CLINICAL STUDY PROTOCOL

Sponsor's Reference Number: FM57

EudraCT Number: 2017-000960-14

TITLE:	A Phase III, dose-ranging, multi-centre, randomised, double-blind, placebo-controlled, home use, parallel group clinical trial of topically-applied glyceryl trinitrate (GTN) for the treatment of erectile dysfunction (ED) with an open label extension
PHASE:	Phase III
DRUG:	MED2005
SPONSOR:	Futura Medical Developments Ltd. Surrey Technology Centre 40 Occam Road Guildford Surrey, GU2 7YG, UK Telephone: +44 (0)1483 685670 Fax: 44 (0)1483 685671
CHIEF INVESTIGATOR:	Dr Rupert Mason
Protocol Version and Date:	Version 7.0 27 July 2018

Information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical/regulatory review of the study, without written authorisation from Futura Medical Developments Ltd (hereinafter known as FMD).

1. PROTOCOL APPROVAL SIGNATURES

Version 7.0, dated 27 July 2018

Sponsor's Approval

This protocol has been approved by Futura Medical Developments Ltd.

Sponsor's Signatories:

Tim Holland, Clinical Development Director, Futura Medical Developments Ltd

Signature: _____ **Date:** _____

Consultant Statistician, Dr Paul Terrill, Cytel

Signature: _____ **Date:** _____

Medical Advisor:
Dr Rupert Mason, Futura Medical Developments Ltd

Signature: _____ **Date:** _____

Investigator's Agreement:

I have read this FMD Protocol No. FM57

A Phase III, dose-ranging, multi-centre, randomised, double-blind, placebo-controlled, home use, parallel group clinical trial of topically-applied glyceryl trinitrate (GTN) for the treatment of erectile dysfunction (ED) with an open label extension

I have fully discussed the objectives of this study and the contents of this protocol with FMD (the Sponsor).

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical/regulatory review of the study, without written authorisation from FMD. It is, however, permissible to provide information to a subject in order to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and with the applicable regulatory requirements.

I understand that FMD may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to FMD.

Principal Investigator:

Printed Name: _____ _____

Signature: _____ **Date:** _____

2. STUDY PERSONNEL

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For complete study administrative structure, see the relevant Sponsor's file. Where applicable, administrative changes are to be documented in the Sponsor's file without requiring formal protocol amendment.

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4. LIST OF ABBREVIATIONS

Abbreviation	Explanation
ABPI	Association of British Pharmaceutical Industry
ACE	Angiotensin Converting Enzyme
ADR	Adverse Drug Reaction
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BP	Blood Pressure
CI	Chief Investigator
CK	Creatine Kinase
C_{max}	Maximum plasma concentration
CRO	Clinical Research Organisation
CRP	C-reactive Protein
CSR	Clinical Study Report
DHP	Data Handling Plan
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	electronic Case Report Form
ED	Erectile Dysfunction
EF	Erectile Function
ePRO	electronic Patient-Reported Outcomes
EU	European Union
FAS	Full Analysis Set
FMD	Futura Medical Developments Ltd
GAQ	Global Assessment Questionnaire
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transpeptidase
GMP	Good Manufacturing Practice
GTN	Glyceryl Trinitrate
HBc	Hepatitis B Core antibodies
HbsAG	Hepatitis B Surface Antigen

HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HR	Heart Rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IIEF	International Index for Erectile Function
IMP	Investigational Medicinal Product
IP	Inorganic Phosphate
IUD	Intrauterine Device
IUS	Intrauterine System
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LDH	Lactate Dehydrogenase
LS	Least-Squares
MCID	Minimal Clinically Important Difference
MedDRA	Medical Dictionary for Regulatory Activities
MNAR	Missing Not At Random
NIH	National Institutes of Health
NO	Nitric Oxide
NSAID	Non-Steroidal Anti-Inflammatory Drug
OLAS	Open-Label Analysis Set
PD	Pharmacodynamic
PDE-5	Phosphodiesterase type 5
PGE 1	Prostaglandin E1
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PI	Principal Investigator
PK	Pharmacokinetic
PP	Per Protocol
PT	Preferred Term
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person

ROC	Receiver Operating Characteristics
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SEAR	Self-Esteem And Relationship questionnaire
SEP	Sexual Encounter Profile
SOC	System Organ Class
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
$T_{1/2}$	Terminal elimination half-life
T_{max}	Time to reach C_{max}
TMF	Trial Master File
ULN	Upper Limit of Normal
US	United States
w/w	Weight in weight

5. STUDY SYNOPSIS

Protocol Ref: FM57	**Study Product:** MED2005

Title of the Study:

A Phase III, dose-ranging, multi-centre, randomised, double-blind, placebo-controlled, home use, parallel group clinical trial of topically-applied glyceryl trinitrate (GTN) for the treatment of erectile dysfunction (ED) with an open label extension

Chief Investigator:

Dr Rupert Mason

Sites:

Approximately 50 investigational sites in countries including Poland, Hungary, Czech Republic, Slovakia, Georgia, Russia, Ukraine, Bulgaria and Latvia.

Study Period (planned):	**Clinical Phase:**
2018–2020	III

Objectives:

Primary Objective

- To demonstrate the efficacy of MED2005 versus placebo in male subjects clinically diagnosed with ED using the erectile function (EF) domain of the International Index for Erectile Function (IIEF), the Sexual Encounter Profile (SEP) Question 2 and the SEP Question 3. The primary objective will be addressed by estimating the following estimand: difference between treatment policies (each MED2005 dose versus placebo) in all subjects who met the study inclusion/exclusion criteria and who were randomised and attempted intercourse post-randomisation at least once, assessed via the change compared to baseline in EF [IIEF-EF], the ability to achieve vaginal penetration [SEP Question 2] and the ability to have successful intercourse [SEP Question 3] over 12 weeks of treatment

Secondary Objectives

- To evaluate the efficacy of MED2005 in male subjects using the Self-Esteem And Relationship (SEAR) questionnaire for men and women, the Global Assessment Questionnaire (GAQ), the additional domains of the IIEF, the Patient Global Impression of Severity (PGI-S), the Patient Global Impression of Change (PGI-C) as well as subjective measures of the time of onset and duration of action (erection) & erection hardness and questions on usage and application of MED2005
- To evaluate the long-term (up to 12 months) efficacy of MED2005
- To evaluate the safety of MED2005 using adverse events (AEs) and standard physico-chemical assessments

Study Design:

A Phase III, dose-ranging, multi-centre, randomised, double-blind, placebo-controlled, home use, parallel group clinical study to evaluate the efficacy and safety of MED2005, a topically applied GTN gel for the treatment of ED. The study will include a screening period, a double-blind phase and an open-label extension phase.

Screening Period: Subjects will be screened for eligibility during a screening period between Day –43 and Day –1. The IIEF questionnaire will be completed by the subject at the start of the screening period at the first site visit (Visit 1) and the EF domain of the IIEF (IIEF-EF; i.e. Questions 1–5 and 15) will be used to determine pre-screening eligibility of the subject. A score of ≤ 25 will be acceptable for inclusion in the screening period of the study. Both the male subject and his female partner will be required to attend Visit 1. Subject and partner training in the use of questionnaires and IMP application will be given at this visit.

During the screening period, subjects and their partners are required to make a minimum of four attempts at sexual intercourse within a 4-week period (without treatment). They will be asked to complete questionnaires to record their experiences after each sexual intercourse attempt (using the SEP [male subjects and their female partners]) and at the end of the 4-week period (using the IIEF and PGI-S [male subjects only] and SEAR [male subjects and their female partners]) according to a prescribed schedule of questionnaires. Subjects who cannot comply with the minimum number of intercourse attempts or who exceed 25 on the IIEF-EF at the end of the screening period will be excluded from the study.

Double-Blind Phase: Eligible subjects will participate in the double-blind phase, comprising a 12-week treatment period (Visits 2, 3, 4 and 5) and a 1-week follow-up visit (Visit 6). The subject and his female partner will be required to attend Visit 2 at the start of the double-blind phase.

During the treatment period subjects will be randomly allocated to receive placebo or one of three doses of MED2005 (0.6 mg GTN, 1.2 mg GTN, 1.8 mg GTN). Subjects will be divided into sub-groups based on their baseline ED severity scores (from the end of the screening period): mild (IIEF-EF domain score of 17–25), moderate (IIEF-EF 11–16) or severe (IIEF-EF ≤ 10). The number of subjects in each of the three baseline ED severity groups will be monitored during the trial in order to have approximately equal numbers in each group.

At home, subjects or their partners should apply the investigational medicinal product (IMP) immediately prior to sexual intercourse and make at least four intercourse attempts in each of the three 4-weekly periods during treatment (Weeks 1–4, 5–8 and 9–12). The subjects and their partners will be asked to complete questionnaires using electronic patient-reported outcomes (ePRO) to record their experiences after each sexual intercourse attempt (using the SEP questionnaire and the onset and duration of action [erection] and erection hardness questions at home [male subjects and their female partners]), and at the end of each of the three 4-week periods during treatment (using the IIEF, PGI-S and PGI-C questionnaires [male subjects only], and the SEAR and GAQ questionnaires [male subjects and their female partners]; to be completed at site visits for subjects and at home for their partners if preferred).

Subjects and their female partners will be monitored for AEs by being asked to complete 4-week diaries at home of untoward signs and symptoms as they experience them (i.e. in real time) throughout the duration of the double-blind phase of the study (from signing of informed consent until the follow-up assessment at Visit 6). The diaries will be reviewed at each study visit.

Subjects will be asked to return to the study site at the end of each of the three 4-week (± 1 week) periods during treatment (i.e. at Visits 3, 4 and 5) to return used and unused IMP, to enable the clinical staff to check compliance and to assess subject health status, including assessment of any AEs and recording concomitant medications. These visits will be optional for the female partners. Subjects and their female partners will be required to attend a follow-up visit (Visit 6) 7 days (± 2 days) after the Week 12 visit (Visit 5).

At the end of the double-blind phase, during Visit 6, subjects and their female partners will be invited to take part in the open-label extension phase at the 0.6% MED2005 (1.8 mg GTN) dose level. Participation in the extension phase will be at the discretion of the individual subject and his partner and if there are still available places. Recruitment will continue until approximately 450 subjects and their female partners have consented. The remaining subjects will be discharged from the study.

Open-Label Extension Phase: The open-label extension phase will comprise 12-months treatment for eligible subjects, with visits every 3 months. For each 3-month period subjects will be dispensed 12 tubes per month (36 tubes at each visit) to allow them to use the tubes as they require. Male subjects will be asked to complete the SEP questionnaire to record their experiences after each sexual intercourse attempt as and when they occur. At each site visit male subjects will be asked to complete the IIEF questionnaire to cover the previous 1 month. Subjects and their female partners will be monitored for AEs by completing diaries of untoward signs and symptoms as they experience them (i.e. in real time) throughout the duration of the open-label extension phase.

Once they have entered the open-term extension phase, male subjects will be asked to return to the study site every 3 months (at Day 180 [Visit 7], Day 270 [Visit 8], Day 360 [Visit 9] and Day 450 [Visit 10]) to enable the clinical staff to check AEs and concomitant medications (in the diaries), SEP questionnaire completed after each intercourse attempt to cover each 3-month period, IIEF to cover previous 1-month period and compliance on IMP usage. Vital signs and a penis examination will be undertaken at each 90 day visit. An electrocardiogram (ECG) will be done at 12 months (Day 450). Visits during the open-label extension phase will be optional for the female partners.

Number of Subjects:

Double-Blind Phase: It is planned to randomise and treat 250 male subjects for each of the four treatment groups, clinically diagnosed with ED, and their female partners (total N = 1000).

Open-Label Extension Phase: It is planned to include a total of 450 male subjects who have completed the double-blind phase of the study, and their female partners.

Diagnosis and Main Criteria for Admission:

Double-Blind Phase: Male subjects aged 18–70 years with a confirmed clinical diagnosis of ED for more than 3 months (according to the National Institutes of Health Consensus Statement 'the inability to achieve or maintain penile erection sufficient for satisfactory sexual performance at least once'), verified by the IIEF-EF domain (a score of ≤ 25 points at the end of the screening period) and involved in a continuous heterosexual relationship with their partner for at least 6 months.

Exclusion criteria include: any significant cardiovascular, pulmonary, hepatic, renal, gastrointestinal, haematological, endocrinological, metabolic, neurological or psychiatric disease; any history of an unstable medical or psychiatric condition or using any medication that, in the opinion of the Principal Investigator (PI), is likely to affect the subject's ability to complete the study or precludes the subject's participation in the study.

Open-Label Extension Phase: Subjects who complete the double-blind phase, were compliant to study procedures and who consent to the open-label extension phase.

Exclusion criteria include: Subsequent to recruitment into the double-blind phase of the study, the development of any significant or serious cardiovascular, pulmonary, hepatic, renal, gastrointestinal, haematological, endocrinological, metabolic, neurological or psychiatric disease which, in the opinion of the PI, renders the subject unfit to continue in the open-label extension phase of the study.

Study Treatments and Mode of Administration:

Double-Blind Phase: Subjects will be randomly allocated in a 1:1:1:1 ratio to receive one of the following gel treatments according to a parallel group design (i.e. subjects will receive one treatment only):

- MED2005 0.2% (w/w) GTN gel to deliver a 0.6 mg dose of GTN
- MED2005 0.4% (w/w) GTN gel to deliver a 1.2 mg dose of GTN
- MED2005 0.6% (w/w) GTN gel to deliver a 1.8 mg dose of GTN
- Placebo vehicle

Randomisation will be carried out on Day 1 of the treatment period of the double-blind phase (Visit 2) according to an interactive voice/web response system (IVRS/IWRS), stratified by baseline ED severity. No stratification by site will be done. During the treatment period, the subjects or their partners will be required to topically apply a single dose (approximately 300 mg) to the glans of the penis and rub in for at least 15 seconds (to ensure thorough distribution of the gel and promote penetration of the active substance) immediately prior to sexual intercourse. Subjects will be asked to leave a washout period of at least 12 hours before the next attempt at sexual intercourse using the IMP gel.

Open-Label Extension Phase: All subjects will receive treatment with MED2005 0.6% (w/w) GTN gel to deliver a 1.8 mg (0.6%) dose of GTN. The gel is to be used as described above for the double-blind phase.

Reference Treatment and Mode of Administration:

Placebo vehicle gel, identical in appearance to the three active MED2005 gels. The placebo gel will be administered as a single dose in the same way and at the same volume as MED2005.

Duration of Treatment:

Double-Blind Phase: Eligible subjects will participate in a 12-week treatment period (Visits 2, 3, 4 and 5) and a 1-week follow-up visit (Visit 6). Subjects will be asked to apply the IMP immediately prior to sexual intercourse and to make at least four intercourse attempts in each of the three 4-weekly periods during treatment (Weeks 1–4, 5–8 and 9–12).

Open-Label Extension Phase: Eligible subjects will participate for a further 360 days of treatment (Visits 7, 8, 9 and 10). Subjects will use the IMP immediately prior to sexual intercourse as they require.

Criteria for Evaluation:

Efficacy Assessments:

Efficacy will be evaluated using questionnaires (IIEF, SEP, SEAR, GAQ, PGI-S, PGI-C) as well as subjective measures of time of onset and duration of action (erection) and erection hardness. The co-primary efficacy outcomes will be the IIEF-EF domain, SEP Question 2 and SEP Question 3, completed by the male subjects. Information on usage and application of the gels will be evaluated.

Safety Assessments:

Safety will be evaluated throughout the double-blind phase using standard assessments including physical examinations and visual examination of the penis, vital signs (blood pressure [BP], heart rate [HR], body temperature), standard clinical laboratory safety tests (haematology, biochemistry, urinalysis), 12-lead ECGs and monitoring of AEs and concomitant medications with paper diaries (potential partner AEs will be captured at site visits or by telephone). Safety will be evaluated throughout the open-label extension phase by monitoring of AEs and concomitant medications with paper diaries (potential partner AEs will be captured at site visits or by telephone), monitoring of vital signs, ECGs, and visual examination of the penis.

