Clinical Study Report

Effect of Semenax™ Capsules on Semen Characteristics

Protocol ID:	DM/100710/SMX/MSD
Investigational Product:	Semenax™ Capsules
Indication:	Male Sexual Dysfunction
Development Phase:	Exploratory
Date first patient enrolled:	17 June 2011
Date last patient completed:	30 March 2012
Investigators: Dr. Abhay Kulkarni, Dr. Devendra Save, Dr. Ambadas Kulkarni, Dr. Ashish P. Badadare, Dr. Neelima V. Jadhav, Dr. Ganesh Avhad	
Sponsor:	Leading Edge Marketing
Sponsor's representative:	Mr. Douglas MacKay, DM Contact Management Ltd. Email: doug@dmcontact.com Tel: +1 250 3838267
Contract Research Organization (CRO):	Vedic Lifesciences Pvt. Ltd.
Report signatory and contact details:	Dr. Navneet Sonawane, Vedic Lifesciences Pvt. Ltd. E-mail: navneet.s@vediclifesciences.com Tel: +91 22 42025706
This study was conducted in full accordance with the study protocol and all applicable laws and regulations, including but not limited to current International conference on harmonization -Good clinical practices (ICH-GCP), Schedule Y and the Indian council for medical research (ICMR) ethical guidelines for biomedical research on human participants.	
Date of report:	Version 1.0 dated 1-Oct-2012

Written by:	Reviewed by:	Approved by:
Dr. Anuradha Kulkarni	Dr. Faisal Khan	Dr. Navneet Sonawane

This report conforms to the ICH-E3 guidelines for structure and content of clinical study reports. This document is the property of DM Contact Management Ltd. and contains confidential information. It may not be forwarded to third parties without explicit written prior consent from DM Contact Management Ltd, either in part or in whole, may not be published or copied in any manner, without prior consent of DM Contact Management Ltd.

1. Synopsis

Name of Sponsor/Company:

Leading Edge Marketing, PO Box CR-56766, Nassau Bahamas

Name of Finished Product: Semenax™

Name of Active Ingredient: Zinc Aspartate, Vitamin E, L-carnitine, Maca, Pine Bark Extract, L-arginine HCL, L-lysine, Catuaba, Epimedium sagitattum, Muira puama, Hawthorn, Cranberry extract, Tribulus terrestris, Avena sativa extract, Sarsaparilla, Swedish Flower Pollen, Pumpkin seed, Butea superba

Title of Study:

Effect of Semenax™ capsules versus placebo on semen characteristics of hypospermic and normospermic men

Investigators:

- Dr. Abhay Kulkarni
  Ayushree Ayurvedic Hospital & Research Centre, 34, Parab Nagar, Near Swami Samaratha Kendra, Nasik Road-422 009, Contact: 0253-2322100 / 9822537240
- Dr. Devendra Save
  Mangirish, Ramkunwar Thakur Road, Near Movie Gem Cinema, Dahisar (East), Mumbai-400 068 Contact: 9820007947
- Dr. Ambadas Kulkarni
  Rajendra Apartment, Rajendra colony, Shastri path, Near Hotel Badshah, Nasik Road-422 101 Contact: 9422245588
- Dr. Ashish P. Badadare
  Giridhar Clinic, Shree Oshiya Corner, Near Telephone exchange, Sukhsagar Nagar, Pune- 411 046 Contact: 9423580971
- Dr. Neelima V. Jadhav
  Sushila Ayurveda Clinic and Research Center, Ground Floor, Vivekananda Apts, Ashok Stambh, Nasik-422 001 Contact: 0253-2310500 / 9823994560
- Dr. Ganesh Avadh
  Swasthya Clinic, Ashwini heights, Sadashiv Peth, Pune. Contact: +91 9623452969

Strictly Confidential

Study centre(s):

There were a total of 6 study sites, all located in India (3 sites in Nashik, 2 sites in Pune and 1 in Mumbai).

Publication (reference): None at the time of writing this report.

Studied period: **Date of first enrolment**: 17 June 2011 **Date of last completed**: 30 March 2012	**Phase of development**: Exploratory

Study objectives and variables:

	Study objectives	**Variables**
Efficacy variables	To assess the effect on the ejaculate volume	• Mean change in the ejaculate volume from Baseline to End-of-treatment (EoT) • Number of patients showing a 20% increase in the ejaculate volume
	To assess the effect on sperm characteristics	• Mean change in sperm count, sperm concentration, sperm motility and sperm morphology from Baseline to EoT
	To assess the effect on sexual function	• Mean change in IIEF-EF and total scores from Baseline to EoT • Mean change in the grade of orgasm intensity from Baseline to EoT • Patient's global efficacy assessment • Investigator's global assessment
Safety variables	To assess the safety and tolerability	• Incidence of clinical AEs' • Laboratory AEs' • Patients' rating of tolerability of treatment

Methodology:

The study was randomized, double-blind and placebo-controlled. Patients were screened

Strictly Confidential

and recruited based on IIEF scores. Based on semen volume at Screening, patients in the Semenax™ and placebo treatment arms were further subdivided into 2 subgroups, namely, hypospermic and normospermic. At Baseline (Day 0), IIEF assessment was done and the Investigational product (IP) was dispensed for a period of 2 months. Subsequent visits were scheduled at Day 30 and Day 60 (End of treatment [EoT1]). After Day 60, both the treatment arms were dispensed placebo capsules for a period of 2 weeks, which was single blinded. The next visit, EoT 2 was scheduled 15-20 days after Day 60. IIEF assessment was done on Day 30 and Day 60, semen analysis was done on Day 60 and EoT 2. Patient's global efficacy assessment, patient's rating for tolerability and laboratory evaluations were done on Day 60. IP accountability and adverse event (AE) monitoring was done on all the visits.

Number of patients analyzed:

A total 63 evaluable cases were available (32 in the Semenax™ and 31 in the placebo arm). The Semenax™ arm included 12 hypospermic and 20 normospermic men whereas the placebo arm comprised of 9 hypospermic and 22 normospermic men.

Diagnosis and main criteria for inclusion:

Men aged 30-60 years with hypospermia (semen volume < 2ml) or normospermia (semen volume 2-5.5 ml) with perceived reduction in ejaculate volume

Test product, dose and mode of administration, batch number:

Semenax™ capsules: 4 capsules twice a day orally for 2 months.

Batch number for Semenax™ and placebo -T - F11040001

Duration of treatment:

2 months (excluding 1 month of Screening period and 20 days follow up period)

Reference therapy, dose and mode of administration, batch number:

Placebo capsules, 4 capsules twice a day orally for 2 months.

Placebo capsules, 4 capsules twice a day orally for 2 weeks for follow up period for both the treatment arms

Batch no-T - F11040001

Strictly Confidential

Analysis sets

No of patients in Intent-To-Treat (ITT) analysis set: 78

No of patients in Per Protocol (PP) analysis set: 63

Statistical methods:

The analysis of efficacy variables was carried out on the PP population. The primary efficacy variable was analyzed using Analysis Of Variance (ANOVA). Secondary efficacy variables were analyzed using ANOVA or Pearson's Chi-square test as applicable. Subgroup analysis was performed for 2 sub-groups: normospermic and hypospermic. Analysis of safety variables, vital parameters and incidence of AEs was done on the ITT population. Mean changes in vital parameters and laboratory hematological tests were analyzed using ANOVA.

Summary:

Efficacy results:

A statistically significant increase was seen in the ejaculate volume in the Semenax™ arm as compared with placebo (Semenax™: 0.49 ± 0.82 versus placebo: -0.21 ± 0.75 [p=0.008]). A higher number of patients in the Semenax™ arm showed a 20% or more increase in ejaculate volume, as compared with placebo (p=0.004). Mean change from Baseline to EoT, in semen parameters was not statistically significant within or across 2 treatment arms. A statistically significant increase was seen in the total IIEF and IIEF-EF score, from Baseline to EoT, within the individual treatment arms but not across the 2 treatment arms. Semenax™ showed statistical significance over placebo with respect to Investigator's global assessment (p=0.02) and patient's global efficacy assessment (Ejaculate volume: p=0.0001). A higher number of patients in the Semenax™ arm showed an increase in orgasm intensity, from Baseline to EoT, as compared with placebo.

Safety results

There were a total of 15 AEs reported during the study and all of them got resolved during the study. They were either mild (n=8) or moderate (n=7) in intensity. Five AEs were probably related to the IP, 1 was possibly related and 9 AEs were not related to the IP. There were no clinically or statistically significant changes observed either in laboratory

Strictly Confidential

parameters or vital signs. Majority of patients rated tolerability to treatment as 'good' in both the arms with no statistical significance (p=0.82) and none of the patients reported tolerability as 'poor' in both the arms.
Conclusion: Semenax™ was clinically superior to placebo in improving ejaculate volume and the intensity of orgasm. Semenax™ did not demonstrate clinical superiority in improving sperm characteristics and IIEF scores. Semenax™ demonstrated as acceptable safety and tolerability profile.
Date of the report: Version 1.0 dated 1-Oct-2012

Strictly Confidential

2. Table of Contents

Strictly Confidential

Strictly Confidential

LIST OF TABLES

Strictly Confidential

LIST OF FIGURES

Strictly Confidential

3. List of Abbreviations

Abbreviations	Full form
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ANOVA	Analysis of variance
BD	Twice a day
BMI	Body mass index
BP	Blood pressure
CBC	Complete blood count
CRF	Case report form
CRO	Contract research organization
EC	Ethics committee
ECG	Electro cardiogram
EoT	End of treatment
ESR	Erythrocyte sedimentation rate
GCP	Good clinical practice
Hb	Hemoglobin
HCl	Hydrochloride
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International conference on harmonization
IEC	Independent ethics committee
IIEF	International index of erectile function
IIEF-EF	International index of erectile function-erectile function
IIEF-OF	International index of erectile function-orgasmic index
IP	Investigational product
IS	Intercourse satisfaction
ITT	Intent to treat
LOCF	Last observation carried forward
OD	Once a day
OS	Overall satisfaction
PP	Per protocol
RBC	Red blood cells

Strictly Confidential

SAE	Serious adverse event
SD	Sexual desire
SD	Standard deviation
SGPT	Serum glutamic pyruvic transaminase
TMF	Trial master file
VLPL	Vedic Lifesciences private limited
WBC	White blood cells
WHO	World health organization

Strictly Confidential

4. Ethics

4.1 Independent Ethics Committee

In order to ensure the safety and rights of study patients, approval for the study was sought from an appropriately constituted Independent ethics committee (IEC), before initiating the study. The name and address of the Ethics committee (EC) for this study is as follows:

Meet Ethics Committee

Maher Nursing Home, GI-2/A,

Shri Krishna Avenue, Shri Krishna nagar,

Borivali East, Sawar Pada corner, Mumbai 400066.

Tel no. 099679 02387/098695 70298/098192 44512

4.2 Ethical conduct of the study

This study was conducted according to International conference on harmonization -Good clinical practices (ICH-GCP), applicable government regulations and institutional research policies and procedures. The study protocol was submitted to a properly constituted IEC, in agreement with applicable regulatory requirements for formal approval of the study. The investigator obtained the EC's written approval for conducting the study and a copy of this documented approval was also provided to the sponsor before commencement of this study.

4.3 Patient information and consent

All study patients were provided an informed consent form (ICF) describing this study and providing sufficient information for them to make an informed decision about their participation in this study. These ICFs were submitted with the protocol for the EC's review and approval.

The formal consent of participating study patients, using the EC approved ICF, was obtained before recruiting these patients. The ICF was signed by the study patients or the study patients' legally acceptable representative and the investigator designated research professional obtaining the consent.

