter no. nil dated 3rd September, 2014. Your clarification has been reviewed. The comments and decision are given below for your information and necessary action accordingly:

Decision: Approved

Yours sincerely
(R.K.Garg)
Member Secretary, IEC
&
Faculty In-charge

DCGI approval of ethics committee



File No. ECR/421/George's/Inst/UP/2013

From

The Drugs Controller General (India)
Directorate General of Health Services

FDA Bhawan, Kotla Road,
New Delhi – 110 002
Dated: 05 JUN 2013

To

The Chairman,
Institutional Ethics Committee,
King George's Medical College,
Office of Research Cell, Administrative Block,
King George's Medical University, U.P., Lucknow,
India.

SUB: - Ethics Committee Registration No. **ECR/ 262 /Inst/UP/2013** issued under Rule 122DD of the Drugs & Cosmetics Rules1945.

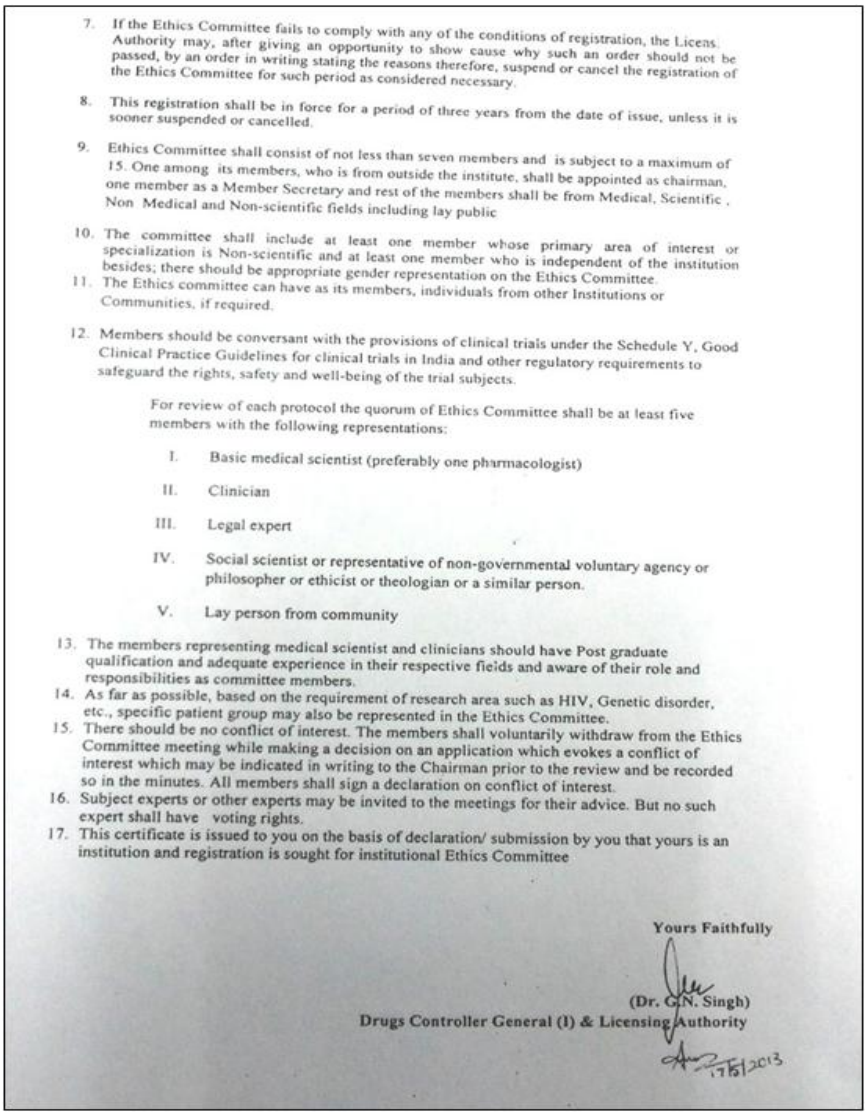
Dear Sir

Please refer to your application no. 498/GAVC, dated 20th March 2013 submitted to this office for the Registration of Ethics Committee.

Based on the documents submitted by you, this office hereby Registers the **INSTITUTIONAL ETHICS COMMITTEE, KING GEORGE'S MEDICAL COLLEGE,** situated at **OFFICE OF RESEARCH CELL, ADMINISTRATIVE BLOCK, KING GEORGE'S MEDICAL UNIVERSITY, U.P., LUCKNOW, INDIA,** with Registration number **ECR/ 262 /Inst/UP/2013** as per the provisions of Rule 122DD of the Drugs and Cosmetics Rules, 1945 subject to the following conditions:

1. This Registration is subject to the conditions specified under Rule 122DD and Appendix VIII of Schedule-Y of Drugs and Cosmetics Act, 1940 and Rules 1945.
2. The Ethics Committee shall review and accord its approval to a clinical trial at appropriate intervals as specified in Schedule Y and the Good Clinical Practice Guidelines for Clinical Trials in India and other applicable regulatory requirements for safeguarding the rights, safety and well being of the trial subjects.
3. In the case of any serious adverse event occurring to the clinical trial subjects during the clinical trial, the Ethics Committee shall analyze and forward its opinion as per procedures specified under APPENDIX XII of Schedule Y.
4. The Ethics Committee shall allow inspectors or officials authorized by the Central Drugs Standard Control Organization to enter its premises to inspect any record, data or any document related to clinical trial and provide adequate replies to any query raised by such inspectors or officials, as the case may be, in relation to the conduct of clinical trial.
5. The licensing authority shall be informed in writing in case of any change in the membership or the constitution of the ethics committee takes place.
6. All the records of the ethics committee shall be safely maintained after the completion or termination of the study for not less than five years from the date of completion or termination of the trial (Both in hard and soft copies).

(Cont...)



7. If the Ethics Committee fails to comply with any of the conditions of registration, the Licens. Authority may, after giving an opportunity to show cause why such an order should not be passed, by an order in writing stating the reasons therefore, suspend or cancel the registration of the Ethics Committee for such period as considered necessary.

8. This registration shall be in force for a period of three years from the date of issue, unless it is sooner suspended or cancelled.

9. Ethics Committee shall consist of not less than seven members and is subject to a maximum of 15. One among its members, who is from outside the institute, shall be appointed as chairman, one member as a Member Secretary and rest of the members shall be from Medical, Scientific , Non Medical and Non-scientific fields including lay public

10. The committee shall include at least one member whose primary area of interest or specialization is Non-scientific and at least one member who is independent of the institution besides; there should be appropriate gender representation on the Ethics Committee.
11. The Ethics committee can have as its members, individuals from other Institutions or Communities, if required.

12. Members should be conversant with the provisions of clinical trials under the Schedule Y, Good Clinical Practice Guidelines for clinical trials in India and other regulatory requirements to safeguard the rights, safety and well-being of the trial subjects.

For review of each protocol the quorum of Ethics Committee shall be at least five members with the following representations:

I. Basic medical scientist (preferably one pharmacologist)

II. Clinician

III. Legal expert

IV. Social scientist or representative of non-governmental voluntary agency or philosopher or ethicist or theologian or a similar person.

V. Lay person from community

13. The members representing medical scientist and clinicians should have Post graduate qualification and adequate experience in their respective fields and aware of their role and responsibilities as committee members.
14. As far as possible, based on the requirement of research area such as HIV, Genetic disorder, etc., specific patient group may also be represented in the Ethics Committee.
15. There should be no conflict of interest. The members shall voluntarily withdraw from the Ethics Committee meeting while making a decision on an application which evokes a conflict of interest which may be indicated in writing to the Chairman prior to the review and be recorded so in the minutes. All members shall sign a declaration on conflict of interest.
16. Subject experts or other experts may be invited to the meetings for their advice. But no such expert shall have voting rights.
17. This certificate is issued to you on the basis of declaration/ submission by you that yours is an institution and registration is sought for institutional Ethics Committee

Yours Faithfully

(Dr. G.N. Singh)
Drugs Controller General (I) & Licensing Authority

17/5/2013

INTRODUCTION

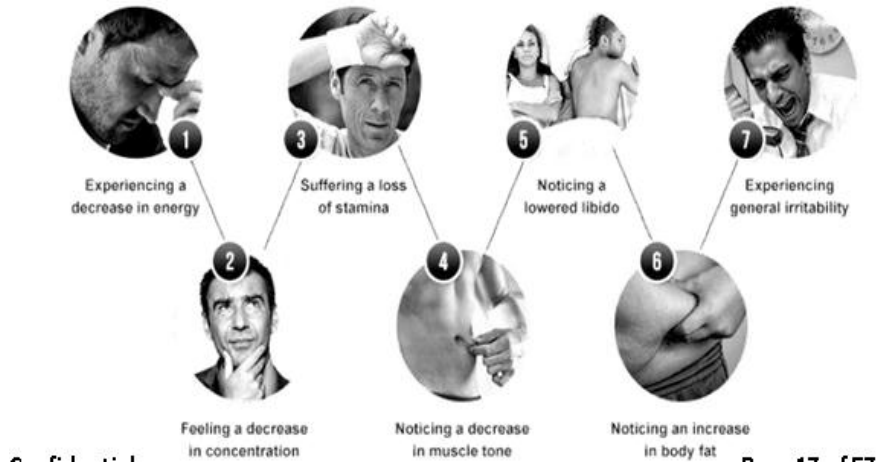
Testosterone deficiency or hypogonadism in men is a disease which involves serious impact on the quality of life of a person due to the inability of testes in men to function properly. This inability of testes results in decreased circulating levels of testosterone in blood. Testosterone is a metabolic and vascular hormone with multiple physiological effects in various target tissues and organs. It is extremely important for maintaining[1]

- Muscle mass and function
- Bone mass
- Body composition

Therefore, testosterone deficiency contributes to the onset and progression of sarcopenia to obesity and ultimately to frailty. Testosterone deficiency is related not only to sarcopenia and frailty, but also to an increased risk of institutionalization, hospitalization, and mortality due

to its following effects[1]

- Reduced lean body mass
- Reduced bone mineral density (BMD)
- Increased fat mass with concomitant changes in body composition
- Reduced physical function and performance
- Reduced cognitive function
- Increased depressive symptoms
- Increased risk of falls and bone fractures
- Metabolic syndrome such as type II diabetes
- Fatigue
- Anaemia



Prevalence of testosterone deficiency

With the increase in prevalence of testosterone deficiency, the effects of hypogonadism worsen. The global prevalence of testosterone deficiency ranges from 10-40% and this prevalence increases with age, ranging from 12% among men in their 50s to 49% among those in 80s and older. Between the ages of 40-70 years, the prevalence of hypogonadism is 52%. The prevalence of testosterone deficiency in middle-aged to elderly men in the United States ranged from 24–39% which is much higher than that observed in other parts of the world. The prevalence of testosterone deficiency in Europe was significantly lower than in the US, ranging from 8–20%. In Asia, the prevalence is estimated to be only 10% which is comparatively much lesser than the other parts of the world.[2]