Statistical Methods:

In general, safety and efficacy variables will be presented by means of descriptive statistics and figures, as appropriate, by treatment (active at each dose level and placebo) and by time point and gender, if applicable.

A Bonferroni correction will be used to take into account that there are three active versus placebo comparisons; i.e. all p-values resulting from comparing the three different MED2005 doses (0.6 mg GTN, 1.2 mg GTN, 1.8 mg GTN) versus placebo will be multiplied by three and statistical significance will then be declared if $p < 0.05$. Corresponding Bonferroni corrected 95% confidence intervals will be produced.

Efficacy Analyses:

Double-Blind Phase: Primary and secondary analyses will be performed on the Full Analysis Set (FAS; all randomised subjects who used medication at least once).

The co-primary efficacy endpoints, assessed in the male subjects, are:

- The change from baseline of the average of the Week 4, Week 8 and Week 12 IIEF-EF domain scores
- The change in percentage of sexual intercourse attempts in which subjects were able to insert their penis into their partner's vagina (SEP Question 2) between baseline and the 12 week treatment period
- The change in percentage of sexual intercourse attempts in which subjects were able to maintain an erection of sufficient duration to have successful intercourse (SEP Question 3) between baseline and the 12 week treatment period

The primary objective will be assessed by testing hypotheses for each MED2005 group (0.6 mg GTN, 1.2 mg GTN or 1.8 mg GTN) separately. The basic statistical model for the primary analysis for all three co-primary endpoints is an analysis of covariance (ANCOVA) including terms for treatment group, site and baseline (as a continuous variable). Baseline ED severity (mild, moderate or severe, based on Visit 2 IIEF-EF) will be included in the analysis of the SEP questions, and will be included in the analysis of IIEF-EF as a sensitivity analysis. The estimated treatment means and differences (MED2005 versus placebo) will be reported as part of this analysis. The objective is for all co-primary endpoints to show superiority of MED2005 to placebo in order to conclude a significant result. No adjustment for multiplicity of the error probability for the individual co-primary endpoints is required. However, the three co-primary endpoints will still be considered in a hierarchy of their importance: IIEF-EF domain, SEP Question 3 and SEP Question 2.

The following secondary efficacy analyses will be performed in a supportive way to describe the effect of treatment:

- The analysis of the three co-primary endpoints will be repeated in the three pre-specified subgroups of ED severity: mild, moderate and severe
- The change in the IIEF-EF domain, SEP Question 2 and SEP Question 3 at each 4-week visit will be analysed
- Responder analyses assessing the proportion of subjects with a specific increase in the IIEF-EF domain from baseline, using a different responder definition defined separately for each baseline severity group
- Responder analyses for SEP Questions 2 and 3 will be conducted in the same way as for the IIEF-EF
- Responder analyses will also be conducted using responder thresholds (that represent meaningful within-patient changes) in the three co-primary endpoints that are determined using anchor-based methods. The thresholds will be defined using a suitable set of data from this study prior to study unblinding.

The following secondary efficacy analyses will be conducted in a more exploratory way:

- The GAQ will be analysed via logistic regression including terms for treatment group, site and baseline ED severity (categorical variable)
- The change in the other domains of the IIEF questionnaire, the other SEP questions (Questions 1, 4 and 5), the overall SEAR questionnaire score, the scores in the two subdomains of the SEAR questionnaire (sexual relationship satisfaction and confidence), the PGI-S at time points 4, 8 and 12 weeks will be analysed using ANCOVA as described for the primary endpoint analysis. The PGI-C will be analysed using an analysis of variance (ANOVA)
- Subjective measures of the time of onset and duration of action (erection) and erection hardness will be analysed using an ANCOVA model fitted to the average of Wilcoxon Rank Scores
- Usage and application question responses will be summarised by treatment group

All efficacy assessments provided by the female partners will be analysed using the same statistical models as for the male subjects.

Open-Label Extension Phase: Efficacy assessments will be summarised, including (where applicable) changes from baseline, where the baseline assessments are the ones prior to the double-blind phase.

Safety Analyses

Summary statistics will be presented for scheduled assessments and change from baseline for vital signs, ECGs and clinical laboratory safety tests.

Dosing duration and frequency will be summarised.

AEs will be listed by system organ class (SOC) and preferred term (PT) classifications assigned to the event using the Medical Dictionary for Regulatory Activities (MedDRA; Version 20.1 or higher). The number of AEs and number (and %) of subjects with AEs will be summarised by SOC and PT. In addition, AEs will be summarised by severity, relationship to treatment, time to onset (from the last dose of IMP prior to AE start date) and duration (offset).

Listings will be presented of serious adverse events (SAEs) and AEs leading to withdrawal.

6. INTRODUCTION

6.1 Background

Erectile dysfunction (ED) is a chronic condition affecting male sexual function and has a significant health economic impact worldwide. It has been surmised that if all men in the United States (US) sought care for ED, the cost of treatment in the US alone would reach $15 billion [1]. Although it can affect all age groups, the frequency of ED increases with age. The probability of ED triples from 5% in men aged 40 years to 15% in men aged 70 years [2]. A recent study which evaluated ED in men aged 40–79 years suggested that the prevalence of ED was highest in men aged 70 years or older [3]. When adjusted for age, patients with cardiovascular disease and diabetes have an increased risk of ED [4]. Given the increase in life expectancy across the western world coupled with higher frequencies of cardiovascular disease and diabetes, it is predicted that by 2025 the global prevalence of ED will be approximately 322 million, which could contribute to a significant cost burden on healthcare systems [5].

ED is a multi-factorial condition with a treatment trajectory compounded because aging men are often affected with several diseases, leading to polypharmacy and treatment regimens that could potentially worsen the ED. According to the National Institutes of Health (NIH) Consensus Development Conference, ED can be defined as 'the persistent inability to achieve or maintain penile erection sufficient for satisfactory sexual performance' [6]. In view of this definition, the NIH also recommends the use of 'erectile dysfunction' as the agreed term instead of 'impotence'.

The treatment of ED usually follows a circuitous route. Erectile function (EF) involves a complex coordination of physiological processes and as such the management of ED reflects this complexity. Evidence suggests that 80% of ED cases are of organic origin [6]. These organic causes are diverse and include, but are not limited to, vascular disorders (such as cardiovascular disease, hypertension), iatrogenic factors (such as hormonal agents, beta-blockers), penile injury/anatomic abnormalities (such as Peyronie's disease, priapism) and endocrine disorders (such as diabetes, hypogonadism). The most frequent organic causes of ED are thought to be vascular in origin and patients frequently present with decreased blood flow to the penis owing to cardiovascular disease [7]. Many cases of ED are characterised as 'vascular' indicating a correlation with cardiovascular risk factors and events [8].

Usually, first-line therapies for the treatment of ED are lifestyle changes (exercise and weight loss) and modifications to risk factors [9], followed by treatment with oral phosphodiesterase type 5 (PDE-5) inhibitors such as sildenafil, tadalafil or vardenafil [10]. Other treatments such as intracavernosal injections [11] and intraurethral suppositories have been used previously; however, these treatments are frequently associated with adverse events (AEs) such as local pain and priapism and poor compliance owing to their invasive nature [12]. Topical prostaglandin E1 (PGE 1) has been used for the treatment of ED [13]. In one study, the treatment was safe, well-tolerated and significantly increased penile blood flow in 8 patients. The treatment has gained popularity owing to its ease of use [14], and the topical administration of alprostadil (a synthetic form of PGE 1) is licensed for the treatment of ED in men aged ≥ 18 years [15]. Owing to their less invasive routes of administration and ease of use, topical therapies approved for other indications have been explored as alternative candidates for the treatment of ED.

Although PDE-5 inhibitors are widely used in ED and their side-effects have been well documented, all PDE-5 drugs are contraindicated in patients taking nitrates (such as glyceryl

trinitrate [GTN], a potent smooth muscle vasodilator) for cardiovascular disease. From an epidemiological perspective this fact has broader implications given the putative link between ED and cardiovascular disease in the elderly.

The vasodilator GTN is a well-known and well documented therapeutic agent. GTN has established clinical use for the prophylaxis of angina. It is usually administered inter-nasally, orally or sublingually as short- or long-acting tablets and sprays, or transdermally via patches or topical ointments. Clinical data for nitric oxide (NO) donors and their impact on ED is less extensive compared with PDE-5 inhibitors; however, available evidence suggests that NO donors, for example topically applied GTN, might be a potentially useful approach to the management of sexual dysfunction [16]. Topical GTN is also licensed for the treatment of anal fissure.

The first case of an organic nitrate improving ED was reported in 1977 in a patient taking sublingual GTN. Since then, several studies have shown that GTN (either as a topical ointment at concentrations ranging from 2 to 10%, or as a topical plaster) is effective in increasing penile tumescence in patients with organic, psychogenic or mixed ED with no significant differences between ED subtypes [17]. Whilst so far there is little empirical evidence on the effect of topical GTN on ED, one study has shown that topical application of a cream containing the NO donor, isorbide dinitrate, is efficacious [18]. In a randomised, double-blind, placebo-controlled study, 21 out of 36 men with ED reported full erection and satisfactory intercourse after 1 week of treatment with an active cream containing aminophylline 3%, isosorbide dinitrate 0.25% and co-dergocrine mesylate 0.05% versus placebo. There were no cases of priapism or significant AEs, and none of the 21 subjects reported complaints from their partner.

6.2 Rationale for Conducting Study

In light of the recent literature, Futura Medical Developments Ltd (FMD) are developing a gel formulation of GTN (MED2005) as a topical treatment for ED delivered using DermaSys®, a versatile and bespoke technology. Of particular interest are subjects who are currently taking chronic oral nitrate therapy, for whom the use of oral PDE-5s are contraindicated.

FMD has conducted three Phase I, dose-ranging clinical studies with MED2005: a pharmacokinetic (PK) study (Study FM33), a pharmacodynamic (PD) study (FM35), which used penile blood flow changes as a surrogate marker of efficacy; a second PK study (Study FM58) and one Phase IIa study in male subjects clinically diagnosed with ED (Study FM53). In view of the results of these studies (see Section 6.3 below), FMD is further developing MED2005 for the intended treatment of ED in male subjects

6.3 Clinical Studies with MED2005

For further details of the clinical studies carried out with MED2005, please refer to the current version of the FMD MED2005 Clinical Investigator's Brochure (IB).

6.3.1 Pharmacokinetics

The Phase I PK study (FM33) demonstrated a dose-response relationship with regard to plasma levels of GTN in 16 healthy male volunteers. The time to reach the maximum plasma concentration (t_{max}) ranged between 6.5 and 9.0 minutes, and the terminal elimination half-life ($t_{1/2}$) was approximately 4 minutes. The second Phase 1 PK study (FM58 PK), the CSR for which has yet to be finalised, demonstrated a dose response relationship with regards to plasma levels in 30 healthy male volunteers. The t_{max} ranged between 10-12 minutes. The data

suggested that MED2005 doses in the range of 0.2%-0.6% may be optimum for further efficacy and safety studies.

6.3.2 Pharmacodynamics

The Phase I volunteer study (FM35) has shown evidence of PD effects supportive of the intended indication. This single-centre, placebo-controlled, double-blind, dose-ranging, crossover study assessed the physiological effects of GTN gels on application to the glans penis in 15 healthy male volunteers. The study, which used Doppler ultrasound to measure penile blood flow, was not powered to produce statistically significant outcomes. However it provided a complex data set from which the following conclusions were drawn:

- MED2005 appeared to stimulate penile blood flow in a number of subjects relative to placebo
- Some vascular changes (penile artery, peak systolic velocity, end diastolic velocity) achieved statistical significance with certain doses at certain time points
- MED2005 at a dose of 0.6 mg appeared to induce a greater effect on blood flow than any of the other doses used
- Dr Paul Sidhu, a Consultant at Kings College Hospital, London and an expert in the use of Doppler ultrasound, commented that the blood flow changes induced by MED2005 were consistent with the erection process and therefore that these data were encouraging in regard to GTN's proposed erectogenic action

6.3.3 Efficacy and Safety

The efficacy and safety of MED2005 was assessed in a recent Phase IIa, multi-centre, randomised, double-blind, placebo-controlled, crossover study in male subjects clinically diagnosed with ED (Study FM53). The application of 0.6 mg MED2005 gel to the glans penis was associated with a statistically significant increase (i.e. improvement) in the EF domain score of the International Index for Erectile Function (IIEF; the primary endpoint) compared with a placebo gel. The efficacy of MED2005 compared with placebo was further supported by the analyses of the secondary efficacy outcome variables.

The tolerability and safety profile of MED2005 appears to be predictable and consistent with the known pharmacological profile of GTN. In Study FM53, 15 mild related headaches were reported in 1023 intercourse attempts and only 2 mild related headaches were reported by the female partners.

The Phase I, healthy volunteer studies FM33, FM35 and FM58 demonstrated a favourable safety profile of MED2005. There was a low incidence of mild transient headache, no clinically significant effects on blood pressure (BP) and no serious adverse events (SAEs). In the Phase IIa study in male subjects clinically diagnosed with ED (FM53), a locally applied dose of MED2005 was considered safe, well-accepted and well-tolerated by the male subjects and their female partners. FMD has also conducted a single-blind, placebo-controlled, dose-ranging study to assess the physiological effects and tolerability of a different GTN gel formulation (Zanafil) applied to the vaginas of a group of healthy, pre-menopausal, female volunteers (Study FM22). No AEs were reported following vaginal application of 0.5 mg and 1 mg doses of GTN gel. This suggests that even if the full dose of MED2005 was transferred to the female partner during sexual intercourse, it would be unlikely to cause any notable tolerability problems.

For further safety information, please refer to the 'Reference Safety Information' of the current version of MED2005 IB.

Additional studies in subjects with ED are required to further demonstrate the efficacy and safety of MED2005. This is the reason for the current study.

6.4 Risk-Benefit Evaluation

6.4.1 Potential Benefits

MED2005 is being developed for the treatment of ED and as such, subjects receiving treatment with MED2005 might benefit from improvements in EF and quality of life for themselves and their partners.

6.4.2 Potential Risks

Preclinical studies demonstrate that GTN does not possess teratogenic potential, has no adverse effects on male or female reproductive organs and is unlikely to have the potential to cause sensitisation or irritation at the intended site of application in men or women.

Published clinical studies and literature reports confirm the pharmacologically predictable tolerability profile of GTN. The most common AEs that have been reported are headache (generally mild and short-lived) and hypotension (not normally symptomatic). The literature reports relative success following the application of GTN transdermal patches or GTN ointment to the shaft of the penis.

GTN has been used in clinical practice in numerous countries for more than 100 years for the treatment of angina pectoris and other cardiovascular conditions. The side-effects of GTN are well documented and reports indicate that the most common undesirable effects include headache, facial flushing and nausea. In subjects treated with GTN ointments, for example for rectal pain or angina prophylaxis, the reported AEs are similar to those documented for other GTN treatments. For the treatment of rectal pain, the most commonly reported treatment-related AEs using Rectogesic® 4 mg/g rectal ointment were dose-dependent increases in headache (57% of subjects) followed by dizziness and nausea [19]. For prophylaxis of angina pectoris, AEs related to Percutol® 2% ointment have also been shown to be dose-related and almost all were the result of vasodilator activity. Headache was the most commonly reported AE [20]. Other commonly reported AEs with GTN 2% ointment include nausea and vomiting. Uncommon side-effects include cardiac disorders (tachycardia, bradycardia [in the presence of syncope]), vascular disorders (hypotension, circulatory collapse), allergic skin disorders (eczema, dermatitis, pruritus, urticaria, non-specific rashes) and immune system disorders (hypersensitivity reactions, anaphylaxis).

The study is designed for careful monitoring of any potential AEs of MED2005.

6.5 Conduct of the Study

This study will be performed in compliance with the protocol, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements including European Union (EU) Good Manufacturing Practice (GMP) requirements for investigational medicinal products (IMPs).