Strictly Confidential

5. Investigators and study administrative structure

The administrative structure of the study has been summarized in Table 1 below

Table 1 Administrative Structure of the Study	
Contract Research Organization (CRO)	Vedic Lifesciences Pvt. Ltd. (VLPL) 118 Morya House, Off Link Road, Andheri (West), Mumbai-400053, India
Project Manager	Mr. Ganesh Shresta
Monitors	Mr. Prasanna Bhanshe Dr. Chetan Metha

Investigator details

- Dr. Abhay Kulkarni
  Ayushree Ayurvedic Hospital & Research Centre, 34, Parab Nagar, Near Swami Samaratha Kendra, Nasik Road-422 009, Phone – 0253-2322100 / 9822537240
- Dr. Devendra Save
  Mangirish, Ramkunwar Thakur Road, Near Movie Gem Cinema, Dahisar (East), Mumbai-400 068 Contact: 9820007947
- Dr. Ambadas Kulkarni
  Rajendra Apartment, Rajendra colony, Shastri path, Near Hotel Badshah, Nasik Road-422 101 Phone – 9422245588
- Dr. Ashish P. Badadare
  Giridhar Clinic, Shree Oshiya Corner, Near Telephone exchange, Sukhsagar Nagar, Pune-411 046 Contact: 9423580971
- Dr. Neelima V. Jadhav
  Sushila Ayurveda Clinic and Research Center, Ground Floor, Vivekananda Apts, Ashok Stambh, Nasik-422 001 Phone - 0253 - 2310500 / 9823994560
- Dr. Ganesh Avhad
  Swasthya Clinic, Ashwini heights, Sadashiv Peth, Pune. Contact: +91 9623452969

Site	**Investigator**	**Study Coordinators**
Nasik	Dr. Abhay Kulkarni	Ms. Amandeep Kaur
Nashik	Dr. Neelima V. Jadhav	Ms. Amandeep Kaur
Nashik	Dr. Ambadas Kulkarni	Dr. Suvarna Bagul

Strictly Confidential

Pune	Dr. Ashish Badadare	Ms. Deepali Sangamnerkar
Mumbai	Dr. Devendra Save	Ms. Priyadarshni Krishnan
Pune	Dr. Ganesh Avhad	Dr. Nachiket Bhalerao
Data Manager		Ms. Ashwini Mate
Medical Writer		Dr. Anuradha Kulkarni

Laboratories

- Chitale Pathology Laboratory,
  Shree Clinic, Bele Park, Opp. Mama Mumngi, Gangapur Road, Nasik-422 005.
  Contact: Dr. Sanjeevani Chitale-+91 9850584832
- N. M. Medical,
  Swastik Building, Chandravarkar Cross Road-2, Borivali (West), Mumbai – 400 092.
  Contact: +91 43425555
- Suburban diagnostics
  Seraph Centre, Opp. BSNL Exchange, Shahu College Road, Off Pune - Satara Road,
  Pune-411 009. Contact: +91 020 41094509

Clinical Trial Supply Manufacturer (Active)	Adroit Pharmaceuticals Pvt. Ltd., 46, Garoba Maidan, Itwari, Nagpur-440 002 Mob-+91 09373107400
Clinical Trial Insurance Company	The Oriental Insurance Co. Ltd. P.B. 7037, A-25/27, Asaf Ali Road, New Delhi–110 002

CRO Contract research organization; VLPL Vedic Lifesciences private limited

Strictly Confidential

6. Introduction

Adequate ejaculate volume is necessary to transport sperms in the female reproductive tract for fertilization1. Ejaculate volume is often overlooked and other parameters are considered as causative factors for infertility. As per World health organization (WHO), the 2 important parameters assessed for fertility are total number of spermatozoa per ejaculate and the sperm concentration, both of which are dependent on ejaculate volume2.

Apart from improving fertility, an increasing number of men are seeking various options to increase their ejaculate volume to increase orgasmic function and enhance sexual gratification3. Many men associate their performance and ability to fulfill partners with ejaculate volume. Aging and consumption of medications like anti depressants are known to decrease ejaculate volume4. Thus there is a growing need to find alternatives to increase ejaculate volume.

Supplements like vitamin C and vitamin E5, zinc6, L-arginine, L-carnitine7, selenium, coenzyme Q10, and folic acid are considered to be effective in increasing ejaculate volume. A plethora of such products are nowadays available which claim to increase ejaculate volume with their regular consumption. However, there seems to be a dearth of scientific evidence to back up this claim or to assess the effect of these products on the ejaculate volume and thereby on orgasmic function. There is an unmet medical need to conduct organized studies to scientifically substantiate such claims.

Therefore, the present study was conducted to gather clinical evidence for substantiating this correlation between increase in ejaculate volume and the resultant improvement in orgasmic function. Semenax^{TM} is a polyherbal formulation which was developed to address the growing need of a safe and efficacious product to increase ejaculate volume. Perceived hypospermia has almost never been investigated, even in patients with sexual problems. The present exploratory study investigated the efficacy and safety of Semenax^{TM} in men with perceived hypospermia in a double-blind, randomized placebo-controlled setting. Additionally, the investigational product was also studied for

Strictly Confidential

its effect on sexual functioning and sperm characteristics in men with perceived hypospermia.

7. Study objectives

7.1 Efficacy Objective

- To assess the effect of Semenax™ versus placebo on the ejaculate volume of hypospermic and normospermic men
- To assess the effect of Semenax™ versus placebo on sperm characteristics, namely: sperm count, sperm morphology and sperm motility
- To assess the effect of Semenax™ versus placebo on sexual function using International index of erectile function (IIEF)
- To assess the effect of Semenax™ versus placebo on orgasm grade.

7.2 Safety objective

- To assess the safety and tolerability of Semenax™ versus placebo.

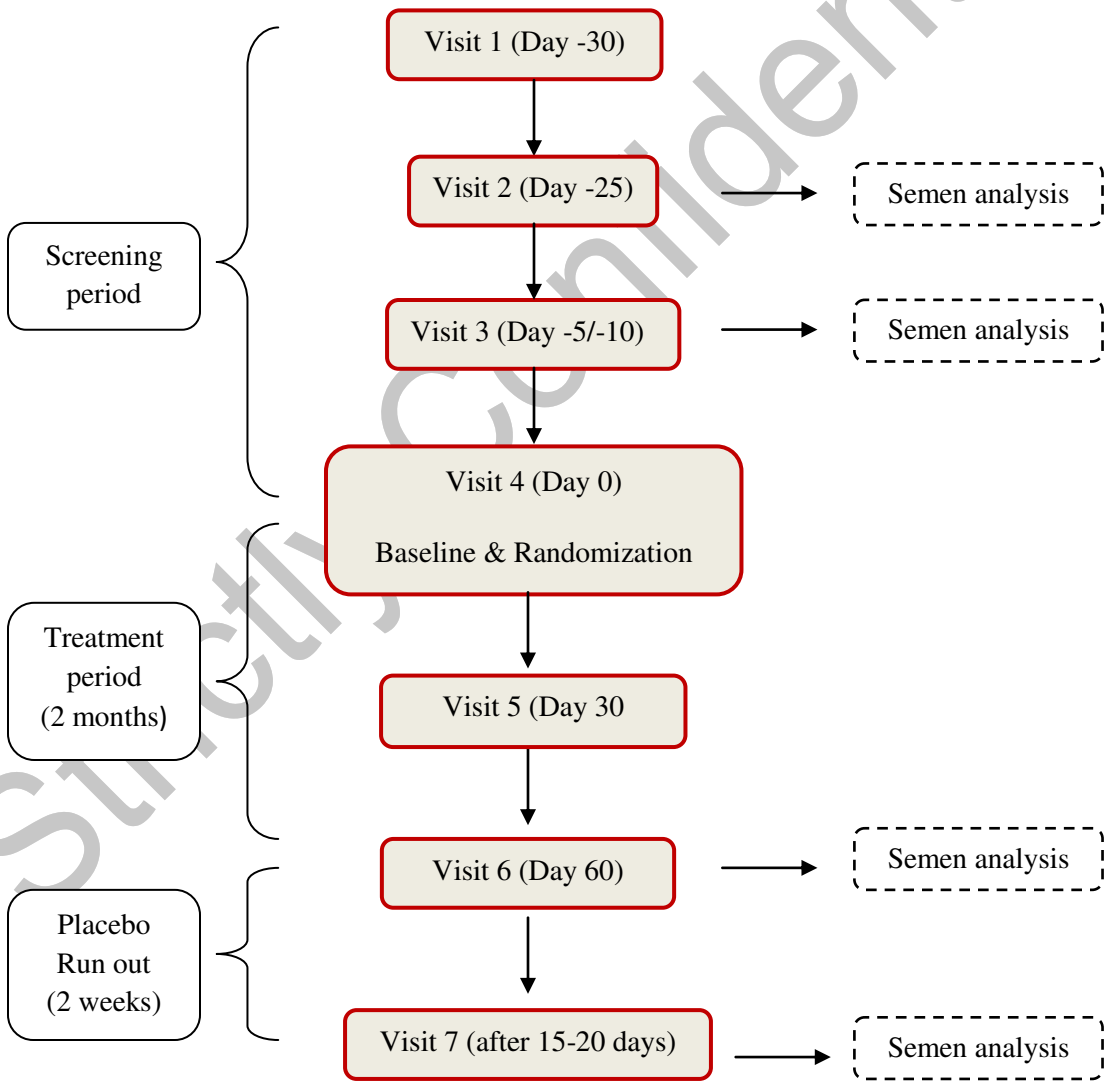
Strictly Confidential

8. Investigational plan

8.1 Overall Study Design and Plan Description

The present study was a randomized double-blind, placebo-controlled, parallel arm, multi centre study to assess the efficacy and safety of Semenax™ capsules on semen characteristics of hypospermic and normospermic men. Figure 1 presents a schematic representation of the study design.

Figure 1 Study design



Strictly Confidential

8.2 Discussion Of Study Design, Including The Choice Of Control Groups

A randomized double-blind, study design was chosen to minimize bias. Two groups (hypospermic and normospermic) were analyzed within each treatment arm. Stratified block randomization was used to ensure homogeneity in randomization. Since the IP is a polyherbal formulation and is being studied in an organized manner for the first time, placebo was used instead of an active comparator. Also an arbitrarily chosen sample size of 60 evaluable patients, with a brief study duration of 2 months was considered appropriate. The patient population chosen was men who perceived themselves as hypospermic irrespective of their clinical status and desire to increase their ejaculate volume. A similar male population also represents the real world target population of the IP. In view of this, increase in ejaculate volume in the study population was chosen as primary study endpoint. Hypospermia is often associated with sexual dysfunctions like erectile dysfunction, reduced orgasmic quality and infertility[8,1]. Hence, the other study endpoints chosen were assessment of sperm characteristics and sexual functioning to assess the effect of IP on fertility and sexual dysfunction.

8.3 Selection Of Study Population

8.3.1 Inclusion Criteria

Patients fulfilling all of the following inclusion criteria were eligible for participation in the study.

1. Men aged 30-60 years, involved in a stable monogamous heterosexual relationship
2. Men with hypospermia (semen volume lower than 2 ml) or normospermia (semen volume 2-5.5 ml) but who perceived a reduction in their ejaculate
3. Men with normozoospermia (sperm concentration >20x10^6 / ml)
4. Men with mild oligozoospermia (sperm concentration10-19.99x10^6/ ml) or moderate oligozoospermia (sperm concentration 4-10x10^6/ ml)
5. Men with mild to moderate impairment of sperm motility and sperm morphology
6. Men with erectile dysfunction [IIEF-Erectile function (IIEF-EF)score < 26]

Strictly Confidential

7. Men with a response score of 3 and above to the IIEF-Orgasmic function (IIEF-OF) question ("When you had sexual stimulation or intercourse how often did you ejaculate?)
8. Men willing to maintain a constant sexual abstinence period of 2 to 3 days each time before producing semen sample and comply with other semen collection procedures.

8.3.2 Exclusion Criteria

Patients fulfilling any of the following exclusion criteria were ineligible for participating in the study.