It has been observed that testosterone deficiency develops more in the population suffering from other metabolic syndrome such as diabetes. In the diabetic population with age between

40-70 years, hypogonadism is as high as 75%. During a cross-sectional study on 900 Indian men with type II diabetes, it was observed that 20.7% (186 out of 900) men were found to be testosterone deficient. 451 out of 900 (50.1%) patients were suffering from initial symptoms of testosterone deficiency.[3,4]

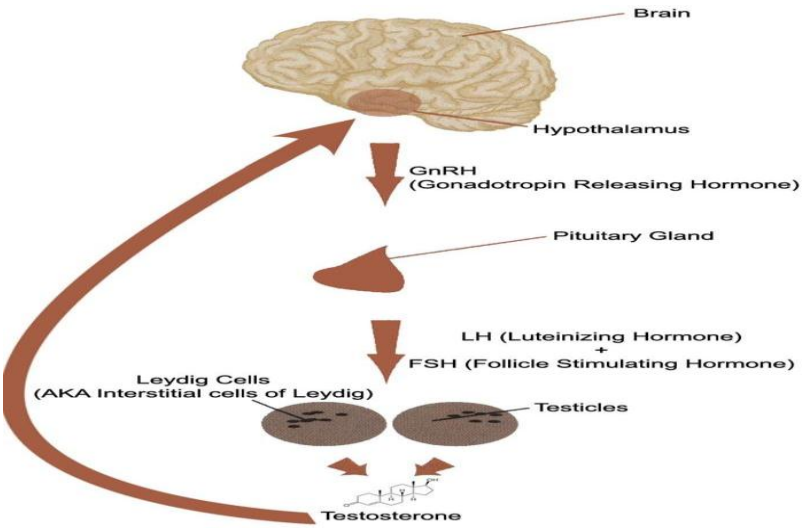
Fillo J *et al.* (2017) also found link between testosterone deficiency and another metabolic syndrome *i.e.* obesity. They conducted their study on 216 males with abdominal obesity. 98 out of 198 (49.5%) males with abdominal obesity and 1/18 (5.5%) males without abdominal obesity had testosterone deficiency. They found that in the group of males with waist circumference more than 120 cm, 87.1% had testosterone deficiency. They observed that males older than 40 years of age with abdominal obesity have a higher incidence of erectile dysfunction and testosterone deficiency.[5]

The total testosterone levels & free testosterone levels help to evaluate the prevalence of testosterone deficiency in men as they are well-known tools to diagnose hypogonadism or testosterone deficiency. Diagnosis of testosterone deficiency in ageing men can be challenging, as symptoms of testosterone deficiency overlap with those of 'normal' physiological ageing. The diagnosis of testosterone deficiency in men is done on the basis of clinical symptoms also along with low serum testosterone levels. The majority of clinical symptoms associated with hypogonadism include decreased libido, decreased frequency of sexual thoughts, decreased frequency or rigidity of nocturnal erections and erectile dysfunction. Other clinical symptoms for diagnosis include fatigue, decreased energy, poor concentration, decreased sense of well-being, depressed mood, decreased vitality and depression. Men who present with signs or symptoms of hypogonadism, the diagnosis is confirmed with laboratory testing which include free testosterone levels lower than 220–345 pmol/l being abnormal.[6,7]

Testosterone replacement therapy has been shown to improve the symptoms of testosterone deficiency as well as overall quality of life (QOL) in men. But this therapy also involves the development of significant risk of adverse events. An increase in serum hematocrit is the most common adverse event, which in extreme cases can lead to serum hyperviscosity, which has been associated with vascular thromboembolic events such as stroke, myocardial infarction and deep vein thrombosis.

Treatments for testosterone deficiency

As in all endocrine disorders, the goal of treatment of hypogonadism is to restore the deficient glandular function. If fertility is the issue and the testis is under-stimulated because of a gonadotropin deficiency, FSH and LH administration is recommended. LH and FSH are the two hormones that exert the signalling process to the third axis point, *i.e.* testes, to begin the synthesis and secretion of Testosterone.



In the other cases, testosterone therapy is advised. As given above, a number of testosterone replacement therapy (TRT) preparations are currently available in the market for the treatment of testosterone deficiency. On the other hand, intramuscular injections of short-acting testosterone derivatives achieve good serum concentrations within 2-3 days with levels returning to baseline in most men by 2 weeks, resulting in an injection schedule of 1-2 weeks. Topical gels or patches provide a more stable serum-testosterone concentration over time than injections. Patches currently available are associated with a high rate of skin reaction and their use has been largely replaced by T gels (Testosterone gels). The main disadvantages of T gels are cost and a black box warning concerning transfer potential to women and children. Testosterone administration should favour formulations that are capable of maintaining stable physiological levels of testosterone over time and devoid of any side effects.[8]

The herbal formulation used in the present study named as "Furosap®" has been examined for its effectiveness in testosterone deficient subjects. It has been chosen because of the components comprising this herbal formulation extracted from herb known as *Trigonella foenum-graecum* which is also known as Fenugreek.

The investigational agent - Furosap®

FUROSAP® is an innovative herbal supplement made through a novel patented process, involving physical separation of active ingredients from the seeds of Fenugreek herb (*Trigonella foenum-graecum*) without affecting the chemical properties of the active fractions. It is a natural and promising dietary supplement. It comprises of Protodioscin as the major fraction. This component helps to boost the testosterone levels via stimulating pituitary gland and improves the medical state of patients suffering from hypogonadism or testosterone deficiency.

Literature on Furosap®

As given in the patent by Goel PK (2008), fenugreek seeds contain furostanolic saponins including protodioscin in a major amount from which Furosap® has been prepared. The protodioscin-rich extract prepared by the inventor by unique process was intended for elevating testosterone levels and promoting anabolic processes and intended to be consumed in well-defined dosage forms e.g. tablets or capsules. Inventor also mentioned the process by which the protodioscin from fenugreek seeds helps in boosting testosterone levels. According to the inventor, the dominant furostanolic saponin - protodioscin is the active ingredient responsible for testosterone-boosting effects. This steroidal saponin appears to stimulate the release of luteinizing hormone from the pituitary gland. LH then travels via the bloodstream to the testicles, where it stimulates testosterone production. Protodioscin is believed to increase dehydroepiandrosterone (DHEA) production also by the adrenal glands. This steroid precursor becomes testosterone.[9]

It has been previously observed by Maheshwari A *et al.* (2017) that the protodioscin- based Furosap® was effective in the management of testosterone deficiency. Protodioscin-enriched extract of fenugreek *i.e.* Furosap® was able to improve free testosterone levels in the patients up to 46%. Sperm profile was also improved in the patients in their study. Their study plan was as given in the below table[10]:

Study title	**Study design**	**Treatment duration** 12 weeks **Treatment dose** 500 mg/day/subject
Efficacy of Furosap™, a novel Trigonella foenum-graecum seed extract, in Enhancing Testosterone Level and Improving Sperm Profile in Male	One-arm, open-labelled, multi-center study in 50 volunteers	

Volunteers		

Thus, being effective in improving testosterone and sperm profile in men in above given study, Furosap® was again tested in the present study to evaluate its effect in the hypogonadism population.

2. AIMS AND OBJECTIVES

The aim of the study was to evaluate the effect of Furosap®, in humans suffering from testosterone deficiency (or hypogonadism) which was achieved by considering following given objectives:

OBJECTIVES

Primary objective

- To assess the efficacy of Furosap® as testosterone booster.

Secondary objective

The secondary objectives of the study included -

- To evaluate the percent of subjects responding to Furosap®
- To demonstrate the effect of Furosap® on safety parameters including cardiovascular functions.
- To identify the effect on mood, mental alertness, reflex erection and overall performance.

End Points

Primary endpoint

- Improvement in testosterone levels
- Improvement in sperm profile

Secondary endpoint

- Improvement in mood, mental alertness, reflex erection and overall performance
- No abnormal change in lipid profile
- No abnormal change in the biochemical parameters and haematological parameters which include:
  - Liver function tests (SGOT, SGPT, ALP)
  - Renal function tests (Urea, creatinine)

- Blood parameters (Hb, TLC, DLC)

3. INVESTIGATIONAL PLAN STUDY DESIGN

This was an open labeled and single armed study. The study was carried out on Indian population suffering from hypogonadism or testosterone deficiency. The study was carried out at King George's Medical University, Lucknow - 226003, Uttar Pradesh, India.

Study Population

1. Eligible age for the study participation: Between 35 to 65 years
2. Gender eligible for study participation: Male

Inclusion Criteria

1. Agrees to written as well as audio-visual informed consent.
2. Ability to understand the risks/benefits of the protocol.
3. Males between 35-65 years of age.
4. Diagnosed with Symptomatic hypogonadism.

Exclusion Criteria

1. Uncooperative Subjects.
2. Impaired hepatic function indicated by SGOT/SGPT >2.5 times the upper limit of normal.
3. Patients suffering from CAD.
4. Abnormal liver or kidney function tests (ALT or AST > 2 times the upper limit of normal; elevated creatinine, males > 125 μmol/L or 1.4mg/dl, females > 110 μmol/L or 1.2mg/dl)
5. History of malignancy.
6. History of hypersensitivity to any of the investigational drugs.
7. Receiving any other testosterone booster therapy/medication/supplement within the last 2 months.
8. History of coagulopathies.
9. High alcohol intake (>2 standard drinks per day).
10. History of psychiatric disorder that may impair the ability of subjects to provide written informed consent.
11. Any medical condition, where the investigator feels participation in the study could be detrimental to the subjects overall well-being.

Stopping Rules

The criteria for the "stopping" of trial or "discontinuation criteria" was only in the case of serious adverse event (as defined in safety assessments clause).

8. TREATMENTS

Screening and treatment of the subjects

The subjects were screened for the clinical study on the basis of given inclusion/exclusion criteria. The investigational product was allotted after screening and enrolment of the study subject. The subjects were followed up after 4 weeks, 8 weeks and 12 weeks. Safety was assessed at each follow-up visit. Subjects complaining of significant symptoms following administration of investigational product were planned to be evaluated for objective parameters of adverse drug reactions. Investigational product was considered to be discontinued in case of any serious adverse drug reaction. Investigational Product.

- **Product name**

Furosap® (Fenugreek seed extract)

- **Batch no.**

FUP0914 & FUP0615

- **Formulation**

Each capsule contained 500mg of investigational product which was to be taken orally per day.

- **Packaging**

Each pack contained 30 capsules.