7. STUDY OBJECTIVES

7.1 Primary Objective

- To demonstrate the efficacy of MED2005 versus placebo in male subjects clinically diagnosed with ED using the EF domain of the IIEF, the Sexual Encounter Profile (SEP) Question 2 and the SEP Question 3. The primary objective will be addressed by estimating the following estimand: difference between treatment policies (each MED2005 dose versus placebo) in all subjects who met the study inclusion/exclusion criteria and who were randomised and attempted intercourse post-randomisation at least once, assessed via the change compared to baseline in EF [IIEF-EF], the ability to achieve vaginal penetration [SEP Question 2] and the ability to have successful intercourse [SEP Question 3] over 12 weeks of treatment

7.2 Secondary Objectives

- To evaluate the efficacy of MED2005 in male subjects using the Self-Esteem And Relationship (SEAR) questionnaire for men and women, the Global Assessment Questionnaire (GAQ), the additional domains of the IIEF, the Patient Global Impression of Severity (PGI-S), the Patient Global Impression of Change (PGI-C) as well as subjective measures of the time of onset and duration of action (erection) and erection hardness and questions on usage and application of MED2005
- To evaluate the long-term (up to 12 months) efficacy of MED2005
- To evaluate the safety of MED2005 using AEs and standard physico-chemical assessments

8. STUDY DESIGN

8.1 Overall Study Design and Plan

This is a Phase III, multi-centre, randomised, double-blind, placebo-controlled, home use, parallel group clinical study to evaluate the efficacy and safety of MED2005, a topically applied GTN gel for the treatment of ED. The study will include a screening period, a double-blind phase and an open-label extension phase.

The study population will comprise male subjects aged between 18 and 70 years clinically diagnosed with ED, and their female partners. A total of 1000 subjects are planned to be randomised and treated in the double-blind phase of the study at a suitable number of sites within Eastern Europe. After completing the final follow-up visit (Visit 6) in the double-blind phase, subjects and their female partners will be invited to take part in the 12-month open-label extension phase. Participation in the extension phase will be at the discretion of the individual subject and his partner. Recruitment will continue until approximately 450 subjects and their partners have consented to participate in the open-label extension phase.

During the double-blind phase, treatment will involve topical self- or partner-administration of a gel to the glans penis prior to attempting sexual intercourse. Subjects will be randomised to receive one of the following gel treatments in a 1:1:1:1 ratio:

- MED2005 0.2% (w/w) GTN gel to deliver a 0.6 mg dose of GTN
- MED2005 0.4% (w/w) GTN gel to deliver a 1.2 mg dose of GTN
- MED2005 0.6% (w/w) GTN gel to deliver a 1.8 mg dose of GTN
- Placebo vehicle

During the open-label extension phase, all subjects will receive MED2005 0.6% (w/w) GTN gel to deliver a 1.8 mg dose of GTN.

Subjects will be screened for eligibility during a screening period between Day –43 and Day –1. The IIEF questionnaire will be completed by the male subjects at the start of the screening period at the first site visit (Visit 1) and the EF domain of the IIEF (IIEF-EF; i.e. Questions 1–5 and 15) will be used to determine the pre-screening eligibility of the subject. A score of ≤ 25 will be acceptable for inclusion in the screening period of the study. Informed consent will be signed by male subjects and their female partners during screening (Visit 1) before they can be admitted into the study. There will also be subject and partner training in the use of questionnaires and IMP application at Visit 1.

During the screening period, at home and after refraining from using other ED treatments for a period of at least 14 days, subjects and their partners are required to make a minimum of four attempts at sexual intercourse, at their convenience but within a 4-week period (without treatment). The subjects and their partners will be asked to complete questionnaires to record their experiences after each sexual intercourse attempt (using the SEP questionnaire at home [male subjects and their female partners]) and at the end of the 4-week period (using the IIEF and PGI-S [male subjects only], and the SEAR [male subjects and their female partners] questionnaires). The IIEF-EF completed at the end of the screening period will be used to confirm eligibility for randomisation. Subjects who cannot comply with the minimum number of intercourse attempts verified by completed SEPs or who exceed 25 on the IIEF-EF will be excluded from the study. This eligibility check will be completed prior to randomisation and dosing. The scores generated from the screening period will be used as an established baseline in the planned analyses.

Eligible subjects will then participate in the double-blind phase, comprising a 12-week treatment period (Visits 2, 3, 4 and 5) and a 1-week follow-up visit (Visit 6). Male subjects will be required to attend all study visits. The female partner will be required to attend Visits 1, 2 and 6; attendance at the other visits (Visits 3, 4 and 5) will be optional.

During the treatment period, subjects will be randomly allocated to receive placebo or one of the three doses of MED2005 (0.6 mg GTN, 1.2 mg GTN or 1.8 mg GTN). Randomisation will be carried out on Day 1 of the treatment period (Visit 2) using an interactive voice/web response system (IVRS/IWRS). Subjects will be stratified for randomisation based on their baseline ED severity scores from the end of the screening period (see Section 9.5 for details). The number of subjects in each of the three baseline ED severity groups (i.e. mild, moderate and severe) will be monitored during the trial in order to have approximately equal numbers in each group.

Training on the application of the IMP will be repeated/ reinforced. Medication will be dispensed on Day 1 of the treatment period (Visit 2): 12 units will be supplied for each 4-week period. At

home, subjects or their partners should apply the dispensed gel immediately prior to sexual intercourse and make at least four intercourse attempts in each of the three 4-weekly periods during treatment (Weeks 1–4, 5–8 and 9–12). Subjects will be asked to leave a washout period of at least 12 hours before the next attempt at sexual intercourse using the IMP. The subjects and their partners will be asked to complete questionnaires using electronic patient-reported outcomes (ePRO) to record their experiences after each sexual intercourse attempt (using the SEP questionnaire and the onset and duration of action [erection] and erection hardness questions at home [male subjects and their female partners]), and at the end of each of the three 4-week periods during treatment (using the IIEF, PGI-S and PGI-C questionnaires [male subjects only], and the SEAR and GAQ questionnaires [male subjects and their female partners]; to be completed at site visits for subjects and at home for their partners if preferred).

Subjects and their female partners will be monitored for AEs by being asked to complete 4-week diaries at home of untoward signs and symptoms as they experience them (i.e. in real time) throughout the duration of their participation in the double-blind phase of the study (from signing of informed consent until the follow-up assessment at Visit 6). The diaries will be reviewed at each study visit.

Subjects will be asked to return to the study site at the end of each of the three 4-week (± 1 week) periods during treatment (i.e. at Visits 3, 4 and 5) to return used and unused IMP, to enable the clinical staff to check compliance and to assess subject health status, including assessment of any AEs and recording concomitant medications. At these visits, dispensed IMP tubes will be visually inspected to check if the tube has been pierced to help assess subject compliance and allow re-training on expressing a dose if deemed necessary. These visits will be optional for the female partners.

Subjects and their female partners will be required to attend a follow-up visit (Visit 6), 7 days (± 2 days) after the Week 12 visit (Visit 5) for safety assessment. At the end of the double-blind phase, during Visit 6, subjects and their partners will be invited to take part in the open-label extension phase. Participation in the extension phase will be at the discretion of the individual subject and his partner. Recruitment will continue until approximately 450 subjects and their female partners have consented. The remaining subjects will be discharged from the study.

The open-label extension phase will comprise 12-months treatment with visits every 3 months. During the extension phase, all subjects will receive MED2005 0.6% (w/w) GTN gel to deliver a 1.8 mg dose of GTN. Treatment will involve topical self- or partner-administration of the gel to the glans penis immediately prior to attempting sexual intercourse. Subjects will be asked to leave a washout period of at least 12 hours before the next attempt at sexual intercourse using the IMP gel. Training on the application of the IMP will be provided and repeated/reinforced as necessary throughout the extension phase.

For each 3-month period subjects will be dispensed 12 tubes per month (36 tubes at each visit) to allow them to use the tubes as they require. Male subjects will be asked to complete the SEP questionnaire to record their experiences after each sexual intercourse attempt as and when they occur. At each site visit male subjects will be asked to complete the IIEF questionnaire to cover the previous 1 month. Subjects and their female partners will also be monitored for AEs by completing diaries of untoward signs and symptoms as they experience them (i.e. in real time) throughout the duration of the open-label extension phase.

Once they have entered the open-label extension phase, subjects will be asked to return to the study site every 3 months (at Day 180 [Visit 7], Day 270 [Visit 8], Day 360 [Visit 9] and Day 450 [Visit 10]) to enable the clinical staff to check AEs and concomitant medications (in the

diaries), SEP questionnaire completed after each intercourse attempt to cover each 3-month period, IIEF to cover previous 1-month period and compliance on IMP usage. Vital signs and a penis examination will be undertaken at each visit. An electrocardiogram (ECG) will be done at 12 months (Day 450). Visits during the open-label extension period will be optional for female partners.

Subject participation in the double-blind phase will comprise 12 weeks of treatment and a 1-week follow-up visit. Subjects who continue in the open-label extension phase will participate for a further 360 days of treatment. The end of the study will be the last visit of the last subject.

Efficacy will be evaluated using questionnaires (IIEF, SEP, SEAR, GAQ, PGI-S, PGI-C) as well as subjective measures of time of onset and duration of action (erection) and erection hardness. Information on usage and application of the gels will be evaluated.

Safety will be evaluated throughout the double-blind phase using standard assessments including physical examinations and visual examination of the penis, vital signs (BP, heart rate [HR], body temperature), standard clinical laboratory testing (haematology, biochemistry, urinalysis), 12-lead ECGs, alcohol and drugs of abuse testing, serology testing, pregnancy testing (females of childbearing potential only) and recording of AEs and concomitant medications with paper diaries (potential partner AEs will be captured at site visits or by telephone). Safety will be evaluated throughout the open-label extension phase by monitoring of AEs and concomitant medications with paper diaries (potential partner AEs will be captured at site visits or via telephone call), monitoring of vital signs, ECGs, and visual examination of the penis.

All assessments are detailed in the schedule of events below (Table 1). The timetable for completion of the questionnaires for evaluating efficacy is detailed in the schedule of questionnaires below (Table 2).

Table 1 Schedule of Events

Assessments/ procedures	Screening period	Double-blind phase					Open-label extension phase				
	Screening	Treatment period				Follow-up[a,b]					
	Day –43 to Day –1	Day 1 Week 1	End of Week 4 (± 1 week)	End of Week 8 (± 1 week)	End of Week 12 (± 1 week)	Visit 5 + 7 days (± 2 days)	Visit 5 + 7 days (± 2 days)	Day 180 (± 7 days)	Day 270 (± 7 days)	Day 360 (± 7 days)	Day 450 (± 7 days)
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10
Male subject attendance	X	X	X	X	X	X	X	X	X	X	X
Female partner attendance	X	X				X					
Informed consent (M+F)	X						X				
Eligibility check	X[c]	X					X				
Medical history	X	X									
Physical examination[d]	X	X			X	X		X	X	X	X
Height, body weight, BMI	X										
Alcohol breath test	X										
Haematology	X		X	X	X						
Biochemistry	X		X	X	X						
Serologies	X										
Endocrinology[e]	X										
Urinalysis	X		X	X	X						
Urine drugs of abuse	X										
Training in the use of subject questionnaire and IMP application[f]	X	X	X	X			X	X	X	X	

Table 1 Schedule of Events

Assessments/ procedures	Screening period	Double-blind phase					Open-label extension phase				
	Screening	Treatment period				Follow-up[a,b]					
	Day –43 to Day –1	Day 1 Week 1	End of Week 4 (± 1 week)	End of Week 8 (± 1 week)	End of Week 12 (± 1 week)	Visit 5 + 7 days (± 2 days)	Visit 5 + 7 days (± 2 days)	Day 180 (± 7 days)	Day 270 (± 7 days)	Day 360 (± 7 days)	Day 450 (± 7 days)
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10
Urine pregnancy test (females of childbearing potential only)[g]		X				X		X	X	X	X
Randomisation		X									
Dispensing of medication supplies[h]		X	X	X			X	X	X	X	
Study drug administration		←	—	—	→		←	—	—	—	→
Return and visual inspection of medication supplies			X	X	X			X	X	X	X
IIEF questionnaire[i]	X[j]	X	X	X	X			X	X	X	X
SEP questionnaire[i, k]	←	—	—	—	→		←	—	—	—	→
SEAR questionnaire[i]	X	X	X	X	X						
GAQ[i]			X	X	X						
PGI-S[i]	X	X	X	X	X						
PGI-C[i]			X	X	X						
Onset/duration of action (erection) and erection hardness questions			←	—	→						
Usage and application					X						

Table 1 Schedule of Events

Assessments/ procedures	Screening period	Double-blind phase					Open-label extension phase				
	Screening	Treatment period				Follow-up[a,b]					
	Day –43 to Day –1	Day 1 Week 1	End of Week 4 (± 1 week)	End of Week 8 (± 1 week)	End of Week 12 (± 1 week)	Visit 5 + 7 days (± 2 days)	Visit 5 + 7 days (± 2 days)	Day 180 (± 7 days)	Day 270 (± 7 days)	Day 360 (± 7 days)	Day 450 (± 7 days)
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10
questions[l]											
Vital signs (BP [supine and standing], HR, body temperature)[m]	X	X	X	X	X	X		X	X	X	X
ECG[n]	X				X						X
Concomitant medications recording[o]	X	X	X	X	X	X		X	X	X	X
AE review[o]	X	X	X	X	X	X		X	X	X	X
Invitation to open-label extension						X					

a Subjects and their female partners will return to the study site to have a follow-up 7 days (± 2 days) after their end of treatment visit in the double-blind phase.
b At the end of the double-blind phase, and after completing their Visit 6 follow-up visit assessments, subjects and their female partners will be invited to take part in the open-label extension phase. Participation in the extension phase will be at the discretion of the individual subject and his partner and subject to availability of places. Visit 6 will be the end of study visit for subjects who do not participate in the open-label extension phase
c Eligibility will include the IIEF questionnaire and ED history.
d A full physical examination (including a penis examination) will be carried out at screening (Visit 1) and a brief examination, focusing on any changes since screening, will be carried out on Day 1 (Visit 2) and all other visits indicated in the table.
e Morning testosterone samples will be taken for male subjects at screening (Visit 1). If the reading is below the laboratory normal range the test should be repeated using an early morning specimen. Repeated low levels indicate the possibility of hypogonadism and the subject should be referred for full investigation and not recruited.
f Training in IMP application and the completion of questionnaires will be carried out at screening (Visit 1). Training in IMP application will be repeated/reinforced on Day 1 of the treatment period (Visit 2), and if deemed necessary also at Visits 3, 4, 6, 7, 8 and 9 (i.e. if the investigator thinks the subject/partner needs re-training on expressing a dose after visually inspecting previously used IMP tubes to check if the tube has been pierced).

g A urine pregnancy test will be completed by female subjects of childbearing potential on Day 1 of the treatment period (Visit 2; at the study site) and at the follow-up visit (Visit 6; either at the study site or at the subject's home if preferred). For subjects participating in the open-label extension phase, a urine pregnancy test will also be completed by female subjects of childbearing potential at Visits 7, 8 9 and 10 (either at the study site or at the subject's home if preferred). The pregnancy test kit will be provided.
h Medication will be dispensed on Day 1 of the treatment period (Visit 2) and at Visits 3, 4, 6, 7, 8 and 9.
i Double-blind phase: Subjects and their partners will be asked to complete questionnaires using ePRO to record their experiences after each sexual intercourse attempt, at the end of the screening period and at the end of each of the three 4-week periods during treatment. Subjects and their female partners should complete the SEP questionnaire and the onset and duration of action (erection) and erection hardness questions at home after each sexual intercourse attempt during the study. The IIEF (male subjects only) and SEAR (male subjects and their female partners) questionnaires will be completed at the end of the screening period (i.e. at the end of the 4-week no-treatment period) and at the end of each of the three 4-week periods during treatment. The PGI-S (male subjects only) will be completed at the end of Visit 1 and Visit 2 and at the end of each of the three 4-week periods during treatment. The GAQ (male subjects and their female partners) and PGI-C (male subjects only) will be completed at the end of each of the three 4-week periods during treatment. The IIEF, SEAR, GAQ, PGI-S and PGI-C will be completed at site visits for subjects; their female partners can complete the SEAR and GAQ at home if preferred.
Open-label extension phase: Male subjects will be asked to complete questionnaires using ePRO to record their experiences after each sexual intercourse attempt and at the end of each of the 3-month periods during treatment. Subjects should complete the SEP questionnaire at home after each sexual intercourse attempt during the study. The IIEF questionnaire to cover the previous 1 month will be completed at each site visit during the study.
j Pre-screening IIEF (i.e. IIEF-EF Questions 1–5 and 15).
k During the screening period (between site Visit 1 and Visit 2), subjects and their female partner will make at least four attempts at sexual intercourse without treatment. Subjects with less than four attempts at sexual intercourse or high IIEF scores (> 25) will be excluded prior to randomisation and entry into the treatment period. Subjects and their partners should complete the SEP questionnaire after each sexual intercourse attempt between Visit 1 and Visit 2.
l Questions on the usage and application of the gels will be completed by the male partner at the end of the treatment period (Visit 5).
m For supine vital sign measurements, the subjects will be required to rest in a supine position for at least 10 minutes prior to their measurements. Standing vital signs measurements will then be taken after 1 minute of standing.
n 12-lead ECG done in triplicate approximately 1 minute apart (subjects will be required to rest in a supine position for at least 10 minutes prior to their ECG measurements).
o AEs will be monitored throughout the duration of study using paper diaries (4-week diaries during the double-blind phase, 3-month diaries during the open-label extension phase) completed by the subjects and their female partners at home as they experience any untoward signs and symptoms (i.e. in real time). Concomitant medications will also be monitored using the diaries. The diaries will be reviewed at study visits and AEs and concomitant medications will be recorded on the appropriate pages of the eCRF. For female partners the AE review can be conducted by telephone.