Exclusion criteria related to semen parameters

Observed for either of the 2 samples produced during Screening

1. Aspermia (no semen)
2. Absence of fructose /low fructose (13 µmol per ejaculate)
3. ph<7.2 or >8.0
4. Excessive red blood cells (hemospermia)
5. Excessive leukocytes or leukospermia
6. Severe impairment of ejaculate volume or sperm concentration or sperm motility or sperm morphology
7. Ejaculate volume>5.5 ml (Includes hyperspermia i.e. >7 ml of ejaculate volume)

Exclusion criteria related to medical conditions

8. Neurological disorders such as multiple sclerosis, demyelination disease, tumors and degenerative conditions etc.
9. Presence of diabetic neuropathy or complications, use of insulin for glycemic control
10. Untreated or uncontrolled hypertension
11. Inflammatory disorders, infections or obstruction of the genital tract

Strictly Confidential

12. Congenital anomalies (spina bifida, spinal dysraphism, congenital bilateral/ unilateral absence of the vas deferens)
13. History of trauma to the pelvic organs or spinal cord injury
14. Surgical history of radical prostatectomy, retroperitoneal lymphadenectomy, bladder neck surgery, pelvic surgery, spinal cord surgery, vasectomy
15. History of mumps orchitis within 3 years of Screening
16. History of cryptorchidism
17. Presence of painful orgasms (dysorgasmia)
18. Known or suspected cases of Klinefelter's syndrome or Kartagener's syndrome
19. Clinical suspicion of varicocele
20. Recent history of a major systemic illness
21. Occurrence of febrile illness (temperature over 102ºF) within 3 months before Screening/ semen sample collection
22. Illnesses (including psychiatric illnesses) that received (within 1 month of Screening) or required treatment with drugs known to affect sexual function (refer to Table 4)
23. Known cases of Human immunodeficiency virus (HIV) , Acquired immunodeficiency syndrome (AIDS) or recent cases of sexually transmitted diseases
24. Men undergoing infertility treatment or assisted reproductive
25. Clinically significant laboratory abnormality at Screening
26. Any other medical condition which in the opinion of the investigator may affect the evaluations of the study

Strictly Confidential

Exclusion criteria related to lifestyle conditions

27. Body mass index (BMI) ≥35 kg/m^2
28. Moderate to heavy alcohol consumption (more than 40-80 grams or 3.5-7 standard drinks, per day). A standard drink is one 12 ounce can of beer or wine cooler, one 5 ounce glass of wine, or 1.5 ounces of distilled spirits
29. Excessive smoking (more than 10 cigarettes per day)
30. Substance abuse (e.g. heroin, methadone, marijuana etc.)
31. Occupational or environmental exposure to risk factors for male reproductive system (e.g. Chronic exposure to heat, ionizing radiation, heavy metals like lead cadmium, certain pesticides like dibromochloropropane, aromatic solvents, driving for prolonged intervals, frequent sauna baths etc.)

Other exclusion criteria

32. Participation in a clinical study 2 months prior to Screening
33. Known hypersensitivity to any ingredient listed in the composition of Semenax™
34. Unwillingness to comply with the protocol stipulated semen collection procedures
35. Medical condition of the female sexual partner (including pregnancy) that may affect the evaluation of the study
36. Unwillingness/inability to provide written informed consent.
37. Drug exposure known to affect sperm characteristics, within 3 months of the first semen analysis (refer to Table 4)

Strictly Confidential

8.3.3 Removal of Patients from Therapy or Assessment

8.3.3.1 Withdrawal criteria

Patients were withdrawn from the study in the following cases:

- Major protocol deviations
- Serious adverse events (SAEs)wherein continuation in the study posed serious risk to the patient
- Patient's unwillingness to continue participation in the study. On such occasions the investigator made a reasonable effort to ascertain the reasons, while fully respecting the study patient's rights
- Study patient or his female partner developed any medical condition which affected the outcome and evaluations of the study
- Any other condition which in the opinion of the investigator justified study patient's withdrawal.

8.3.3.2 Lost to follow up

A study patient was considered as lost to follow up if he did not report for the scheduled study visit (including the window period of ± 7 days for Day 30 and Day 60 visit) and remained untraceable.

8.3.3.3 Protocol deviation

Following were deemed as major protocol deviations warranting withdrawal of the study patients:

- Recruitment of a patient into the study even though he had not satisfied 1 or more inclusion criteria
- Study patient was assigned to the wrong treatment arm
- Consumption of less than 85% of the total dose that needed to be consumed in the period between study visits of Day 0, Day 30 and Day 60
- Study patient reporting later than 7 days for the scheduled study visits on Day 30 and Day 60
- Introduction of a medication (other than study medication) that could potentially affect the seminal parameters

Strictly Confidential

- Patient who developed withdrawal criteria during the study but was not withdrawn
- Non-adherence to abstinence period of 2-3 days was also considered as a protocol deviation. In such cases study patient was asked to return for a repeat sample after completing the protocol specified abstinence period. If the study patient continued to falter on the abstinence period, he was withdrawn from the study.

8.4 Treatments

8.4.1 Treatments Administered

Capsules Semenax™ or matching placebo

8.4.2 Identity of Investigational Product(s)

Semenax™ (capsules), the Investigational product (IP) of the present study is a proprietary formulation containing various herbs, vitamin E and zinc. The details of IP are given in Table 2.

Table 2 Details of Investigational product

Name of IP	Semenax™ (capsules) and matching placebo capsules
Dosage	4 capsules twice daily for 2 months
Route of administration	Orally
Batch number	T-F11040001
Name and address of the manufacturer	Adroit Pharmaceuticals Pvt. Ltd., 46, Garoba Maidan, Itwari, Nagpur-440002 Mob-+91 09373107400

The detailed composition of Semenax™ capsule used in this study has been presented in the Table 3. Matching placebo capsules were prepared using carboxy methyl cellulose.

Strictly Confidential

Table 3 Composition of 8 Semenax™ capsules	
Active Ingredients	**Quantity in mg**
Zinc Aspartate (20% elemental zinc)	030.000
Vitamin E (Dl-Alpha Tocopherol Acetate)	120.000 IU
L-carnitine	500.000
Maca (root)	400.000
Pine Bark Extract	300.000
L-arginine HCL	250.000
L-lysine	250.000
Catuaba (bark)	200.000
Epimedium Sagitattum (leaf)	150.000
Muira Puama (bark)	100.000
Hawthorn (berry)	050.000
Cranberry extract (seed)	050.000
Tribulus Terrestris (vine)	050.000
Avena Sativa extract (seed)	050.000
Sarsaparilla (root)	050.000
Swedish Flower Pollen	050.000
Pumpkin (seed)	030.000
Butea Superba	500.000
Other Ingredients: Cellulose, gelatin, vegetable stearate, silicon dioxide	

Hcl Hydrochloride

8.4.3 Method of Assigning Patients to Treatment Arms

Study patients were assigned to treatment (active or placebo) in a ratio1:1, using stratified block randomization according to a computerized randomization schedule. Randomly permuted blocks of 4 patients each were generated using the statistical software, Stats Direct Version 2.7.8) separately for each stratum (normospermic or hypospermic). The randomization codes were secured in tamper-evident sealed envelopes at the respective sites. Each chit had the study patient ID & the treatment allocated. The master

Strictly Confidential

randomization chart was sealed in an envelope and maintained in the trial master file (TMF).

8.4.4 Selection of Doses in the Study

Semenax™ or matching placebo capsules were administered at a dose of 4 capsules twice daily for 2 months.

8.4.5 Selection and Timing of Dose for each Patient

The product is already marketed with a recommended daily dosage of 3600 mg and the same dosage was used for evaluation in the present study. The recommended dosage was achieved through administration of 4 capsules twice daily.

8.4.6 Blinding

This was a double-blind study. Study patients, investigators, monitors and data analysts remained blinded to the treatment assignments. Independent personnel not involved in the execution and analysis of the study undertook blinding procedures at the IP manufacturing unit, to ensure that the placebo and Semenax™ capsules were indistinguishable. Placebo and Semenax™ capsules were matched for appearance and packed in identical containers with identical labels.

8.4.7 Prior and Concomitant Therapy

The list of concomitant medications prohibited during and 3 months prior to the study is given in the Table 4.

Strictly Confidential

Table 4 List of prohibited drugs

a) Drugs adversely affecting semen quality

Recreational/ Illicit drugs
- Alcohol
- Cigarettes
- Marijuana
- Opiates
- Cocaine

Antihypertensive
- Spironolactone
- Methyl dopa
- Reserpine

Psychotherapeutic agents
- Antipyschotics
- Tricyclic antidepressants
- Phenothiazines

Antiepileptic
- Carbamazepine
- Oxcarbazepine
- Valproate

Chemotherapeutic agents
- Alkylating agents
- Antimetabolites
- Vinca alkaloids

Hormones
- Anabolic steroids
- Testosterone
- Antiandrogens
- Progesterone
- Estrogens

Antibiotics
- Nitrofurantoin
- Erythromycin
- Tetracyclines
- Gentamycin

Miscellaneous
- Cimetidine
- Cyclosporine
- Colchicine
- Allopurinol
- Sulfasalazine

b) Drugs used in the treatment of male infertility/ sexual dysfunction

Chlomiphene citrate, Human chorionic gonadotropin, Imipramine, Pseudoephedrine Phosphodiestarase type-5 inhibitors, Ingredients listed in Semenax™

c) Anticoagulants

Strictly Confidential

8.4.8 Treatment Compliance

For ensuring adequate treatment compliance, study patients were properly instructed regarding study procedures before they signed the ICF. The investigator informed the patients of their obligations and responsibilities during the study. At each visit, the record of dispensed and returned medication was maintained. Consumption of any concomitant medication was recorded in the case report form (CRF).

8.5 Efficacy and Safety Variables

8.5.1 Efficacy and Safety Measurements Assessed and Flow Chart

Efficacy variables:

1. Mean change in the ejaculate volume from Baseline to End of treatment (EoT) as compared with placebo
2. Number of patients showing a 20% increase in ejaculate volume as compared with placebo
3. Mean change in sperm count, sperm motility and sperm morphology from Baseline to EoT as compared with placebo
4. Mean change in IIEF-EF and total scores from Baseline to EoT as compared with placebo. (Refer to Appendix Section 15.2 Table 31 for the IIEF questionnaire used to assess IIEF-EF and total score.)
5. Change in the grade of orgasm intensity from Baseline to EoT as compared with placebo

   Subject graded orgasm quality on the following scale:

   - Grade1-weak or poor
   - Grade 2-moderate or fair
   - Grade 3-good or strong
   - Grade 4-very good or very strong
   - Grade 5-most powerful or excellent

6. Patients' global efficacy assessment

At EoT, patients rated efficacy by responding either "Yes" or "No" to 2 global efficacy questions:

- "Did the treatment improve your ejaculate volume?''

Strictly Confidential

- "Did the treatment improve your orgasm quality?"

7. Investigators' Global assessment.

Based on the improvement in ejaculate volume, IIEF scores and orgasmic quality; investigators performed a global assessment of efficacy as below:

- Excellent: Improvement in semen volume, IIEF scores and orgasm quality
- Very Good: Improvement in semen volume and IIEF scores or orgasm quality
- Good: Improvement in semen volume but no improvement in IIEF scores or orgasm quality
- Fair: No improvement in semen volume, but improved IIEF scores or orgasm quality
- Poor: No improvement in any of the above parameters

Safety Variables:

1. Clinical adverse events (AEs) elicited from medical history and physical examination including measurement of vitals(pulse, systolic and diastolic blood pressure) and systemic examination
2. Laboratory AEs elicited from changes in the following:
   (Complete blood count [CBC], Erythrocyte sedimentation rate [ESR], Serum glutamic pyruvic transaminase [SGPT], serum creatinine, routine urine, Electro cardiogram [ECG])
3. Patients' rating of tolerability of treatment.

Visit specific schedule for efficacy and safety variables is listed out in Table 5.