- **Storage**

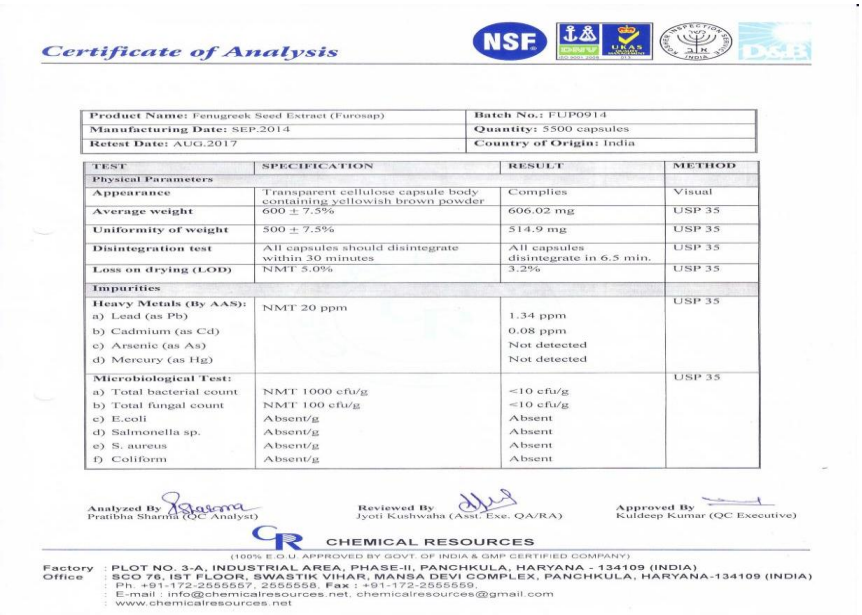
The investigational product was stored at room temperature in a cool and dark place and protected from direct sunlight, as instructed.

- **Accountability procedure**

Allocation of the investigational product was done by the site staff only. Distribution of the product was maintained in the IP accountability log provided by the sponsor to the site staff. Each entry was maintained separately with the date/signature of the principal investigator & study coordinator. The person responsible for the distribution of the product was instructed to sign on the IP accountability log.

- **Concomitant medication**

All concomitant prescription medications taken during the study by the participants were recorded on the case report forms (CRFs). Reported medications included concomitant prescription medications, over-the-counter medications (OTC) and non-prescription medications taken at the time of adverse events (all grades) too.



Certificate of Analysis

Product Name: Fenugreek Seed Extract (Furosap)	**Batch No.:** FUP0914
Manufacturing Date: SEP.2014	**Quantity:** 5500 capsules
Retest Date: AUG.2017	**Country of Origin:** India

TEST	SPECIFICATION	RESULT	METHOD
Physical Parameters			
Appearance	Transparent cellulose capsule body containing yellowish brown powder	Complies	Visual
Average weight	600 ± 7.5%	606.02 mg	USP 35
Uniformity of weight	500 ± 7.5%	514.9 mg	USP 35
Disintegration test	All capsules should disintegrate within 30 minutes	All capsules disintegrate in 6.5 min.	USP 35
Loss on drying (LOD)	NMT 5.0%	3.25%	USP 35
Impurities			
Heavy Metals (By AAS): a) Lead (as Pb) b) Cadmium (as Cd) c) Arsenic (as As) d) Mercury (as Hg)	NMT 20 ppm	 1.34 ppm 0.08 ppm Not detected Not detected	USP 35
Microbiological Test: a) Total bacterial count b) Total fungal count c) E.coli d) Salmonella sp. e) S. aureus f) Coliform	 NMT 1000 cfu/g NMT 100 cfu/g Absent/g Absent/g Absent/g Absent/g	 <10 cfu/g <10 cfu/g Absent Absent Absent Absent	USP 35

Analyzed By Pratibha Sharma (QC Analyst) Reviewed By Jyoti Kushwaha (Asst. Exe. QA/RA) Approved By Kuldeep Kumar (QC Executive)

CHEMICAL RESOURCES

(100% E.O.U. APPROVED BY GOVT. OF INDIA & GMP CERTIFIED COMPANY)

Factory : PLOT NO. 3-A, INDUSTRIAL AREA, PHASE-II, PANCHKULA, HARYANA - 134109 (INDIA)
Office : SCO 76, IST FLOOR, SWASTIK VIHAR, MANSA DEVI COMPLEX, PANCHKULA, HARYANA-134109 (INDIA)
Ph. +91-172-2555557, 2555558. Fax : +91-172-2555559.
E-mail : info@chemicalresources.net, chemicalresources@gmail.com
www.chemicalresources.net

Certificate of analysis (COA)

Certificate of Analysis

Product Name: Fenugreek Seed Extract (Furosap)	**Batch No.:**FUP0914
Manufacturing Date: SEP.2014	**Quantity:** 120 packs x 30 caps
Retest Date: AUG.2017	**Country of Origin:** India

TEST	SPECIFICATION	RESULT	METHOD
Physical Parameters			
Appearance	Transparent cellulose capsule body containing yellowish brown powder	Complies	Visual
Average weight	600 ± 7.5%	606.02 mg	USP 35
Uniformity of weight	500 ± 7.5%	514.9 mg	USP 35
Disintegration test	All capsules should disintegrate within 30 minutes	All capsules disintegrate in 6.5 min.	USP 35
Loss on drying (LOD)	NMT 5.0%	3.2%	USP 35
Impurities			
Heavy Metals (By AAS):	NMT 20 ppm		USP 35
a) Lead (as Pb)		1.34 ppm	
b) Cadmium (as Cd)		0.08 ppm	
c) Arsenic (as As)		Not detected	
d) Mercury (as Hg)		Not detected	
Microbiological Test:			USP 35
a) Total bacterial count	NMT 1000 cfu/g	<10 cfu/g	
b) Total fungal count	NMT 100 cfu/g	<10 cfu/g	
c) E.coli	Absent/g	Absent	
d) Salmonella sp.	Absent/g	Absent	
e) S. aureus	Absent/g	Absent	
f) Coliform	Absent/g	Absent	

Remarks: The above analysis results comply with the specification.

Analyzed By Pratibha Sharma (QC Analyst)

Reviewed By Rajan Singh (Asst. Exe.QA/RA)

Approved By Kiran Tiwari (Head R&D)

CHEMICAL RESOURCES

(100% E.O.U. APPROVED BY GOVT. OF INDIA & GMP CERTIFIED COMPANY)

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: Ph. +91-172-2555557, 2555558, **Fax :** +91-172-2555559,
: E-mail : info@chemicalresources.net, chemicalresources@gmail.com
: www.chemicalresources.net

Certificate of Analysis

Product Name: Fenugreek Seed Extract (Furosap)	**Batch No.:** FUP0615
Manufacturing Date: JUN.2015	**Quantity:** 100 packs x 30 capsules
Best before: MAY.2018	**Country of Origin:** India

TEST	SPECIFICATION	RESULT	METHOD
Physical Parameters			
Appearance	Transparent cellulose capsule body containing yellowish brown powder	Complies	Visual
Average weight	600 ± 7.5%	617.27 mg	USP 37
Uniformity of weight	500 ± 7.5%	520.19 mg	USP 37
Disintegration test	All capsules should disintegrate within 30 minutes	All capsules disintegrate in 6.5 min.	USP 37
Loss on drying (LOD)	NMT 5.0 %	3.9 %	USP 37
Impurities			
Heavy Metals (By AAS):	NMT 20 ppm		USP 37
a) Lead (as Pb)		0.456 ppm	
b) Cadmium (as Cd)		0.07 ppm	
c) Arsenic (as As)		Not detected	
d) Mercury (as Hg)		Not detected	
Microbiological Test:			USP 37
a) Total bacterial count	NMT 1000 cfu/g	200 cfu/g	
b) Total fungal count	NMT 100 cfu/g	Absent	
c) E.coli	Absent/g	Absent	
d) Salmonella sp.	Absent/g	Absent	
e) S. aureus	Absent/g	Absent	
f) Coliform	Absent/g	Absent	

Remarks: The above analysis results comply with the specification.

Analyzed By Satish Kumar (Sr. Exe. QC)

Reviewed By Rajan Singh (Asst. Exe.QA/RA)

Approved By Kiran Tiwari (Head R & D)

CHEMICAL RESOURCES

(100% E.O.U. APPROVED BY GOVT. OF INDIA & GMP CERTIFIED COMPANY)

Factory : PLOT NO. 3-A, INDUSTRIAL AREA, PHASE-II, PANCHKULA, HARYANA - 134109 (INDIA)
Office : SCO 76, IST FLOOR, SWASTIK VIHAR, MANSA DEVI COMPLEX, PANCHKULA, HARYANA-134109 (INDIA)
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: E-mail : info@chemicalresources.net, chemicalresources@gmail.com
: www.chemicalresources.net

9. EFFICACY EVALUATION

The efficacy of investigational product (Furosap®) in testosterone deficient patients was evaluated by the laboratory investigations. The following investigations were done at baseline, follow-up month (4 and 8 weeks) and end of the study (12 weeks):

Assessment of Efficacy

- Scoring chart evaluation (Evaluation of mental alertness, mood, reflex erection & overall performance) (Annexure I)
- Frequency of sexual intercourse evaluation

The following laboratory investigations were also done after intervals along with the above given evaluations for efficacy analysis:

i. At Baseline

- Free testosterone
- Total testosterone
- DHEA-S levels
- Fasting blood sugar
- Fasting lipid profile (TC, LDL, HDL, TG, VLDL)
- Semen examination (Sperm count, sperm motility, sperm morphology)

ii. Follow-up Month (1st and 2nd)

- Semen examination (Sperm count, sperm motility, sperm morphology)
- Fasting lipid profile (TC, LDL, HDL, TG, VLDL)

iii. End of study (3rd Month)

- Free testosterone
- Total testosterone
- DHEA-S levels
- Fasting blood sugar
- Fasting lipid profile (TC, LDL, HDL, TG, VLDL)
- Semen examination (Sperm count, sperm motility, sperm morphology)

10. SAFETY EVALUATION

Safety of the investigational product of the enrolled subjects was evaluated by following laboratory investigations during baseline and final follow-up (12 weeks):

- Blood urea nitrogen (BUN)
- Haemoglobin (Hb)
- Total Leukocyte count (TLC)
- Differential Leukocyte Count (DLC)
- Serum Glutamic Oxaloacetic Transaminase (SGOT)
- Serum Glutamic-Pyruvic Transaminase (SGPT)
- Serum Alkaline Phosphatase (ALP)

Assessment of Safety

Safety was assessed at each follow-up visit. Investigational product was planned to be discontinued in case of any serious adverse reaction followed by management of patient according to the clinical condition.

