A CLINICAL STUDY REPORT VIGRX PLUS In Male Sexual Health

PROTOCOL ID: VL/080305/DM

SPONSOR **Leading Edge Marketing**

PO Box CR-56766, Suite 1210
Nassau Bahamas

Sponsor's Contact Person **Mr. Doug MacKay**

DM Contact Management Ltd.
Tel: (250) 383-8267 extension 447
Fax: (250) 383-0896

CRO **Vedic Lifesciences Pvt. Ltd.**

118, Morya House, Off. New Link Road, Andheri (West),
Mumbai – 400053.
India.
Tel: 022-42025700

DATE: 08/05/2010

SYNOPSIS

Name of sponsor company : Leading Edge Marketing

Name of finished product : VigRX Plus capsules

Name of active ingredients:
Panax ginseng (Korean Red Ginseng)
Serenoa repens (Saw Palmetto)
Crataegus rivularis (Hawthorne)
Ginkgo biloba
Turnera diffusa (Damiana)
Tribulus terrestris
Erythroxylum catuaba
Ptychopetalum olacoides (Muira Puama)
Cuscuta chinensis
Epimedium sagittatum
Bioperine (extract from Piper nigrum fruit)

Title of the study: A triple blind, placebo controlled, randomized study to evaluate the safety and efficacy of VigRX Plus capsules as a dietary supplement to improve erectile function and maintain Male Sexual Health.

Investigators and study centres:

1)Dr. Gaurang Shah
Jivdaya Hospital,Dharmoday bldg, Jivdaya lane, L.B.S. Marg, Ghatkopar (W), Mumbai86.INDIA.Mob: 9821019432.

2)Dr. R. K. Shimpi
Dept. of Urology,Noble Hospital, 153,Magarpatta City Road, Hadapsar,Pune-411 013. INDIA.Mob : 9822059799

3)Dr. Suresh Patankar
Institute of urology,Survey no. 32/2A, Erandwane, Behind Mehendale garage,Gulwani Maharaj road, Pune-4.INDIA.Mob : 9881256992

4)Dr. Manoj Chaudhari
169, Parvati gaon, Bhaghirathi Medical Foundation, Pune – 400009, Phone. 9225571450

5)Dr. Vilas Sabale
First floor, Vithal Acrade, Near Rupee bank, Pune Nasik Highway,Bhosari, Pune-411039 Mobile: 9822004630

Study period:
Date of first enrollment: 07/05/2009
Date of last completed: 17/12/2009

Phase of study : Therapeutic exploratory

Objectives

Primary objective

To evaluate the efficacy of VigRXPlus capsules as a dietary supplement to improve erectile function as assessed by Erectile function subscale of IIEF Questionnaire (IIEF-A) from baseline to end of treatment as compared to placebo.

Secondary objectives

- To evaluate the efficacy of VigRX Plus capsules as a dietary supplement for Male Sexual Health as assessed by IIEF (Total) (International Index of Erectile Function) questionnaire from baseline to end of treatment as compared to placebo
- To evaluate the efficacy of VigRX Plus capsules as a dietary supplement for Male Sexual Health as assessed by IIEF-B questionnaire (sum of all the subscales of IIEF except erectile function subscale) from baseline to end of treatment as compared to placebo
- To evaluate the impact of VigRX Plus capsules as a dietary supplement for Male Sexual Health as assessed by EDITS questionnaire (Patient & Partner version) as compared to placebo
- To evaluate the safety of VigRX Plus capsules as a dietary supplement for Male Sexual Health from baseline to end of treatment as compared to placebo
- To assess the effect of VigRX Plus on the sperm count, motility, semen volume from baseline to end of treatment.
- To assess the effect of VigRX Plus on Serum testosterone from baseline to end of treatment as compared to placebo

Diagnosis and main criteria for inclusion

1. Male subjects aged between 25-50 years
2. Subject having a monogamous, heterosexual relationship
3. Male subjects with IIEF-A score 11 to 23 & IIEF-B score 21 to 35 at screening visit & baseline visit
4. Subject provides written informed consent and comes for regular follow up

Methodology

75 males between 25-50 years of age were recruited to get 60 completed cases. Subjects with an IIEF erectile function domain score of 11-23 and remaining domains score of 21-35 were eligible for the study. For each subject the study terminated after a maximal period of 84 days from enrollment and included 5 follow up visits. After consenting to participate subjects were put on 15 days wash-out period before being administered the investigational product or placebo. On baseline visit (Day 1), medical history and physical examination were performed, IIEF Total questionnaire was assessed and the trial medications were dispensed. At all the follow-up visits (at an interval of 28 days) each subject was administered a new IIEF (Total) and an EDITS questionnaire. Each subject received another supply of the trial medications during these visits. On Day 28 and Day 84 EDITS questionnaire partner version scores were obtained from partners who consented for the same. Additionally at these visits subjects rated the tolerability of the treatment they received. At the end of treatment investigator's global assessment of therapy and subject's opinion on continuing with the trial medication was obtained.

Read more info on http://www.vigrxplusdirect.com/

Number of patients planned: 60 completed cases

Number of patients analysed :75

Test product, dose and mode of administration, batch number

VigRX Plus -2 capsules (each containing 360 mg of active composition) twice a day with meals for 12 weeks, Batch No: VP01.

Reference therapy: Placebo 2 capsules twice a day with meals for 12 weeks

Batch No: VX01,

Criteria for evaluation:

Primary efficacy evaluation

Improvement in IIEF-A (Erectile function domain of the International Index of Erectile Function) score for erectile function domain as compared to placebo

Secondary efficacy evaluation:

- Increase in total score of quality of sexual life questionnaire-IIEF (Total) as compared to placebo

Secondary efficacy evaluation (continued)

- Improvement in IIEF-B (other than the erectile function domain) score as compared to placebo
- Satisfaction with treatment (EDITS Patient & partner version) as compared to placebo
- Improvement in Semen Analysis Parameters as compared to placebo
- Improvement in Serum Testosterone (Total) levels , as compared to placebo Safety

Monitoring of adverse events. Clinical examination, Assessment of vitals and laboratory parameters.

Statistical methods

Analysis for safety was done on an intention-to treat population. This included subjects who received at least one dose of treatment post randomization and for whom at least one post baseline measurement was available. Missing data were imputed using last observation carried forward (LOCF) method.

Analysis of efficacy was primarily done on a per protocol data set constituting of subjects completing all the protocol required visits. Changes from baseline in IIEF scores were assessed using analysis of covariance (ANCOVA). Data on EDITS (patient and partner versions) were analysed by independent sample t test. Chi-square test was used to analyse investigators' assessment and subjects opinion across the two groups. All statistical tests were applied at 5% level of significance.

Results

Efficacy

Treatment with VigRX Plus resulted in a statistically significant increase ($p<0.0001$) of IIEF-A, IIEF-B and IIEF-Total scores as compared to placebo, on Day 84 (end of treatment).In subjects treated with VigRX Plus, mean increases from baseline to end of treatment for IIEF-A, IIEF-B and IIEF-Total were 9, 20.1 and 11.56 respectively. The corresponding increases in the placebo group were 0.62, 1 and 0.68.Treatment satisfaction as assessed by EDITS (patient version) was statistically significantly higher in the VigRX Plus group as compared to placebo on Day 28, Day 56 and Day 84. At the end of treatment, mean EDITS score was 82.31 in the VigRX Plus group and 36.78 in the placebo group.

Results (continued)

Female partners reciprocated the satisfaction levels experienced by their male counterparts treated with VigRX Plus, with the mean EDITS (partner version) score of 69.58 in the VigRX Plus group being statistically greater than that of 25.5 in the placebo group.

There was no statistically significant difference in the sperm count, semen volume and sperm motility between the two treatment groups. Serum Testosterone levels did not change significantly in any of the study groups.

At the end of study, global assessment of therapy by investigator clearly saw a superiority of outcomes in subjects receiving VigRX Plus as compared to those receiving placebo, with statistical significance. Subjects' opinion was also statistically significant in favour of VigRX Plus.

Safety

VigRX Plus and placebo both were safe and well tolerated in the study. Changes in laboratory and vital signs were clinically insignificant. The only serious adverse event reported in this study was when one subject from the VigRX Plus group suffered from infection due to malarial parasite and was subsequently withdrawn from the study.

Conclusion

In conclusion, use of VigRX Plus for twelve weeks was significantly better than placebo in improving erectile function in subjects with sexual dysfunction. It was also significantly superior to placebo in improving the other aspects of sexual health such as libido, intercourse satisfaction, orgasmic function and overall satisfaction. The enhancement of sexual function was endorsed by female partners of subjects receiving VigRX Plus. VigRX Plus was safe and well tolerated in subjects with male sexual dysfunction.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CRF	Case Report Form
ECG	Electrocardiogram
ESR	Erythrocyte Sedimentation Rate
ED	Erectile Dysfunction
EDITS	Erectile Dysfunction Inventory of Treatment Satisfaction
Hb	Haemoglobin

IEC	Independent Ethics Committee
IIEF	International Index of Erectile Function
ITT	Intent To Treat
ICH	International Conference on Harmonisation
IP	Investigational Product
LOCF	Last Observation Carried Forward
NAION	Non arteritic anterior optic neuropathy
SAE	Serious Adverse Event
SGPT	Serum Glutamic Pyruvic Transaminase

LIST OF TABLES AND GRAPHS

1 ETHICS

The study was conducted in accordance with International Conference of Harmonization's (ICH)-Good Clinical Practices (GCP) and the applicable regulatory requirements of India. Prior to study initiation, the study protocol and amendments were submitted to an appropriately constituted Independent/ Institutional Ethics Committee (IEC), in agreement with local legal prescriptions, for formal approval of the study conduct. The study commenced only after an affirmative decision of the EC/IRB concerning the conduct of the study was made in writing to the investigator and a copy provided to the sponsor. Freely given informed consent was obtained from study participants and their female partners prior to their entry into the trial.

Study Site	**Ethics Committee**

Dr. Gaurang Shah Jivdaya Hospital, Dharmoday bldg, Jivdaya lane, L.B.S. Marg, Ghatkopar(W), Mumbai-86. Mob: 9821019432.	Independent Ethics Committee 4, Sharavati, Worli Sea Face, Worli, Mumbai 400030. Tel : 91-22-65748188 Fax : 91-22-24966602
Dr. Suresh Patankar Institute of urology, Survey no. 32/2A, Erandwane, Behind Mehendale garage, Gulwani Maharaj road, Pune-4. Mob : 9881256992	Ethical Committee, AMAI Charitable Trust C/O Institute of Urology S.No. 32/2A, Erandwane, Behind Mehendale Garage, Gulwani Maharaj Street, Pune 411004.
Dr. R. K. Shimpi Dept. of Urology, Noble Hospital, 153,Magarpatta City Road, Hadapsar, Pune 411 013. Mob : 9822059799	Ethical Committee, Noble hospital, 153,Magarpatta City Road, Pune - 411013. Tel: (020)66285000 / 66295000 Fax: (020)66285199

2 INTRODUCTION

It has been reported from various studies in the general population and primary care that around 15-20% of men describe some sort of sexual problem [1]. Erectile dysfunction is one of the most common forms of sexual disorder and according to a survey, the Massachusetts Male Aging Study, 52% of men beyond 40 years of age may have some degree of erectile failure[2].