Strictly Confidential

Strictly Confidential

Table 5	**Visit specific schedule**						
	Screening visit 1 (Day-30)	**Screening visit 2 (Day-25)**	**Screening visit 3 (Day-5/-10)**	**Baseline visit (Day 0)**	**Follow up visit (Day 30)**	**EOT(1) (Day 60)**	**EOT(2) 15-20 days from EOT(1)**
Systemic examination	x	-	-	x	x	x	-
Efficacy variables							
Semen analysis	-	x	x	-	-	x	x
IIEF	x	-	-	x	x	x	-
Orgasmic Quality	-	-	-	x	x	x	-
Patient's global efficacy assessment	-	-	-	-	-	x	-
Investigator's global assessment	-	-	-	-	-	-	x
Safety variables							
Vitals	x	-	-	x	x	x	-
CBC	-	-	x	-	-	x	-
ESR	-	-	x	-	-	x	-
ECG	-	-	x	-	-	x	-
SGPT	-	-	x	-	-	x	-
Serum Creatinine	-	-	x	-	-	x	-
Urine routine	-	-	x	-	-	x	-
Patient's assessment of tolerability	-	-	-	-	-	x	-
AE Monitoring	-	-	-	x	x	x	x

AE Adverse event; CBC Complete blood count; ECG Electrocardiogram; EOT End of treatment; ESR Erythrocyte sedimentation rate; IIEF International index of erectile function; SGPT Serum glutamic pyruvic transaminase

Strictly Confidential

8.6 Data Quality Assurance

The following steps were taken to ensure collection of accurate, consistent, complete and reliable data:

- Before initiation of the study, an investigators' meeting was held in order to facilitate the discussion and resolution of various scientific, operational and other issues that were foreseen. During the meet and individual site initiation visits, the study personnel were trained on the protocol, CRF filling rules and administration of the IIEF questionnaire to ensure appropriate and standardized capture of data
- Monitoring visits were made by the Contract research organization (CRO) personnel to ensure that the data collected was accurate, complete, in compliance with the protocol requirements and consistent with the source documents. A co monitoring visit was also conducted by the project manager at each site
- An internal audit was performed by the quality assurance department to verify whether the study documents are in accordance with the protocol and GCP
- Semen analysis was done as per WHO recommendations and all the laboratory personnel were trained to ensure uniformity during sample collection and analysis.

8.7 Statistical Methods Planned In The Protocol And Determination Of Sample Size

8.7.1 Statistical and Analytical Plans

Table 6 presents the study hypotheses.

Table 6	**Study hypotheses**
Null hypothesis	As per the null hypothesis, no difference existed in the semen volume and sperm characteristics between the 2 groups, from Baseline to EoT
Alternate hypothesis	As per the alternate hypothesis, there did exist a difference in the semen volume and sperm characteristics between the 2 groups, from Baseline to EoT

EoT End of treatment

Strictly Confidential

Analysis Sets

For analysis, 2 types of study population were defined as follows:

The intention-to-treat (ITT) population consisting of all patients who received the study drug and reported for at least 1 post-baseline IIEF evaluation or at least 1 EoT semen analysis. Last observation carried forward (LOCF) imputation method was used to handle missing data

The per-protocol (PP) population comprising of patients who reported for all protocol stipulated study visits and did not have any major protocol deviations related to the evaluation of efficacy (for primary efficacy endpoint only).

The ITT analysis set was chosen for conducting protocol determined analysis of safety and the PP analysis set was chosen for conducting protocol determined analysis of efficacy.

Statistical Methods

1. Descriptive statistics included absolute counts, mean, standard deviation (SD), minimum, and maximum.
2. Baseline characteristics of the 2 arms were compared using analysis of variance (ANOVA).
3. Subgroup analysis was performed for 2 sub-groups: normospermic and hypospermic
4. ANOVA was used to analyze the mean changes in semen parameters and total IIEF scores
5. Pearson's Chi-square test was applied to analyze the change in the grade of orgasms
6. Remaining secondary efficacy variables (number of patients in whom the ejaculate volume increased by 20%, responses to global efficacy questions, patient's tolerability assessment and investigator's global assessment) were analyzed using Chi-square test
7. Mean changes in vital parameters, laboratory hematological and urine tests from Baseline to EoT were compared across the arms by ANOVA.
8. All statistical tests were performed at 5% level of significance
9. All clinical AEs were presented as a detailed tabulated patient listing
10. No interim analysis was done for the study

8.7.2 Determination of Sample Size

Since this was the first study of Semenax™, no statistical method was applied for calculation of the sample size. An arbitrarily chosen sample size of 60 evaluable patients, with 30 in each treatment arm, was considered appropriate to detect a statistical difference between

Strictly Confidential

Semenax™ and placebo. Ninety six participants were enrolled (48 in each arm) to get 60 evaluable cases.

8.8 Changes In The Conduct Of The Study Or Planned Analyses

8.8.1 Changes in the conduct of the study

There have been no changes in the conduct of the study.

8.8.2 Changes in the planned analyses

There have been no changes to the planned analyses.

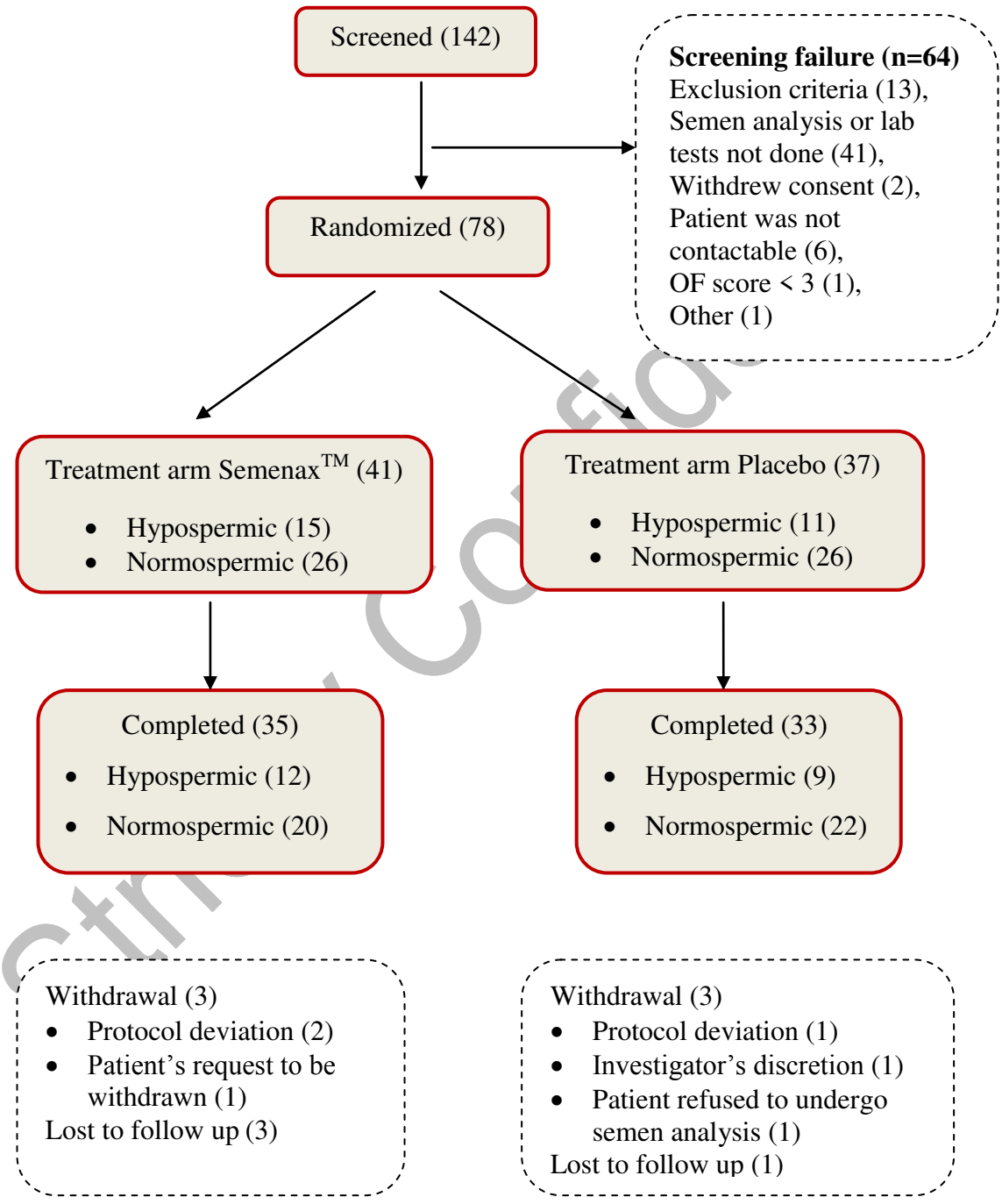
Strictly Confidential

9. Study Patients

9.1 Disposition of Patients

The disposition of study patients is shown in **Error! Not a valid bookmark self-reference.**.

Figure 2 **Disposition of study patients**



OF Orgasmic function

A total of 142 study patients were screened for the study; out of which 64 were Screening failures. The most common reasons for screening failure were exclusion criteria (13) and semen analysis or lab tests not done (41). The remaining 78 study patients were randomized to receive either Semenax™ (n=41) or Placebo (n=37) arm. Both treatment arms had 2 subgroups based on the ejaculate volume - hypospermic and normospermic. A comparable number of hypospermic and normospermic men were included in both the treatment arms. Out of the 78 study patients randomized to the 2 treatment arms, a total of 6 study patients were withdrawn from the study (3 in each treatment arm) and 4 study patients were lost to follow up (3 in Semenax™ and 1 in placebo). The most common reason for withdrawal from both the arms was protocol deviations. The total number of completed study patients was 68 and was comparable across both the arms (35 in Semenax™ and 33 in the placebo arm).

9.2 Protocol Deviations

There were 9 protocol deviations during the study. Two of them were major; where 1 patient did not adhere to the abstinence period before semen analysis at EoT and the other lost the IP bottle and reported low IP compliance. Other deviations were minor with no impact on study results.

A brief summary of all protocol deviations has been presented in the Appendices Section 15.1.2,Table 29.

Strictly Confidential

10. Efficacy Evaluation

10.1 Data Sets Analyzed

Table 7 presents a summary of the data sets analyzed in the study and the reasons for exclusion of study patients from the analysis sets.

Table 7 Analysis sets	
Total patients recruited	78
Number of patients in the ITT analysis set • Analysis of vitals • Patient's tolerability assessment • Analysis of laboratory parameters	 78 73 (Withdrawal of 5 patients before Day 60) 69 (Laboratory assessments not done for 9 patients)
Number of patients who completed the study	68
Reasons for exclusion of patients from the completed analysis set	• Withdrawal of patients (6) • Lost to follow up (4)
Number of patients in the PP analysis set for all efficacy variables	63
Number of patients excluded from the PP analysis set	5
Reasons for exclusion of patients from the PP analysis set	Protocol deviations (5)

IIEF International index of erectile function; ITT Intent to treat; PP Per protocol

Strictly Confidential

10.2 Demographic And Other Baseline Characteristics

Demographic and baseline characteristics of both the arms are presented in the Table 8.

Table 8 Demographic and baseline characteristics

	Semenax™ (n=41)		Placebo (n=37)	
	Hypospermic (n=15)	Normospermic (n=26)	Hypospermic (n=11)	Normospermic (n=26)
Age Mean (SD)	38.60 (9.03)	37.96 (6.60)	36.73 (8.24)	35.88 (6.73)
Pre existing conditions (n)	0	3 • Hyperacidity • Psoriasis • Joint pain	0	4 • Hypertension • Peptic Disease • URTI • Hyperacidity
Concomitant medication (n)	0	2	0	2
BMI (kg/m^2) Mean (SD)	25.05 (4.13)	24.08 (3.48)	25.66 (2.88)	24.91 (3.60)
Ejaculate volume Mean (SD)	1.36 (0.39)	3.22 (0.89)	1.38 (0.34)	3.08 (0.77)
Total IIEF score Mean (SD)	43.40 (8.97)	43.62 (8.38)	45.18 (7.37)	43.92 (7.44)

BMI Body mass index; IIEF International index of erectile function; SD Standard deviation; URTI Upper respiratory tract infection

The 2 treatment arms as well as the subgroups based on semen volume were comparable to each other with respect to demographic and key Baseline characteristics.

10.3 Measurement Of Treatment Compliance

Table 9 summarizes patients' compliance to study treatment.