Definitions Adverse Reaction

WHO technical report no 498 (1972) "a response to a drug which is noxious and unintended, and which occurs at normal doses normally used in man for prophylaxis, diagnosis, or therapy of a disease, or for the modification of physiological function"

"All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions".

Adverse Events / Adverse Experience

Any untoward medical occurrence that may present during the clinical study with the product at the same time does not necessarily have a causal relationship with this treatment.

"Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment".

Serious Adverse Event or Reaction

A serious adverse event or reaction is any untoward medical occurrence that at any dose:

- Results in death

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is life-threatening
- Congenital anomaly/birth defect.

Reporting of Adverse Events

At the time of screening of subjects any clinical abnormality should be noted as All Ready Exist (ARE) condition in the CRF's. The adverse event will be considered only if it matches the above defined criteria or any new clinical finding in the subjects or abnormal laboratory values, not to ARE conditions.

All the adverse events should be reported as mentioned in the schedule Y of the drug and cosmetics act and rules 1940.

Reporting to the Sponsor

All the serious adverse events will be reported by the principal investigator to the sponsor via phone call within 24 hours and details of clinical findings at the time of SAE's will be sent to the sponsor via fax within 24 hours.

Reporting to the Ethics Committee (EC)

All the serious adverse events will be reported by the principal investigator to the EC within 7 working Days.

Ethical Justification

There was no additional financial burden on the study participants as the cost of the study and procedures will be borne by the sponsor. In case of development of untoward medical incident related to the investigational product, the investigators and the sponsor will take responsibility for the management.

11. RESULTS

Demographic parameters

Average age of the study population was 39.05 years, with minimum age of 35 years and maximum age of 60 years.

Average height of the study population was 171.73 cm, with minimum height of 155 cm and maximum height of 198 cm.

Average BMI and pulse of the study population was 23.37 kg/m^2 and 71.28 per minute, respectively.

Table 1: Statistical data of demographic parameters of study population.

PARAMETERS	Mean ± Std. Deviation	Minimum	Maximum
Age (years)	39.05 ± 5.60	35.00	60.00
Height (cm)	171.73 ± 9.85	155.00	198.00
BMI (kg/m^2)	23.37 ± 3.67	10.63	36.00
Pulse (per minute)	71.28 ± 2.22	70.00	80.00

Body weight (Kg)

The mean body weight of the study population was 69.08 kg at baseline. This mean weight was significantly increased to 69.16 kg at Visit 1 and remained stable on the further visits *i.e.* at Visit 2 (69.11 kg) and Visit 3 (69.03 kg).

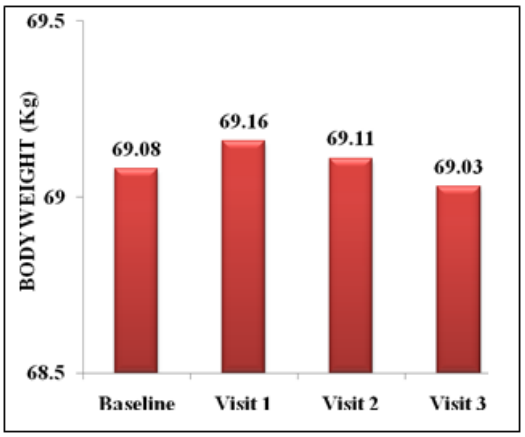


Fig 1: Mean body weight of the study population.

Table 2: Statistical data of mean body weight of study population.

BODY WEIGHT	Mean ± Std. Deviation	t-value	p-value
Baseline	69.08 ± 7.79		
Visit 1 (4 Weeks)	69.16 ± 7.65	1.469	0.145
Visit 2 (8 Weeks)	69.11 ± 7.73	0.961	0.339
Visit 3 (12 Weeks)	69.03 ± 7.83	1.408	0.163

Blood Pressure (mmHg)

The systolic blood pressure (SBP) and diastolic blood pressure (DBP) of the study population on screening were 113.83 mmHg and 85.06 mmHg, respectively. The mean SBP was significantly decreased to 112.10 mmHg and mean DBP was decreased to 81.51 mmHg on completion of the treatment.

Table 3: Statistical data of mean blood pressure of study population.

BLOOD PRESSURE	Mean ± Std. Deviation	t-value	p-value
SBP baseline	113.83 ± 5.93	2.70	0.008
SBP on completion of treatment	112.10 ± 5.59		
DBP baseline	85.06 ± 7.16	4.73	0.000
DBP on completion of treatment	81.51 ± 3.86		

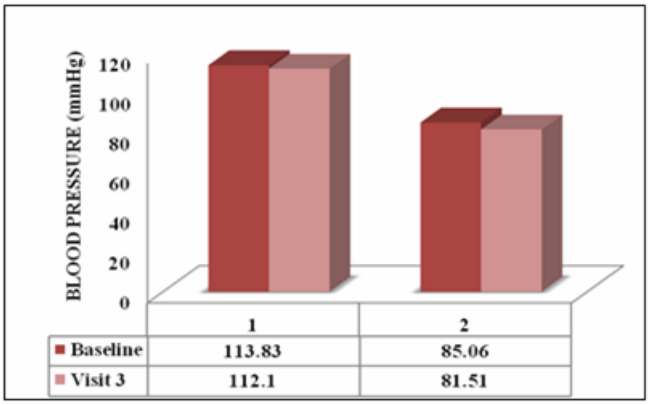


Fig 2: Mean SBP (1) & DBP (2) of the study population.

A. EFFICACY EVALUATION

Frequency of sexual intercourse (Days/month)

The mean frequency of sexual intercourse was 10.10 days/month at baseline which was increased significantly to 11.08 days/month on Visit 1 (after 4 weeks of treatment with investigational product). This was further increased to mean 12.25 days/month after 8 weeks of treatment on Visit 2. On completion of the treatment (Visit 3), the mean frequency of sexual intercourse was increased more to 14.01 days/month.

This frequency of sexual intercourse was observed to be increased up to 38.71% till the completion of the treatment in the study population.

Table 4: Statistical data of mean frequency of sexual intercourse of study population.

FREQUENCY OF SEXUAL INTERCOURSE (Days/month)	Mean ± Std. Deviation	t-value	p-value
Baseline	10.10 ± 2.85		
Visit 1 (4 Weeks)	11.08 ± 2.20	5.751	0.000
Visit 2 (8 Weeks)	12.25 ± 2.17	10.009	0.000
Visit 3 (12 Weeks)	14.01 ± 2.74	12.017	0.000

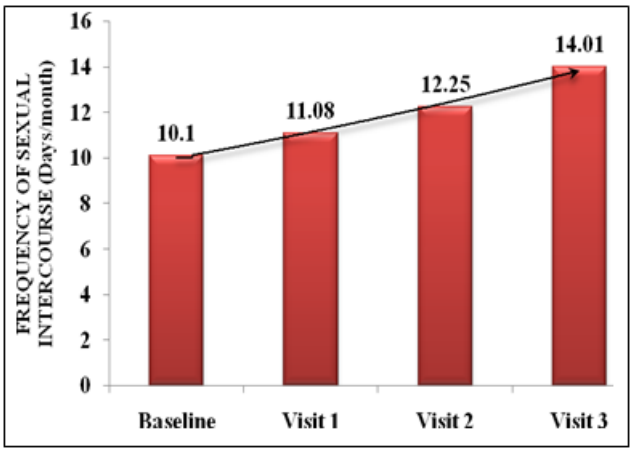


Fig 3: Mean frequency of sexual intercourse of the study population Free testosterone levels (pg/ml).

The mean free testosterone level of the study population at baseline was 11.28 pg/ml which was significantly increased to 19.50 pg/ml in 88.6% of the study population till the completion of the treatment with investigational product.

Mean free testosterone levels were increased up to 72.87% in the study population till the completion of the treatment.

Table 5: Statistical data of mean free testosterone levels of study population.

FREE TESTOSTERONE (pg/ml)	Mean ± Std. Deviation	t-value	p-value
Baseline	11.28 ± 8.86	8.456	0.000
Visit 3 (12 Weeks)	19.50 ± 9.73		

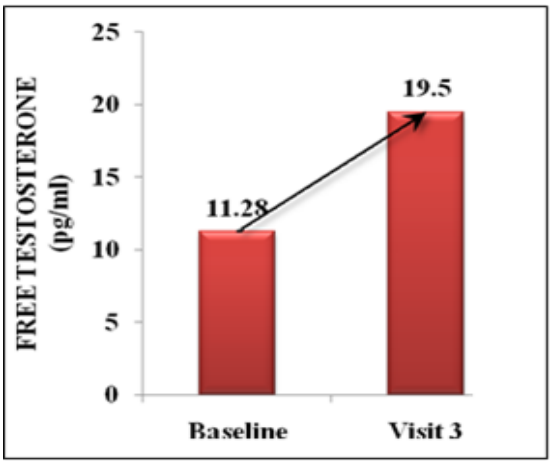


Fig 4: Mean free testosterone levels of the study population Total testosterone (ng/dl).

It was observed that the mean total testosterone level of the study population was 386.79

ng/ml at baseline which was significantly increased to 495.27 ng/ml in 85.2% of study population till the completion of the treatment with investigational product.

In the study population, 28.04% increase in total testosterone levels was observed till the completion of the treatment.

Table 6: Statistical data of mean total testosterone levels of study population.

TOTAL TESTOSTERONE (ng/ml)	Mean ± Std. Deviation	t-value	p-value
Baseline	386.79 ± 161.90	7.776	0.000
Visit 3 (12 Weeks)	495.27 ± 144.03		

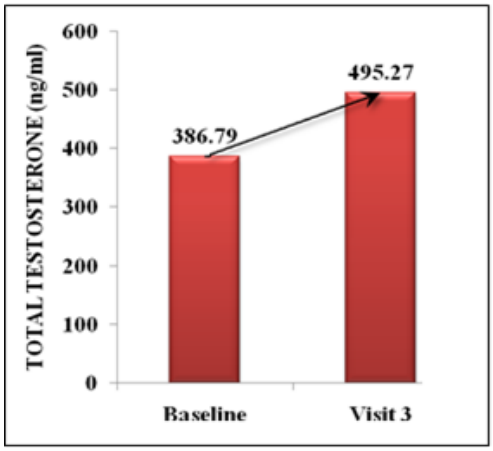


Fig 5: Mean total testosterone levels of the study population.

DHEA-S levels (µg/dl)

The mean DHEA-S level of the study population at baseline was 197.32 µg/dl which was significantly decreased to 182.96 µg/dl till the completion of the treatment.

Table 7: Statistical data of mean DHEA-S levels of study population.