Current pharmacologic treatment of male sexual dysfunction includes a number of interventions; including oral phosphodiesterase type 5 (PDE5) inhibitors and intracorporeal agents with vasodilatory effects[3]. PDE5 inhibitors (e.g Sildenafil) for erectile dysfunction have revolutionised the treatment of male sexual dysfunction and are among the best selling drugs worldwide[4]. While normal sexual function involves successful integration of biological, psychological, and interpersonal influences[3], Sildenafil is known only to facilitate erections and not restore sexual desire (does not work without sexual stimulation), overcome sexual resistance or treat relational discord [4].

The use of Sildenafil necessitates caution in cardiac failure and when used within six months of acute myocardial infarction and stroke. It is inadvisable in patients with unstable angina pectoris. The co-administration of Sildenafil with organic nitrates, for example, glyceryl trinitrate or isosorbide dinitrate, is unsafe. The relative contraindications to Sildenafil in cardiovascular disease are uncontrolled hypertension and impaired cardiac reserve. The most common side effects are headache, flushing (due to vasodilation), and dyspepsia (due to relaxation of the smooth muscle of the gastroesophageal sphincter with reflux [5]. Further, several cases of non-arteritic anterior ischaemic optic neuropathy (NAION) have been reported since 2005 in users of PDE5 inhibitor agents. Following a series of such case reports, WHO and FDA have labeled the association between use of PDE5 inhibitors and risk of NAION as "possibly" causal [6].

While concerns of safety and limited efficacy still remain as longstanding treatment gaps in current therapy for male sexual dysfunction, several herbal therapies have provided suggestive evidence of efficacy in controlled clinical trials. The present study was therefore undertaken to evaluate the safety and efficacy of an herbal formulation VigRX Plus containing Korean red ginseng a widely used herbal ingredient and others in subjects with male sexual dysfunction. The study was based on the initial aphrodisiac activity exhibited by VigRX Plus in significantly reducing the ejaculation latency and post ejaculatory interval in male albino rats when compared to vehicle control. Treatment with VigRX Plus had resulted in a significant increase in ejaculation frequency on day 7 and a non significant increase on day 14 with marginal increase in testosterone concentration in serum and number of spermatogonia cells in seminiferous tubules of testes. (Unpublished report).

A set of preclinical studies[7] (at two different doses and duration) of an earlier marketed herbal combination VigRX, (devoid of 3 additional ingredients-Tribulus, Damiana, and Bioperine that are present in VigRX Plus) in a Sprague-Dawley rat model demonstrated a marked enhancing effect on the sexual activity of rats. In vitro assays determined that VigRX is able to inhibit the enzyme Rho-kinase. Also, VigRX was shown to be free from pharmaceutical adulterants, including phosphodiesterase type 5 (PDE -5) inhibitors and related analogues.

With the accrued preclinical evidence it was imperative to investigate the role of VigRx Plus in humans. Hence, in the present study, efficacy and safety of VigRX Plus was explored in human male subjects with sexual dysfunction.

3 STUDY OBJECTIVES

Primary objectives

To evaluate the efficacy of VigRX Plus capsules as a dietary supplement to improve erectile function as assessed by Erectile function subscale of IIEF Questionnaire (IIEFA) from baseline to end of treatment as compared to placebo. Index) questionnaire as compared to placebo

Secondary objectives

- To evaluate the efficacy of VigRX Plus capsules as a dietary supplement for Male Sexual Health as assessed by IIEF (Total) (International Index of Erectile Function) questionnaire from baseline to end of treatment as compared to placebo
- To evaluate the efficacy of VigRX Plus capsules as a dietary supplement for Male Sexual Health as assessed by IIEF-B questionnaire (sum of all the subscales of IIEF except erectile function subscale) from baseline to end of treatment as compared to placebo
- To evaluate the impact of VigRX Plus capsules as a dietary supplement for Male Sexual Health as assessed by EDITS questionnaire (Patient & Partner version) as compared to placebo
- To evaluate the safety of VigRX Plus capsules as a dietary supplement for Male Sexual Health from baseline to end of treatment as compared to placebo
- To assess the effect of VigRX Plus on the sperm count, motility, semen volume from baseline to end of treatment.
- To assess the effect of VigRX Plus on Serum testosterone from baseline to end of treatment as compared to placebo.

4 INVESTIGATIONAL PLAN

4.1 OVERALL STUDY DESIGN AND CHOICE OF CONTROL GROUP

This was a multicentre, triple blind, randomized, parallel group study of VigRX in subjects with male sexual dysfunction. The control used for this study was placebo.

4.2 METHODOLOGY

This was a twelve week study wherein subjects after a wash out period of 7/15 days, were randomized to receive either VigRX Plus or placebo capsules (Fig1) After their entry into the trial, eligible subjects were administered IIEF questionnaires for baseline assessment of sexual dysfunction. Safety assessment through medical history, vitals and systemic examination, monitoring of adverse events were performed at baseline and each follow up visit. Follow up visits were scheduled on Day 28, Day 56, Day 84 of study. At each of these visits, in addition to the IIEF evaluation subjects administered an EDITS (patient version) questionnaire to assess treatment satisfaction. EDITS (partner version) data on female partners of trial subjects was acquired on day 28 and day 84. Efficacy evaluation by semen analysis parameters (semen volume, sperm count, and semen motility) and serum testosterone was done at screening visit and at end of treatment.

Laboratory evaluation and ECG were scheduled at start and end of treatment. Global assessment of therapy by investigator, subjects' opinion and assessment of tolerability were performed at treatment end (Day 84).

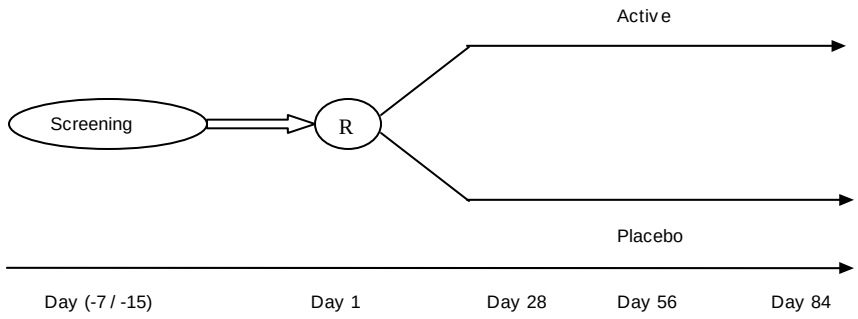
A detailed schedule of study visits and procedures are displayed in Table 1

Table 1. Visit specific schedule

Parameters	Screening (Day -7/-15)	WASHOUT PERIOD (DAY – 7 / DAY 15)	Baseline (Day 1)	Day 28	Day 56	Day 84
Subject Informed Consent	X		-	-	-	-
Subject's Female Partner Informed Consent	-		-	X	-	-
Vitals	X		X	X	X	X
Systemic Examination	X		X	X	X	X
TSH	X		-	-	-	-

S. Prolactin	X		-	-	-	-
S. Testosterone	X		-	-	-	X
CBC & ESR	X		-	-	-	X
ECG	X		-	-	-	X
Serum Creatinine	X		-	-	-	X
Urine Routine	X		-	-	-	X
RBS	X		-	-	-	-
SGPT	X		-	-	-	X
Semen Analysis	X		-	-	-	X
IIEF T Questionnaire	X		X	X	X	X
EDITS Questionnaire (patient version)	-		-	X	X	X
EDITS Questionnaire (partner version)	-		-	X	-	X
Subject Diary	-		X	X	X	X
Dispensing of Study Medication	-		X	X	X	-
Monitoring of Adverse / Serious Adverse Events	-		X	X	X	X
IP compliance	-		-	X	X	X
Global assessment by the investigator	-		-	-	-	X

Fig 1 : Study design



4.3 SELECTION OF STUDY POPULATION

4.3.1 INCLUSION CRITERIA

Patients satisfying all of the following inclusion criteria were to be included in the study

1. Male aged between 25-50 years
2. Subject having a monogamous, heterosexual relationship
3. Male subjects with IIEF-A score 11 to 23 & IIEF-B score 21 to 35 at screening visit & baseline visit
4. Subject provides written informed consent and comes for regular follow up

4.3.2 EXCLUSION CRITERIA

Patients meeting any of the following exclusion criteria were to be excluded from the study

1. Subjects with major psychiatric disorders
2. Has a history of stroke, myocardial infarction, coronary artery disease, cardiac failure, angina, life-threatening arrhythmia within the past 6 months.
3. Has a history of diabetes
4. Has a history of spinal cord injury or a radical prostatectomy or radical pelvic surgery.
5. Has anatomical deformity of the penis which has a severe effect on sexual functioning
6. Is a k/c/o HIV / AIDS
7. Is know to suffer from sexually transmitted diseases(STDs) at screening visit
8. Chronic Alcoholics showing withdrawal symptoms or subjects having medication (opiates etc) or drug (marijuana, cocaine etc)/ Nicotine/Caffeine dependence
9. Is using medications that are known to cause sexual dysfunction (cimetidine, spironolactone, thiazides, β-adrenergic blockers, anti- depressants etc.)
10. Has a major illness that in the opinion of the investigator would interfere with the conduct of the study.
11. Has participated in a clinical drug study within the last 30 days prior to entering this study.

12. Subject with Liver dysfunction as evidenced by SGPT level of 1.5 X ULN.
13. Subject with Renal dysfunction as evidenced by Serum Creatinine level of 1.5 X ULN.
14. Has an abnormal thyroid stimulating hormone (TSH) level lower than 30% of LLN or more than 30% of ULN.
15. Has erectile dysfunction caused by neurological or endocrine factors such as hyperprolactinemia or low serum testosterone levels (<200 ng/dl).
16. Subjects already taking any medications for the study indication & do not wish to discontinue the same
17. Subject not ready to sign the consent & unable to comply with the protocol
18. Subjects whose female partners are Pregnant

4.3.3 WITHDRAWAL CRITERIA

Subjects meeting any of the following criteria were to be withdrawn from the study

- Earnest request of the subject assigning a reason for the same.
- Discretion of the Investigator.
- Repeated protocol criteria deviations.
- Serious adverse events where continuation of study possess serious risk to the subject.
- Subject has consumed less than 80% of the total dose that needs to be consumed in the period between follow-ups and in the opinion of the investigator needs to be withdrawn from the study
- Subject consumes any other medicines used for the treatment of Sexual Dysfunction.
- Subject consumes any medications that are mentioned in the list of prohibited medications.