Table 9 Treatment Compliance

Time points	Semenax™ (n=32) Mean (SD)	Placebo (n=31) Mean (SD)
Day 0 – Day 30	97.18 (4.83)	96.68 (3.59)
Day 30 – Day 60	93.21 (17.56)	93.66 (17.92)

ANOVA Analysis of variance; SD Standard deviation

Strictly Confidential

The compliance to study treatment was comparable across the 2 treatment arms with no statistically significant difference observed between the 2 arms. The compliance across the treatment arms was higher than the protocol specified compliance threshold of 85%.

10.4 Analysis of Efficacy (PP population)

10.4.1 Mean change in the ejaculate volume from Baseline to EoT (PP population)

Descriptive statistics of the variable ejaculate volume has been presented in Section 13.1 in Table 26.

Mean change in the ejaculate volume from Baseline to EoT, within and between the treatment arms has been presented in Table 10.

Table 10 Mean change in ejaculate volume from Baseline to EoT as per ANOVA (PP population)

Time	Semenax™ (n=32)	Placebo (n=31)	p value
Mean (SD) at Baseline	2.49 (1.14)	2.64 (1.00)	
Mean (SD) at EoT	2.97 (1.44)	2.43 (1.13)	
Change from Baseline to EoT	0.49 (0.82)	-0.21 (0.75)	0.0008
p value Baseline to EoT	0.14	0.44	

ANOVA Analysis of variance; EoT End of treatment; SD Standard deviation

At EoT, there was an increase in the ejaculate volume in the Semenax™ group, whereas the placebo group showed a reduction. This change was statistically significant when compared across the 2 treatment arms (p=0.0008).

Analyses conducted on hypospermic and normospermic subgroups have been presented in Table 11.

Strictly Confidential

Table 11	**Sub group analysis of mean change in ejaculate volume from Baseline to EoT as per ANOVA (PP population)**		
Hypospermic subgroup analysis (n=21)			
Time	Semenax™ (n=12)	Placebo (n=9)	p value
Mean (SD) at Baseline	1.32 (0.39)	1.50 (0.23)	0.24
Mean (SD) at EoT	1.77 (0.87)	1.50 (0.67)	0.46
Change from Baseline to EoT	0.44 (0.81)	0.00 (0.74)	0.21
p value Baseline to EoT	0.12	0.99	
Normospermic subgroup analysis (n=42)			
Time	Semenax™ (n=20)	Placebo (n=22)	p value
Mean (SD) at Baseline	3.19 (0.80)	3.11 (0.79)	0.77
Mean (SD) at EoT	3.70 (1.21)	2.82 (1.06)	0.02
Change from Baseline to EoT	0.51 (0.85)	-0.30 (0.75)	0.002
p value Baseline to EoT	0.12	0.30	

ANOVA Analysis of variance; EoT End of treatment; SD Standard deviation

An increase in ejaculate volume, from Baseline to EoT, was observed in the normospermic subgroup within the Semenax™ arm but this increase was not statistically significant. However, a statistically significant improvement of ejaculate volume was noted across the 2 treatment arms (p=0.002). The mean change in ejaculate volume, from Baseline to EoT did not show statistical significance within the Semenax™ and placebo treatment arms (p=0.12 for Semenax™ and p=0.30 for placebo). There were no clinically or statistically significant changes noted in the hypospermic subgroup.

10.4.2 Number of patients showing a 20% increase in the ejaculate volume from Baseline to EoT in the PP population

Patients showing a 20% or greater increase in the ejaculate volume from Baseline to EoT have been referred to as "*20% responders*" and those with an increase in ejaculate volume below the 20% threshold have been referred to as "*non responders*". The total number of 20% responders and non responders in the PP population and in the subgroup population has been presented in Table 12.

Strictly Confidential

Table 12	**Number of patients showing a 20% increase in the ejaculate volume from Baseline to EoT on PP population**		
Total population (n=63)	Semenax™ (n=32)	Placebo (n=31)	P value by chi square test
20% Responders* (n)	16	5	0.004
Non responders* (n)	16	26	
Hypospermic subgroup (n=21)	Semenax™ (n=12)	Placebo (n=9)	
20% Responders (n)	7	3	0.26
Non responders (n)	5	6	
Normospermic subgroup (n=42)	Semenax™ (n=20)	Placebo (n=22)	
20% Responders (n)	9	2	0.01
Non responders (n)	11	20	

*Patients showing a 20% or greater increase in the ejaculate volume from Baseline to EoT have been referred to as "*20% responders*" and those with an increase in ejaculate volume below the 20% threshold have been referred to as "*non responders*".

In the PP population, the number of 20% responders was higher in the Semenax™ arm as compared with the placebo arm, with a statistically significant difference being reported between the 2 treatment arms (p=0.004). In the hypospermic subgroup, though the number of 20% responders was higher in Semenax™ than the placebo arm (7 in Semenax™ and 3 in placebo); the difference was not statistically significant (p=0.26). In contrast to its hypospermic counterpart, a statistically significant number of patients in the normospermic subgroup, showed a 20% increase in ejaculate volume (9 in Semenax™ and 2 in placebo arm and p=0.01).

10.4.3 Mean change in sperm count, sperm motility and sperm morphology from Baseline to EoT (PP population)

Table 13 presents mean change in sperm count, sperm motility and sperm morphology, from Baseline to EoT for total PP population. No statistically significant change was noted in these parameters, from Baseline to EoT, within and across the 2 treatment arms.

Strictly Confidential

Table 13	Mean change in sperm parameters from Baseline to EoT on total PP population as per ANOVA			
	Time	Semenax™ (n=32)	Placebo (n=31)	p value
Sperm count	Mean (SD) at Baseline	64.91 (46.55)	52.46 (37.26)	0.25
	Mean (SD) at EoT	72.48 (41.02)	49.19 (41.18)	0.03
	Change from Baseline to EoT	7.58 (31.47)	-3.27 (27.49)	0.15
	p value Baseline to EoT	0.49	0.74	
Progressive motility	Mean (SD) at Baseline	58.13 (20.01)	55.29 (17.38)	0.55
	Mean (SD) at EoT	55.27 (17.39)	49.84 (15.44)	0.20
	Change from Baseline to EoT	-2.86 (16.45)	-5.45 (12.73)	0.49
	p value Baseline to EoT	0.54	0.20	
Non progressive motility	Mean (SD) at Baseline	8.13 (6.63)	8.82 (5.34)	0.65
	Mean (SD) at EoT	10.20 (8.33)	9.27 (5.63)	0.61
	Change from Baseline to EoT	2.08 (3.73)	0.45 (3.44)	0.08
	p value Baseline to EoT	0.27	0.75	
Sperm morphology	Mean (SD) at Baseline	82.02 (21.77)	88.23 (15.42)	0.20
	Mean (SD) at EoT	86.05 (13.65)	86.19 (15.31)	0.97
	Change from Baseline to EoT	4.03 (18.06)	-2.03 (6.58)	0.08
	p value Baseline to EoT	0.38	0.60	

ANOVA Analysis of variance; EoT End of treatment; SD Standard deviation

Table 14 and Table 15 present the analyses performed on the hypospermic and normospermic subgroups respectively. The subgroup analyses were performed to determine the mean change from Baseline to EoT; in sperm count, motility and morphology. The analysis involving the hypospermic subgroup, demonstrated a statistically significant difference between the 2 treatment arms for sperm morphology (p=0.05), where the normal forms increased in the Semenax™ group and decreased in the placebo group. Sperm counts in the hypospermic subgroup within both the treatment arms increased as compared with Baseline. This increase was more in the Semenax™ group as compared to placebo, but was not statistically significant. In the same subgroup, a reduction was observed in progressive sperm motility, from Baseline to EoT, within the treatment arms. However, in this regard, it is

Strictly Confidential

important to note that this reduction was neither clinically significant nor statistically relevant.

The analysis performed on the normospermic subgroup also revealed a few important differences from Baseline to EoT. The placebo arm witnessed a reduction in sperm count from Baseline to EoT, whereas an increase was seen in the Semenax™ arm. In the placebo arm, the normospermic subgroup analysis revealed a marginal reduction, from Baseline to EoT, in the number of sperms with normal morphology. On the other hand, the number of morphologically normal sperms increased, from Baseline to EoT, in the Semenax™ arm. However, the difference between the 2 treatment arms with respect to sperm morphology was not statistically significant.

Table 14 Mean change in sperm parameters from Baseline to EoT on hypospermic subgroup as per ANOVA

	Time	Semenax™ (n=12)	Placebo (n=9)	p value
Sperm count	Mean (SD) at Baseline	85.26 (58.66)	53.66 (35.66)	0.17
	Mean (SD) at EoT	89.28 (47.80)	53.78 (40.34)	0.09
	Change from Baseline to EoT	4.02 (24.59)	0.12 (26.20)	0.73
	p value Baseline to EoT	0.86	0.99	
Progressive motility	Mean (SD) at Baseline	56.67 (21.38)	51.28 (18.54)	0.55
	Mean (SD) at EoT	53.13 (17.65)	43.33 (18.75)	0.24
	Change from Baseline to EoT	-3.54 (12.54)	-7.94 (10.06)	0.40
	p value Baseline to EoT	0.66	0.38	
Non progressive motility	Mean (SD) at Baseline	10.42 (8.65)	11.50 (7.62)	0.77
	Mean (SD) at EoT	12.08 (9.40)	12.50 (8.29)	0.92
	Change from Baseline to EoT	1.67 (3.89)	1.00 (4.36)	0.71
	p value Baseline to EoT	0.66	0.79	
Sperm morphology	Mean (SD) at Baseline	83.17 (14.31)	86.17 (21.10)	0.70
	Mean (SD) at EoT	84.42 (13.62)	81.44 (18.32)	0.67
	Change from Baseline to EoT	1.25 (4.96)	-4.72 (8.45)	0.05
	p value Baseline to EoT	0.83	0.62	

ANOVA Analysis of variance; EoT End of treatment; SD Standard deviation

Strictly Confidential

Table 15	Mean change in sperm parameters from Baseline to EoT on normospermic subgroup as per ANOVA			
	Time	Semenax™ (n=20)	Placebo (n=22)	p value
Sperm count	Mean (SD) at Baseline	52.69 (33.54)	51.97 (38.71)	0.95
	Mean (SD) at EoT	62.41 (33.72)	47.32 (42.31)	0.21
	Change from Baseline to EoT	9.71 (35.40)	-4.65 (28.48)	0.15
	p value Baseline to EoT	0.37	0.71	
Progressive motility	Mean (SD) at Baseline	59.00 (19.66)	56.93 (17.06)	0.72
	Mean (SD) at EoT	56.55 (17.57)	52.50 (13.45)	0.40
	Change from Baseline to EoT	-2.45 (18.70)	-4.43 (13.76)	0.70
	p value Baseline to EoT	0.68	0.34	
Non progressive motility	Mean (SD) at Baseline	6.75 (4.80)	7.23 (3.77)	0.47
	Mean (SD) at EoT	9.08 (7.65)	7.95 (3.59)	0.54
	Change from Baseline to EoT	2.33 (3.71)	0.23 (3.08)	0.05
	p value Baseline to EoT	0.26	0.84	
Sperm morphology	Mean (SD) at Baseline	81.32 (25.56)	89.07 (12.94)	0.22
	Mean (SD) at EoT	87.03 (13.92)	88.14 (13.91)	0.80
	Change from Baseline to EoT	5.70 (22.59)	-0.93 (5.51)	0.19
	p value Baseline to EoT	0.39	0.82	

ANOVA Analysis of variance; EoT End of treatment; SD Standard deviation

Strictly Confidential

10.4.4 Mean change in IIEF-Total and Erectile Function subscale scores from Baseline to EoT (PP population)

Table 27**Error! Reference source not found.** presents descriptive statistics for the total IIEF score on Day 0, Day 30 and Day 60.

Table 16 presents mean change from Baseline to EoT of total IIEF and IIEF-EF score for the total PP population.