DHEA-S levels (µg/dl)	Mean ± Std. Deviation	t-value	p-value
Baseline	197.32 ± 74.39	3.050	0.003
Visit 3 (12 Weeks)	182.96 ± 65.13		

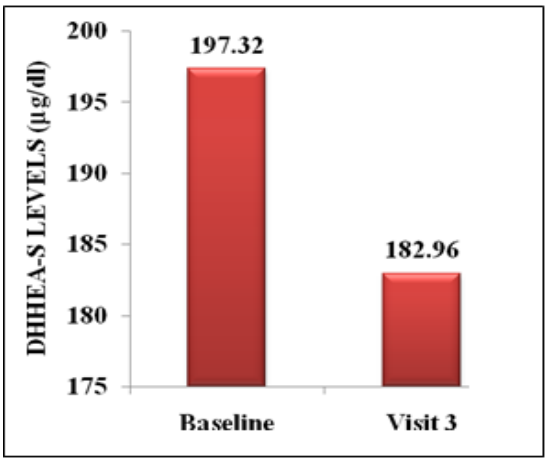


Fig 6: Mean DHEA-S levels of the study population Sperm count (Million/cc).

The mean sperm count of the study population was 46.15 million/cc at baseline which was significantly increased to 51.63 million/cc in 14% of the study population after consumption of investigational product till 4 weeks (Visit 1). On Visit 2 (after 8 weeks), the mean sperm count was significantly increased more to 56.10 million/cc in 19.3% of the study population. On completion of the treatment mean sperm count was significantly increased further to 62.22 million/cc in 22.7% of the study population. The sperm count was increased up to 34.82% in the study population.

Table 8: Statistical data of mean sperm count of study population.

SPERM COUNT (Million/cc)	Mean ± Std. Deviation	t-value	p-value
Baseline	46.15 ± 27.56		
Visit 1 (4 Weeks)	51.63 ± 25.55	5.387	0.000
Visit 2 (8 Weeks)	56.10 ± 26.66	6.754	0.000
Visit 3 (12 Weeks)	62.22 ± 25.008	10.064	0.000

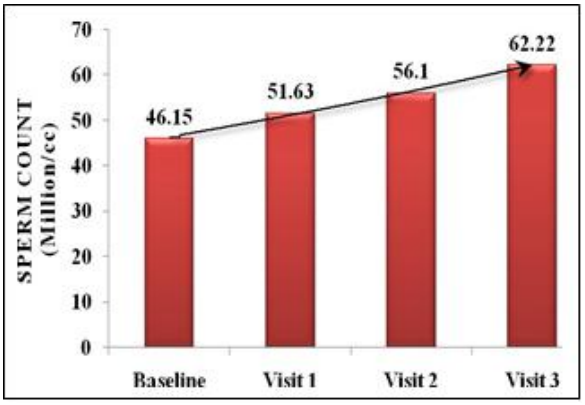


Fig 7: Sperm count of the study population Sperm motility (%).

The sperm motility indicates percentage of motile sperm in the semen sample. The sperm

motility of study population was observed to be significantly increased with the progress in treatment. The mean sperm motility of the study population was 47.12% at baseline which was increased to 48.26% on Visit 1 *i.e.* after 4 weeks. On Visit 2, the mean sperm motility observed to be significantly increased to 51.65% in the study population. On completion of the treatment (Visit 3), the mean sperm motility was further increased to 55.35%. The increase in sperm motility was statistically significant. The sperm motility was observed to be improved up to 17.46% in the study population till the completion of the treatment.

Table 9: Statistical data of mean sperm motility of study population.

SPERM MOTILITY (%)	Mean ± Std. Deviation	t-value	p-value
Baseline	47.12 ± 23.478		
Visit 1 (4 Weeks)	48.26 ± 22.145	1.236	0.220
Visit 2 (8 Weeks)	51.65 ± 22.520	3.072	0.003
Visit 3 (12 weeks)	55.35 ± 21.975	6.288	0.000

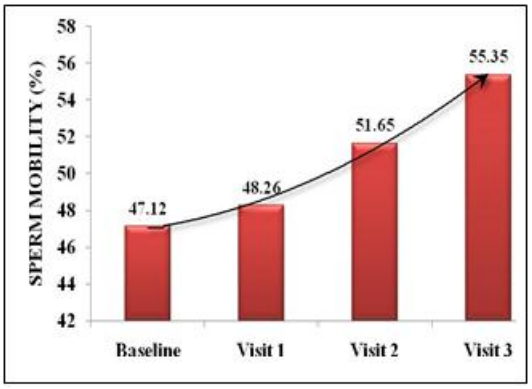


Fig 8: Sperm motility of the study population.

Abnormal sperm morphology (%)

Abnormal sperm morphology in percent indicates the percent of abnormal sperms observed microscopically in a semen sample. On screening, average percent of sperms with abnormal morphology were 32.79, which were significantly reduced to 30.64% & 29.46 % on Visit 1 & Visit 2, respectively. On completion of the treatment, mean percent of sperms with abnormal morphology were significantly reduced to 26.62% in the study population.

It was observed that the abnormal sperm morphology was decreased up to 18.81% in the study population till the completion of the treatment.

Table 10: Statistical data of mean abnormal sperm morphology of study population.

RM MORPHOLOGY (%)	Mean ± Std. Deviation	t-value	p-value
Baseline	32.79 ± 19.996		
Visit 1 (4 Weeks)	30.64 ± 18.585	1.232	0.221
Visit 2 (8 Weeks)	29.46 ± 17.754	1.519	0.133
Visit 3 (12 weeks)	26.62 ± 17.130	2.656	0.009

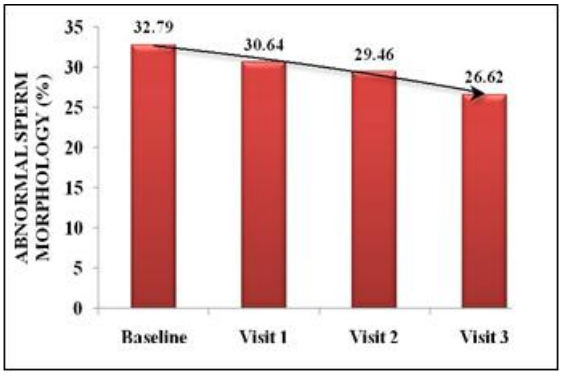


Fig 9: Abnormal sperm morphology of the study population Mental alertness.

The mean score of mental alertness in the study population was 5.22 at baseline which was increased to 5.41 on Visit 1 and further increased to 5.94 on Visit 2 in the study population. On completion of the treatment, the mean score of mental alertness was observed to be increased to 6.51 as compared to baseline score in the study population.

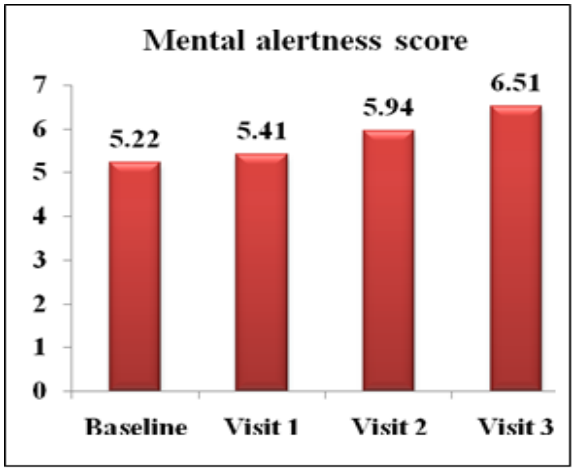


Fig 10: Mental alertness score of the study population.

Percent population with improvement in mental alertness

This improvement in mental alertness of study population was also observed in different age groups. In the group between 35-40 years of age, 18.3% population improved their mental alertness till Visit 1 which was increased to 55.4% of population till Visit 2 and further increased to 76.8% of population till the completion of the treatment.

In the group between 41-50 years of age, maximum number of population showed improvement in mental alertness from the treatment. On Visit 1, 23.10% population improved their mental alertness which was increased to improvement in 80% of population till Visit 2 and further increased to 92% of population till the completion of the treatment.

In the group between 51-60 years of age, 33.3% population improved mental alertness till Visit 1. On Visit 2, the percent of population with improvement in mental alertness was increased up to 66.7% which was further increased to 83.3% of population till the completion of the treatment.

As the overall study population is considered, 21.5% of population showed improvement in mental alertness till Visit 1 (4 weeks), 63.6% of population showed improvement in mental alertness till Visit 2 (8 weeks) and 81.8% of total population showed improvement in mental alertness till the completion of the treatment.

It was observed that mental alertness increased up to 24.71% in the study population till the completion of the treatment.

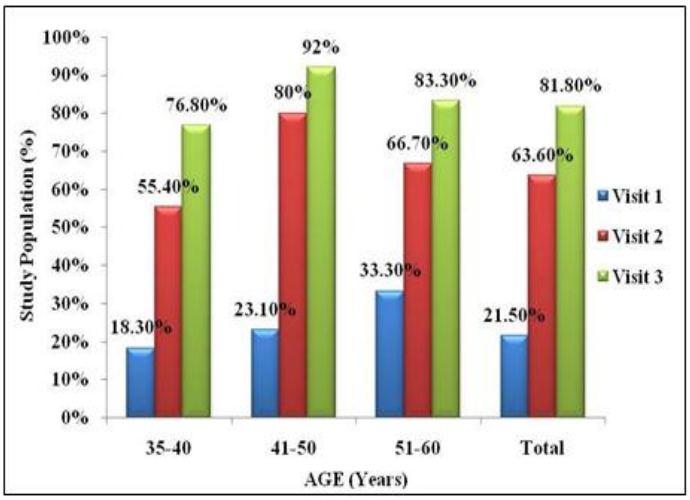


Fig 11: Age-wise population (%) with improvement in mental alertness Mood.

The mean score of mood in the study population was 4.98 at baseline. On Visit 1 (4 weeks), the mean score was slightly increased to 5.55 in 57% of study population which was further increased to 6.08 on Visit 2 (8 weeks) in 84.1% of the study population. On completion of the treatment, the mean score of mood was increased to 6.68 in 95.5% of the study population as compared to baseline score.

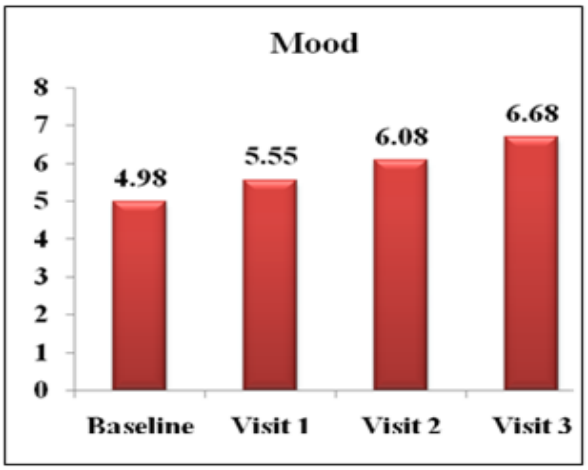


Fig 12: Mean mood score of the study population.