4.3.4 DROP OUT / LOST TO FOLLOW UP CRITERIA

Subject was to be considered as a dropout if he does not report for the follow up within – 5 or + 5 days of his scheduled visit day but does report to investigator later and in the opinion of the investigator needs to be consider as drop out.

Subject was to be considered as a lost to follow up if he does not report to investigator at all after a particular follow up visit during therapy period**.**

4.4 TREATMENTS ADMINISTERED

4.4.1 IDENTITY OF INVESTIGATIONAL PRODUCT

Each capsule of VigRX Plus contains the following

Table 2.Composition of VigRX Plus

Ingredients (Latin Names)	Part used	Actual wt / caps (mg)
Panax ginseng (Korean Red Ginseng)	Root	100.000
Serenoa repens (Saw Palmetto)	Berry	100.000
Crataegus rivularis (Hawthorne)	Berry	100.000
Ginkgo biloba	Leaf	100.000
Turnera diffusa (Damiana)	Leaf	100.000
Tribulus terrestris	Vine	075.000
Erythroxylum catuaba	Bark	050.000
Ptychopetalum olacoides (Muira Puama)	Bark	050.000
Cuscuta chinensis	Seed	025.000
Epimedium sagittatum	Leaf	015.000
Bioperine (extract from Piper nigrum fruit)	-	005.000
Total amount		720.000

Additional ingredients: dicalcium phosphate, cellulose, croscarmellose sodium, stearic acid, silicon dioxide, magnesium stearate, FD&C Red #40

Presentation: White plastic bottles each containing 128 capsules

Placebo capsules were similar to IP in appearance and were made up of CMC (Carboxymethyl cellulose)

4.4.2 DOSES AND ADMINISTRATION

VigRX Plus and placebo were to be taken orally with meals at a dose of 2 capsules twice daily for 12 weeks. Each capsule contained 360 mg of the active composition mentioned above. The IP and placebo were administered to subjects in the following regimen.

Table 3. Treatment regimen

Group	Morning	Night	Route of Administration	Treatment Duration
VigRX Plus	2Capsules* of VigRX Plus	2 Capsules* of VigRX Plus	ORAL (Capsules to be taken with meals)	12 weeks (from day 1 to day 84)
Placebo	2 Capsules of Placebo	2 Capsules of Placebo		

**Each capsule contained 360 mg of the active composition of VigRx Plus*

4.4.3 BLINDING AND RANDOMISATION

A total of 72 subjects were expected to be recruited from the investigator's clinical practices or referring physicians. Each subject satisfying the inclusion/exclusion criteria was to be recruited in the study and be assigned to one of the treatment groups according to a randomization schedule. A research coordinator, who was not directly involved in trial-related activities, performed the randomization and blinding to avoid bias.

4.4.4 PRIOR AND CONCOMITANT THERAPY

During the course of the study, the subjects were prohibited from consuming any other medication used in the treatment of Male Sexual Dysfunction. A list of medications prohibited in the study is provided in Appendix 10.1.1. No other herbal medication other than that dispensed during the study was allowed. Subjects who were required to take medicines for any other complaints were to do so only in consultation with the Investigator. Use of any concomitant medication was to be recorded in the case report form (CRF). Subjects were not advised any specific lifestyle & dietary changes upon enrolment in the study & throughout the duration of the study.

4.4.5 TREATMENT COMPLIANCE

In order to ensure treatment compliance, adequate instructions were to be given to subjects regarding trial procedures during the informed consent process. Subjects were provided with a memory card for follow up visits and test requisition forms for laboratory investigations. At each visit, a record of dispensed and returned medication was to be maintained to determine subject's compliance to treatment.

4.5 EFFICACY AND SAFETY VARIABLES

4.5.1 PRIMARY EFFICACY VARIABLES

4.5.1.1 INTERNATIONAL INDEX OF ERECTILE FUNCTION -ERECTILE FUNCTION DOMAIN (IIEF-A)

It is an internationally accepted instrument described by Rosen et al [8] for measuring erectile dysfunction and monitoring response to treatment.

The erectile function domain (items1-6 of the index) designated as IIEF A in this study was used to measure erectile dysfunction. It provided information on the subject's ability to achieve and maintain an erection. The erectile function domain consists of six

questions concerning erection frequency (question [Q]1), erection firmness (Q2), frequency of partner penetration (Q3), frequency of maintaining erection after penetration (Q4), ability to maintain erection to completion of intercourse (Q5), and confidence in achieving and maintaining erection (Q6), all during the previous 4 weeks. The primary efficacy variable consisted of the change in mean erectile function domain score (IIEF A) from baseline to end point.

4.5.2 SECONDARY EFFICACY VARIABLES

4.5.2.1 INTERNATIONAL INDEX OF ERECTILE FUNCTION- TOTAL (IIEF-TOTAL)

The IIEF addresses the relevant domains of male sexual function (erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction), is psychometrically sound, and has been linguistically validated in 10 languages. This questionnaire is readily self-administered in research or clinical settings. The IIEF demonstrates the sensitivity and specificity for detecting treatment-related changes in patients with erectile dysfunction[8].

Each item on the IIEF questionnaire is scored on 5 point Likert scale. Scores for each domain are variable and total score range is 5 to 75. Maximum possible score for erectile function is 30. The complete IIEF questionnaire is provided as Appendix 10.1.3

4.5.2.2 INTERNATIONAL INDEX OF ERECTILE DYSFUNCTION (OTHER THAN THE ERECTILE FUNCTION DOMAIN)-(IIEF B)

The section of the international index other than the erectile function domain, designated as IIEF B in this study, was used to measure other aspects of sexual dysfunction besides erectile dysfunction. It gives information on, orgasmic function, sexual desire, intercourse satisfaction and overall sexual satisfaction in a subject.

4.5.2.3 ERECTILE DYSFUNCTION INVENTORY OF TREATMENT SATISFACTION (EDITS- Patient and Partner version)

Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) was developed by Althof, Corty et al [9] to examine the degree of satisfaction with different treatment modalities for ED. Separate questionnaires are available for both the subject and the

subject's partner. With the partner version EDITS allows partner satisfaction an important determinant—especially for sexual dysfunction but seldom evaluated to be measured and investigated.

4.5.2.4 SEMEN ANALYSIS

Semen analysis is a measure to determine the semen quality in terms of the ability of sperm to accomplish fertilization. A semen analysis does not diagnose fertility or infertility but provides a relative measure of semen quality compared to the general population of men. Since it is the sperm that is of importance to male fertility, semen quality involves both sperm quantity and quality.

Most available studies on oral phosphodiesterase inhibitors demonstrate a significant increase in sperm motility and viability both in vivo and in vitro, which seems to be enhanced at low doses and reduced at high concentrations [10]. In the current study semen analysis of subjects was conducted at screening and end of treatment to investigate whether administration of the VigRX Plus has any modifying effect on seminal parameters

The following parameters were measured in semen analysis:

- Volume and consistency of semen
- Sperm count: Sperm count measures the concentration of sperm in a man's ejaculate. Anything over 20 million sperm per milliliter is considered normal.
- Sperm motility describes the ability of sperm to move properly towards an ovum. A more specified measure is *motility grade*, where the motility of sperm are divided into four different grades:

Grade IV: Sperm with progressive motility. These are the strongest and swim fast in a straight line.

Grade III: (non-linear motility): These also move forward but tend to travel in a curved or crooked motion.

Grade II: These have non-progressive motility because they do not move forward despite the fact that they move their tails

Grade I: These are immotile and fail to move at all

The percentage of each motility grade was recorded after 1h, 2h, 3h and 6h of collection.

4.5.2.5 SERUM TESTOSTERONE

While the role of testosterone in mediating penile erection may be largely unknown, routine testing of serum testosterone has been recommended for initial evaluation of ED. In this study serum testosterone levels were evaluated for changes from baseline to endpoint (Day 84) across the two study groups.

4.5.2.6 GLOBAL ASSESSMENT OF THERAPY BY INVESTIGATOR

Global assessment of therapy was made by the investigator, based on the criteria described below:

Table 4. Criteria for global assessment by investigator

Excellent	Improvement in all the IIEF-A, IIEF-B, EDITS (patient & partner versions) Questionnaires , Semen Analysis & Serum testosterone
Very Good	Improvement in IIEF-A, IIEF-B, EDITS (patient version) Questionnaires & Semen Analysis
Good	Improvement in IIEF-A, IIEF-B, EDITS (patient version) Questionnaires
Fair	Improvement in IIEF-A & IIEF-B Questionnaires
Poor	No Improvement

4.5.2.7 SUBJECT'S OPINION

At the end of the study period, subjects were asked if they preferred to continue using of the study product in future, for their sexual dysfunction

4.5.3 APPROPRIATENESS OF MEASUREMENTS

The International Index of Erectile Function (IIEF) is a widely used, multi-dimensional self-report instrument for the evaluation of male sexual function. It is has been recommended as a primary endpoint for clinical trials of erectile dysfunction (ED) and for diagnostic evaluation of ED severity. The IIEF was developed in conjunction with the clinical trial program for Sildenafil, and has since been adopted as the 'gold standard' measure for efficacy assessment in clinical trials of ED and its use in classifying ED severity and prevalence. The IIEF meets psychometric criteria for test reliability and validity, has a high degree of sensitivity and specificity, and correlates well with other measures of treatment outcome. It has demonstrated consistent and robust treatment

responsiveness in studies in USA, Europe and Asia, as well as in a wide range of etiological subgroups[11].

Limitations[11]- The IIEF focuses only on current sexual functioning and provides superficial assessment of domains of sexual functioning other than erection. It does not provide any specific information about the partner relationship or sexual functioning of the partner. It could be argued that these are important areas for assessment in clinical practice. It was thus important to include EDITS questionnaire to assess treatment satisfaction of the partner.

4.5.4 SAFETY AND TOLERABILITY VARIABLES

Safety was assessed primarily through incidence of adverse events (AE), clinical and laboratory evaluation of the subject.

4.5.4.1 ADVERSE EVENTS

An adverse event is defined as any untoward medical occurrence in a subject who has been administered an investigational product and does not necessarily have a causal relationship. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with the use of the IP whether or not related to the IP.

Adverse events were further classified into serious and non-serious. Definition of serious adverse events (SAE) is described in Appendix 10.1.2 of this report. All adverse events whether serious or non serious, whether observed or reported by the patient were to be evaluated by the investigator and recorded in the AE section of the subject's case report form. Adverse event reporting required the severity of the event, treatment administered, any change in study drug, investigator attribution to study drug and outcome status to be documented in the CRF.