Strictly Confidential

Table 16 Mean change in total IIEF and IIEF-EF score from Baseline to EoT on total PP population as per ANOVA

	Time	Semenax™ (n=32)	Placebo (n=31)	p value
Total IIEF score	Mean (SD) at Baseline	43.37 (8.81)	43.42 (7.18)	0.98
	Mean (SD) at EoT	50.94 (9.41)	48.55 (7.31)	0.27
	Change from Baseline to EoT	7.56 (5.64)	5.13 (7.36)	0.15
	p value Baseline to EoT	0.002	0.01	
IIEF-EF score	Mean (SD) at Baseline	17.19 (4.04)	17.65 (3.19)	0.62
	Mean (SD) at EoT	20.47 (3.58)	20.03 (3.18)	0.61
	Change from Baseline to EoT	3.28 (3.03)	2.39 (3.52)	0.28
	p value Baseline to EoT	0.001	0.005	

ANOVA Analysis of variance; EF Erectile function; EoT End of treatment; IIEF International index of erectile function; PP Per protocol; SD Standard deviation

A statistically significant change was observed from Baseline to EoT in both treatment arms for the total IIEF score (Semenax™: p=0.002, placebo: p=0.01) and IIEF-EF score (Semenax™: p=0.001, placebo: p=0.005). However, there was no statistically significant difference between the 2 treatment arms (Total IIEF: p=0.15, IIEF-EF: p=0.28).

Table 17 presents analyses of total IIEF and IIEF-EF score, from Baseline to EoT, in hypospermic and normospermic subgroups.

Strictly Confidential

Table 17	Sub group analysis of total IIEF and IIEF-EF score from Baseline to EoT on PP population as per ANOVA			
Hypospermic PP population (n=21)				
	Time	Semenax™ (n=12)	Placebo (n=9)	p value
Total IIEF score	Mean (SD) at Baseline	43.58 (9.62)	45.11 (7.34)	0.70
	Mean (SD) at EoT	49.58 (9.05)	48.44 (4.61)	0.73
	Change from Baseline to EoT	6.00 (5.08)	3.33 (6.67)	0.31
	p value Baseline to EoT	0.13	0.26	
IIEF-EF score	Mean (SD) at Baseline	17.08 (4.48)	17.89 (4.40)	0.69
	Mean (SD) at EoT	19.67 (3.84)	20.22 (2.54)	0.71
	Change from Baseline to EoT	2.58 (2.50)	2.33 (3.77)	0.86
	p value Baseline to EoT	0.14	0.19	
Normospermic PP population (n=42)				
	Time	Semenax™ (n=20)	Placebo (n=22)	p value
Total IIEF score	Mean (SD) at Baseline	43.25 (8.54)	42.73 (7.17)	0.83
	Mean (SD) at EoT	51.75 (9.77)	48.59 (8.26)	0.26
	Change from Baseline to EoT	8.50 (5.87)	5.86 (7.64)	0.22
	p value Baseline to EoT	0.006	0.01	
IIEF-EF score	Mean (SD) at Baseline	17.25 (3.88)	17.55 (2.67)	0.77
	Mean (SD) at EoT	20.95 (3.43)	19.95 (3.46)	0.35
	Change from Baseline to EoT	3.70 (3.29)	2.41 (3.50)	0.23
	p value Baseline to EoT	0.003	0.01	

ANOVA Analysis of variance; EF Erectile function; EoT End of treatment; IIEF International index of erectile function; PP Per protocol; SD Standard deviation

Strictly Confidential

In the hypospermic subgroup, there was no statistically significant change for both the parameters. However, in the normospermic subgroup there was statistically significant increase from Baseline to EoT, for both the parameters in both the treatment arms (Total IIEF score: Semenax™ p=0.006, placebo p=0.01 and IIEF-EF score: Semenax™ p=0.003, placebo p=0.01) but did not demonstrate significance across the 2 treatment arms (Total IIEF score: p=0.22 and IIEF-EF score: p=0.23).

10.4.5 Change in the grade of orgasm intensity (PP population)

Patients were asked to grade their orgasm intensity at Baseline and EoT on a 5 point scale. Patients with increase of 1 or more points on the grade scale were considered as "*responders"* whereas patients who did not show any change on this scale were referred to as "*non responders*".

Table 18 presents a summary of change in orgasm intensity from Baseline to EoT for the total PP population and both the sub groups.

Table 18 Change in grade of orgasm intensity (PP population)

Total PP population (n=63)			
	Semenax™ (n=32)	Placebo (n=31)	p value using Pearson's chi – square test
Responders*	21	13	0.06
Non responders*	11	18	
Hypospermic subgroup (n=21)			
	Semenax™ (n=12)	Placebo (n=9)	
Responders	7	4	0.53
Non responders	5	5	
Normospermic subgroup (n=42)			
	Semenax™ (n=20)	Placebo (n=22)	
Responders	14	9	0.06
Non responders	6	13	

*Patients with increase of 1 or more points on the grade scale were considered as "*responders"* whereas patients who did not show any change on this scale were referred to as "*non responders*".

There were a total of 34 responders with an improvement in the grade of orgasm intensity. The number of responders was higher in Semenax™ arm (n=21) than placebo (n=13) but the difference was not statistically significant (p=0.06). For both the hypospermic and normospermic subgroups, number of responders was higher in Semenax™ arm than the placebo arm but did not reach statistical significance (Hypospermic subgroup: p=0.53, Normospermic subgroup: p=0.06)

Strictly Confidential

10.4.6 Investigators' global assessment

Based on the improvement in ejaculate volume, IIEF scores and orgasmic quality, investigators rated the efficacy of the product at EoT on a 5 point scale from 'Excellent to Poor'.

Table 19 presents summary of investigators' global assessment for the total PP population

Table 19 Investigators' global assessment from Baseline to EoT (PP population)

Rating	Semenax™ (n=32)	Placebo (n=31)	p value using chi- square test
Excellent	14	3	0.02
Very good	3	11	
Good	4	5	
Fair	8	10	
Poor	3	2	

The number of patients scoring 'Excellent' was higher in the Semenax™ arm (n=14 or 43.75%) than placebo (n=3 or 9.68%). The analysis showed a statistically significant difference (p=0.02) between the 2 treatment arms.

Table 20 presents subgroup analysis of Investigators' global assessment.

Strictly Confidential

Table 20	**Subgroup analysis for investigators' global assessment**		
Hypospermic population (n=21)			
Rating	Semenax™ (n=12)	Placebo (n=9)	p value using chi- square test
Excellent	4	1	0.46
Very good	1	0	
Good	2	2	
Fair	4	3	
Poor	1	3	
Normospermic population (n=42)			
Rating	Semenax™ (n=20)	Placebo (n=22)	p value using chi- square test
Excellent	10	2	0.05
Very good	2	2	
Good	2	3	
Fair	4	9	
Poor	2	6	

In the hypospermic subgroup analysis, there was no statistically significant difference (0.46) between the 2 treatment arms. However, in the normospermic subgroup there was a significant difference (p=0.05) between the 2 treatment arms. The number of patients with an 'excellent rating' was 10 (50%) for the Semenax™ arm and 2 (9.09%) for the placebo arm.

10.4.7 Patients' global efficacy assessment

Study patients were asked to assess the efficacy of the product based on improvement in the ejaculate volume and orgasmic quality.

Table 21

Table 21	**Patients' global efficacy**

presents the summary of patients' global efficacy.

Table 21	**Patients' global efficacy**			
		Semenax™ (n=32)	Placebo (n=31)	p value using chi square test
Improvement in ejaculate volume	Yes	21	5	0.0001
	No	11	26	
Improvement in	Yes	23	15	0.06

Strictly Confidential

orgasm quality	No	9	16	

The number of patients with improvement in ejaculate volume and orgasm intensity was higher in the Semenax™ arm as compared with placebo. Improvement in ejaculate volume was statistically significant (p=0.0001) whereas improvement in orgasmic quality just missed to reach statistical significance (p=0.06).

Table 22 presents a summary of subgroup analysis for improvement in ejaculate volume and orgasm quality.

Table 22 Subgroup analysis for patients' global assessment

Hypospermic PP population (n=21)				
		Semenax™ (n=12)	Placebo (n=9)	p value using chi square test
Improvement in ejaculate volume	Yes	7	1	0.03
	No	5	8	
Improvement in orgasm quality	Yes	8	5	0.60
	No	4	4	
Normospermic PP population (n=42)				
		Semenax™ (n=20)	Placebo (n=22)	p value using chi square test
Improvement in ejaculate volume	Yes	14	4	0.001
	No	6	18	
Improvement in orgasm quality	Yes	15	10	0.05
	No	5	12	

In the hypospermic subgroup, a statistically significant improvement in ejaculate volume (p=0.03) was noted in the Semenax™ arm as compared with placebo. On the other hand no statistically significant difference (p=0.60) was noted between the 2 treatment arms with respect to orgasm quality. In the normospermic subgroup, Semenax™ demonstrated statistical significance for both these parameters over placebo (Ejaculate volume: p=0.001, Orgasmic quality: p=0.05)

Strictly Confidential

10.4.8 Statistical/analytical issues

10.4.8.1 Handling of dropouts or missing data

LOCF imputation method was used to handle missing data.

10.4.8.2 Use of an "Efficacy Subset" of patients

Hypospermic and normospermic efficacy subsets of the study population were used for the analysis of all efficacy variables

10.4.9 Efficacy conclusions

Semenax™ demonstrated a statistically significant increase in ejaculate volume over placebo. Total IIEF and IIEF-EF score showed statistically significant increase from Baseline to EoT within both the treatment arms. However, a statistically significant increase was not observed between the 2 treatment arms with respect to semen parameters, total IIEF score and IIEF-EF score. Analysis of Investigators' global assessment showed a statistically significant difference between the 2 treatment arms. Results of patients' global efficacy assessment favored Semenax™ with a statistically significant difference being noted across the 2 treatment arms with respect to improvement in the ejaculate volume. Statistical significance in favor of Semenax™ was missed by a negligible margin with respect to improvement in orgasm quality.

Strictly Confidential

11. Safety Evaluation

11.1 Adverse Events

A total of 15 AEs were reported during the study. The AEs were either mild (n=8) or moderate (n=7) in intensity. Five AEs were probably related to the IP, 1 was possibly related and 9 AEs were unrelated to the IP.

All AEs resolved during the study. Four AEs in4 patients resolved without any medications. Other 11 AEs were resolved during the study with appropriate medication prescribed by the investigator without any sequelae. A brief summary of all the AEs is given in Appendix 15 Section 15.1.3 (refer to Table 30)

11.2 Deaths, Other Serious Adverse Events, And Other Significant Adverse Events

There were no deaths, SAEs or other significant AEs during the study.

11.3 ECG analysis (ITT population)

There were no abnormal ECG findings at EoT.

11.4 Clinical Laboratory Evaluation (ITT population)

There were no clinically relevant or statistically significant changes observed in any of the laboratory parameters from Baseline to EoT, in either treatment arm or when compared between 2 treatment arms.