Abbreviations: AE=adverse events, BMI=body mass index, BP=blood pressure, ECG=electrocardiogram, eCRF=electronic case report form; ED=erectile dysfunction, ePRO=electronic patient-reported outcomes, F=female, GAQ=Global Assessment Questionnaire, HR=heart rate, IIEF=International Index for Erectile Function questionnaire, IMP=investigational medicinal product, M=male, PGI-C=Patient Global Impression of Change, PGI-S=Patient Global Impression of Severity, SEAR=Self-Esteem And Relationship questionnaire, SEP=Sexual Encounter Profile questionnaire.

Table 2 Schedule of Questionnaires

Questionnaire	Participant	Schedule
IIEF	Male only	• At the start of the screening period (Visit 1) to determine pre-screening eligibility of the subject (pre-screening IIEF i.e. Questions 1–5 and 15 only) • At Day 1 Week 1 (Visit 2) without treatment • At the end of each of the three 4-week periods during treatment in the double-blind phase (Visits 3, 4 and 5) • At each of the 3-month visits to cover the previous 1 month in the open-label extension phase (Visits 7, 8, 9 and 10)
SEP	Male and Female Male only	• After each sexual intercourse attempt during the 4-week screening period (without treatment): minimum of 4 sexual course attempts (between Visit 1 and 2) • After each sexual intercourse attempt during each of the three 4-weekly periods during treatment (between Visits 2 to 5) in the double-blind phase • After each sexual intercourse attempt during the open-label extension phase
SEAR	Male and Female	• At the end of the 4-week screening period (without treatment; end of Visit 1) • At the end of each of the three 4-week periods during treatment in the double-blind phase (Visits 3, 4 and 5)
GAQ	Male and Female	• At the end of each of the three 4-week periods during treatment in the double-blind phase (Visits 3, 4 and 5)
PGI-S	Male only	• At the end of Visit 1 and Visit 2 • At the end of each of the three 4-week periods during treatment in the double-blind phase (Visit 3, 4 and 5)
PGI-C	Male only	• At the end of each of the three 4-week periods during treatment in the double-blind phase (Visit 3, 4 and 5)
Onset and duration of action (erection) and erection hardness	Male and Female	• After each sexual intercourse attempt in each of the three 4-weekly periods during treatment in the double-blind phase (Visits 2 to 5)
Usage and application	Male only	• At Visit 5

Abbreviations: GAQ=Global Assessment Questionnaire, IIEF=International Index for Erectile Function questionnaire, PGI-C=Patient Global Impression of Change, PGI-S=Patient Global Impression of Severity, SEAR=Self-Esteem And Relationship questionnaire, SEP=Sexual Encounter Profile questionnaire.

8.2 Rationale for Study Design

8.2.1 Discussion of Study Design

This study will evaluate the efficacy and safety of three doses of topically applied GTN gel compared with a placebo vehicle gel in male subjects clinically diagnosed with ED and their female partners.

The randomised, double-blind, placebo-controlled features of the study design are intended to reduce the effect of selection bias on the results. The parallel group design means that multiple treatment arms are more practical and concerns about possible carryover effects are eliminated (compared with a crossover design). However, the main issue with using parallel

groups is the effect of inter-subject variability. The random allocation of a matching placebo is intended to define the placebo response and therefore clarify the effects of GTN.

In addition, there will be a 12-month open-label extension phase starting at the end of the double-blind phase for approximately 450 patients. The safety and efficacy of the long-term use of 0.6% MED2005 (1.8 mg GTN) in subjects with ED and their female partners will be evaluated in the open-label extension phase.

8.2.2 Choice of Subjects

The study will be conducted in adult male subjects clinically diagnosed with ED and verified by the IIEF-EF domain (a score of ≤ 25 points at the end of the screening period), and their female partners. Adult males with ED are the target population for the future intended use of MED2005. The selection criteria are defined in such a way that subjects eligible for participation in the study will be known to be free from any significant illness which could potentially confound the study results.

8.2.3 Rationale for Study Drug Dose and Schedule

The justification for choice of doses to be tested in this study was based on PK and clinical data generated in earlier developmental studies with MED2005, and the clinical use of a 2.5 mg gel of GTN in a related FMD product.

FMD has previously tested the following doses of MED2005:

FMD study	Dose	Phase	Number of Volunteers/Patients
FM33	MED2003 0.075 mg, 0.1 mg, 0.25 mg, 0.5 mg MED2004 0.75 mg MED2005 1.2 mg	I	16 healthy volunteers
FM35	MED2003 0.01 mg, 0.075 mg, 0.25 mg MED2005 0.6 mg	I	15 healthy volunteers
FM53	MED2005 0.6 mg	IIa	232 patients
FM58	MED2005 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg	I	30 healthy volunteers

In the FM58 PK study, MED2005 0.6 mg, 1.2 mg, and 1.8 mg demonstrated similar or lower PK values than the sublingual tablet comparator (Nitrostat 1.8mg GTN); however, in some of the PK parameters the MED2005 2.4 mg was slightly higher compared to Nitrostat. There were no safety concerns for any of the studied doses of MED2005.

FMD currently market a condom based product with an ancillary medicinal substance. The class III medical device incorporates a topical gel which contains 2.5 mg GTN in a non-aqueous base and is used to help maintain an erection. Users are exposed to the topical application of 2.5 mg of GTN under the occlusion of the device. The extended clinical use of a 2.5 mg GTN gel in a class III has a validated satisfactory safety record.

Therefore MED2005 0.6 mg, 1.2 mg, and 1.8 mg were selected for the double-blind phase of this study. For the open-label extension phase, all subjects will be provided with MED2005 1.8 mg as this dose is expected to have the greatest efficacy and provide the most significant information on safety and efficacy.

During the double-blind phase subjects are asked to make at least four intercourse attempts using the IMP in each of the three 4-weekly period during treatment in order to get a reasonable assessment of the efficacy and safety of MED2005 versus placebo.

The open-label extension phase is designed to assess long-term safety of MED2005 as it might be used once it is on the market. Therefore, subjects will be asked to use the IMP as and when they wish to and medication use will be assessed as part of the open-label analyses.

8.2.4 Choice of Route and Rate of Administration

In the double-blind phase of this study, the subject or their female partner will topically apply one of the three MED2005 gels (0.6 mg GTN, 1.2 mg GTN or 1.8 mg GTN) or the placebo vehicle gel to the glans penis. In the open-label extension phase, all subjects will receive treatment with the 0.6% MED2005 gel to deliver a dose of 1.8 mg GTN.

The IMP will be self- or partner-applied at home. This is the intended method of administration after licensing. Subjects or their partners will be required to apply a single dose (approximately 300 mg) of gel to the glans of the penis and rub for at least 15 seconds (to ensure thorough distribution of the gel and promote penetration of the active substance) immediately prior to sexual intercourse. Subjects will be asked to leave a washout period of at least 12 hours before the next attempt at sexual intercourse using the IMP.

8.2.5 Monitoring and Communication of AEs

AEs will be monitored throughout the duration of the study from signing of the Informed Consent Form (ICF) at screening (Visit 1) until the final study visit. AEs of any untoward signs and symptoms for both the subject and his female partner will be documented in paper diaries to be completed at home by the subjects and their partners as they experience them (i.e. in real time) during each 4-week period in the double-blind phase and each 3-month period in the open-label extension phase and reviewed regularly by the Principal Investigator (PI) or his/her delegate (potential partner AEs will be captured at site visits or by telephone). If any information relating to the study product becomes available after the submission of a final protocol to the Competent Authority which may impact on the conduct of the study, including but not limited to the risk and benefit evaluations underpinning approvals and subject consent, FMD shall notify the study site in writing as soon as practically possible and the parties will agree, in writing, what steps need to be taken, if any.

8.2.6 Study Principal Investigator, Site Facilities and Personnel

This multi-centre study will be conducted at approximately 50 investigational sites in countries including Poland, Hungary, Czech republic, Slovakia, Georgia, Russia, Ukraine, Bulgaria and Latvia. At all sites, the study will be conducted by an experienced PI and well-trained medical, clinical and technical staff with experience in the conduct of clinical studies. The study is designed to closely monitor, treat and communicate potential expected adverse reactions (based on the known mode of action of the IMP) as well as potential unexpected AEs.

8.3 Stopping Criteria

The study will be discontinued if any unacceptable safety findings are identified. This decision will be made jointly by the Chief Investigator (CI) (or deputy) and the Sponsor. A written document signed by the CI (or deputy) and Sponsor will be produced ratifying the decision.

Please see Section 9.6 for possible reasons for discontinuation of an individual subject

The PI and the Sponsor will have joint judgment of an unacceptable tolerability profile (stopping criteria) based on the frequency and intensity of observed AEs (including SAEs and treatment-related AEs).

Any subject suffering from a clinically relevant AE will be monitored closely and provided with the appropriate medical care and follow-up.

9. SELECTION AND WITHDRAWAL OF SUBJECTS

9.1 Number and Source of Subjects to be Studied

It is planned to randomise and treat 1000 male subjects clinically diagnosed with ED, along with their female partners, in the double-blind phase of the study. Additional subjects may be randomised if there are a substantial number of dropouts to ensure that sufficient data are available for analysis; this would be detailed in a protocol amendment. Subjects will be identified and recruited through volunteer databases, site/clinician recruitment and/or advertisements as necessary.

For the open-label extension phase, it is planned to include a total of 450 male subjects and their female partners.

9.2 Inclusion Criteria

All subjects must meet all of the following inclusion criteria to be eligible for the study (following screening [Visit 1], an eligibility check will be carried out on Day 1 of the treatment period [Visit 2]):

1. Subject is a male aged between 18 and 70 years inclusive, at screening
2. Confirmed clinical diagnosis of ED for more than 3 months according to the NIH Consensus Statement (‘the inability to achieve or maintain penile erection sufficient for satisfactory sexual performance at least once’)
3. Subject answers ‘yes’ to the question regarding the presence of residual EF over the past 3 months: ‘*At home over the past 3 months, have you experienced at least some growth of your penis in response to: (1) mechanical stimulation by yourself or your partner, or (2) visual stimulation?*’
4. Subject has been involved in a continuous heterosexual relationship for at least 6 months prior to screening
5. Documented written informed consent from both subject and his female partner
6. If the male subject's female partner is of childbearing potential from the time of first sexual intercourse attempt during the screening period until the last administration of study treatment, then the couple must have been using a medically acceptable form of contraception for at least 3 months prior to entering the study, and agree to continue such use for at least 1 month after the last study drug administration

   Acceptable methods of contraception are listed below; it should be noted that condoms, femidoms, diaphragms, caps or hormone rings are not permitted as a form of contraception in this study:

   - Surgical sterilisation of the male partner (vasectomy with documentation of azoospermia if possible)
   - The female partner has undergone documented tubal ligation (female sterilisation)
   - The female partner uses combined hormone injectables

- The female partner uses medically prescribed hormonal implants
- The female partner has undergone documented placement of an intrauterine device (IUD) or intrauterine system (IUS)
- The female partner uses combined oral contraceptives
- The female partner uses progesterone only contraceptives
- The female partner uses combined hormonal patches

Other than for male/female sterilisation, if any of these above listed methods are being used then their effectiveness must be determined by the PI or their delegate, taking into consideration the compliance and tolerance of the female partner with this method of contraception.

Subjects who are or wish to become pregnant will not be included in the study.

7. Subject and his female partner are capable of understanding and complying with the requirements of the protocol and must have signed the ICF prior to participation in any study-related procedures
8. Low IIEF-EF scores (≤ 25) during the screening period

To continue in the open-label extension phase of the study, subjects must meet the following inclusion criteria at the follow-up visit of the double-blind phase (Visit 6):

1. Subject and his female partner complete the double-blind phase
2. Subject and his female partner were compliant to study procedures during the double-blind phase
3. Documented written informed consent from both subject and his female partner
4. If the male subject's female partner is of childbearing potential from the time of first sexual intercourse attempt during the screening period until the last administration of study treatment, then the couple must have been using a medically acceptable form of contraception for at least 3 months prior to entering the study, and agree to continue such use for at least 1 month after the last study drug administration

   Acceptable methods of contraception are listed below; it should be noted that condoms, femidoms, diaphragms, caps or hormone rings are not permitted as a form of contraception in this study:

   - Surgical sterilisation of the male partner (vasectomy with documentation of azoospermia if possible)
   - The female partner has undergone documented tubal ligation (female sterilisation)
   - The female partner uses combined hormone injectables
   - The female partner uses medically prescribed hormonal implants
   - The female partner has undergone documented placement of an intrauterine device (IUD) or intrauterine system (IUS)
   - The female partner uses combined oral contraceptives
   - The female partner uses progesterone only contraceptives
   - The female partner uses combined hormonal patches

Other than for male/female sterilisation, if any of these above listed methods are being used then their effectiveness must be determined by the PI or their delegate, taking into consideration the compliance and tolerance of the female partner with this method of contraception.

Subjects who are or wish to become pregnant will not be included in the study.