4.5.4.2 CLINICAL AND LABORATORY EVALUATION

Physical examinations and monitoring of vital signs (systolic and diastolic blood pressure, respiration rate and pulse rate) were to be conducted at screening, baseline and at each follow up visit. Laboratory evaluations consisting of haematological, clinical

chemistry and urinalysis parameters were required at the screening visit and at the end of treatment phase on Day 84. In addition, a 12-lead Electrocardiogram (ECG) was to be performed at these visits. Any clinically significant abnormality in any of the above mentioned safety parameters was to be recorded as an adverse event in the respective pages of the CRF.

4.5.4.3 TOLERABILITY

In addition to the above mentioned safety parameters, subjects were asked to rate the tolerability of the IP based on the following criteria at the end of the treatment: Table 5. Assessment of tolerability

Good	No side effects
Fair	Mild to moderate side effects
Poor	Severe side effects requiring withdrawal of subject

4.6 DATA QUALITY ASSURANCE

Before study initiation, it was ensured that the protocol -stipulated study procedures were well-understood by the investigator and his study staff .The study was monitored regularly for compliance to ICH-GCP, protocol and regulatory requirements. At each monitoring visit, CRF entries were verified by comparing them with the source documents before retrieving the case report forms. The monitor was to ensure that the investigator maintained accurate, timely, and complete records.

4.7 STATISTICAL METHODS

4.7.1 SAMPLE SIZE ESTIMATION

For this exploratory pilot study, it was estimated that a sample size of 60 subjects would be sufficient to detect a difference in IIEF scores between VigRX Plus and placebo group at a significance level of 5%.

4.7.2 ANALYSIS POPULATIONS

Two types of populations were identified for analysis

Intention –To -Treat Population (ITT) population were subjects who were recruited into the study and who received at least one dose (or any portion of a dose) of study medication. Analysis of safety variables were done for the ITT population.

Per-Protocol (PP) population consisted of completed subjects i.e. all subjects who completed the study according to the following definition:

Definition for a completed case: Subject was considered a completed case if he fulfilled at least 84 days of treatment. (w.r.t. IIEF & EDITS patient version) Note:

- For this study even those subjects whose female partners did not participate, were considered as completed subjects & their data were to be analyzed.
- EDITS partner version assessment was to be done for only those female partners who gave informed consent and for whom data was available.

Drop out, withdrawal and protocol deviation cases were to be reported and described.

Missing, unused and spurious data were to be identified and appropriately taken care of during the final analysis. Missing data was to be inserted using the last observation carried forward (LOCF) method.

4.7.3 HYPOTHESES

The null hypothesis (H_0) was that no difference exists in both primary and secondary end points between both the groups and the alternative hypothesis (H_A) was that there exists a difference between the groups

Primary hypothesis:

1. The score of IIEF-A will increase from baseline to Day 84.
2. This increase will be more in the active group as compared to placebo group.

Secondary hypotheses:

The secondary hypotheses to be investigated were

- Levels of secondary response variables improve from Day 1 up to day 84 (to be tested per variable).
- The safety variables (CBC, ESR, Liver Profile, Renal Profile, & ECG) may not change from screening to day 84

4.7.4 METHODS OF ANALYSIS

- The final analysis was performed at the end of the study (Day 84) after database lock.

- Basic statistic evaluations include mean, standard deviation, median, min-max, etc…
- All efficacy and safety variables were exploratively analyzed and descriptively evaluated. Thereby the structure equality of the 2 arms was especially verified. Thus, initially univariate and co-variate analysis of all the variables (qualitative, quantitative and ordinal) was carried out to determine the basic features of data like range, central tendency, spread etc. Then all the variables were compared across the groups to see the broad differences between them.
- Descriptive statistics (mean, standard deviation and N for continuous and count variables; median, range and N for discrete variables) of the primary response variable (IIEF - A) and each of the secondary response variables was done using all data available.
- The primary endpoint the Erectile Function subscale of International Index of Erectile Function Questionnaire (IIEF-A) was compared between the treatment and placebo groups at baseline & end of treatment. Secondary Efficacy variables (IIEF-total, IIEF-B, EDITS Patient & Partner version, Semen Analysis, S. Testosterone) were also compared between the treatment and placebo groups at baseline & end of treatment. These were the quantitative variables and were mainly assessed by quantitative statistics. Adequate statistical tests such as the t test (paired for before and after data, unpaired if between the two groups), chisquare test, U-test, ANOVA, ANCOVA etc, were applied. Friedman/ Wilcoxon (for before and after data) Mann-Whitney (between the two groups) nonparametric test were used to confirm these results.
- Nominal variables in the study such as global assessment of therapy were assessed by the chi-square test.
- All statistical tests were performed at 5% significance level ($p < 0.05$).
- For demographic and other remaining variables (vital parameters, clinical examination, and lab tests which include Complete Blood Count (CBC), ESR, SGPT, Creatinine and Routine Urine) are concerned, initially univariate analysis was carried out. They were then compared across the groups by adequate statistical tests such as the t test, chi-square test, U-test, etc.
- Adverse/Serious Adverse Events were analysed using appropriate statistical test.

- The following statistical softwares were used: - SPSS 15, PEPI, EPI INFO 2000 and MS Excel XP.

Interim Analysis and Data Monitoring

No interim analysis was planned for the trial.

5 STUDY PATIENTS

5.1 DISPOSITION OF PATIENTS

Out of 108 patients screened, 78 were recruited into the study. Failure to meet the stipulated IIEF scores and laboratory abnormalities were the major reasons for screening failures (Table 6). The eligible subjects were randomized to receive either VigRX Plus or placebo. While one subject from the placebo group (VL/DM/63) was withdrawn due to his unwillingness to continue participation in the study after Day 56, two others(VL/DM/37and VL/DM/20 were lost to follow up after Day 28 and Day 56.

Fig 2.displays the disposition of subjects in the study.

Table 6. Reasons for screening failure

Site ID	IIEF	Laboratory abnormalities	Other
VL/DM/01	4	3	0
VL/DM/02	0	6	2
VL/DM/03	1	0	1
VL/DM/04	0	2	1
VL/DM/05	3	3	2

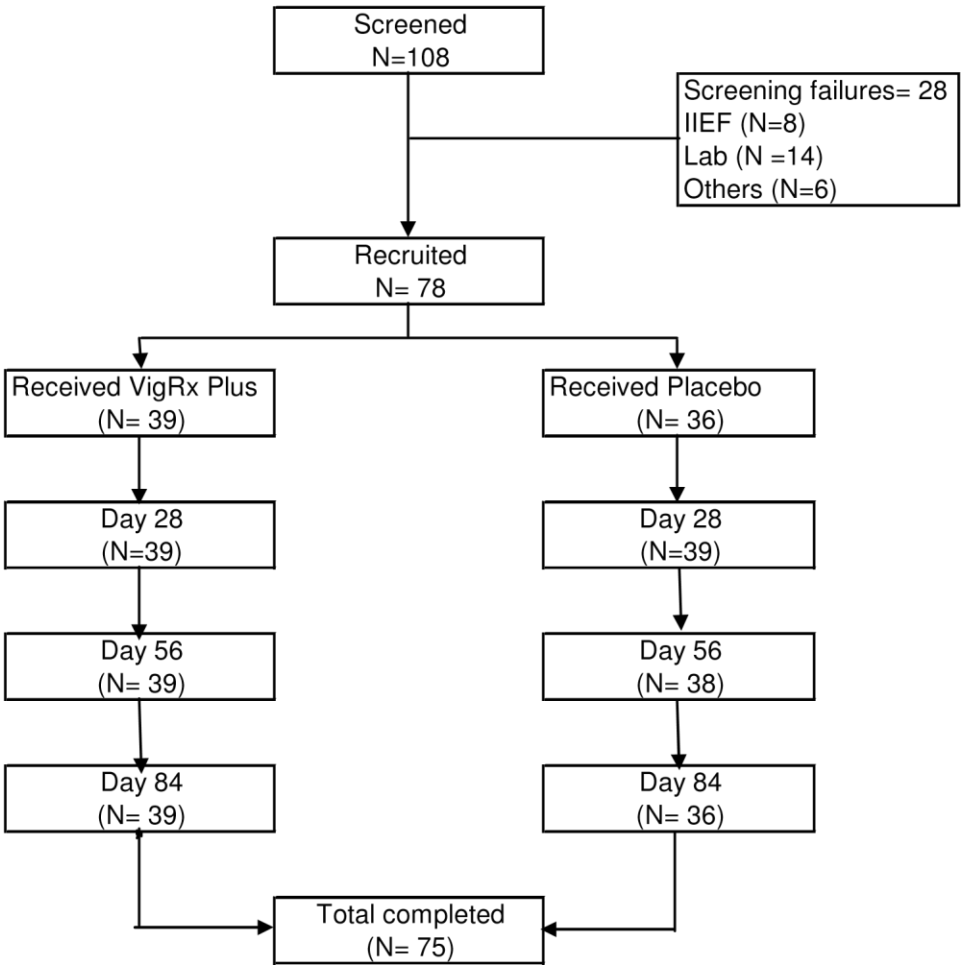


Fig 2. Disposition of patients

5.2 PROTOCOL DEVIATIONS

There were no major protocol violations which led to withdrawal of subjects from the study. A majority of the protocol deviations were related to due to delay in scheduled laboratory test or tests not conducted due to various reasons. Appendix 10.2.1 summarizes the protocol deviations at each study site.

6 EFFICACY EVALUATION

6.1 DATA SETS ANALYSED

Analysis of safety (vital parameters) was done on an ITT population consisting of data on 78 subjects in whom at least one post baseline measurement was available. Analysis of

laboratory parameters however was done only on subjects in whom complete data was available for screening and end of treatment visit.

Efficacy evaluation was performed on a per-protocol data set of completed cases, in which data on all the protocol stipulated visits was available for IIEF and EDITS questionnaires. Analysis of all other efficacy parameters were done for subjects in whom complete data is available for the respective parameter

6.2 DEMOGRAPHIC CHARACTERISTICS

The two study groups appeared to be well balanced in terms of mean age of their subjects. (Table 7)

Table 7. Demographic characteristics

Demographic characteristics	VigRx Plus (N=39)	Placebo (N=39)
Age (yrs.)	35.23 ± 13.24	34.33 ± 11.78
Values are expressed as mean ± 2SD		

6.3 PRE-EXISTING CONDITION/CONCOMITANT MEDICATIONS USED IN STUDY

A list of concomitant medications used in the study is provided in Appendix 10.3. All concomitant medications used were indicated for pre-existing conditions of the subjects or for treatment of adverse events.

6.4 EFFICACY RESULTS

6.4.1 PRIMARY EFFICACY MEASURES

6.4.1.1 IIEF A

Treatment with VigRX Plus showed a statistically significant (p=<0.0001) increase of IIEF A erectile function scores from baseline to endpoint at Day 84 as compared to placebo.