A summary of all the laboratory parameters assessed in the ITT population has been presented in Table 23

Strictly Confidential

Table 23 Mean change in laboratory parameters from Baseline to EoT as per ANOVA in ITT population (n=69)

		Semenax™ (n=36)	Placebo (n=33)	p value
RBC (mill/c.mm)	Mean (SD) at Baseline	4.88 (0.50)	4.97 (0.47)	
	Mean (SD) at EoT	4.75 (0.49)	4.91 (0.58)	
	Change from Baseline to EoT	-0.12 (0.38)	-0.06 (0.49)	0.52
	p value Baseline to EoT	0.29	0.66	
WBC (per c.mm)	Mean (SD) at Baseline	7.44 (1.97)	7.89 (1.52)	
	Mean (SD) at EoT	11.94 (19.06)	10.54 (12.28)	
	Change from Baseline to EoT	4.50 (19.11)	2.66 (12.33)	0.64
	p value Baseline to EoT	0.16	0.22	
Hb (mg/dl)	Mean (SD) at Baseline	13.81 (1.14)	13.99 (1.53)	
	Mean (SD) at EoT	13.67 (1.10)	13.96 (1.53)	
	Change from Baseline to EoT	-0.14 (0.74)	-0.04 (0.74)	0.57
	p value Baseline to EoT	0.59	0.92	
Hematocrit (%)	Mean (SD) at Baseline	41.94 (3.16)	42.84 (4.01)	
	Mean (SD) at EoT	41.29 (3.13)	41.75 (4.78)	
	Change from Baseline to EoT	-0.66 (2.51)	-1.09 (3.17)	0.37
	p value Baseline to EoT	0.38	0.32	
Platelets (thou/µL)	Mean (SD) at Baseline	206.16 (98.31)	192.10 (107.46)	
	Mean (SD) at EoT	210.07 (117.42)	185.88 (101.36)	
	Change from Baseline to EoT	3.91 (73.44)	-6.22 (37.05)	0.48
	p value Baseline to EoT	0.88	0.81	
Neutrophils (%)	Mean (SD) at Baseline	56.40 (8.83)	55.99 (7.84)	
	Mean (SD) at EoT	55.94 (9.24)	57.95 (7.93)	
	Change from Baseline to EoT	-0.46 (8.05)	1.96 (9.14)	0.25
	p value Baseline to EoT	0.83	0.32	
Basophils (%)	Mean (SD) at Baseline	0.00 (0.02)	0.06 (0.24)	
	Mean (SD) at EoT	0.02 (0.17)	0.08 (0.27)	
	Change from Baseline to EoT	0.03 (0.17)	0.02 (0.29)	0.99
	p value Baseline to EoT	0.37	0.70	
Lymphocytes (%)	Mean (SD) at Baseline	38.39 (9.01)	38.74 (7.90)	
	Mean (SD) at EoT	37.78 (9.95)	36.47 (8.77)	
	Change from Baseline to EoT	-0.61 (8.49)	-2.26 (8.21)	0.41
	p value Baseline to EoT	0.79	0.27	

Strictly Confidential

Monocytes (%)	Mean (SD) at Baseline	2.87 (2.67)	2.60 (3.11)	
	Mean (SD) at EoT	3.45 (2.84)	3.00 (2.45)	
	Change from Baseline to EoT	0.58 (1.88)	0.40 (2.47)	0.74
	p value Baseline to EoT	0.38	0.56	
Eosinphils (%)	Mean (SD) at Baseline	2.33 (2.27)	2.34 (1.83)	
	Mean (SD) at EoT	2.80 (2.20)	2.79 (2.52)	
	Change from Baseline to EoT	0.47 (2.46)	0.45 (1.79)	0.98
	p value Baseline to EoT	0.38	0.41	
ESR (mm at end of 1 hour)	Mean (SD) at Baseline	10.61 (7.79)	11.97 (11.74)	
	Mean (SD) at EoT	12.14 (7.61)	12.85 (10.49)	
	Change from Baseline to EoT	1.52 (7.87)	0.88 (8.86)	0.75
	p value Baseline to EoT	0.40	0.75	
SGPT (IU/L)	Mean (SD) at Baseline	29.91 (13.16)	32.50 (14.99)	
	Mean (SD) at EoT	28.39 (14.23)	25.64 (9.95)	
	Change from Baseline to EoT	-1.53 (13.01)	-6.85 (15.98)	0.13
	p value Baseline to EoT	0.64	0.03	
Serum Creatinine (mg/dl)	Mean (SD) at Baseline	0.98 (0.19)	0.94 (0.17)	
	Mean (SD) at EoT	0.99 (0.15)	0.95 (0.16)	
	Change from Baseline to EoT	0.01 (0.17)	0.01 (0.16)	0.96
	p value Baseline to EoT	0.81	0.77	
P computed using ANOVA				

ANOVA Analysis of variance; EoT End of treatment; ESR Erythrocyte sedimentation rate; Hb Hemoglobin; RBC Red blood cells; SD Standard deviation; SGPT Serum glutamic pyruvic transaminase; WBC White blood cell

11.5 Vital signs, physical findings and other observations related to safety (ITT population)

There were no clinically relevant or statistically significant changes observed in any of the vital signs at EoT. Table 24 presents a brief summary on mean change in vital signs, from Baseline to EoT, noted in the ITT population.

Strictly Confidential

Table 24 Mean change in vital signs from Baseline to EoT as per ANOVA in ITT population (n=78)

		Semenax™ (n=41)	Placebo (n=37)	p value
Pulse	Mean (SD) at Baseline	75.51 (3.91)	75.84 (3.81)	
	Mean (SD) at EoT	75.63 (4.56)	74.00 (4.99)	
	Change from Baseline to EoT	0.12 (5.31)	-1.84 (6.54)	0.15
	p value Baseline to EoT	0.90	0.08	
Systolic BP	Mean (SD) at Baseline	122.49 (5.72)	123.62 (10.17)	
	Mean (SD) at EoT	120.68 (6.84)	124.81 (9.30)	
	Change from Baseline to EoT	-1.80 (6.28)	1.19 (8.94)	0.09
	p value Baseline to EoT	0.20	0.60	
Diastolic BP	Mean (SD) at Baseline	78.00 (5.79)	80.59 (5.63)	
	Mean (SD) at EoT	77.85 (4.82)	79.62 (4.69)	
	Change from Baseline to EoT	-0.15 (7.62)	-0.97 (6.18)	0.60
	p value Baseline to EoT	0.90	0.42	

ANOVA Analysis of variance; BP Blood pressure; EoT End of treatment; SD Standard deviation

11.6 Patient's tolerability (ITT population)

Patients were asked to rate their tolerability to treatment at EoT on a rating scale of good, fair and poor. The majority of study patients rated their tolerability of the IP as 'good' in both the groups with no statistical significance (p=0.82) between the 2 treatment arms. None of the patients reported tolerability as 'poor' in both the treatment arms. These findings have been summarized in Table 25.

Table 25 Patient's tolerability on ITT population (n=73)

Rating	Semenax™ (n=38)	Placebo (n=35)	p value using chi square test
Good (n)	33	31	0.82
Fair (n)	5	4	
Poor (n)	0	0	

11.7 Safety Conclusions

There was no major safety concern during the study. Most AEs were unrelated to the IP, of mild to moderate intensity and were resolved during the study. The IP was safe and well tolerated by the study patients.

Strictly Confidential

12. Discussion and overall conclusions

12.1 Discussion

The current study was a pilot, exploratory, randomized, double-blind and placebo-controlled clinical investigation to assess the safety and efficacy of Semenax™ in men with perceived hypospermia.

A statistically significant increase in the ejaculate volume was observed in the Semenax™ arm and in its normospermic subgroup, as compared with placebo, from Baseline to EoT. Though the ejaculate volume in the hypospermic subgroup increased from Baseline to EoT in the Semenax™ arm, it could not achieve statistical significance over placebo. A higher number of patients in the Semenax™ arm showed a 20% increase in ejaculate volume from Baseline to EoT (20% responders), as compared with the placebo arm (16 [50%] in Semenax™ and 5 [16.13%] in placebo). This was also statistically significant (p=0.004). Subgroup analysis showed a statistically significant increase in the number of 20% responders in the normospermic subgroup. No clinically relevant or statistically significant changes were seen in the sperm characteristics within or across the treatment arms and within the subgroups in the 2 treatment arms.

A statistically significant increase in the IIEF total score and IIEF-EF score was noted from Baseline to EoT, within the individual treatment arms. However, this difference was not statistically significant when compared across the 2 treatment arms. The normospermic subgroup also achieved similar results. The number of patients with increase in grade of orgasm intensity was also higher in the Semenax™ arm than placebo. Analysis of the investigators' global assessment of therapy and patients' assessment, both demonstrated a statistically significant advantage obtained with the use of Semenax™ over placebo. In the overall appraisal of efficacy results, Semenax™ was more efficacious than placebo in increasing ejaculate volume and in improving sexual function.

Semenax™ was well tolerated by patients during the study. All 15 AEs were mild to moderate in intensity and were successfully resolved during the study. None of the laboratory parameters, ECG and vital signs showed any clinically relevant or statistically significant change from Baseline to EoT. Patients' tolerability was also rated as 'good' by most of them (33 [86.84%] in Semenax™ and 31 [88.57%] in placebo).

Strictly Confidential

Previous published preclinical studies have shown the efficacy of polyherbal mixtures in the treatment of male sexual dysfunction[9]. In clinical studies too, herbal formulations have shown great promise in improving ejaculate volume and sperm characteristics[10,11]. A similar clinical study conducted by Jiang H *et al* reported an 18.13% increase in ejaculate volume at the end of the study[11]. The current study has also shown a comparable 19.68% increase in the ejaculate volume in the Semenax™ arm.

The present study could not show statistically significant increase in IIEF scores or improvement in semen parameters. IIEF scoring is very subjective in nature and IIEF assessment is considered as a good tool to record male sexual history. It lacks the ability to diagnose, assess and compare the improvement in male sexual function[12,13]. Lack of improvement in semen parameters, in the current study, is perhaps attributable to a small sample size and a short study duration.

Several herbs have been traditionally used and acknowledged for their role in male sexual dysfunction and impotence[14]. Many of the ingredients of Semenax™ are also traditionally known to improve male sexual performance, increase ejaculate volume and improve fertility. Few clinical studies have shown the efficacy of the individual ingredients of Semenax™ such as Maca[15], L carnitine, L arginine[7] and Zinc[6], in improving seminal characteristics. However, this was the first study to provide preliminary clinical evidence in support of the claims of Semenax™. The label claim of Semenax™ has been substantiated through this study since Semenax™ has shown efficacy in increasing the ejaculate volume over placebo in a short duration of 2 months. In order to detect a change in semen parameters and IIEF scores with the use of Semenax™, it is recommended to conduct a study of a longer duration and on a larger sample size. Further larger studies to evaluate long term efficacy and safety of Semenax™, with an active comparator with similar ingredients or placebo are essential to furnish more scientific evidence.

12.2 Overall conclusions*:*

Semenax™ was clinically superior to placebo in improving ejaculate volume and the intensity of orgasm. Semenax™ did not demonstrate clinical superiority in improving sperm characteristics and IIEF scores. Semenax™ demonstrated an acceptable safety and tolerability profile.

Strictly Confidential

13. Tables, figures and graphs referred to but not included in the text

13.1 Descriptive statistics

Descriptive statistics for semen volume for PP population is presented in Table 26

Table 26 Descriptive statistics of semen volume (PP population)

		Semenax™ (n=32)	Placebo (n=31)
Day 0	Mean	2.49	2.64
	SD	1.14	1.00
	Min	0.48	1.11
	Max	4.64	4.72
	Median	2.50	2.39
Day 60	Mean	2.97	2.43
	SD	1.44	1.13
	Min	0.64	0.82
	Max	6.76	5.78
	Median	2.83	2.28

Max Maximum; Min Minimum; PP Per protocol; SD Standard deviation

Strictly Confidential

Descriptive statistics for IIEF total score for PP population is presented in Table 27.