9.3 Exclusion Criteria

Subjects are prohibited from participating in the study if they meet any of the following exclusion criteria (following screening [Visit 1], an eligibility check will be carried out on Day 1 of the treatment period [Visit 2]):

1. Any significant or serious cardiovascular, pulmonary, hepatic, renal, gastrointestinal, haematological, endocrinological, metabolic, neurological or psychiatric disease which, in the opinion of the PI, renders the subject unfit to take part in the study
2. Subject has any history of an unstable medical or psychiatric condition or using any medication that, in the opinion of the PI, is likely to affect the subject's ability to complete the study or precludes the subject's participation in the study

   Certain concomitant medications; e.g. other vasodilators, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, beta blockers, diuretics, anti-hypertensives, tricyclic anti-depressants and major tranquillisers, as well as the consumption of alcohol, may potentiate the BP lowering effects of MED2005; therefore, the PI must consider this carefully and include subjects at their discretion
3. Any presence of a symptomatic, active urinary tract infection diagnosed by the PI or their delegate at screening or during the study
4. Any presence of chronic indwelling urethral catheterisation or penile anatomical abnormalities (e.g. penile fibrosis) that would significantly impair EF
5. Any history of operations for Peyronie's disease
6. Primary hypoactive sexual desire or any history of hypogonadism
7. Any history of radical prostatectomy
8. Any history of severe/uncontrolled diabetes
9. Subjects taking two or more anti-hypertensives for the treatment of BP
10. Hypersensitivity to GTN or to any of the excipients, or idiosyncratic reactions to other organic nitrates
11. Concomitant treatment with sildenafil citrate, tadalafil, vardenafil and other PDE-5 inhibitors
12. Subjects taking Alpha blockers
13. Subjects receiving testosterone pellets
14. Any penile surgery except circumcision
15. Any treatment with acetyl cysteine within 6 months
16. Any treatment with dihydroergotamine within 6 months
17. Postural hypotension, hypotension or uncorrected hypovolaemia, as the use of GTN in such states could produce severe hypotension or shock

18. Increased intracranial pressure (e.g. head trauma or cerebral haemorrhage) or inadequate cerebral circulation
19. Any history of migraine or recurrent headache
20. Aortic or mitral stenosis
21. Hypertrophic obstructive cardiomyopathy
22. Constrictive pericarditis or pericardial tamponade
23. Closed-angle glaucoma
24. Subjects with nursing partners, known pregnant partners or with partners who wish to become pregnant during the course of the study
25. Confirmed positive results from urine drug screen (amphetamines, benzodiazepines, cocaine, cannabinoids, opiates, barbiturates, tricyclic antidepressants and methadone) or from the alcohol breath test at screening (for clarification, **any** positive result from the urine drug screen or alcohol breath tests at screening will mean the subject will be excluded from the study). In the instance that a subject is using medication which may give a positive result, exclusion will be at the PI's discretion
26. Subject has recent (last 12 months) clinical evidence of alcoholism or drug abuse.
27. Subject has a positive screen for hepatitis B, consisting of hepatitis B surface antigen (HBsAG), hepatitis C antibody, and human immunodeficiency virus (HIV)
28. Any clinically significant abnormal laboratory, vital signs or other safety findings as determined by medical history, physical examination or other evaluations conducted at screening or on admission
29. Subjects unwilling to cease use of vacuum devices, intracavernosal injections, PDE-5s or other therapy for ED for the entire course of the study
30. Unwillingness of the subject or their partner to agree to make the required attempts at sexual intercourse during treatment period
31. Any history of unresponsiveness to PDE-5 treatment or significant side-effects, excluding visual disturbances, with PDE-5s
32. Fewer than four attempts at sexual intercourse during the screening period
33. Subjects or their partners who are illiterate or are unable to understand the language in which the questionnaires are available
34. Subject has received any investigational product during the 90 days prior to dosing for this study
35. Subject or his partner cannot communicate reliably with the PI
36. Subjects with severe premature ejaculation (little or no control of ejaculation at the time of penetration)

Subjects are prohibited from participating in the open-label extension phase of the study if they meet any of the following exclusion criteria at the follow-up visit of the double-blind phase (Visit 6):

1. Subsequent to recruitment into the double-blind phase of the study, the development of any significant or serious cardiovascular, pulmonary, hepatic, renal, gastrointestinal, haematological, endocrinological, metabolic, neurological or psychiatric disease which, in the opinion of the PI, renders the subject unfit to continue in the open-label extension phase of the study

2. Subject using any medication that, in the opinion of the PI, is likely to affect the subject's ability to complete or participate in the open-label phase of the study.

   NB The concomitant medications listed as exclusion criteria for the study apply to the open-label extension phase. Certain concomitant medications; e.g. other vasodilators, calcium channel blockers, ACE inhibitors, beta blockers, diuretics, anti-hypertensives, tricyclic anti-depressants and major tranquillisers, as well as the consumption of alcohol, may potentiate the BP lowering effects of MED2005; therefore, the PI must consider this carefully and include subjects at their discretion

3. Any presence of a symptomatic, active urinary tract infection diagnosed by the PI or their delegate at the start of the open-label extension phase
4. Subsequent to recruitment into the double-blind phase of the study, the development of postural hypotension, hypotension or uncorrected hypovolaemia, increased intracranial pressure or inadequate cerebral circulation, any clinically significant vital signs or other safety findings as determined by medical history, physical examination or other evaluations conducted at Visit 6 prior to recruitment to the open-label phase

9.4 Subject Restrictions

Subjects and their female partners will have to comply with the following restrictions:

- Blood donation will not be allowed at any time during the study and up to 3 months (90 days) after completion of the study
- Male subjects should not donate sperm and their female partners should not donate egg(s) from the time of the first administration of IMP until 3 months after the last administration of IMP
- Condoms, femidoms, diaphragms, caps or hormone rings are not permitted as a form of contraception in this study

9.5 Subject Inclusion and Randomisation

Subjects who sign the ICF for the study at Visit 1 and undergo screening procedures will be identified during screening by a unique screening number. Subjects who fulfil the eligibility criteria will be assigned consecutive subject numbers and randomised before study medication is dispensed on Day 1 of the treatment period (Visit 2).

Subjects will be randomised to receive one of the following gel treatments in a 1:1:1:1 ratio according to a parallel group design (i.e. subjects will receive one treatment only):

- MED2005 0.2% (w/w) GTN gel to deliver a 0.6 mg dose of GTN
- MED2005 0.4% (w/w) GTN gel to deliver a 1.2 mg dose of GTN
- MED2005 0.6% (w/w) GTN gel to deliver a 1.8 mg dose of GTN
- Placebo vehicle

Subjects will be stratified for randomisation based on their baseline ED severity scores from the end of the screening period:

- Mild (IIEF-EF domain score of 17–25)
- Moderate (IIEF-EF domain of 11–16)
- Severe (IIEF-EF domain ≤ 10)

It is intended to randomise an approximately equal number of subjects for each baseline severity group. No stratification by site will be done as, with four treatment groups and three baseline ED severity strata, it is not deemed feasible without risking overall balance for treatments.

If a subject discontinues from the study, the subject number will not be re-used and the subject will not be allowed to re-enter the study.

Randomisation will be carried out using an IVRS/IWRS.

For the open-label extension phase, eligible subjects who sign the ICF for the extension phase at Visit 6 will continue in the study. All subjects will receive MED2005 0.6% (w/w) GTN gel to deliver a 1.8 mg dose of GTN.

9.6 Withdrawal of Subjects

Each subject (and their female partners) will be informed of their right to withdraw from the study at any time and for any reason. The reasons for any subject withdrawal will be recorded on the electronic Case Report Form (eCRF).

9.6.1 Criteria for Withdrawal from Study Drug

Subjects (and their female partners) may be withdrawn from the study drug at any time. All subjects who withdraw from the study drug during the double-blind phase will be asked to continue completing the IIEF and SEP questionnaires in order to address the primary efficacy objective of difference between treatment policies.

A PI will withdraw a subject from study drug at any time for any of the following reasons:

- If a subject experiences a serious or intolerable AE, that prevents them from continuing.
- If a subject incurs a significant protocol violation which impacts on their safety (this will be discussed on a case-by-case basis with the Sponsor).
- At the request of the Sponsor.
- If it is considered that the subject's health is composed by remaining in the study or the subject is not sufficiently cooperative.

9.6.2 Criteria for Withdrawal from the Study

Subjects (and their female partners) are free to withdraw from the study at any time, without prejudice (withdrawal of consent).

Subjects may be withdrawn from the study at any time; however, once treatment has commenced, every attempt should be made to continue with the safety and IIEF and SEP questionnaires up to the end of the double-blind phase to ensure the safety of the subject and in order to address the primary efficacy objective of difference between treatment policies.

Reasons for withdrawing a subject from the study can include:

- Voluntary discontinuation by the subject and/or his female partner, who are free to discontinue participation in the study at any time
- Severe non-compliance to the protocol as judged by the PI and/or Sponsor
- Any other reason as judged by the PI

9.6.3 Procedures for Subject Withdrawal

Subjects who withdraw from the study (and their female partners) should always be asked about their reason(s) for withdrawal and the presence of any AEs. Study-related AEs will be monitored closely and provided with the appropriate medical care and follow-up.

10. STUDY AND CONCOMITANT TREATMENTS

10.1 Investigational Medicinal Product

The IMP under study is MED2005, a gel formulation of GTN currently under development by FMD as a topical treatment for ED. The matching placebo used will be the vehicle gel containing no active ingredients.

During the double-blind phase, MED2005 (at three strengths: 0.2% GTN gel, 0.4% GTN gel and 0.6% GTN gel) or placebo (vehicle gel) will be provided in single unit dose aluminium tubes with 800 mg of gel in every tube packed in cartoon boxes of 4 tubes per box. For each subject, 12 units will be supplied for each of the three 4-week periods during treatment (Weeks 1–4, 5–8 and 9–12).

During the open-label extension phase, MED2005 0.6% GTN gel will be provided in single unit dose aluminium tubes with 800 mg of gel in every tube packed in cartoon boxes of 4 tubes per box. For each 3-month period of the extension phase, 12 units per month (36 tubes at each visit [Visits 6, 7, 8 and 9]) will be supplied to each subject to allow them to use the tubes as they require.

Each 800 mg filled tube will contain sufficient gel to apply a single dose (approximately 300 mg) of MED2005 (0.2%, 0.4% or 0.6%) or placebo at each application. Subjects and their female partners will be trained on the application of the gel to the glans of the penis and cautioned not to use more than one tube of gel per sexual intercourse event. Subjects will be asked to leave a washout period of at least 12 hours before the next attempt at sexual intercourse using the IMP. The placebo gel will be identical in appearance to the three active MED2005 gels and will be administered in the same way and at the same volume as MED2005.

The IMP will be clearly labelled with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries.

10.2 Methods of Assigning Subjects to Treatment Groups

See Section 9.5 above for details of randomisation.

10.3 Drug Accountability

The PI, trained delegate or pharmacy staff (as applicable) is responsible for the correct storage of the study medication according to the manufacturer's recommendations. The medication made available for this clinical study must be used in accordance with the protocol and must only be handled by the pharmacist or other authorised personnel. The pharmacy staff must maintain complete and accurate records, showing the receipt and disposition of all supplies of the study medication. These records must include a master record which lists the date of receipt of all study medication and the quantities received, and a dispensing record which includes all quantities dispensed, the subject numbers to whom the medication was dispensed, the date of each dispensing and the identification of the dispenser. IMP will not be destroyed without prior written confirmation from the Sponsor. The Clinical Research Organisation (CRO) will be responsible for coordinating the destruction of any unused medication at the sites.

Written proof of destruction must be kept in the Sponsor Oversight File and/or the Trial Master File (TMF) and Investigator Site File.

At site visits at the end of each of the three 4-week periods during treatment in the double-blind phase (i.e. at Visits 3, 4 and 5) and at the end of each of the 3-month periods during the open-label extension phase (i.e. at Visits 7, 8, 9 and 10), subjects will be asked to return used and unused tubes of IMP to enable the clinical staff to check treatment compliance. Clinical staff will examine the IMP tubes visually to check if the tube has been pierced to help assess subject compliance and allow re-training on expressing a dose if deemed necessary.

10.4 Blinding

10.4.1 Methods for Ensuring Blinding

During the double-blind phase of the study both the subjects and the investigators will be unaware (blinded) which of the four treatments (0.2% GTN gel, 0.4% GTN gel, 0.6% GTN gel or placebo gel) each subject will be administered. All four treatments will be identical in appearance; i.e. they will be supplied in identical 800 mg filled aluminium tubes each containing sufficient gel to apply a single dose of approximately 300 mg of identical clear, translucent gels with no smell.

Randomisation will be carried out using an IVRS/IWRS.

Subjects should remain blinded to the double-blind treatment during the open-label extension phase.

Blinding is not applicable for the open-label treatment.

10.4.2 Methods for Unblinding the Study

In an emergency, details of the assigned treatment allocation can be obtained from the IVRS/IWRS. This should not be done except in medical emergencies when the appropriate management of the subject necessitates knowledge of the treatment randomisation. The PI or delegate must document and report to FMD any break of the treatment allocations. FMD retains the right to obtain knowledge of the treatment allocations for SAEs suspected to be causally-related to MED2005 and that potentially require expedited reporting to the Regulatory Authorities and/or Ethics Committees (ECs). Treatment allocations will not be exposed for the planned analyses of the double-blind phase until all decisions on the evaluability of the data from each individual subject and his partner have been made and documented.

10.5 Prior and Concomitant Medications

Subjects stabilised for a minimum of 3 months on long-term nitrate therapies such as other GTN products, isosorbide dinitrate and amyl or butyl nitrate for the treatment/prevention of angina can, at the discretion of the PI, continue their medication and enter the study.

Prescription or non-prescription medication is allowed at the discretion of the PI as long as it does not have a negative impact on the safety of the subject or the integrity of the study data.

Use of non-steroidal anti-inflammatory drugs (NSAIDs) and acetylsalicylic acid are permitted for the treatment of AEs.

Details of previous and concomitant medications will be recorded throughout the study on the appropriate pages of the eCRF.

10.5.1 Prohibited Medications

Subjects are prohibited from taking the following medications:

- Androgens (e.g. testosterone), trazodone or anti-androgens
- Any therapy for ED, including within 14 days of screening
- Subjects taking an alpha blocker
- Phosphodiesterase inhibitors; e.g. sildenafil, tadalafil and vardenafil
- Acetyl cysteine
- Heparin
- Dihydroergotamine

During the course of the study, subjects should not take any medication which, in the opinion of the PI, could interfere with the treatment procedure, recovery or assessments of safety and effectiveness.

10.6 Treatment Compliance

During the double-blind phase subjects will be asked to return to the study site at the end of each of the three 4-week (± 1 week) periods during treatment (i.e. at Visits 3, 4 and 5) to return used and unused tubes of IMP, to enable the clinical staff to check compliance and to assess subject health status. At these visits, IMP tubes will be examined visually to check if the tube has been pierced to help assess subject compliance and allow re-training on expressing a dose if deemed necessary.

During the open-label extension phase, subjects will be asked to return to the study site at the end of each of the 3-month (± 1 week) periods during treatment (i.e. at Visits 7, 8, 9 and 10) to return used and unused IMP, to enable the clinical staff to check compliance and to assess subject health status. At these visits, IMP tubes will be examined visually to check if the tube has been pierced to help assess subject compliance and allow re-training on expressing a dose if deemed necessary.

11. STUDY ASSESSMENTS AND SCHEDULES

11.1 Schedule of Assessments

All study assessments are detailed in the schedule of events (Table 1) and the schedule of questionnaires (Table 2) and described in detail below.

11.1.1 Pre-screening Assessments

At their first site visit (Visit 1), all subjects will be required to complete the IIEF. The IIEF-EF will be used to determine the pre-screening eligibility of the subject. A score of ≤ 25 will be acceptable for inclusion in the main screening period of the study.

11.1.2 Screening Assessments (Visit 1)

Visit 1 must be attended by the male subject and his female partner. Following written informed consent, the following assessments should be carried out during the screening period between Day –43 and Day –1:

- Eligibility check
- Medical history (including history of ED and surgical history)
- Full physical examination (including height, weight and body mass index [BMI])
- Alcohol breath test
- Urine drugs of abuse screen
- Vital signs (BP, HR and body temperature)
- Laboratory safety assessments (haematology, biochemistry and urinalysis)
- 12-lead ECG (in triplicate, approximately 1 minute apart)
- Serology
- Endocrinology
- Training in the use of subject questionnaires and IMP application
- AE review
- Prior and concomitant medications and procedures
- SEAR questionnaire (male subject and his female partner)
- PGI-S (male subject only)

During the screening period (between site Visits 1 and 2), subjects and their partners are required to make a minimum of four attempts at sexual intercourse (without treatment) within a 4-week period at their convenience. The following assessments should be carried out during this time:

- SEP questionnaire (to be completed by the subject and his partner at home after each sexual intercourse attempt)
- Pre-screening IIEF questionnaire (i.e. IIEF-EF Question 1 to 5 and 15 only) to be completed by the subject at the end of the screening period on site, to confirm eligibility.

Subjects who cannot comply with the minimum number of intercourse attempts or who exceed 25 on the IIEF-EF will be excluded from the study before randomisation and dosing.