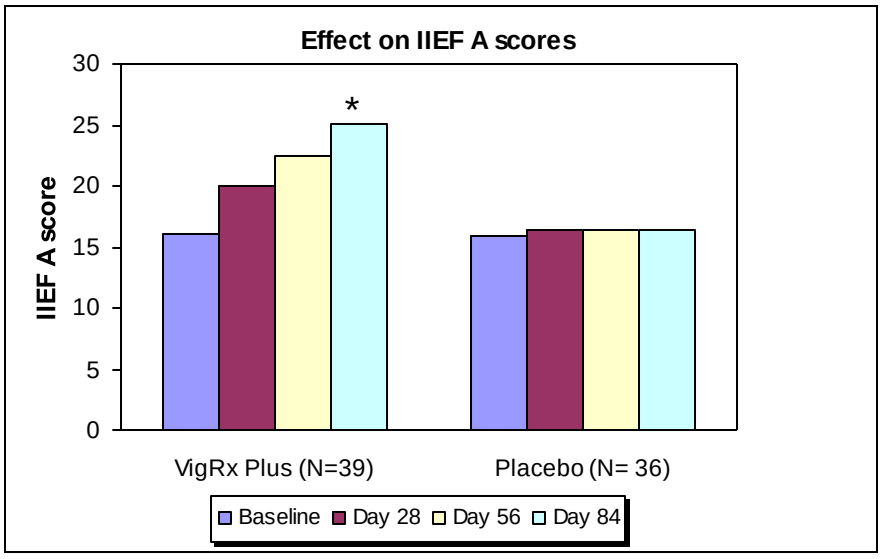
In subjects receiving VigRX Plus the ability to penetrate the partner (Q3 of IIEF) and maintain erection after penetration (Q4 of IIEF) saw a greater improvement than in those receiving placebo (Table 8).

Table 8. Responses to IIEF question 3 and 4

	Baseline	Day 84	Improvement
Ability to penetrate the partner (Q3 of IIEF)			
VigRX Plus (N=39)	2.69 ± 1.12	4.12 ± 1.6	58.97 %
Placebo (N=36)	2.64 ± 1.08	2.63 ± 1.38	4.86 %
Ability to maintain erection after penetration(Q4 of IIEF)			
VigRX Plus (N=39)	2.56 ± 1.1	4.02 ±1.62	62.82 %
Placebo (N=36)	2.44 ± 1.1	2.66 ± 1.34	10.18 %
IIEF scores are expressed as Mean ±2SD			

Table 9. Effect on IIEF scores

	Baseline	Day 28	Day 56	Day 84
IIEF A				
VigRX Plus (N=39)	16.08 ± 5.82	20.03 ± 6	22.46 ± 7.14	25.08 ± 9.12
Placebo (N= 36)	15.86 ± 6.48	16.33 ± 6.98	16.39 ± 7.42	16.47 ± 8.5
IIEF TOTAL				
VigRX Plus (N=39)	42.56 ± 10.18	52.15 ± 10.96	58.05 ± 14.54	63.13 ± 20.12
Placebo (N= 36)	42.47 ± 10.20	43.86 ± 10.66	43.69 ± 6.95	43.86 ± 16.9
IIEF B				
VigRX Plus (N=39)	26.49 ± 5.92	32.13 ± 6.34	35.59 ± 8.46	38.05 ± 11.38
Placebo (N= 36)	26.61 ± 5.82	27.53 ± 6.36	27.31 ± 8.58	27.39 ± 9.84
IIEF scores are expressed as mean ± 2SD				

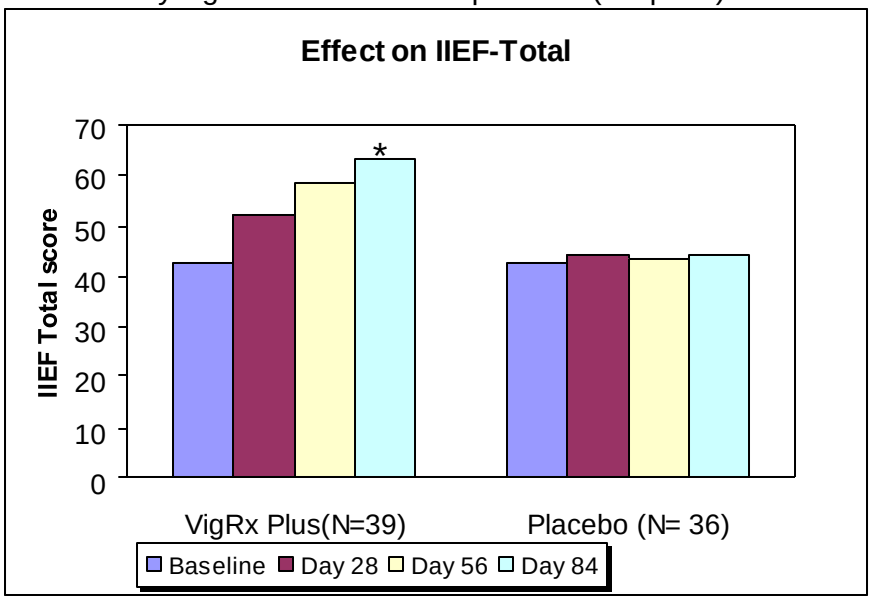


Graph 1.Effect on IIEF A scores.*p=<0.0001 indicates significantly different from baseline, as compared to placebo by ANCOVA

6.4.2 SECONDARY EFFICACY PARAMETERS

6.4.2.1 IIEF TOTAL SCORE

Effect of VigRX Plus in increasing total IIEF scores from baseline to end of treatment (at Day 84) was statistically significant over that of placebo. (Graph 2.)



Graph 2.Effect on IIEF Total scores. *p<0.001indicates significantly different from baseline as compared to placebo, by ANCOVA.

6.4.2.2 IIEF B

On Day 84, subjects of the VigRX Plus group saw a statistically significant increase (p=<0.0001) of IIEF B scores from baseline as compared to placebo. Improvement in IIEF B scores is described in Table 9.

Orgasmic function

Subjects on VigRX Plus saw a greater improvement of orgasmic function than in those on placebo as assessed by the increase in question 10 and 11 of the international index.

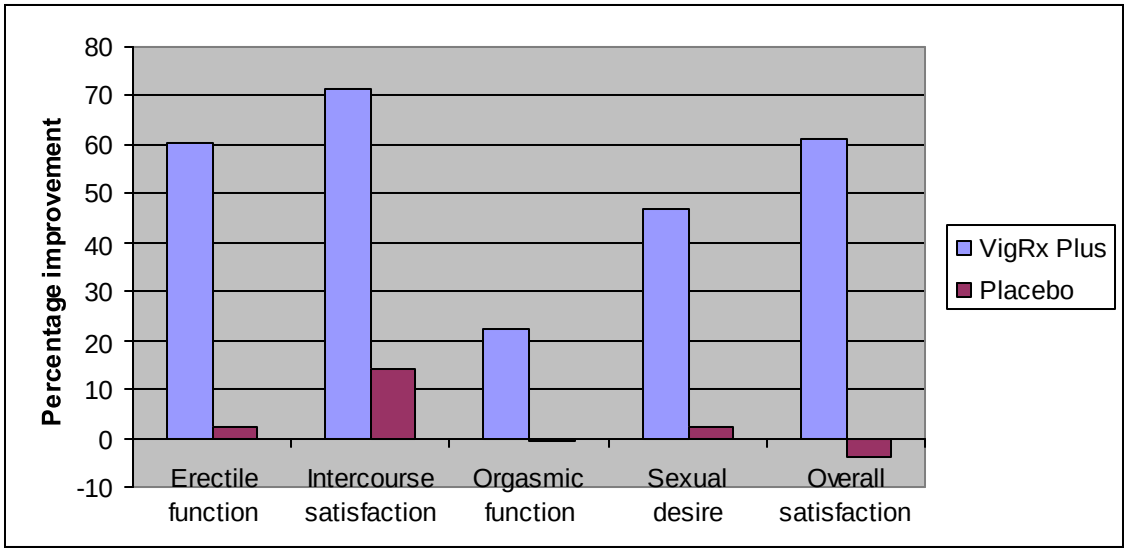
Sexual desire

Enhancement of sexual desire was greater in subjects of the VigRX Plus group as compared to those of the placebo group. Overall satisfaction

Scores of overall satisfaction were higher in the VigRX Plus than in the placebo group.

Table 10. Effect on IIEF domains

IIEF DOMAINS		VigRX Plus (N=39)			Placebo (N=36)		
		Baseline (Mean±2SD)	Day 84 (Mean±2SD)	Improvement	Baseline (Mean±2SD)	Day 84 (Mean±2SD)	Improvement
Erectile function	Q1-6	16.08 ± 5.82	25.08 ± 9.12	60.35%	15.86 ± 6.48	16.47 ± 8.5	2.07 %
Intercourse satisfaction	Q7	1.92±1.06	3.17±1.37	71.43%	1.94±2.42	2.38±1.29	14.03%
	Q8	2.69±0.56	4.20±0.8		2.61±1.08	2.66±1.34	
	Q9	2.66±0.52	4.20±0.80		2.58±1.1	2.66±1.34	
Orgasmic function	Q 10	4.58±0.49	4.84±0.36	22.49%	4.44±1.2	4.58±1.20	-0.46%
	Q 11	3.25±0.63	4.38±0.93		3.33±1.58	3.19±2.28	
Sexual desire	Q12	3.17±0.55	4.51±0.68	47%	3.25±1.26	3.22±1.52	2.08%
	Q13	3.17±0.55	4.53±0.68		3.22 ±1.26	3.19±1.48	
Overall satisfaction	Q14	2.82±0.50	4.10±0.91	61%	2.94±0.82	2.91±1.1	-3.7%
	Q15	2.64±0.70	4.07±0.87		2.66±1.34	2.55±2.04	
IIEF scores are expressed as Mean±2 SD							



Graph 3. Percentage improvement in IIEF domains

6.4.2.3 EDITS

Patient version

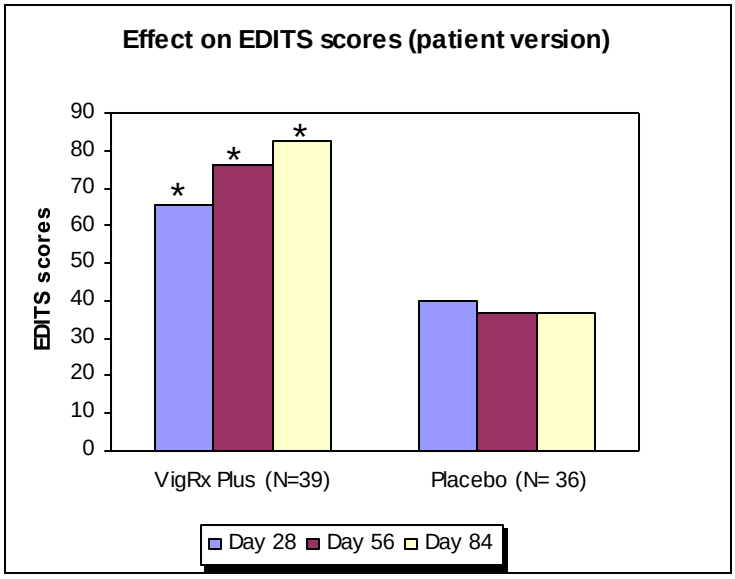
In subjects receiving VigRX Plus, EDITS scores on Day 28, 56 and 84 were statistically significantly higher($p<0.0001$) than that in those receiving placebo.