Percent population with improvement in mood

This improvement in mood of study population was also observed in different age groups. In the group between 35-40 years of age, 55.3% population improved their mood till Visit 1 which was increased to 76.80% of population till Visit 2 and further increased to 92.9% of population till the completion of the treatment.

In the group between 41-50 years of age, maximum number of population showed improvement in mood from the treatment. On Visit 1, 65.40% population improved their mood which was increased to improvement in the complete enrolled population (100%) till Visit 2 and further remained stable in complete study population (100%) till the completion of the treatment.

In the group between 51-60 years of age, 50% population improved mood till Visit 1. On Visit 2, the percent of population with improvement in mood was increased up to 83.3% which was further observed in complete enrolled population (100%) of study till the completion of the treatment.

It was observed that mood score increased up to 34.13% in the study population till the completion of the treatment.

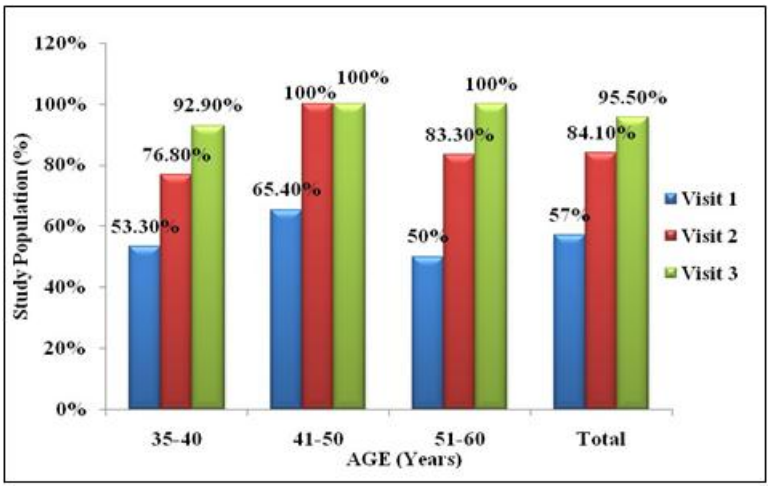


Fig 13: Age-wise population (%) with improvement in mood Reflex erection.

It was observed that the mean score of reflex erection was 4.72 at baseline in the study population. On Visit 1 (4 weeks), the mean score was increased to 5.24 in 47.3% of the study population. This score was further increased slightly to 5.85 in 75% of the study population on Visit 2 (8 weeks). On completion of the treatment, the mean score was increased to 6.62 in 90.9% of the study population.

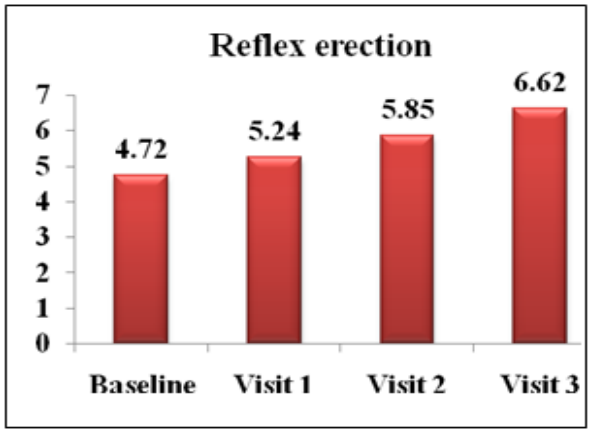


Fig 14: Mean reflex erection score of the study population.

Percent population with improvement in reflex erection

This improvement in reflex erection of study population was observed in different age groups. In the group between 35-40 years of age, 46.70% population improved reflex erection till Visit 1 which was increased to 73.20% of population till Visit 2 and further increased to 89.30% of population till the completion of the treatment.

In the group between 41-50 years of age, 46.2% population improved their reflex erection till Visit 1 which was increased to improvement in 76% of study population till Visit 2 and

further increased to 92% till the completion of the treatment.

In the group between 51-60 years of age, maximum study population showed improvement in reflex erection. On Visit 1, 66.70% study population improved reflex erection. As the treatment was progressed till Visit 2, the complete study population (100%) showed improvement in Reflex erection which was also remained same (100% population) till the completion of the treatment in this age group.

It was observed that reflex erection was increased up to 40.25% in the study population till the completion of the treatment.

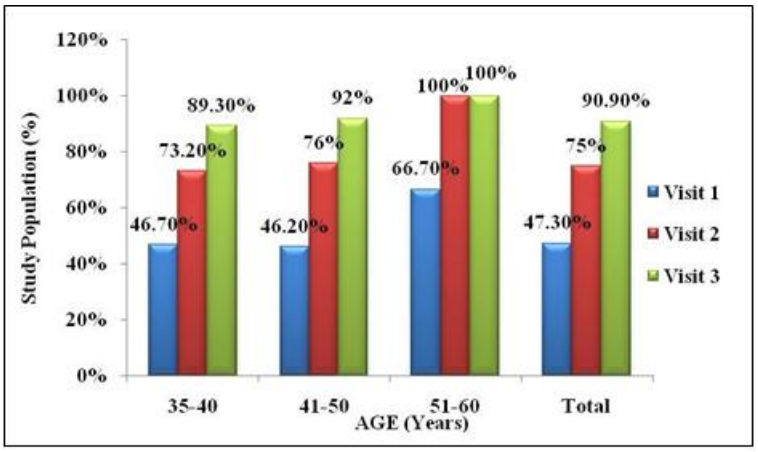


Fig 15: Age-wise population (%) with improvement in reflex erection Overall performance.

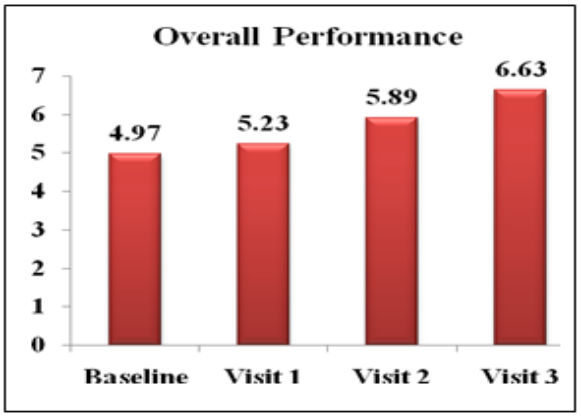


Fig 16: Mean overall performance score of the study population.

The mean score of overall performance of the study population was 4.97 at baseline. On Visit 1 (4 weeks), this mean score was increased to 5.23 in the 28% of study population. This score was further increased to 5.89 in 78.4% of study population at Visit 2 (8weeks). On

completion of the treatment, 98.9% of population showed the increase in mean score of 6.63.

Percent population with improvement in overall performance

The overall performance was observed in different age groups of study population. In the group between 35-40 years of age, 30% population improved overall performance till Visit 1 which was increased to 73.20% of population till Visit 2 and further increased to 98.20% of population till the completion of the treatment.

In the group between 41-50 years of age, 19.20% population improved their overall performance till Visit 1 which was increased to improvement in 88% of study population till Visit 2. As the treatment progressed till Visit 3, the complete study population (100%) of this age group showed improvement in overall performance.

In the group between 51-60 years of age, 33.3% study population showed improvement in overall performance till Visit 1 which was increased in 83% of study population till Visit

2. As the treatment was progressed till Visit 3, the complete study population (100%) of this age group showed improvement in overall performance.

As the whole study population is considered, 28% study population showed improvement in overall performance till Visit 1, 78% population showed improvement in overall performance till Visit 2 and 98.9% of study population showed improvement in overall performance till the completion of the treatment.

It was observed that overall performance was increased up to 33.40% in the study population till the completion of the treatment.

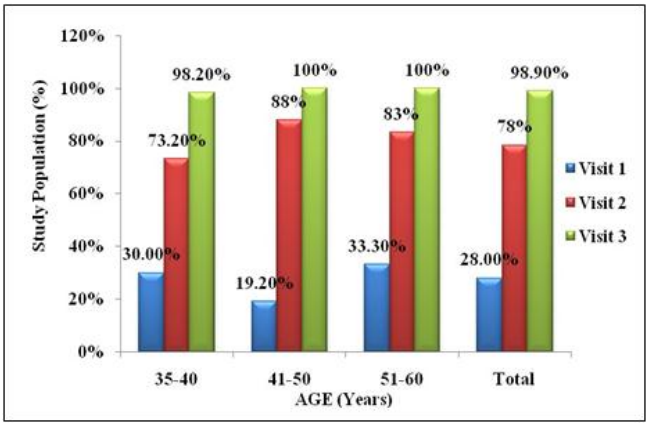


Fig 17: Age-wise population (%) with improvement in overall performance Fasting.

blood sugar (mg/dl)

At baseline, the mean fasting blood sugar level of the study population was 106.95 mg/dl which was observed to be significantly decreased to 102.51 mg/dl till the completion of the treatment.

Table 11: Statistical data of mean fasting blood sugar levels of study population.

FASTING BLOOD SUGAR (mg/dl)	Mean ± Std. Deviation	t-value	p-value
Baseline	106.95 ± 35.183	1.859	0.066
Visit 3 (12 Weeks)	102.51 ± 26.445		

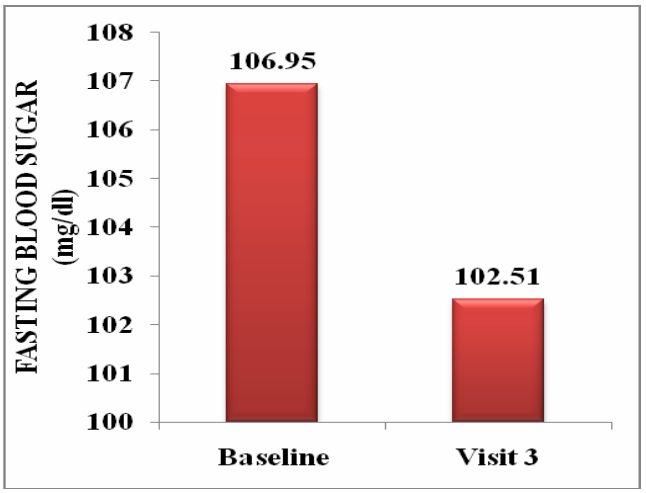


Fig 18: Mean fasting blood sugar levels of the study population.

B. SAFETY EVALUATION

LIVER FUNCTION TESTS

Serum glutamic oxaloacetic transaminase (SGOT) activity (U/L)

A significant decrease in the mean SGOT activity was observed on completion of the treatment. The values remained within the normal range (0-37 U/L).