Table 27 Descriptive statistics of IIEF total score (PP population)

		Semenax™ (n=32)	Placebo (n=31)
Day 0	Mean	43.38	43.42
	SD	8.81	7.18
	Min	29.00	32.00
	Max	66.00	57.00
	Median	42.00	42.00
Day 30	Mean	47.13	45.26
	SD	9.12	6.65
	Min	31.00	32.00
	Max	71.00	60.00
	Median	45.50	46.00
Day 60	Mean	50.94	48.55
	SD	9.41	7.31
	Min	36.00	31.00
	Max	72.00	62.00
	Median	49.00	49.00

IIEF International index of erectile function; Max Maximum; Min Minimum; PP Per protocol; SD Standard deviation

Strictly Confidential

14. Reference List

1. Roberts M., Jarvi K. Steps in the investigation and management of low semen volume in the infertile man. *Can Urol Assoc J*. 2009; 3(6): 479–485
2. Slama R, Eustache F, Ducot B, Jensen TK, Jørgensen N, Horte A *et al*. Time to pregnancy and semen parameters: a cross-sectional study among fertile couples from four European cities. *Hum Reprod,* 2002; 17: 503-515.
3. Thompson M. Why Are Men Choosing to Increase Ejaculate Volume? Accessed on 30-7-2012 from http://ezinearticles.com/?Why-Are-Men-Choosing-to-Increase-Ejaculate-Volume?&id=4042820
4. Baldwin D, Mayers A. Sexual side-effects of antidepressant and antipsychotic drugs. *Advances in Psychiatric Treatment*. 2003; 9: 202-210
5. Rolf C, Cooper TG, Yeung CG, Nieschlag E. Antioxidant treatment of patients with asthenozoospermia or moderate oligoasthenozoospermia with high-dose vitamin C and vitamin E: a randomized, placebo-controlled, double-blind study. *Hum. Reprod.* 1999; 14 (4): 1028-1033.
6. Kumar N, Verma RP, Singh LP, Varshney VP, Dass RS. Effect of different levels and sources of zinc supplementation on quantitative and qualitative semen attributes and serum testosterone level in crossbred cattle (Bos indicus x Bos taurus) bulls. *Reprod Nutr Dev*. 2006; 46(6):663-75
7. Moradi M, Moradi A, Alemi M, Ahmadnia H, Abdi H, Ahmadi A, *et al*. Safety and Efficacy of Clomiphene Citrate and L-Carnitine in Idiopathic Male Infertility, A Comparative Study. *Urol J*. 2010; 7:188-93.
8. Seidman SN, Roose SP. The Relationship Between Depression and Erectile Dysfunction. Accessed on 1-8-2012 from http://www.hawaii.edu/hivandaids/The%20Relationship%20Between%20Depression%20and%20Erectile%20Dysfunction.pdf
9. Frydrychová S, Opletal L, Macáková K, Lustyková A, Rozkot M, Lipenský J. Effects of herbal preparation on libido and semen quality in boars. *Reprod Domest Anim*. 2011 (4):573-8.
10. Song FW, Zhong WD. Clinical efficacy of Shengjing capsule on patients with oligoasthenospermia. *Zhonghua Nan Ke Xue*. 2009 ;15(8):762-4.

Strictly Confidential

11. Jiang H, Shang XJ, Guo J, Li Z, Zhao LM, Shao Y *et al.* Multi-centered clinical trial of Fufang Xuanju capsule for oligoasthenospermia. *Zhonghua Nan Ke Xue.* 2008 ;14(8):755-8.

12. Kassouf W, Carrier S. A comparison of the International Index of Erectile Function and erectile dysfunction studies**.** *BJU Int*. 2003;91(7):667-9.

13. Blander DS, Sánchez-Ortiz RF, Broderick GA. Sex inventories: can questionnaires replace erectile dysfunction testing? *Urology*. 1999;54(4):719-23.

14. . Mugisha MK Origa HO. Traditional herbal remedies used in the management of sexual impotence and erectile dysfunction in western Uganda. *Afr Health Sci*. 2005; 5(1): 40–49.

15. Gonzales GF , Cordova A , Gonzales C , Chung A , Vega K , Villena A . Lepidium meyenii (maca) improved semen parameters in adult men. Asian J Androl . 2001;3(4):301-303.

Strictly Confidential

15. APPENDICES

15.1 Patient Data Listings

15.1.1 Discontinued patients

Table 28	List of patients discontinued from the study
Sub ID	**Reason for discontinuation**
SMX01	Lost to follow up
SMX04	Withdrawn
SMX34	Lost to follow up
SMX40	Withdrawn
SMX63	Withdrawn
SMX64	Lost to follow up
SMX66	Withdrawn
SMX67	Withdrawn
SMX73	Lost to follow up
SMX81	Withdrawn
Patients who completed the study but are not included in the PP analysis set	
SMX18	Low treatment compliance
SMX39	Low treatment compliance
SMX42	Low treatment compliance
SMX75	Low treatment compliance
SMX80	Low treatment compliance

Strictly Confidential

15.1.2 Protocol deviations

Table 29		Protocol deviations		
Sub ID	**Day**	**Deviation**	**Action**	**Impact**
SMX01	Day 30	Patient did not return the IP bottle and hence IP compliance could not be calculated	Patient's verbal information about IP compliance was considered	none
SMX15	Day 60	Patient's EoT I visit was delayed by 9 days	Semen analysis was done on the visit patient reported	none
SMX15	Day 60	Patient's EoT II visit was delayed by 25 days	Semen analysis was done on the visit patient reported	none
SMX16	Day 60	Patient did not adhere to the abstinence period of 2-3 days	none	Major impact on semen analysis
SMX16	Day 60	Patient's EoT I visit was delayed by 8 days	none	none
SMX18	Day 30	Patient lost the IP bottle	none	Major impact on IP compliance
SMX18	Day 60	Patient's EoT visit was delayed by 10 days	none	none
SMX22	Day 0	Patient's Screening visit was delayed by 1 day	none	none
SMX66	Day 60	Patient did not go for laboratory tests	none	Excluded from PP population

EoT End of treatment; IP Investigational product

Strictly Confidential

15.1.3 Adverse event listings

Table 30 AE listing

	SubID	AE Description	AE start date	AE stop date	AE intensity	Relationship to study drug	Treatment given to manage the AE	Outcome
Semenax	SMX09	fever	4/22/2012	4/23/2012	Mild	Not related	Tab paracetamol 500mg BD	Resolved
	SMX55	constipation	4/4/2012	4/6/2012	Mild	Not related	Ayurvedic proprietary medicine (Softovac Powder)	Resolved
		epigastric pain	4/11/2012	4/14/2012	Moderate	Not related	Dicyclomine10mg, acetaminophen 400mg and dextropropoxyphene 65mg OD, Pantoprazole 40mg and Domperiode 10mg OD	Resolved
		abdominal pain	5/8/2012	5/11/2012	Moderate	Probable	T-Dicylomine 20mg and paracetamol 500mgBD, T-Ranitidine 150mg BD	Resolved
	SMX05	swelling of both the feet	10/10/2011	10/14/2011	Mild	Not related	Local application of diclofenac sodium gel BD	Resolved
	SMX10	headache	12/13/2011	12/14/2011	Mild	Possible	none	Resolved
	SMX15	hyperacidity	6/30/2011	7/1/2011	Moderate	Probable	Tab pantoprazole 40mg OD	Resolved
	SMX31	fever and common cold	12/22/2011	12/25/2011	Moderate	Not related	Cefixime 200mg BD, paracetamol 500mg BD, chlorphenaramine maleate 2mg BD, pseudoephidrine 60mg BD, caffeine 30mg BD	Resolved
	SMX58	abdominal pain	5/24/2012	5/26/2012	Moderate	Probable	T-Dicyclomine Hcl 20mg, paracetamol 500mg	Resolved

Strictly Confidential

							and T ranitidine 150mg BD	
	SMX78	headache	8/13/2011	8/14/2011	Mild	Not related	none	Resolved
	SMX83	eye irritation and itching on both hands	9/17/2011	9/24/2011	Mild	Not related	none	Resolved
Placebo	SMX08	gastric irritation	4/21/2012	4/24/2012	Moderate	Not related	Tab pantoprazole 40mg BD	Resolved
	SMX27	backache since 3-4 days	1/19/2012	1/24/2012	Moderate	Not related	Tab aceclofenac 100mg OD, Paracetamol 500mg OD	Resolved
	SMX32	Hyperacidity	10/28/2011	10/30/2011	Mild	Probable	Tab rabeprazole 20mg BD	Resolved
	SMX40	stomach bloating	6/25/2011	7/10/2011	Mild	Probable	none	Resolved

AE Adverse event; BD Twice a day; OD Once a day

Strictly Confidential

15.2 International Index of Erectile Function questionnaire

The score was assessed on Day 0, Day 30 and Day 60 based on the response over the 4 weeks.

Table 31 IIEF questionnaire

ERECTILE FUNCTION [EF] DOMAIN						
VISIT DAY				Day 0	Day 30	Day 60
1	How often were you able to get an erection during sexual activity?	No sexual activity	0			
		Almost never or never	1			
		A few times (much less than half the time)	2			
		Sometimes (about half the times)	3			
		Most times (much more than half the time)	4			
		Almost always or always	5			
2	When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	No sexual activity	0			
		Almost never or never	1			
		A few times (much less than half the time)	2			
		Sometimes (about half the times)	3			
		Most times (much more than half the time)	4			
		Almost always or always	5			
3	When you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?	Did not attempt intercourse	0			
		Almost never or never	1			
		A few times (much less than half the time)	2			
		Sometimes (about half the times)	3			
		Most times (much more than half the time)	4			
		Almost always or always	5			
4	During sexual intercourse, how often were you able to maintain erection after you had penetrated your partner?	Did not attempt intercourse	0			
		Almost never or never	1			
		A few times (much less than half the time)	2			
		Sometimes (about half the times)	3			
		Most times (much more than half the time)	4			
		Almost always or always	5			
5	During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	Did not attempt intercourse	0			
		Extremely difficult	1			
		Very difficult	2			
		Difficult	3			
		Slightly difficult	4			
		Not Difficult	5			
6	How do you rate your confidence that you could get and keep an erection?	Very low or none at all	1			
		Low	2			
		Moderate	3			
		High	4			

Strictly Confidential

		Very high	5			
TOTAL SCORE [EF] =						
INTERCOURSE SATISFACTION [IS]						
VISIT DAY				Day 0	Day 30	Day 60
7	How many times have you attempted sexual intercourse?	No attempts	0			
		0-1 attempts	1			
		2-3 attempts	2			
		4-5 attempts	3			
		6-7 attempts	4			
		> 7 attempts	5			
8	When you attempted sexual intercourse, how often was it satisfactory for you?	Did not attempt intercourse	0			
		Almost never or never	1			
		A few times (much less than half the time)	2			
		Sometimes (about half the times)	3			
		Most times (much more than half the time)	4			
		Almost always or always	5			
9	How much have you enjoyed sexual intercourse?	No intercourse	0			
		No enjoyment	1			
		Not very enjoyable	2			
		Fairly enjoyable	3			
		Highly enjoyable	4			
		Very highly enjoyable	5			
TOTAL SCORE [IS] =						
ORGASMIC FUNCTION [OF]						
VISIT DAY				Day 0	Day 30	Day 60
10	When you had sexual simulation or intercourse, how often did you ejaculate?	No sexual stimulation or intercourse	0			
		Almost never or never	1			
		A few times (much less than half the time)	2			
		Sometimes (about half the times)	3			
		Most times (much more than half the time)	4			
		Almost always or always	5			
11	When you had sexual stimulation or intercourse, how often did you have the feeling of orgasm or climax?	No sexual stimulation or intercourse	0			
		Almost never or never	1			
		A few times (much less than half the time)	2			
		Sometimes (about half the times)	3			
		Most times (much more than half the time)	4			
		Almost always or always	5			
TOTAL SCORE [OF] =						
SEXUAL DESIRE [SD]						
VISIT DAY				Day 0	Day 30	Day 60
12	How often have you felt sexual desire?	Almost never or never	1			
		A few times (much less than half the time)	2			
		Sometimes (about half the times)	3			

Strictly Confidential

		Most times (much more than half the time)	4			
		Almost always or always	5			
13	How would you rate your level of sexual desire?	Very low or none at all	1			
		Low	2			
		Moderate	3			
		High	4			
		Very high	5			
TOTAL SCORE [SD] =						
OVERALL SATISFACTION [OS]						
				Day 0	Day 30	Day 60
14	How satisfied have you been with your overall sex life?	Very dissatisfied	1			
		Moderately dissatisfied	2			
		About equally satisfied and dissatisfied	3			
		Moderately satisfied	4			
		Very satisfied	5			
15	How satisfied have you been with your sexual relationship with your partner?	Very dissatisfied	1			
		Moderately dissatisfied	2			
		About equally satisfied and dissatisfied	3			
		Moderately satisfied	4			
		Very satisfied	5			
TOTAL SCORE [OS] =						
TOTAL IIEF SCORE [EF+OF+IS+SD+OS] =						

EF Erectile function; IS Intercourse satisfaction; OF Orgasmic function; OS Overall satisfaction, SD Sexual desire

Strictly Confidential

https://malehealthreview.com/semenax