The results of EDITS (patient and partner version) are summarized in Table 11 and 12.

Table 11. Effect on EDITS (patient version)

	Day 28	Day 56	Day 84
VigRX Plus (N=39)	65.44 ± 36.28	76.10 ± 40.92	82.31 ± 40.46

Placebo (N= 36)	40.17 ± 32	36.61 ± 39.6	36.78 ± 45.06
EDITS(patient version) scores are expressed as Mean ±2SD			



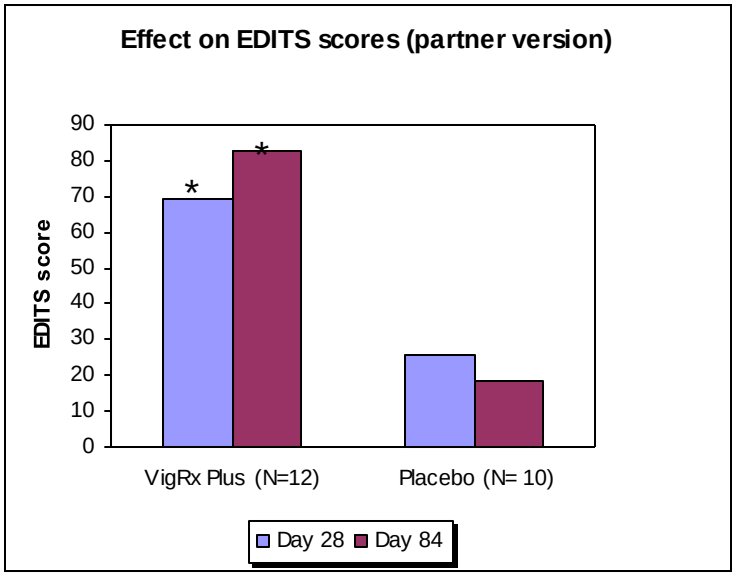
Graph 4.Effect on EDITS (patient version) scores. *p<0.001indicates significantly higher than placebo, by independent sample t test

Partner version

Female partners of subjects receiving VigRX Plus reported statistically significantly higher (p<0.0001) scores than those of subjects receiving placebo.

Table 12. Effect on EDITS (partner version)

	Day 28	Day 84
VigRX Plus (N=12)	69.58 ± 34.24	82.75 ± 19.6
Placebo (N= 10)	25.50 ± 20.24	18.50 ± 18.88
EDITS(partner version)scores are expressed as Mean±2SD		



Graph 5.Effect on EDITS scores (partner version). *p<0.001indicates significantly higher than placebo, by independent sample t test

6.4.2.4 SEMEN ANALYSIS

Sperm count

The mean sperm count in the VigRX Plus group decreased from 49.45 million/ml at baseline to 47.15 million/ml on day 84 (Table 13). The change however was not statistically significant as compared to placebo.

Semen volume

The semen volume in both study groups increased from baseline to day 84. The increase in the VigRX Plus group was not statistically significant as compared to placebo.

Sperm motility

There was no statistically significant difference between the VigRX Plus and placebo groups with respect to changes in the sperm motility when compared from baseline to end of treatment. (Table 14)

Table 13.Effect on sperm count and semen volume

	Sperm count (million per ml)		Semen volume (ml)	
	Baseline	Day 84	Baseline	Day 84
VigRX Plus (N=22)	49.45 ± 55.7	47.15 ± 50.62	1.75 ± 1.26	2.11 ± 1.06

Placebo (N=18)	58.29 ± 60.04	63.97 ± 41.66	1.97 ± 1.4	2.22 ± 1.76
Values for sperm count are expressed as Mean±2SD				

Table 14. Effect on sperm motility

		VigRX Plus				Placebo			
Visit	Sperm Motility (%)	Grade of Sperm motility				Grade of sperm motility			
		IV	III	II	I	IV	III	II	I
Screening	After 1 hr	45±50.68	25±30.54	11±9.24	18±40.10	51±341	24±29.14	11±9.44	17±23.24
	After 2 hr	42±84.46	28±31.9	11±11.52	19±42.98	47±28.7	28±31.22	13±13.22	17±22.02
	After 3 hr	38±23.14	25±35.44	16±15.4	21±44.52	44±23.34	29±29.94	17±14.26	19±21.06
	After 6 hr	33±19.38	21±26.76	19±21.36	25±47.1	37±24.70	24±25.76	23±20.88	21±21.98
Day84	After 1 hr	48±17.39	24±26.54	15±9.98	13±13.32	51±45.22	27±25.02	17±18.94	15±21.74
	After 2 hr	43±17.98	28±25.4	16±12.66	16±17.34	43±51.1	27±26.32	19±20.76	21±21.68
	After 3 hr	36±30.88	31±29.1	19±7.26	16±14.16	38±51.64	30±31.62	20±18.26	23±24.30
	After 6 hr	29±15.52	30±35.78	20±17.54	20±18.7	33±48.86	29±42.0	20±19.08	24.62

6.4.2.5 SERUM TESTOSTERONE

The serum testosterone levels in subjects receiving VigRX Plus were not statistically significant with respect to change from screening to end of treatment as compared to placebo. (Table 15)

Table 15. Effect on Serum testosterone

	Serum testosterone (ng/dL) Screening	Serum testosterone (ng/dL) Day 84
VigRX Plus (N=37)	544.46 ± 415.28	527.66 ± 310.94
Placebo (N=25)	518.1 ± 395.02	471.75 ± 320.76

S. Testosterone values are expressed as Mean ± 2SD

6.4.2.6 GLOBAL ASSESSMENT OF THERAPY BY INVESTIGATOR

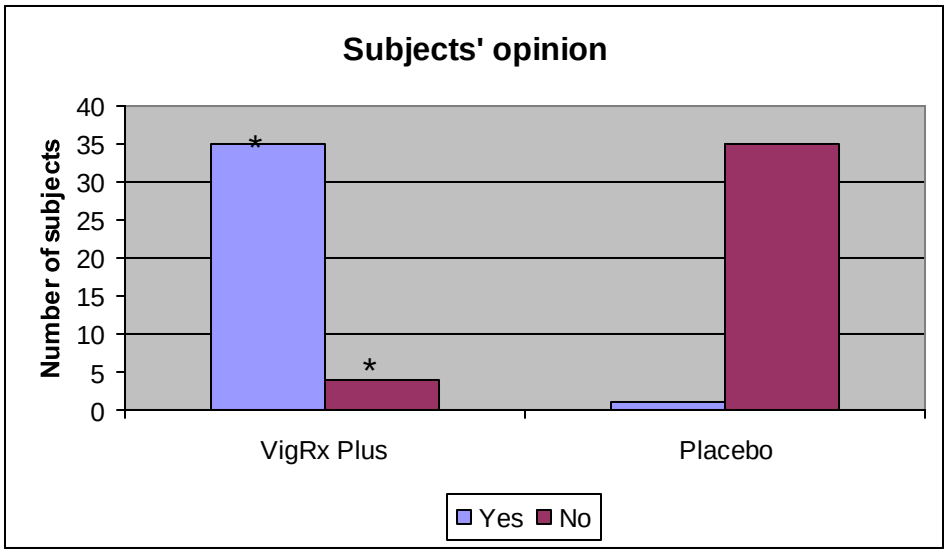
Global assessment of therapy by investigator on Day 84 saw a statistically significant superiority ($p<0.0001$) of VigRX Plus over placebo when analysed by Chi-square test.

Table 16. Global assessment of therapy by Investigator

Global assessment of therapy	VigRX Plus	Placebo
Excellent	8 (20.15%)	--
Very Good	18 (46.15%	--
Good	11(28.21%)	2(5.56%)
Fair	----	8(22.22%)
Poor	2(5.13%)	26(72.22%)

6.4.2.7 SUBJECT'S OPINION

At the end of treatment (Day 84), the proportion of subjects in the VigRX Plus group who wished to continue receiving the trial medication, was statistically significantly higher than those in the placebo group.



Graph 6.Subjects opinion. *$p<0.0001$indicates significantly different as compared to placebo, by Chi-square test

7 SAFETY EVALUATION

7.1 EXTENT OF EXPOSURE

96.15% of the study population had a maximum exposure to VigRX Plus at a dose of 2 capsules per day for 84 days. The least exposure to VigRX Plus was for 28 days and occurred in only one subject.

7.2 ADVERSE EVENTS

7.2.1 SUMMARY OF ADVERSE EVENTS

Out of a total of 23 adverse events occurring in the study, 11 were reported from the VigRX Plus group and 12 from placebo group. The most common (7/23) adverse event was fever of mild severity, with the incidence of the event being similar in both study groups. A listing of adverse events by treatment group is displayed in Table 17. One serious adverse event occurred during the entire course of the study. Subject DM05 receiving VigRX Plus suffered from infection due to malarial parasite (Plasmodium Vivax). The event was severe in intensity and led to hospitalization of the subject. Initially reported at the Day 84 visit, the event resolved after a period of eight days on 16.08 09. The investigator withdrew the subject from the study, but did not consider the event as related to the study medication.