11.1.3 Double-Blind Phase: Treatment Period Assessments

The following assessments should be carried out during the 12-week treatment period (including site Visits 2, 3, 4, and 5).

11.1.3.1 Day 1, Week 1 (Visit 2)

At Site:

Visit 2 must be attended by the male subject and his female partner.

- Eligibility check
- Medical history check
- Brief physical examination (focusing on any changes since screening)
- Repeated/reinforced training in the use of IMP application
- Urine pregnancy test (female partners of childbearing potential only)
- Randomisation
- Dispensing of medication supplies
- Vital signs (BP, HR, body temperature)
- AE review
- Concomitant medications monitoring
- IIEF questionnaire (male subject only)
- SEAR questionnaire (male subject and his female partner; can be completed by female partners at home if preferred)
- PGI-S (male subject only)

11.1.3.2 Treatment Weeks 1–4

At Home:

- Study drug administration
- SEP questionnaire (male subject and his female partner; after each sexual intercourse attempt)
- Onset and duration of action (erection) and erection hardness questions (male subject and his female partner; after each sexual intercourse attempt)
- AE completion and concomitant medication recording (using paper diaries)

At Site (End of Week 4 ±1 week; Visit 3):

Visit 3 must be attended by the male subject; attendance by his female partner is optional.

- Return of medication supplies (including visual inspection of IMP tubes)
- Repeated/reinforced training in the use of IMP application (if deemed necessary)
- Laboratory safety assessments (haematology, biochemistry and urinalysis)
- Vital signs (BP, HR, body temperature)
- IIEF questionnaire (male subject only)
- SEAR questionnaire (male subject and his female partner; can be completed by female partners at home if preferred)
- GAQ (male subject and his female partner; can be completed by female partners at home if preferred)

- PGI-S (male subject only)
- PGI-C (male subject only)
- Dispensing of medication supplies
- AE review
- Concomitant medications monitoring

11.1.3.3 Treatment Weeks 5–8

At Home:

- Study drug administration
- SEP questionnaire (male subject and his female partner; after each sexual intercourse attempt)
- Onset and duration of action (erection) and erection hardness questions (male subject and his female partner; after each sexual intercourse attempt)
- AE completion and concomitant medication recording (using paper diaries)

At Site (End of Week 8 ±1 week; Visit 4):

Visit 4 must be attended by the male subject; attendance by his female partner is optional.

- Return of medication supplies (including visual inspection of IMP tubes)
- Repeated/reinforced training in the use of IMP application (if deemed necessary)
- Laboratory safety assessments (haematology, biochemistry and urinalysis)
- Vital signs (BP, HR, body temperature)
- IIEF questionnaire (male subject only)
- SEAR questionnaire (male subject and his female partner; can be completed by female partners at home if preferred)
- GAQ (male subject and his female partner; can be completed by female partners at home if preferred)
- PGI-S (male subjects only)
- PGI-C (male subjects only)
- Dispensing of medication supplies
- AE review
- Concomitant medications monitoring

11.1.3.4 Treatment Weeks 9–12

At Home:

- Study drug administration
- SEP questionnaire (male subject and his female partner; after each sexual intercourse attempt)
- Onset and duration of action (erection) and erection hardness questions (male subject and his female partner; after each sexual intercourse attempt)
- AE completion and concomitant medication recording (using paper diaries)

At Site (End of Week 12 ±1 week; Visit 5):

Visit 5 must be attended by the male subject; attendance by his female partner is optional.

- Return of medication supplies (including visual inspection of IMP tubes)
- Full physical examination
- Laboratory safety assessments (haematology, biochemistry and urinalysis)
- Vital signs (BP, HR, body temperature)
- 12-lead ECG (in triplicate, approximately 1 minute apart)
- IIEF questionnaire (male subjects only)
- SEAR questionnaire (male subject and his female partner; can be completed by female partners at home if preferred)
- GAQ (male subject and his female partner; can be completed by female partners at home if preferred)
- PGI-S (male subjects only)
- PGI-C (male subjects only)
- Usage and application questions
- AE review
- Concomitant medications monitoring

11.1.4 Double-Blind Phase: Follow-up Assessments (Visit 5 + 7 days [± 2 days]; Visit 6)

Visit 6 must be attended by the male subject and his female partner. The following assessments should be carried out during the follow-up period, 7 days (± 2 days) after the Week 12 visit (Visit 5):

- Brief physical examination
- Urine pregnancy test (female partners of childbearing potential only; can be done at home if preferred)
- Vital signs (BP, HR, body temperature)
- AE review
- Concomitant medications monitoring

Following completion of these assessments, subjects may be invited to participate in the open-label extension phase of the study. See Section 11.1.5 for open-label extension phase assessments.

11.1.5 Open-Label Extension Phase Assessments

At the end of the double-blind phase follow-up visit (Visit 6) subjects and their female partners who meet the eligibility criteria and consent to continue in the open-label extension phase of the study will be provided with medication supplies and repeated/reinforced training in the use of questionnaires and IMP application will be provided if required.

11.1.5.1 Study Days 91–180

At Home:

- Study drug administration
- SEP questionnaire (male subject only; after each sexual intercourse attempt)
- AE completion and concomitant medication recording (using paper diaries)

At Site (Day 180 ± 7 days; Visit 7):

Visit 7 must be attended by the male subject; attendance by his female partner is optional.

- Brief physical examination (including a penis examination)
- Urine pregnancy test (female partners of childbearing potential only; can be done at home if preferred)
- Repeated/reinforced training in the use of IMP application (if deemed necessary)
- Dispensing of medication supplies
- Return of medication supplies (including visual inspection of IMP tubes)
- IIEF questionnaire (male subject only)
- Vital signs (BP, HR, body temperature)
- AE review
- Concomitant medications monitoring

11.1.5.2 Study Days 181–270

At Home:

- Study drug administration
- SEP questionnaire (male subject only; after each sexual intercourse attempt)
- AE completion and concomitant medication recording (using paper diaries)

At Site (Day 270 ± 7 days; Visit 8):

Visit 8 must be attended by the male subject; attendance by his female partner is optional.

- Brief physical examination (including a penis examination)
- Urine pregnancy test (female partners of childbearing potential only; can be done at home if preferred)

- Repeated/reinforced training in the use of IMP application (if deemed necessary)
- Dispensing of medication supplies
- Return of medication supplies (including visual inspection of IMP tubes)
- IIEF questionnaire (male subject only)
- Vital signs (BP, HR, body temperature)
- AE review
- Concomitant medications monitoring

11.1.5.3 Study Days 271–360

At Home:

- Study drug administration
- SEP questionnaire (male subject only; after each sexual intercourse attempt)
- AE completion and concomitant medication recording (using paper diaries)

At Site (Day 360 ± 7 days; Visit 9):

Visit 9 must be attended by the male subject; attendance by his female partner is optional.

- Brief physical examination (including a penis examination)
- Repeated/reinforced training in the use of IMP application (if deemed necessary)
- Dispensing of medication supplies
- Return of medication supplies (including visual inspection of IMP tubes)
- IIEF questionnaire (male subject only)
- Vital signs (BP, HR, body temperature)
- AE review
- Concomitant medications monitoring

11.1.5.4 Study Days 361–450

At Home:

- Study drug administration
- SEP questionnaire (male subject only; after each sexual intercourse attempt)
- AE completion and concomitant medication recording (using paper diaries)

At Site (Day 450 ± 7 days; Visit 10):

Visit 10 must be attended by the male subject; attendance by his female partner is optional.

- Brief physical examination (including a penis examination)
- Urine pregnancy test (female partners of childbearing potential only; can be done at home if preferred)
- Return of medication supplies (including visual inspection of IMP tubes)
- IIEF questionnaire (male subject only)

- Vital signs (BP, HR, body temperature)
- 12-lead ECG (in triplicate, approximately 1 minute apart)
- AE review
- Concomitant medications monitoring

11.2 Efficacy Assessments

The efficacy of MED2005 will be assessed using the following subject-centred questionnaires at the time points described in the schedule of events (Table 1):

- The co-primary efficacy endpoints:
  - The IIEF-EF domain of the IIEF questionnaire, completed by the male subjects
  - Question 2 of the SEP questionnaire, completed by the male subjects
  - Question 3 of the SEP questionnaire, completed by the male subjects
- Secondary efficacy endpoints:
  - The SEAR questionnaire, completed by the male subjects and their female partners
  - Global assessment via completion of the GAQ, completed by the male subjects and their female partners
  - The additional domains of the IIEF questionnaire, completed by the male subjects
  - The other SEP questions (Questions 1, 4 and 5), completed by the male subjects
  - The SEP questions completed by the female partners
  - The PGI-S scale, completed by the male subjects
  - The PGI-C scale, completed by the male subjects
  - Time of onset and duration of action (erection) and erection hardness, completed by the male subjects and their female partners
  - Questions on the usage and application of the gels, completed by the male subjects

The IIEF, PGI-S, PGI-C and usage and application questions will be completed by the male subjects only. The SEP, SEAR, GAQ and time of onset and duration of action (erection) and erection hardness questions will be completed by both the subject and his female partner. For further details, please refer to APPENDIX 1.

11.2.1 International Index for Erectile Function (IIEF) Questionnaire

The IIEF was developed and validated in 1996–1997 as part of the sildenafil clinical study program [21] and in 1999, the IIEF was recommended by the 1st International Consultation on Erectile Dysfunction as the efficacy endpoint of choice for clinical studies in ED [22]. The IIEF has been validated, is widely used in numerous countries and has demonstrated specificity for detecting treatment-related changes in EF [23]. The IIEF consists of 15 questions divided into five domains of sexual function: EF (six questions), orgasmic function (two questions), sexual desire, (two questions), intercourse satisfaction (three questions) and overall satisfaction (two questions). A score of 0 to 5 is awarded to each of the 15 questions [21].

In this study, subjects will be asked to complete the IIEF at pre-screening, at the end of the screening period and at the end of each of the three 4-weekly periods during treatment in the double-blind phase (i.e. Visits 3, 4 and 5 [end of Weeks 4, 8 and 12]). The co-primary endpoint of this study will be the change from baseline (the end of the screening period) to the final on-treatment visit (Visit 5, end of Week 12) in the IIEF-EF domain.

During the open-label extension phase subjects will be asked to complete the IIEF to cover the previous 1 month period at Visits 7, 8, 9 and 10.

Further details of the IIEF are provided in Section 18.1.

11.2.2 Sexual Encounter Profile (SEP) Questionnaire

The SEP questionnaire consists of 5 items addressing the sexual events a subject experiences when attempting intercourse. The SEP questionnaire has been validated and is widely used in clinical studies as a measure of the efficacy of ED therapy. After each sexual encounter subjects will answer five yes or no questions in their SEP diary. Of particular interest will be Question 2: '*Were you able to insert your penis into your partner's vagina?'* and Question 3: '*Did your erection last long enough for you to have successful intercourse?*'.

In this study, subjects and their partners will be asked to complete the SEP questionnaire after each sexual intercourse attempt during the screening period (without treatment) and during each of the three 4-weekly periods during treatment in the double-blind phase (i.e. Weeks 1–4, 5–8 and 9–12). Questions 2 and 3 of the SEP questionnaire will be co-primary efficacy endpoints along with the IIEF-EF.

During the open-label extension phase male subjects will be asked to complete the SEP questionnaire after each sexual intercourse attempt.

Further details of the male and female versions of the SEP questionnaire are provided in Section 18.2.

11.2.3 Self-Esteem And Relationship (SEAR) Questionnaire

The SEAR questionnaire has strong psychometric properties that support its validity and reliability for measuring sexual relationship satisfaction, confidence and particularly self-esteem in men with ED [24]. An adapted SEAR questionnaire has also been shown to be a useful tool in women [25]. It consists of 14 items investigating two dimensions: sexual relationship satisfaction (8 items) and confidence (6 items; subdivided into self-esteem and overall relationship satisfaction). All items are scored on a 5-point Likert-type scale. A higher score signifies a more favourable response for all 14 items.

In this study, subjects and their partners will be asked to complete the SEAR questionnaire at the end of the screening period and at the end of each of the three 4-weekly periods during treatment in the double-blind phase (i.e. Visits 3, 4 and 5 [end of Weeks 4, 8 and 12]). The SEAR questionnaire results will be part of the secondary efficacy endpoint analyses. Further details of the SEAR are provided in Section 18.3.

11.2.4 Global Assessment Questionnaire (GAQ)

The GAQ allows the subject to rate (yes or no) the improvement in EF and has been used to assess efficacy outcomes after treatment with tadalafil in men with ED following spinal cord injury [26] and to evaluate the efficacy of udenafil for ED [27]. Subjects will complete GAQ Question 1 '*Has the treatment you have been taking improved your erectile function?*' and if

necessary Question 2 '*If yes, has the treatment improved your ability to engage in sexual activity?*'.

In this study, subjects and their partners will be asked to complete the GAQ at the end of each of the three 4-weekly periods during treatment in the double-blind phase (i.e. Visits 3, 4 and 5 [end of Weeks 4, 8 and 12]). The GAQ results will be part of the secondary efficacy endpoint analyses. Further details of the male and female versions of the GAQ are provided in Section 18.4.

11.2.5 Patient Global Impression (PGI) Scales

The global assessment tools the PGI-S and PGI-C were included to assess the subjects' overall perception of their condition. The PGI-S and PGI-C are both 1-item questionnaires using balanced Likert scales that ask the subject to rate the severity of a specific condition (the PGI-S, a single-state 5-point categorical scale) or to rate at a particular timepoint the perceived change in his condition in response to treatment (the PGI-C, a transitional 7-point categorical scale).

The PGI scales were modelled on the Clinical Global Impression scales developed in the 1970s. They are simple, direct and easy to use and can be tailored to specific conditions and disease parameters. The PGI scales have previously been validated for use in a number of conditions including urinary incontinence and chronic pain [28, 29]. The PGI-C has also been validated for the evaluation of patient satisfaction (i.e. EF) after placement of a penile prosthesis [30].

In this study, subjects will be asked to complete the PGI-S at the end of Visit 1 and Visit 2, after completing the IIEF; and the PGI-S and PGI-C at the end of each of the three 4-weekly periods during treatment in the double-blind phase (i.e. Visits 3, 4 and 5 [end of Weeks 4, 8 and 12]). The PGI results will be part of the secondary efficacy endpoint analyses. Further details of the PGI scales are provided in Section 18.5.

11.2.6 Onset and Duration of Action (Erection) and Erection Hardness Questions

The subjects and their partners will be asked questions about the onset and duration of their/their partner's erection and erection hardness in conjunction with the SEP after each sexual intercourse attempt during each of the three 4-weekly periods during treatment in the double-blind phase (i.e. Weeks 1–4, 5–8 and 9–12). Further details of the onset and duration of action (erection) and erection hardness questions are provided in Section 8.

11.2.7 Usage and Application

Questions on the usage and application of the gels will be completed once by the subject at the end of the treatment period in the double-blind phase (Visit 5):

1. Who applied the gel most of the time? You/Your partner
2. Did you/your partner find the tube easy to use? Yes/No
3. Did you/your partner find the gel easy to apply? Yes/No
4. Would you have preferred to use a different applicator such as a pad? Yes/No
5. Did you incorporate the application of the gel as part of your foreplay? Yes/No
6. Did you like using the gel? Liked a lot/Mostly liked/Neither liked or disliked/Disliked/Disliked a lot.

11.3 Safety Assessments

The sum total of these safety assessments listed in this section identifies the Princeton III “low risk subjects”.

11.3.1 Adverse events

See Section 12 for full details of AE reporting and recording.

11.3.2 Physical Examination

Subjects will receive a full physical examination at screening (Visit 1). Full physical examinations will include assessments of general appearance, skin, head and neck, lymph nodes, thyroid, abdomen, musculo-skeletal, cardiovascular, respiratory and neurological systems. The physical examination will also include a penis examination. Circumcision status will be recorded in the eCRF. Height, body weight and BMI will be calculated as part of the screening physical examination.