Table 12: Statistical data of mean AST/SGOT activity of study population.

T/SGOT (U/L)	Mean ± Std. Deviation	t-value	p-value
Baseline	31.83 ± 9.570	4.252	0.000
Visit 3 (12 Weeks)	28.31 ± 6.819		

Serum glutamic pyruvic transaminase (SGPT) activity (U/L)

There was significant decrease in the mean SGPT activity in the study population on completion of the treatment. The values remained within the normal range (13-40 U/L).

Table 13: Statistical data of mean ALT/SGPT activity of study population.

T/SGPT (U/L)	Mean ± Std. Deviation	t-value	p-value
Baseline	38.95 ± 18.137	3.704	0.000
Visit 3 (12 Weeks)	33.98 ± 14.522		

Serum alkaline phosphatase (ALP) activity (U/L)

There was significant decrease in the mean ALP activity in the study population on completion of the treatment. The values remained within the normal range till the last visit (53-128 U/L).

Table 14: Statistical data of mean ALP activity of study population.

ALP (U/L)	Mean ± Std. Deviation	t-value	p-value
Baseline	97.22 ± 25.020	3.531	0.001
Visit 3 (12 Weeks)	89.84 ± 23.132		

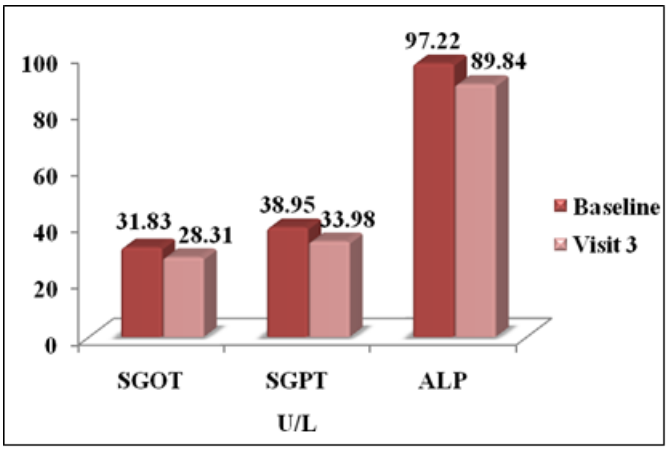


Fig 19: Liver function test parameters of the study population.

RENAL FUNCTION TESTS

Blood Urea Nitrogen (BUN) levels

In the study population, the mean BUN levels were remained significantly same (approx) till the completion of the treatment.

Table 15: Statistical data of mean BUN levels of study population.

BUN (mg/dl)	Mean ± Std. Deviation	t-value	p-value
Baseline	12.02 ± 3.530	2.987	0.004
Visit 3 (12 Weeks)	12.78 ± 3.532		

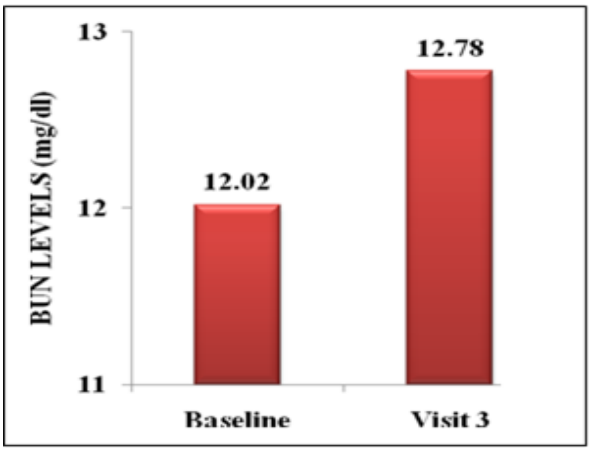


Fig 20: Mean BUN levels of the study population.

LIPID PROFILE

Total cholesterol levels (mg/dl)

At baseline, the mean total cholesterol levels of the study population were 182.41 mg/dl which were decreased significantly to 176.34 mg/dl till Visit 1 (after 4weeks of treatment). On Visit 2 (8 weeks), the mean cholesterol levels significantly fall to 175.36 mg/dl. On completion of the treatment, mean cholesterol levels of the study population were 175.24 mg/dl. The total cholesterol levels remained under normal range (125-200 mg/dl).

Table 16: Statistical data of mean total cholesterol levels of study population.

TOTAL CHOLESTEROL (mg/dl)	Mean ± Std. Deviation	t-value	p-value
Baseline	182.41 ± 31.574		
Visit 1 (4 Weeks)	176.34 ± 32.613	2.667	0.009
Visit 2 (8 Weeks)	175.36 ± 27.461	2.760	0.007
Visit 3 (12 weeks)	175.24 ± 29.706	2.290	0.024

Triglyceride levels (mg/dl)

There was non-significant change in the mean triglyceride levels of the study population till the completion of the treatment.

Table 17: Statistical data of mean triglyceride levels of study population.

TRIGLYCERIDES (mg/dl)	Mean ± Std. Deviation	t-value	p-value
Baseline	151.14 ± 99.070		
Visit 1 (4 Weeks)	147.09 ± 79.940	0.469	0.640
Visit 2 (8 Weeks)	143.73 ± 71.533	0.801	0.425
Visit 3 (12 weeks)	144.41 ± 70.218	0.581	0.562

HDL cholesterol levels (mg/dl)

The mean HDL cholesterol levels of the study population remained almost same till the completion of the treatment as compared to the baseline levels. They remained within the normal range (35-80 mg/dl).

Table 18: Statistical data of mean HDL cholesterol levels of study population.

HDL CHOLESTEROL (mg/dl)	Mean ± Std. Deviation	t-value	p-value
Baseline	44.85 ± 11.154		
Visit 1 (4 Weeks)	42.45 ± 9.469	2.407	0.018
Visit 2 (8 Weeks)	43.87 ± 9.484	1.340	0.184
Visit 3 (12 weeks)	46.47 ± 10.033	1.638	0.105

LDL cholesterol levels (mg/dl)

The mean LDL cholesterol levels of the study population were 106.21 mg/dl at baseline which were significantly decreased to 103.11 mg/dl after 4 weeks of treatment with investigational product. They were further decreased slightly to 102.98 mg/dl till 8 weeks of treatment. On completion of the treatment, the mean LDL cholesterol levels fall significantly further to 98.11 mg/dl.

Table 19: Statistical data of mean LDL cholesterol levels of study population.

LDL CHOLESTEROL (mg/dl)	Mean ± Std. Deviation	t-value	p-value
Baseline	106.21 ± 26.153		
Visit 1 (4 Weeks)	103.11 ± 24.771	1.689	0.095
Visit 2 (8 Weeks)	102.98 ± 23.601	1.594	0.115
Visit 3 (12 weeks)	98.11 ± 21.623	4.254	0.000

VLDL levels (mg/dl)

There was non-significant change in the mean VLDL levels of the study population till the completion of the treatment.

Table 20: Statistical data of mean VLDL cholesterol levels of study population.

VLDL CHOLESTEROL (mg/dl)	Mean ± Std. Deviation	t-value	p-value
Baseline	30.17 ± 19.839		
Visit 1 (4 Weeks)	29.67 ± 14.657	0.332	0.741
Visit 2 (8 Weeks)	28.65 ± 12.538	1.029	0.307
Visit 3 (12 weeks)	28.50 ± 13.939	0.745	0.458

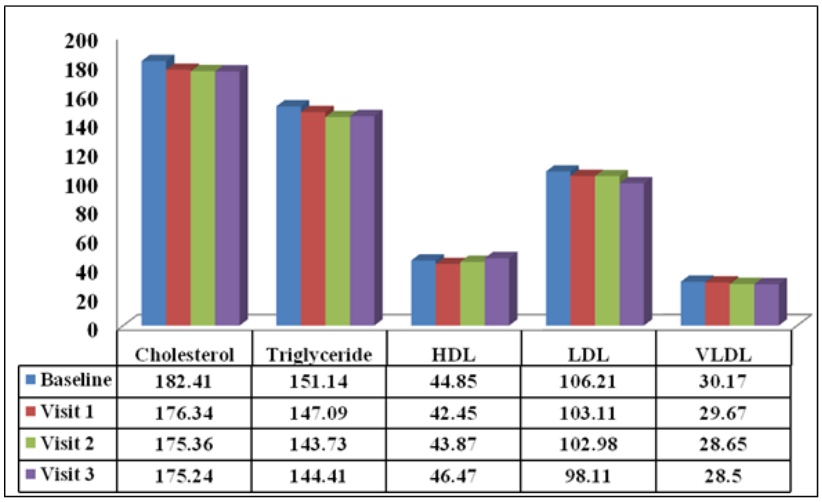


Fig 21: Lipid profile of the study population.

Effect on Hemogram

Hemoglobin (Hb) levels (g/dl)

There was non-significant increase in hemoglobin levels in the study population on completion of the treatment as compared to baseline levels.

Table 21: Statistical data of mean hemoglobin levels of study population.

HEMOGLOBIN (g/dl)	Mean ± Std. Deviation	t-value	p-value
Baseline	14.31 ± 1.470	1.186	0.239
Visit 3 (12 Weeks)	16.03 ± 13.500		

Total leukocyte count (× 10^3 /microlitre)

No significant change in the total leukocyte count was observed on completion of the treatment as compared to baseline levels.

Table 22: Statistical data of mean total leukocyte count of study population.

TOTAL LEUKOCYTE COUNT (× 10^3 / microlitre)	Mean ± Std. Deviation	t-value	p-value
Baseline	7.09 ± 2.183	1.186	0.239
Visit 3 (12 Weeks)	7.12 ± 2.145		

Differential leukocyte count (%)

No significant change in the Neutrophil count, Lymphocyte count and Basophil count was observed on completion of the treatment. A significant increase in Monocyte count and decrease in Eosinophil count was observed on completion of the treatment.

Table 23: Statistical data of mean differential leukocyte count of study population.