Table17. Incidence of adverse events

Group	Subject ID	Description of AE	Severity	Onset	Relation to IP
VigRX Plus					
1	DM02	Pruritus	Mild	Day 28	Probable
2	DM04	Acidity	Mild	Day 28	Probable
3	DM05	Malaria	Severe	Day 84	Not related
4	DM08	Chest Pain	Mild	Day 28	Probable
5	DM11	Fever	Mild	Day 28	Not related
6	DM11	Fever	Mild	Day 84	Not related
7	DM19	Fever	Mild	Day 28	Not related
8	DM19	Bodyache	Mild	Day 28	Not related
9	DM62	Sticky discharge from urine	Mild	Day 84	Possible
10	DM82	Sticky discharge from urine	Moderate	Day 84	Possible

11	DM85	Fever	Mild	Day 1	Not related
Placebo					
12	DM01	Cough and cold	Mild	Day 84	Not related
13	DM03	Fever	Mild	Day 28	Not related
14	DM06	Oedema of both lower extremities	Mild	Day 28	Probable
15	DM09	Cough	Mild	Day 28	Not related
16	DM09	Fever	Mild	Day 28	Not related
17	DM09	Fever	Mild	Day 56	Not related
18	DM09	Cough	Mild	Day 56	Not related
19	DM10	Acidity	Mild	Day 84	Not related
20	DM10	Cough	Mild	Day 84	Not related
21	DM17	Acidity	Moderate	Day 84	Probable
22	DM17	Cold and cough	Mild	Day 84	Not related
23	DM17	Oedema of fingers	Mild	Day 84	Not related

7.3 CLINICAL LABORATORY EVALUATION

7.3.1 VITAL PARAMETERS

Table 18 displays the values for vital parameters assessed at baseline and end of treatment. In both study groups, there was a statistically significant increase of pulse rate as compared to baseline. The increases however were not clinically significant. No other significant changes of vital parameters were observed in any of the study groups.

Table 18. Assessment of vital parameters

	Pulse rate (per min)		**Respiration rate** (per min)		**Systolic blood pressure** (mm Hg)		**Diastolic blood pressure** (mmHg)	
	Baseline	Day84	Baseline	Day84	Baseline	Day84	Baseline	Day84
VigRx Plus (N= 39)	74.82 ± 12.8	78.54* ± 12.04	17.97 ± 2.54	18.21 ± 1.96	120.56 ± 17.46	120.77 ± 13.64	78.62 ± 10.42	79.69 ± 9.64
Placebo (N=39)	75.72 ± 10.46	78.05* ± 9.92	18.41 ± 4.1	18.62 ± 3.3	122.21 ± 13.98	121.44 ± 12.98	79.95 ± 9.82	80.05 ± 9.2

Values of vital parameters are expressed as Mean ± 2SD. * p< 0.05 is significant as compared to baseline by paired - t test.

7.3.2 LABORATORY EVALUATION

7.3.2.1 HAEMATOLOGICAL PARAMETERS

Changes in the values of haematological parameters are displayed in Table 19.

No significant changes were observed in any of the laboratory safety variables in subjects receiving VigRx Plus. In those receiving placebo, a statistically significant change occurred in the Day 84 values of a few laboratory parameters when compared to baseline. Mean eosinophils count increased whereas total RBC count, haemoglobin (Hb), and ESR decreased significantly ($p<0.05$) in the placebo group. These changes however were not of clinical importance.

Table 19. Assessment of laboratory (blood) parameters

	Hemoglobin (g/dl)		**Total RBC** (mill/mul)		**Total WBC** (thou/mul)	
	Baseline	Day 84	Baseline	Day 84	Baseline	Day 84
VigRX Plus (N=36)	14.92±2.52	14.94±2.32	5.10±0.86	5.07±0.76	7.50±3.7	7.14±3.66
Placebo (N=25)	15.31±1.82	14.94±1.88*	5.09±0.92	4.86±1.12*	7.33±3.5	7.11±3.06
	Neutrophils		**Monocytes**		**Eosinophils**	
	Baseline	Day 84	Baseline	Day 84	Baseline	Day 84

VigRX Plus (N=36)	60.33±20.1	58.36±16.94	5.72±4.1	6.11±4.68	4.53±10.24	4.11±6.94
Placebo (N=25)	59.52±22.72	57.96±21.7	4.84±3.44	5.08±3.92	3.56±5.8	5.72±10.28
	Basophils(%)		**Lymphocytes(%)**		**ESR**	
	Baseline	Day 84	Baseline	Day 84	Baseline	Day 84
VigRX Plus (N=36)	0.36±0.98	0.42±1.1	29±17.56	31±14.2	3.92±6.28	3.22±6.12
Placebo (N=25)	0.32±0.96	0.20±0.41	30.32±16.46	31.04±14.92	3.32±2.92	2.80±5.8*
	Serum creatinine(mg/dl)		**Platelet count**		**SGPT**	
	Baseline	Day 84	Baseline	Day 84	Baseline	Day 84
VigRX Plus (N=36)	0.89±0.26	0.90±0.38	255.64±140.76	274.06±121.06	24.72±22.24	26.42±26.72
Placebo (N=25)	0.90±0.3	0.97±0.4	243.43±113.12	250.13±90.06	26.16±20.66	26.40±22.48

Values of laboratory parameters are expressed as Mean ± 2SD. * p< 0.05 is significant as compared to baseline by Wilcoxon signed rank test.

7.3.2.2 URIINE ANALYSIS

There was no incidence of any clinically significant findings in the urine routine tests of both study groups.

7.3.3 ECG RESULTS

No clinically significant abnormalities of ECG were reported in any of the study groups.

7.4 TOLERABILITY

There was no statistically significant difference found between the tolerability of treatment in the two study groups.

Table 20. Assessment of tolerability

Overall assessment of tolerability	**VigRX Plus**	**Placebo**
Very good	31(79.49%)	28(77.78%)
Good	8(20.51%)	5(13.89%)
Fair	---	3(8.33%)

8 DISCUSSION AND CONCLUSION

The present study was designed to evaluate the efficacy and safety of VigRX plus capsules in erectile dysfunction and male sexual health. Erectile dysfunction is known to affect over half of all men between 50 and 70 years of age, and by the age of 40, about 40% of men may suffer from some form of erectile dysfunction[12]. Although the advent of PDE5 inhibitors has revolutionized the medical management of sexual dysfunction, a major limitation to this therapy, along with safety concerns, is the inability to improve sexual desire in men. In this study an attempt was made to address this treatment gap by evaluating the effect of VigRX Plus in male subjects with sexual dysfunction.

Assessment of efficacy was based on patient reported measures; clinician reported measures and laboratory evidence. In combination, these outcome measures aimed at evaluating the various aspects that determine the quality of sexual function in men.

The erectile function domain of international index of erectile function (IIEF) was the primary efficacy parameter of this study. The instrument is widely accepted by regulatory agencies and scientific journals as a valid and reliable measure of sexual functioning in men. Treatment with VigRX Plus for 12 weeks led to enhanced quality of erectile function as evidenced by a statistically significant increase(p=<0.0001) of the IIEF A scores as compared to placebo. The ability to penetrate and maintain erections improved by 58% and 62.82% in the VigRX Plus group and 4.86% and 10.18% in the placebo group.

Improvement in other domains of the international index as assessed by the increase in IIEF B scores, was also statistically significantly higher (p=<0.0001) with VigRX Plus than with placebo. Increases in IIEF scores for sexual desire and intercourse satisfaction were greater in subjects receiving VigRX Plus than in those receiving placebo. While orgasmic function and overall satisfaction enhanced by 22.49% and 61% respectively in VigRX Plus group, the parameters failed to find any improvement in the placebo group.

Overall, the differences in outcomes between the two groups clearly established that

VigRX Plus was superior to placebo in improving the erectile function of men. The findings are consistent with effectiveness of Korean red ginseng in treating ED in randomized controlled trials[13]

Here, it is noteworthy to mention that the improvement of IIEF scores achieved by VigRX Plus are at least comparable, if not equivalent to those reported by Sildenafil in an open label study of twelve weeks[14]. A mean improvement of 60.35% in erectile function with VigRX Plus in this study is comparable with a 66% improvement noted with Sildenafil in the open label study. Further more, in subjects treated with VigRx Plus the increase in sexual desire (47%) was even higher than that reported with Sildenafil (13%) in the same study. Because Sildenafil and other PDE5 inhibitors do not produce but only facilitate erections[15], the effect of VigRX Plus in improving sexual desire is of considerable worth and may prove useful for initiation of sexual stimulation –a critical step in the sexual response cycle of men.

Another important finding of this study was that treatment satisfaction of patients was corroborated by partner evaluations. Female partners of VigRX Plus treated men showed significantly higher levels ($p<0.0001$) of treatment satisfaction (EDITS -partner version) than those of placebo treated men. Since partner satisfaction is considered as one of the important determinants of sexual dysfunction, improved EDITS (patient and partner version) scores with VigRX Plus are predictive of a potential value of VigRX Plus as a long term ED therapy.

The beneficial effect of VigRX Plus was further confirmed as a significantly larger proportion of men elected to continue receiving VigRX Plus after end of the study period. Global efficacy assessment by investigator was also in favour of VigRX Plus.

VigRX Plus did not demonstrate any significant effect on the semen analysis parameters. A possible explanation could be the small number of observations obtained for this parameter due to socio-cultural influences. Considering the favourable effect of VigRX Plus on the spermatogonial cells (unpublished preclinical study) further investigation of VigRX Plus on semen parameters in an adequately sized sample is necessitated.

Sexual disorders in males, especially erectile dysfunction and decreased libido, have often been investigated for their relationship with testosterone- the male hormone. Despite the well-established role of testosterone in enhancing libido, its exact contribution to erections in men remains unclear[16]. VigRX Plus in this study showed an improvement in erectile function scores and a concurrent increase in libido but without any significant change in the serum testosterone levels. It could be therefore inferred upon that effect of VigRX Plus is not due to any testosterone mediated mechanism. Besides, the evidence of a Rho-kinase inhibiting activity in an in vitro assay as mentioned earlier in this report, suggests a potential mechanism for this product and its evaluation in future studies.

Safety of VigRX Plus as demonstrated in this study is desirable in the event of concerns with current pharmacological therapies. Although Sildenafil and other PDE5 inhibitors are effective and well tolerated in the treatment of most patients with ED, patients taking nitrate medications and /or certain alpha-blockers cannot take selected PDE5 inhibitors. With no major adverse effects attributable to VigRX Plus in this study, and no significant difference occurring in the tolerability of treatment between the two groups, VigRXPlus in this study proved to be safe in subjects with sexual dysfunction.

A limitation of this study is that it excluded patients with organic causes and risk factors of ED including vascular disease, diabetes mellitus, hypertension etc. Because most men with ED have an organic cause, the results of this study are not generalizable to a larger ED population. Thus evaluation of VigRx Plus in subjects with an underlying cause of ED is warranted in further studies.

Conclusion

In conclusion, use of VigRX Plus for twelve weeks was significantly better than placebo in improving erectile function in subjects with sexual dysfunction. It was also significantly superior to placebo in improving the other aspects of sexual health such as libido, intercourse satisfaction, orgasmic function and overall satisfaction. The enhancement of sexual function was endorsed by female partners of subjects receiving VigRX Plus. VigRX Plus was safe and well tolerated in subjects with male sexual dysfunction.