Subjects will receive a brief physical examination that will focus on any changes since screening at Visits 2, 5 and 6 in the double-blind phase and at Visits 7, 8, 9 and 10 in the open-label extension phase.

11.3.3 Laboratory Safety Assessments

Standard clinical laboratory safety assessments will be collected during screening and throughout the double-blind phase of the study. All laboratory safety assessments are detailed in Table 3 and described in detail below.

Table 3 Laboratory Safety Variables

Biochemistry	**Haematology**
Aspartate aminotransferase (AST)	Haemoglobin
Alanine aminotransferase (ALT)	Haematocrit
γ-glutamyl transpeptidase (GGT)	Erythrocytes
Alkaline phosphatase (ALP)	Mean cell haemoglobin
Total bilirubin (if > upper limit of normal [ULN] also direct and indirect bilirubin)	Mean corpuscular haemoglobin concentration
Cholesterol	Mean corpuscular volume
Triglycerides	White blood cell count
Creatine phosphokinase (Creatine Kinase [CK], and CK-Myocardial B if CK is elevated)	Differential blood count, platelets
Lactate dehydrogenase (LDH)	
Amylase (if > 1.5 × ULN, also pancreatic isoamylase)	Erythrocyte sedimentation rate after 1 hour
Creatinine	**Urinalysis**
Uric acid	pH
Urea	Glucose
Albumin	Proteins
Total protein	Ketones
Potassium	Bilirubin
Sodium	Urobilinogen
Calcium	Nitrite
Chloride	Blood
Glucose	Leukocytes
Inorganic phosphate (IP)	Specific gravity
C-reactive protein (CRP)	Urine microscopy*
Serology (at screening only)	**Urine Drugs of Abuse**
HIV-I and HIV-II antibodies	Amphetamines
HBsAG	Barbiturates
Hepatitis C virus (HCV) antibodies	Benzodiazepines
Hepatitis B core antibodies (HBc) (immunoglobulin G [IgG], and immunoglobulin M [IgM] if IgG is positive)	Cannabinoids
Endocrinology	Opiates
Testosterone	Cocaine
	Methadone
	Tricyclic antidepressants

* If deemed necessary, based on a clinically significant positive urinalysis test, microscopic examination of sediment and/or culture will be performed.

11.3.3.1 Haematology and Biochemistry

Blood samples for determination of haematology and biochemistry safety variables will be taken at screening (Visit 1) and at the end of each of the three 4-weekly periods during treatment in the double-blind phase (i.e. Visits 3, 4 and 5 [end of Weeks 4, 8 and 12]).

The date and time of collection will be recorded on the appropriate eCRF. The analyses will be done at a central laboratory using routine methods.

Clinical laboratory values outside the reference limits, which are suspected to be of any clinical significance, will be repeated. Subjects with suspected clinically significant results confirmed on repeated sampling should not be included in the study; or, if the subject is already included, they should be followed until test normalisation or for as long as the PI considers necessary.

11.3.3.2 Urinalysis

Urine samples for determination of urinalysis safety variables will be taken at screening (Visit 1) and at the end of each of the three 4-weekly periods during treatment in the double-blind phase (i.e. Visits 3, 4 and 5 [end of Weeks 4, 8 and 12]). Urinalysis will be performed by the site using a dipstick method.

11.3.3.3 Serology

All subjects will be tested for HBsAG, HCV antibodies, HBc antibodies and HIV-1 and HIV-2 antibodies at screening (Visit 1). This is done for the safety of the study personnel. If a subject has a positive result from any of these tests, he will be referred for further examination and treatment and will not be included in the study. These samples will be analysed by a central laboratory.

11.3.3.4 Endocrinology

Morning testosterone samples will be taken for the male subjects at screening (Visit 1). If the reading is below the laboratory normal range the test should be repeated using an early morning specimen. Repeated low levels indicate the possibility of hypogonadism and the subject should be referred for full investigation and not recruited.

11.3.3.5 Urine Drugs of Abuse

Urine samples will be tested for drugs of abuse by the site at screening (Visit 1). If a subject fails the drugs of abuse screen they will be excluded from the study. A repeat drug screen can only be done when methodological reasons are believed to have led to a false positive. Borderline positive results, unless covered by the preceding condition, are to be considered as positive and the subject will be excluded from the study. If a subject is found to be positive due to medication; e.g. flu/cold remedies, any medication containing an opioid, they may undergo a repeat drug screen if they are still within the screening window.

11.3.3.6 Alcohol Breath Test

An alcohol breath test will be carried out at screening (Visit 1), using an alcometer.

11.3.3.7 Urine Pregnancy Test

During the double-blind phase, female partners of childbearing potential will be required to perform a urine pregnancy test on Day 1 of the treatment period (Visit 2; at the study site) and at the follow-up visit (Visit 6; at the study site or at the subject's home if preferred [photographs of a negative urine pregnancy test will be accepted]).

During the open-label extension phase, female partners of childbearing potential will be required to perform a urine pregnancy test on Day 180 (± 7 days), Day 270 (± 7 days), Day 360 (± 7 days) and Day 450 (± 7 days). The pregnancy test may be performed at the study site or at the subject's home if preferred (photographs of a negative urine pregnancy test will be accepted).

Additional urine pregnancy tests may be performed at the PI's discretion.

The pregnancy test kit will be provided.

11.3.4 Vital Signs

11.3.4.1 Blood Pressure and Heart Rate

Supine and standing BP and HR will be measured at screening (Visit 1), during the double-blind phase on Day 1 of the treatment period (Visit 2), at the end of each of the three 4-weekly periods during treatment (i.e. Visits 3, 4 and 5 [end of Weeks 4, 8 and 12]) and at the follow-up visit (Visit 6), and during the open-label extension phase at Visits 7, 8, 9 and 10. For supine vital signs measurements, subjects will be required to rest in a supine position for at least 10 minutes prior to their measurements. Standing vital signs measurements will then be taken after 1 minute of standing.

11.3.4.2 Body Temperature

Body temperature (tympanic) will be measured (a single measurement) in degrees Celsius using an automated thermometer at screening (Visit 1), during the double-blind phase on Day 1 of the treatment period (Visit 2), at the end of each of the three 4-weekly periods during treatment (i.e. Visits 3, 4 and 5 [end of Weeks 4, 8 and 12]) and at the follow-up visit (Visit 6), and during the open-label extension phase at Visits 7, 8, 9 and 10.

11.3.5 12-lead ECGs

12-lead ECGs will be recorded at screening (Visit 1), at the end of the final treatment period in the double-blind phase (Visit 5, end of Week 12) and in the open-label extension phase on Day 450 (Visit 10).

ECG recordings will be made after the subject has been resting in a supine position for at least 10 minutes. The subjects should avoid postural changes during the ECG recordings and clinical staff will ensure that subjects are awake during the recording. At each time point, the ECG will be recorded in triplicate. The triplicates will be performed at approximately 1 minute intervals.

ECG printouts may be filed in the subject's eCRF for medical safety reviews. If possible, the same recorder will be used for any one subject. Each ECG recorder will be set up to the required technical specifications and containing the information required to identify the records. Each ECG recording will be clearly identified (with Subject ID, scheduled time relative to dose, and the actual time of ECG recording). All recorded ECGs will be reviewed by a PI or Sub-Investigator and documented in the eCRF. If a subject shows an abnormal ECG at any stage during the study, additional safety recordings (including the use of 5- or 12-lead Holter equipment) may be made and the abnormality followed to resolution if required. The PI should ensure all relevant staff are fully trained in carrying out ECG recordings.

11.4 Other Assessments

11.4.1 Informed Consent

Informed consent will be signed by both partners during screening (Visit 1) before they can be admitted into the study. To continue into the open-label extension phase, informed consent must be signed by both partners at Visit 6.

11.4.2 Eligibility

Eligibility will be assessed at pre-screening and screening (Visit 1) and then confirmed on Day 1 of the treatment period in the double-blind phase (Visit 2).

Eligibility will include the IIEF questionnaire (completed pre-screening for eligibility of the subject to enter the main screening period and at the end of the screening period to confirm eligibility for randomisation and dosing) and ED history. Subjects with less than four attempts at sexual intercourse or high IIEF scores (> 25) during the screening period will be excluded prior to entry into the treatment period.

Eligibility to participate in the open-label extension phase will be assessed at the follow-up visit (Visit 6) after completion of the assessments in the double-blind phase and will be subject to availability of places.

11.4.3 Medical History

Medical history will be checked and recorded at screening (Visit 1) and on Day 1 of the treatment period in the double-blind phase (Visit 2). Medical history will include history of ED and surgical history.

11.4.4 Volume of Blood Sampling

The maximum blood volume will not exceed 50 mL per subject during the study.

11.4.5 Training

Efficacy Questionnaires

Subjects will be trained in the use of the efficacy questionnaires at screening (Visit 1). The training will be repeated/reinforced on Day 1 of the treatment period in the double-blind phase (Visit 2).

IMP Application

Subjects and their female partners will be trained in the application of the IMP at screening (Visit 1). The training will be repeated/reinforced during the double-blind phase on Day 1 of the treatment period (Visit 2), and if deemed necessary also at Visits 3, 4 and 5 (i.e. if the investigator thinks the subject/partner needs re-training on expressing a dose after visual inspection of previously used IMP tubes to check if the tube has been pierced). Training will be repeated/reinforced during the open-label extension period if required.

Training will be conducted using a model of a phallus and will describe the method required for both circumcised and non-circumcised men. An assessment of physical capability will also be conducted and application training tailored to their needs.

The couple will be instructed on how to operate the aluminium tubes, how to apply the single dose of MED2005 to the glans penis (by the man or the woman) and the length of time it should

be rubbed in prior to sexual intercourse (at least 15 seconds). A description and diagram of this process will be supplied to the subjects in the application instructions. Subjects will also be asked to avoid oral stimulation of the penis for at least 5 minutes post application and reminded to return all drug materials for accountability.

12. ADVERSE EVENTS

AEs will be monitored throughout the duration of the study from signing of the ICF at screening (Visit 1) until the final study visit. Study site personnel will report any AE, whether observed by the investigator or reported by the subject.

12.1 Adverse Events

12.1.1 Definitions

The definitions of AEs, adverse drug reactions (ADRs), SAEs and suspected unexpected serious adverse reactions (SUSARs) are given below. It is of the utmost importance that all staff involved in the conduct of clinical research are familiar with the contents of this section.

Adverse Event

An AE is any untoward medical occurrence (including the deterioration of a pre-existing medical condition) in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. In clinical studies, an AE can include an undesirable medical occurrence occurring at any time, from the date informed consent was signed until the end of their participation in a study; i.e. the subject has discontinued or completed the study.

The causality of AEs (i.e. their relationship to study treatment) will be assessed by the PI who, in completing the relevant eCRF, must answer ‘yes’ or ‘no’ to the question: ‘Do you consider that there is a reasonable possibility that the event may have been caused by the study medication?’.

The following factors should be considered when deciding if there is a ‘reasonable possibility’ that an AE may have been caused by the study medication (that is, there are facts/evidence or arguments to suggest a causal relationship):

- Time course and exposure to suspect drug: Has the subject or their female partner actually received the suspect drug? Does the AE have a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile: Is the AE consistent with previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR, could the AE be anticipated from its pharmacological properties?
- No alternative cause: The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors
- Laboratory tests: A specific laboratory investigation (if performed) has confirmed the relationship?

A ‘reasonable possibility’ could be considered to exist for an AE where one or more of these factors exist.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of the drug?
- Is there a known mechanism?

Ambiguous cases should be considered as being a 'reasonable possibility' of a causal relationship unless further evidence becomes available to refute this.

Adverse Drug Reaction

An ADR is any AE where a causal relationship with the IMP is at least a reasonable possibility; i.e. the relationship cannot be ruled out.

Serious Adverse Event

An SAE is an AE occurring during any study period (i.e. screening, treatment and follow-up, open-label extension), and at any dose of the investigational product or placebo, that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above

The causality of SAEs; i.e. their relationship to study treatment, will be assessed in the same way as for non-serious AEs.

Note that SAEs that could be associated with any study procedure should also be reported.

Suspected Unexpected Serious Adverse Reactions

A SUSAR is any SAE where a causal relationship with the IMP is at least a reasonable possibility, but is not listed in the 'Reference Safety Information' section (Section 7) of the IB.

12.1.2 Recording of Adverse Events

AEs will be collected from the signing of the ICF at screening (Visit 1) until the end of the study. Any AEs that are unresolved at the subject's last AE assessment during the study (i.e. at the subject's final study visit) are to be followed-up by the PI for as long as medically indicated, but without further recording in the eCRF. FMD retains the right to request additional information for any subject and/or their female partner with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Subjects and their partners will be monitored for AEs by being asked to complete paper diaries of untoward signs and symptoms as they experience them (i.e. in real time) throughout the duration of the study. The diaries will be reviewed at study visits and AEs entered into the eCRF. If preferred, the AEs for female partners can be followed up by telephone.

AEs spontaneously reported by the subject or their female partner and/or in response to an open question 'Have you had any health problems during the study day/since your previous visit?' from the study personnel, or revealed by observation, will be recorded during site visits throughout the study.

Findings and values related to physical examinations and measurements of ECG, vital signs, (BP, HR, temperature) and laboratory variables will be defined as AEs if they are considered clinically relevant deteriorations compared with baseline and pre-dose values, as judged by the PI.

12.1.3 Assessment of Adverse Events

12.1.3.1 Adverse Event Intensity

The following variables will be recorded for each AE: Onset, resolution, maximum intensity, action taken, outcome, causality (yes or no) and whether it constitutes an SAE or not.

The intensity rating is defined as:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity (as in mild, moderate or severe) whereas seriousness is defined by the criteria in Section 12.1.1 (i.e. it is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning). An AE of severe intensity will not necessarily meet the criteria for an SAE. For example, nausea that persists for several hours may be considered severe nausea, but is not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be classified as an SAE.

In case of an overdose (accidental or deliberate), all symptoms associated with it should be reported as AEs.

12.1.3.2 Adverse Event Causality

For each AE one of the following categories will be selected based on medical judgement, consideration of the definitions below and all contributing factors.

ADR-related

Related

A clinical event, including a clinically significant abnormal laboratory test or other measurement, which occurs in a plausible time relationship to study drug administration, and which concurrent disease or other drugs or chemicals cannot explain.

Probably related

A clinical event, including a clinically significant abnormal laboratory test or other measurement, with a reasonable time sequence to study drug administration, and is unlikely to be attributed to concurrent disease or other drugs or chemicals.

Possibly related

A clinical event, including a clinically significant abnormal laboratory test or other measurement, with a reasonable time sequence to study drug administration, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Non-ADR-related

Unrelated

A clinical event, including a clinically significant abnormal laboratory test or other measurement, with little or no temporal relationship with study drug administration. Typically explained by extraneous factors (e.g. concomitant disease, environmental factors or other drugs or chemicals).

12.1.3.3 Outcome

The PI or their delegate will follow up all AEs wherever possible until the symptom has resolved or stabilised.

The date of confirming outcome will be recorded. The course of AEs will be assessed using the following outcomes as a guide:

1. Recovered: The AE has resolved and the subject returned to his/her condition prior to onset
2. Recovering: The AE has almost resolved and the subject is returning to his/her condition prior to onset
3. Not recovered: Even on the final day of observation, the AE had not resolved and the subject's condition remained unchanged. In case of death, the subject died of other causes not related to the AE from which there was no recovery
4. Recovered with sequelae: The AE resolved, but the subject has sequelae
5. Fatal: The subject died.
6. Unknown: The AE could not be categorised as per above

12.1.4 Reporting of Serious AEs

If any SAE/SUSAR occurs, the PI will take appropriate action immediately and will strive to identify the cause(s) of the event(s).

Any SAE will be notified by the PI to the Pharmacovigilance Service Provider and Study Monitor designated by the Sponsor within 24 hours by email or fax.

Assessment of causality (relatedness) and seriousness will be made by the site Physician. The FMD Medical Advisor will not be able to downgrade the opinion of the site Physician with regards to causality or seriousness. Assessment of expectedness of the SAE will be conducted by the FMD Medical Advisor with reference to the 'Reference Safety Information' section (Section 7) of the IB.