NTIAL LEUKOCYTE COUNT (%)	Mean ± Std. Deviation	t-value	p-value
Lymphocytes at baseline	30.46 ± 6.860	0.709	0.480
Lymphocytes on Visit 3 (12 Weeks)	29.80 ± 7.365		
Neutrophils at baseline	60.10 ± 7.588	1.057	0.293
Neutrophils on Visit 3 (12 Weeks)	61.22 ± 7.812		
Monocytes at baseline	4.07 ± 2.373	2.928	0.004
Monocytes on Visit 3 (12 Weeks)	4.93 ± 3.179		
Basophils at baseline	0.23 ± 0.224	0.137	0.892
Basophils on Visit 3 (12 Weeks)	0.23 ± 0.313		
Eosinophils at baseline	4.97 ± 4.028	2.745	0.007
Eosinophils on Visit 3 (12 Weeks)	3.82 ± 2.765		

Efficacy conclusions

On completion of the study, following efficacy conclusions were made

i. **Frequency of sexual intercourse:** A significant increase in frequency of sexual intercourse was observed in the study population after 12 weeks of complete treatment. 38.71% increase in the frequency of sexual intercourse was observed.

ii. **Free testosterone levels:** 88.6% of study population showed significant increase in free testosterone levels. On completion of the treatment, 72.87% increase in free testosterone levels was observed in the patients.

iii. **Total testosterone levels:** On the other hand, total testosterone levels increased significantly up to 28.04% in the study population. These positive effects were seen in 85.02% of the study population.

iv. **Sperm profile:** The sperm profile was greatly improved in the enrolled testosterone deficient patients. The sperm count was increased up to 34.82% in the study population. The sperm motility was also observed to be improved in 17.46% of study population. Whereas, abnormal sperm morphology was efficiently decreased up to 18.81% in the study population.

v. **Scoring chart:** It was also observed that various parameters of scoring chart showed improvements till the completion of the treatment. 81.8% of study population showed improvement in mental alertness, 95.5% of study population showed improvement in mood, 90.9% of study population showed improvement in reflex erection and 98.9% study population showed great improvement in overall performance.

Safety conclusions

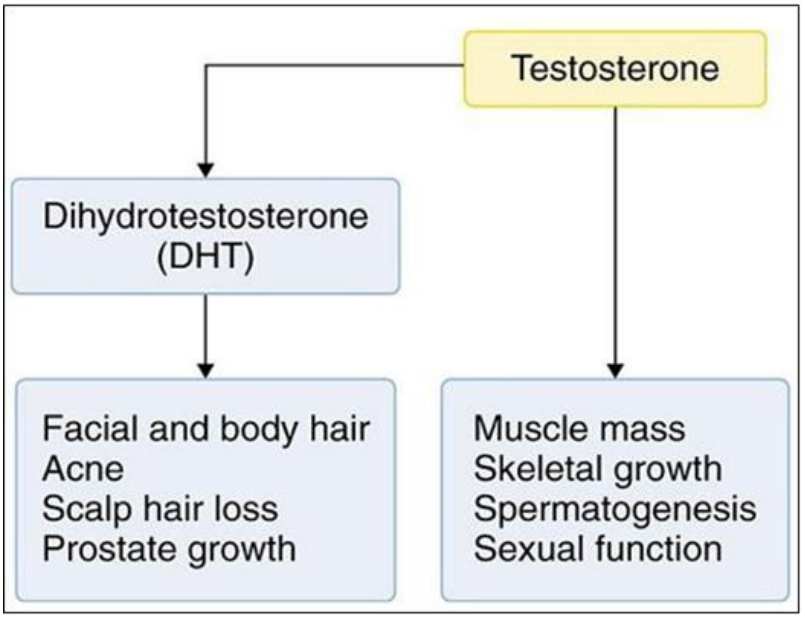
On completion of the study, following safety conclusions were made:

i. No significant change in the liver function tests (serum SGOT, SGPT & ALP activities) was observed.
ii. No significant change in BUN level was observed.
iii. No significant change in the hematological parameters was observed on completion of the treatment.

DISCUSSION

Hypogonadism or testosterone deficiency is the condition in which the gonads in men become unable to generate required amounts of testosterone in body. Generally, it develops with aging and mostly prone at the age above 50 years. This decline in testosterone levels continues throughout life, if not treated well.

Testosterone hormone is responsible for the proper development of male sexual characteristics. Testosterone is also important for maintaining muscle bulk, adequate levels of red blood cells, bone growth, a sense of well-being and sexual function. Thus, without adequate testosterone, a man may lose his sex drive, experience erectile dysfunction, feel depressed, have a decreased sense of well-being and have difficulty concentrating.



Testosterone is produced in the testes by testicular Leydig cells, which is closely regulated by the hypothalamic pituitary gonadal (HPG) axis *via* production of luteinizing hormone (LH). Failure in this delicate balance can result in primary or secondary hypogonadism. Once

produced, testosterone circulates systemically either protein bound or unbound. Approximately 20–25% is loosely protein bound to albumin and can uncouple to join free serum testosterone (1–2%), making 'bioavailable' free testosterone.

The remainder is tightly protein bound by sex hormone-binding globulin (SHBG) and is physiologically inactive. Biologically active testosterone can then bind androgen-binding protein within Sertoli cells to maintain intratesticular testosterone for spermatogenesis, convert to more potent androgens in non-testicular tissue such as dihydrotestosterone (DHT) *via* 5α-reductase enzyme, or convert to estrogen *via* aromatase enzyme. The failure in any of these pathways results in testosterone deficiency.

The mechanism by which the gonads become unable to perform their function is not clearly understood but it is hypothesized that gonadotropin-releasing hormone (GnRH) is responsible for this inability of gonads. Beside this, other causes of testosterone deficiency may include injury, infection or loss of testicles, chemotherapy, medications especially for treating enlarged prostate, chronic kidney failure, stress, alcoholism, abdominal obesity, etc.

In the present study, men suffering from testosterone deficiency or hypogonadism were enrolled. The mean age of the study population was 39.05 years and their mean body weight was recorded to be 69.08 kg.

Frequency of sexual intercourse

In testosterone deficiency or hypogonadism, it has been observed that the sexual activities decrease with the progress in disease. This decrease in sexual activities acts as one of the symptoms of hypogonadism. The frequency of sexual intercourse is directly associated with the testosterone levels in men. It has been proved by many scientific studies that the restoration of testosterone levels results in increasing the frequency of sexual intercourse. In the present study also, it has been observed that the frequency of sexual intercourse was increased significantly in the patients during early stages of treatment *i.e.* as observed by clinical examination after 4 weeks. This increase was progressively improved with the progress in treatment. At the end of the treatment, it was observed that the frequency of sexual intercourse was increased up to 38.71% in the study population as the Furosap® treatment was completed (after 12 weeks).

Free testosterone levels

When the testosterone is released by the leydig cells in the testes then, it is divided into three forms inside body. Free testosterone is one of those forms of testosterone which is also known as bio-available testosterone as it is the active form of testosterone to be used by the body. All the activities for which testosterone is responsible inside body are carried out by free testosterone. Free testosterone is available to bind to receptors in the brain, muscle and other organs of the body.

Thus, during testosterone deficiency, the free testosterone levels are highly affected and they act as marker to detect the clear condition of the patient.

In the present study, it was observed that the free testosterone levels significantly improved up to 72.87% in the study population till the completion of the treatment. Furosap® effectively improved these free testosterone levels in the study population after 12 weeks as compared to the baseline levels.

Total testosterone levels

Total testosterone level is a measure of the total amount of testosterone generated by the testicle. It is the measure of circulating testosterone that includes both diffusible and protein-bound forms.

Total testosterone pays major role in hypogonadism. If total testosterone level is low then it shows that the testicles are not producing sufficient testosterone. On the other hand, if total testosterone is high but bio-available testosterone is low, then, it shows that the testicle is producing sufficient amounts of testosterone but it is not available to the body. Both these conditions produce hypogonadism or testosterone deficiency.

The results of the present study showed that the total testosterone levels of the study population improved by 28.04% in the study population. The increase in total testosterone levels could be because of improved the production of testosterone in the body.

DHEA-S levels

DHEA-S or dehydroepiandrosterone sulphate is an endogenous steroid produced by adrenal glands. It is converted to testosterone by the body after synthesis. It helps to evaluate the functioning of adrenal glands.

It is associated with testosterone deficiency. In some cases, it has been observed that DHEA-S is converted back to DHEA by the body which further act as androgen and inhibits the binding of testosterone to its receptor. Thus, causes testosterone deficiency.

DHEA-S levels in the present study were observed to be decreased as the treatment progressed with Furosap® in the study population. But the DHEA-S was decreased very slightly i.e. 7.27% and remained in normal range in the study population till the completion of the treatment.

Fasting blood sugar

According to the researchers, low testosterone levels raise the sugar levels in blood. It is postulated that the rise in blood sugar levels is due to the insulin resistance caused by the deficiency in testosterone levels.

In insulin resistance, the body produces insulin but doesn't use it properly. As a result, glucose builds up in the blood rather than being absorbed by cells. This condition leads to diabetes.

The results of the present study indicate that the fasting sugar levels of the study population fall to required reference range on completion of the treatment. The normalization of testosterone levels in the study population caused normalisation of insulin cycle and results in fall in fasting sugar levels.

Sperm profile

Low testosterone levels highly influence the sperm production in males. As the deficiency of testosterone worsens, the sperm production also decreases. As the sperm production decreases, it further shows the decrease in sperm count. In the present study also, it has been seen that the sperm count of some of the subjects in the study population was 0 million/cc.

The sperm motility in the testosterone deficient patients also gets affected. If the testosterone deficient subjects produce sperms in minor quantity, maximum of them have been observed to be non-motile with abnormal morphology.

In the absence of testosterone or the androgen receptor, spermatogenesis does not proceed beyond the meiosis stage. The major cellular target and translator of testosterone signals to developing germ cells is the Sertoli cell. In the Sertoli cell, testosterone signals can be

translated directly to changes in gene expression or testosterone can activate kinases that may regulate processes required to maintain spermatogenesis. Thus, testosterone is required in large concentrations to maintain the process of spermatogenesis.

In the present study, the increase in free testosterone levels in the patients resulted in improvement in their sperm profile. On completion of the treatment with Furosap®, the sperm count was improved up to 34.82% and sperms become motile and the improvement was up to 17.46% as compared to the baseline values in the study population. The abnormal sperms were decreased up to 18.81% in the study population till the completion of the treatment. This shows that the improvement in testosterone levels by Furosap® in the study population was effective to improve their sperm profile, too.

Scoring chart

The scoring chart for the testosterone deficient patients includes parameters such as mental alertness, mood, reflex erection and overall performance. These parameters are also dependent on testosterone levels in the body. The deficiency in testosterone levels leads to poor quality of life which majorly affects these parameters. The scores for each parameter indicate the medical state of the hypogonadal men.

In the present study, as the treatment with Furosap® was progressed, the testosterone levels were improved which in turn improved the score for each parameter.

Mental alertness was improved up to 24.71% as compared to the baseline values. Mood was improved up to 34.13% and reflex erection was also improved up to 40.25%. This concludes the improvement in overall performance of the study population after treatment which was recorded to be up to 33.40%.

There was no significant change in liver function tests, renal function tests and hematological parameters, suggesting the investigational product Furosap® was safe for human consumption.

CONCLUSION

Furosap® was effective in testosterone deficient patients as it was able to improve testosterone levels, frequency of sexual intercourse, sperm profile, mental alertness, mood,

reflex erection and overall performance in the whole study population. Furosap® was also safe for human consumption along with its effectiveness.

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