9 REFERENCES

1. Alain Gregoire ABC of sexual health BMJ. 1999 January 23; 318(7178): 245–247.
2. Johannes CB, Kleinman KP, McKinlay JB. Journal of Urology. 2000;163 (2):460463. Incidence of erectile dysfunction in men 40 to 69 years old: longitudinal results from the Massachusetts Male Aging study
3. Segraves RT. CNS Spectr. 2003 Mar;8(3):225-9.Pharmacologic management of sexual dysfunction: benefits and limitations
4. Leiblum SR. After sildenafil: bridging the gap between pharmacologic treatment and satisfying sexual relationships. J Clin Psychiatry. 2002;63 Suppl 5:17-22; discussion 23-5).
5. Peter H.C. Lim, P. Moorthy, Kenneth G.F.Benton. The Clinical Safety of Viagra. Annals of the New York Academy of Sciences Volume 962 Issue Nitric Oxide: Novel sections, deleterious effects, and clinical potential. Pages 378 – 388.
6. Helen V Danesh-Meyer, Leonard A Levin, Erectile dysfunction drugs and risk of anterior ischaemic optic neuropathy: casual or causal association? Br J Ophthalmol 2007;91:1551-1555.
7. Y. Smitasiri, P. D'Souza, J. Neal-Kababick, A. G. Schauss. The Open Natural Products Journal 2010,pp.10-19 (10) Volume 3, ISSN:1874-8481
8. R.Rosen, A.Riley, G.Wagner, I.Osterloh, J.Kirkpatrick, A.Mishra. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction.*Urology*, Volume 49, Issue 6, Pages 822-830
9. Althof et al .EDITS Development of questionnaires for evaluating satisfaction with treatments for erectile dysfunction. UROLOGY ***53*** *(4), 1999*
10. T Mostafa, *International Journal of Impotence Research* 20, 530-536 (November/December 2008)
11. R C Rosen, J C Cappelleri and N Gendrano III The International Index of Erectile Function (IIEF): a state-of-the-science review International Journal of Impotence Research August 2002, Volume 14, Number 4, Pages 226-244

12. Jacob Rajfer, MD, Thomas Magee, PhD, and Nestor Gonzalez-Cadavid, PhD Future Strategies for Treating Erectile Dysfunction Rev Urol. 2002; 4(Suppl 3): S48–S53
13. Dai-Ja Jang, Myeong Soo Lee, Byung-Cheul Shin,Young-Cheoul Lee, and Edzard Ernst, Br J Clin Pharmacol. 2008 October; 66(4): 444–450. Red ginseng for treating erectile dysfunction: a systematic review
14. Leonard S. Marks, Catherine Duda, Frederick J Dorey, Maria Luz Macairan, and Paul Bryan Santos.Treatment of erectile dysfunction with Sildenafil. Urology 53 (1), 1999.
15. .Culley C. Carson, MD *Psychosomatic Medicine* 66:664-671 (2004) Erectile Dysfunction: Evaluation and New Treatment Options
16. Mikhail N. Does testosterone have a role in erectile function? Am J Med. 2006 May;119 (5):373-82.

10 APPENDICES

10.1 STUDY INFORMATION

10.1.1 LIST OF CONCOMITANT MEDICATIONS PROHIBITED

Medications know to cause Male Sexual Dysfunction such as:

Antihypertensives & Diuretics:
Hydrochlorothiazide, Furosemide, Bumetanide, Methyldopa, Clonidine, Guanabenz, Guanfacine,Verapamil, Nifedipine, Hydralazine, Enalapril, Lisinopril, Metoprolol, Propranolol, Atenolol, Losartan,Spironolactone etc
Antidepressants, anti-anxiety drugs and antiepileptic drugs
Fluoxetine, Sertraline, Amitriptyline, Amoxipine, Clomipramine, Nortriptyline Phenelzine, Chlordiazepoxide, Clorazepate, Diazepam, Imipramine, Lorazepam, Oxazepam, Phenytoin.
Antihistamines
Diphenhydramine, Hydroxyzine, Meclizine, Promethazine Non-steroidal anti-inflammatory drugs
Naproxen, Indomethacin
Parkinson's disease medications
Biperiden, Benztropine, Trihexyphenidyl, Procyclidine, Bromocriptine, Levodopa
Antiarrythmics :Digoxin
Disopyramide (Norpace)
Histamine H_2-receptor antagonists Cimetidine, Nizatidine OHA- Pioglitazone Anti-androgens (ketoconazole, spironolactone)

10.1.2 DEFINITION OF SERIOUS ADVERSE EVENT

A serious adverse is defined as an adverse event which:

- results in death
- is life threatening
- requires in patient hospitalization or prolongation of hospitalization
- results in permanent or persistently significant disability
- is a congenital anomaly or birth defect

10.1.3 IIEF QUESTIONNAIRE

	Question	Response	Points

Erectile function			
	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 time)	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 time)	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 time)	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 your erection after you had penetrated (entered) 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 time)	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
		very high	5
Intercourse Satisfaction			
7	How many times have you attempted sexual intercourse?	no attempts	0
		1-2 attempts	1
		3-4 attempts	2
		5-6 attempts	3
		7-10 attempts	4
		>= 11 attempts	5
8		did not attempt intercourse	0
		almost never or never	1

	When you attempted sexual intercourse, how often was it satisfactory for you?	a few times (much less than half the time)	2
		sometimes (about half the time)	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
Orgasmic Function			
	10 When you had sexual intercourse, how often did you never ejaculate?	no sexual stimulation or intercourse	0
		simulation or almost never or	1
		a few times (much less than half the time)	2
		sometimes (about half the time)	3
		most times (much more than half the time)	4
		almost always or always	5
	11 When you had sexual intercourse, how often did you or never the feeling of orgasm or climax?	no sexual stimulation or intercourse	0
		stimulation or have almost never	1
		a few times (much less than half the time)	2
		sometimes (about half the time)	3
		most times (much more than half the time)	4
		almost always or always	5
Sexual Desire			
	12 How often have you felt sexual desire? a few times (much less	almost never or never	1
		than half the time)	2
		sometimes (about half the time)	3
		most times (much more than half the time)	4
		almost always or always	5
	13 How would you rate your level of sexual desire? low	very low or none at all	1
			2

		moderate	3
		high	4
		very high	5
Overall Satisfaction			
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

10.2 TABLES REFERRED TO BUT NOT INCLUDED IN THE TEXT

10.2.1 PROTOCOL DEVIATIONS

Subject No	**Reason for deviation**
Dr. Gaurang Shah	
DM06& DM07	IP not returned on Day 28 visit
DM10	IP not returned on Day 28 visit
DM01,DM05,DM07,DM59,DM60 and DM61	Extended washout period
DM01, DM04, DM07 and DM62	Delay in laboratory testing and Semen analysis
DM08	The subjects IP compliance calculation was 75 % when calculated at Day 84
DM09	IP not returned on Day 56 visit
DM62	IP not returned on Day 28 visit
DM03	ECG and Semen Analysis not performed
DM05	Delay in laboratory testing for Day 84 visit was by more than 15 days
DM05	ECG and Semen analysis not performed
DM06	Laboratory testing not performed for Day 84 visit
DM07	ECG report of Day 84 is lost from the site and thus no ECG reporting is mentioned in the CRF

DM08	Semen Analysis not done for the subject
DM10	IP compliance as 73.80% for Day 84 visit
DM60	IP compliance as 75.64% when calculated on Day 84 visit
DM10, DM60 and DM61	Laboratory testing not performed for Day 84 visit
DM59	ECG and Semen Analysis not performed
Dr. Manoj Chaudhari	
DM31	Subject enrolled in the study with out of normal range TSH levels. Accepted Lower limit – 0.245 units. Subject value – 0.24 units.
DM31	Subject unable to give semen sample even after repeated attempts.
DM32	Semen analysis not performed
DM22, DM24, DM31, DM32,DM88 and DM47, DM57, DM67 and DM68.	Semen analysis not performed.
Dr. Patankar	
DM50	IP not returned on day 28 visit.
DM50	Delay in Laboratory evaluation
DM50	IP not returned
DM51	Delay in Laboratory evaluation
Dr. Pensalwar	
DM19	IP not returned on day 28 visit
DM17, DM19, DM20, DM80, DM84	IP not returned on day 28 visit
DM15	IP not returned on day 56 visit
DM11 and DM12	Day 84 visit delayed by 12 days
DM19, DM20, DM80 and DM84.	IP not returned on day 28 visit
DM16	Subject reported 13 days early for Day 28 visit
Dr. Sable	
DM036,DM037	Extended wash out period

DM042	Extended wash out period
DM40,DM42	IP not returned on day 28 visit
DM45	IP not returned on day 28 visit
DM38. DM41, DM42, DM43, DM44.	Laboratory testing was not done within +3 or -3 days of scheduled visit.
DM45	Laboratory testing for Day 84 visit

10.2.2 LISTING OF PATIENTS RECEIVING INVESTIGATIONAL PRODUCT

ID	Initials
DM02	RDS
DM04	TSP
DM05	RSC
DM08	ASS
DM11	SMS
DM12	PMV
DM13	SAS
DM14	MFS
DM18	DNK
DM19	VBK
DM21	RCT
DM23	SNR
DM25	MMT
DM28	AMP
DM30	PKP
DM31	RRW
DM33	CKR
DM39	ADB
DM40	MUM
DM41	NBG
DM42	RBB
DM46	NMM
DM49	HPM
DM54	NJP
DM57	UAK
DM59	IFG
DM62	DBG
DM64	DGP
DM67	SSN
DM68	SDL
DM70	AKG
DM71	YVZ
DM74	PVM
DM80	JBC

DM81	SAW
DM82	SRM
DM85	MRJ
DM88	SSK
DM90	DEP

10.3 PRE-EXISTING CONDITION/CONCOMITANT MEDICATION USED IN THE STUDY

ID	Initials	Concomitant Medication (CM)	CM Dose	CM Start Date	CM End Date	CM Indication
DM03	PMS	Paracetamol	500 mg bd	7/2/2009	10-07-2009	Fever
DM06	TCV	Diclofenac gel	Twice a day	12/26/2008	Ongoing	Backache
DM10	BKG	Pentamazole	150 mg OD	10/4/2009	10-10-2009	Acidity
		Tab Cetrizine	50 mg O.D.	10/9/2009	Ongoing	Cough
DM11	SMS	Tab-Paracetamol	500 mg B.D.	7/16/2009	17-07-2009	Fever
		Tab-Diclofenac	100 mg	9/30/2009	01-10-2009	Fever
DM17	JBC	Pentaprazole	100 mg BD	10/13/2009	22-10-2009	Acidity
DM19	VBK	Paracetamol	500 mg BD	8/18/2009	21-08-2009	Fever
		Diclofenac	50 mg B.D.	8/18/2009	21-08-2009	Body pain
DM84	SRK	Pentaprazole	100 mg OD	11/1/2009	Ongoing	Acidity
DM85	MRJ	Paracetamol	500 mg	8/10/2009	13-08-2009	Fever

Note: The term 'ongoing' in the above table refers to pre-existing conditions