The initial report will be followed up by a full written report within three working days or five calendar days, whichever comes first, unless no further information is available. A follow-up report and any subsequent reports will be provided as soon as possible when new information becomes available. Occurrence of SUSARs will be notified to the Regulatory Authority by the

Pharmacovigilance Service Provider or their delegate within 7 days (for fatal and life-threatening SUSARs) or 15 days (for all other SUSARs).

SAEs/SUSARs must be recorded and reported whether or not the PI considers the SAE/SUSAR to be related to the IMP.

Photocopies of results, consultant report(s), a summary of the outcome of the reaction and the PI's opinion of the IMP's relationship to the SAE/SUSAR will accompany the SAE form if and when available.

12.1.1 Reporting and Follow-Up of Pregnancy

Any pregnancy in the female partner will be notified by the PI to the Pharmacovigilance Service Provider and Study Monitor designated by the Sponsor within 24 hours by email or fax. Pregnancy will be followed to outcome.

13. QUALITY ASSURANCE AND QUALITY CONTROL

13.1 Quality Assurance and Quality Control

To ensure GCP compliance and compliance with all applicable regulatory requirements, the Sponsor or site may conduct a quality assurance (QA) audit. A regulatory inspection of this study may be carried out by regulatory agencies. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the PI and the site will agree to allow the auditor/inspector direct access to all relevant documents and to allocate their time and the time of their staff to the auditor/inspector to discuss any findings or relevant issues. Quality control (QC) procedures at the site will be implemented to ensure data recorded into the eCRFs are accurate before eCRFs are sent for data entry purposes.

13.2 Monitoring

During the study, a person designated by FMD will have regular contact with the study sites, including visits to:

- Provide information and support to the PI
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled appropriately and that IMP accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (e.g. clinic charts)
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented and reported to the subject

The FMD Clinical Project Manager will be available between visits if the PI, or other staff at the site, need information and advice about the study conduct.

13.3 Blinded Review Meeting

Once all subjects have completed Visit 6 and after discrepancy management and critical QC of the data are complete and before database lock for the double-blind phase, a blinded review of the study data will be performed to identify minor and major protocol deviations. In particular, in this meeting, subjects (and/or specific data) to be excluded from the per protocol (PP) set will be identified.

Once all subjects have completed the open-label extension phase and after discrepancy management and critical QC of the data are complete and before database lock for the open-label extension phase, a review of the study data will be performed to identify minor and major protocol deviations.

14. STATISTICAL ANALYSES

Further details of the proposed statistical analysis will be documented in the statistical analysis plan (SAP), which will be written following completion of the protocol and finalised prior to the breaking of the blind.

In general, safety and efficacy variables will be presented by means of descriptive statistics and figures, as appropriate, by treatment (active at each dose level and placebo) and by time point and gender, if applicable. Continuous variables will be summarised using the number of non-missing observations, mean, standard deviation (SD), median, first and third quartiles, minimum and maximum. Categorical variables will be presented using number of subjects and percentages. For ordered categorical variables, cumulative percentages may also be presented. Raw data will be listed.

Baseline values will be the last assessments prior to randomisation at Visit 2 unless stated otherwise.

A Bonferroni correction will be used to take into account that there are three active versus placebo comparisons; i.e. all p-values resulting from comparing the three different MED2005 doses (0.6 mg GTN, 1.2 mg GTN, 1.8 mg GTN) versus placebo will be multiplied by three and statistical significance will then be declared if $p < 0.05$. Corresponding Bonferroni corrected 95% confidence intervals will be produced.

The objective for the double-blind phase is for all co-primary endpoints to show superiority of MED2005 to placebo in order to conclude a significant result of the study. For this objective, no adjustment for multiplicity of the error probability for the individual co-primary endpoints is required. However, the three co-primary endpoints will still be considered in a hierarchy of their importance, with the testing order being IIEF-EF domain, SEP Question 3 and SEP Question 2.

The objective of the open-label extension phase is to evaluate the safety of long-term (up to 12 months) use of MED2005. In addition, the long-term efficacy of MED2005 will be evaluated. Both safety and efficacy will be evaluated in the subset of subjects who completed the double-blind phase and took part in the open-label extension phase. Descriptive statistics will be based on observed data. In case of any randomisation/treatment errors, any summaries split by treatment group will be produced according to treatment received.

Once all subjects have completed the double-blind phase (Visit 6), the database will be locked, treatment groups unblinded and the analysis of the double-blind phase will be performed using all data from the screening and double-blind treatment phases. A second analysis will be performed once all applicable subjects have completed the open-label extension phase.

14.1 Analysis Sets

The following analysis sets will be used for the statistical analysis of the double-blind phase:

- The **randomised set** will consist of all subjects who were randomised to a treatment
- The **safety set** will consist of all subjects in the randomised set who made use of the medication at least once. In the case of randomisation/treatment errors, subjects will be analysed according to treatment received

- The **full analysis set** (FAS) will consist of all subjects in the randomised set who made use of the medication at least once. In the case of randomisation/treatment errors, subjects will be analysed according to randomised treatment

  Primary and secondary analyses will be performed on the FAS.

- The **per protocol set** (PP) will consist of all subjects in the FAS who completed the 12-week treatment period without major protocol violations and who have valid IIEF, SEP Question 2 and SEP Question 3 assessments at Week 12 (Visit 5)

Analysis sets will be identified prior to the unblinding of the study data. The efficacy analysis will be performed as randomised; i.e. a subject will be assigned to the treatment he was initially allocated, irrespective of what treatment was actually applied, and whether or not treatment was discontinued while questionnaire data was collected (see Section 9.6 Withdrawal of Subjects).

In order to assess the consistency of results, sub-group analyses will also be performed according to three subject baseline ED severity groups:

- Mild (IIEF-EF domain score of 17–25)
- Moderate (IIEF-EF domain of 11–16)
- Severe (IIEF-EF domain of ≤ 10)

The following analysis set will be used for the statistical analysis of the open-label extension phase:

- The **open-label analysis set** (OLAS) will consist of all subjects who made use of medication at least once during the open-label extension.

14.2 Demographic and Baseline Measurements

Assessments made at screening and at baseline of the treatment period will be summarised overall and for each treatment group. These assessments will include demographic and other relevant baseline characteristics (such as medical history, physical examination and the assessments made during the screening period). There will be no formal comparison of baseline data; that is, no statistical hypothesis testing.

14.3 Prior and Concomitant Medication

Prior and concomitant medication will be summarised overall and by treatment. For further information, please also refer to Section 10.5.

14.4 Number of Intercourse Attempts

Use of study medication and number of intercourse attempts will be summarised by treatment and 4-week period. Mean and median number of intercourse attempts will be given as well as an absolute and relative number of subjects tabulated by number of intercourse attempts.

14.5 Efficacy Evaluation

14.5.1 Efficacy Measures

For a list of efficacy assessments, see Section 11.2.

Summary statistics for all efficacy measures will be given by treatment, 4-week period (double-blind phase) and 3-month period (open-label extension phase) and gender (where applicable), for actual values and changes from baseline. Individual components of composite scores (but not domains) will not be summarised unless otherwise stated. Individual components as well as domains will be presented in listings together with the scores used in the analysis.

The co-primary efficacy outcomes will be change from baseline to 12 weeks of treatment in the IIEF-EF domain, SEP Question 2 and SEP Question 3 at Week 12.

Listings and summary statistics for the IIEF-EF, SEP Question 2 and SEP Question 3 will also be provided for the subsets in the open-label extension phase of the study.

14.5.2 Handling of Missing Values

Full details on the handling of missing values in analyses of all analysis sets, including rules applied to incomplete questionnaires and planned additional analyses, will be defined in the SAP. Only the main principles are given for the analyses on the FAS here.

Summary statistics will present the number of missing values and then will be based on non-missing values.

Any missing values in efficacy questionnaire data that occur during the treatment period and are then followed by observed data shall be treated as missing at random and imputed using a corresponding multiple imputation approach.

All subjects who are withdrawn from the study will be asked to continue with the IIEF and SEP questionnaires if possible. These data will be used as part of the analysis for estimating the treatment effect over 12 weeks, according to the randomised treatment policy.

There can be remaining missing values for the primary endpoints for subjects who leave the study and provide no further questionnaire data. For these subjects, missing values will be handled using a control-based multiple imputation approach. The imputation model for the missing observations in both the MED2005 and placebo (control) groups will be constructed from the control group only (missing not at random [MNAR]). This assumes that efficacy results post withdrawal, for subjects who withdraw, would have mirrored those seen in the placebo group and thus lose any potential MED2005 treatment benefit.

Additional estimands/tests of treatment effect, beyond the primary treatment policy estimand, may be addressed, including exploring other ways of handling missing values, such as fitting repeated measures mixed models.

Summary statistics will present the number of observed values and will then be based on the non-missing values for the open-label extension phase.

14.5.3 Primary Analysis

The co-primary efficacy endpoints, assessed in the male subjects, are:

1. The change from baseline of the average of the Week 4, Week 8 and Week 12 IIEF-EF domain scores
2. The change in percentage of sexual intercourse attempts in which subjects were able to insert their penis into their partner's vagina (SEP Question 2) between baseline and the 12 week treatment period
3. The change in percentage of sexual intercourse attempts in which subjects were able to maintain an erection of sufficient duration to have successful intercourse (SEP Question 3) between baseline and the 12 week treatment period

Baseline for the IIEF-EF score is the assessment at Visit 2, baseline for SEP Questions 2 and 3 is the percentage in the screening, treatment free, 4-week period.

The primary objective will be assessed by testing the following hypotheses for each MED2005 dose group (0.6 mg GTN, 1.2 mg GTN or 1.8 mg GTN) and each co-primary endpoint separately, using the FAS:

Null hypothesis (H0): There is no difference in the mean change from baseline in the IIEF-EF domain, SEP Question 2 and SEP Question 3 for the MED2005 treatment group compared with placebo.

$$H0: \mu (MED2005) = \mu (placebo)$$

Alternative hypothesis (H1): There is a difference in the mean change from baseline in the IIEF-EF domain, SEP Question 2 and SEP Question 3 for the MED2005 treatment group compared with placebo.

$$H1: \mu (active) \neq \mu (placebo)$$

Each comparison will be carried out at the two-sided 5% level of statistical significance after a Bonferroni correction (p-values multiplied by three). Efficacy will be stated if all null hypotheses for the co-primary endpoints are rejected. However, the three co-primary endpoints will still be considered in a hierarchy of their importance, with the testing order being IIEF-EF domain, SEP Question 3 and SEP Question 2.

The statistical model for the primary analysis of the IIEF-EF will be an analysis of covariance (ANCOVA) including terms for treatment group, site and baseline (as a continuous variable). The statistical model for the primary analyses of SEP Question 2 and SEP Question 3 will be an ANCOVA including terms for treatment group, site, baseline (as a continuous variable) and baseline ED severity (categorical variable). As the endpoints are change from baseline assessment, the respective baselines for each endpoint are included in the analyses. Baseline ED severity, used as part of the randomisation scheme, is a categorical grouping of the baseline IIEF-EF and as such is not included in the primary analysis of the IIEF-EF as it already appears in the model as a continuous variable. A sensitivity analysis will be performed including baseline ED severity (categorical variable) in addition to the variables included in the primary analysis. The estimated treatment means and differences (MED2005 versus placebo) will be reported as part of this analysis.

14.5.4 Other Efficacy Variables

All other efficacy variables will be analysed in a supportive way to describe the effect of treatment. Secondary analyses will also be performed on the FAS and with the ANCOVA approach.

Double-blind phase:

The following secondary efficacy analyses will be conducted:

- The analysis of the three co-primary endpoints will be repeated in the three pre-specified subgroups of ED severity: mild, moderate and severe as specified in Section 14.1
- The change in the IIEF-EF domain, SEP Question 2 and SEP Question 3 at each 4-week visit will be analysed
- Responder analyses assessing the proportion of subjects with a specific increase in the IIEF-EF domain from baseline, using a different responder definition defined separately for each baseline severity group, will be conducted. A responder is defined as having an increase of ≥ 2, ≥ 5 and ≥ 7 for the mild, moderate and severe subjects, respectively (published Minimal Clinically Important Difference [MCID] according to Rosen *et al*. 2011 [31])
- Responder analyses for SEP Questions 2 and 3 will be conducted in the same way as for the IIEF-EF. A responder is defined as having an increase of –1.3%, 16.7% and 27.3% for SEP Question 2 and 5.0%, 23.3% and 17.0% for SEP Question 3 for patients with mild, moderate and severe baseline ED, respectively (published MCID according to Araujo *et al*. 2012 [32])
- Responder analyses will also be conducted using responder thresholds (that represent meaningful within-patient changes) in the three co-primary endpoints that are determined using a suitable set of data from this study, prior to study unblinding. Receiver operating characteristics (ROC) analyses will be performed to define the thresholds using the PGI-S and PGI-C as anchors, with the thresholds chosen to balance sensitivity and specificity, supplemented with both empirical cumulative distribution functions and probability density functions. The thresholds defined from these analyses will be included in the final SAP prior to breaking the blind.

The following secondary efficacy analyses will be conducted in a more exploratory way making use of the FAS data in the selected doses and placebo over both stages:

- The GAQ will be analysed via logistic regression including terms for treatment group, site and baseline ED severity (categorical variable)
- The change in the other domains of the IIEF questionnaire, the other SEP questions (Questions 1, 4 and 5), the overall SEAR questionnaire score, the scores in the two subdomains of the SEAR questionnaire (sexual relationship satisfaction and confidence) and the PGI-S at time points 4, 8 and 12 weeks will be analysed using ANCOVA as described for the primary endpoint analysis for SEP Questions 2 and 3. The PGI-C will be analysed using an analysis of variance (ANOVA)
- Subjective measures of the time of onset and duration of action (erection) and erection hardness will be analysed using Wilcoxon ranks for each intercourse attempt, averaged across intercourse attempts within each 4-week period for each subject. The averaged Wilcoxon rank data will be analysed using ANCOVA as described for the primary endpoint analysis

- Usage and application question responses will be summarised by treatment group

All efficacy assessments provided by the female partners will be analysed using the same statistical models as for the male subjects.

Opel-label extension phase:

Summary statistics for all efficacy measures will be given for actual values and changes from baseline (where applicable), where the baseline assessments are the ones prior to the double-blind phase. Individual components of composite scores (but not domains) will not be summarised unless otherwise stated. Individual components as well as domains will be presented in listings together with the scores used in the analysis.

Summaries of responders at each Visit will be given using the same responder definitions as per the analysis of double-blind phase.

14.6 Evaluation of Safety

Safety assessments will include physical examinations, vital signs (BP, HR, body temperature), standard clinical laboratory safety tests (haematology, biochemistry, urinalysis), 12-lead ECGs and monitoring of AEs pre- and post-treatment. Safety analysis will be based on the safety set for the double-blind phase and the OLAS for the open-label extension phase. Missing values will not be imputed.

Dosing duration and frequency will be summarised.

14.6.1 Vital Signs

Vital signs will be summarised for each treatment group by visit. Summary statistics will be provided for actual values and change from baseline, where the baseline value is the last value prior to dosing.

14.6.2 Clinical Laboratory Safety Tests

The results of clinical laboratory tests and change from baseline will be summarised for each treatment group by visit, where the baseline value is the last value prior to dosing. Values outside the normal ranges will be flagged and summarised.

14.6.3 ECGs

ECGs will be summarised for each treatment group by visit. Summary statistics will be provided for actual values (based on the mean of the triplicate readings for each subject) and change from baseline, where the baseline is defined as the mean of the values recorded at the screening (Visit 1) ECG.

14.6.4 Adverse Events

All AEs will be listed by system organ class (SOC) and preferred term (PT) classifications assigned to the event using the Medical Dictionary for Regulatory Activities (MedDRA) (Version 20.1 or higher). The number of AEs and number (and %) of subjects with AEs will be summarised by SOC and PT. In addition, AEs will be summarised by severity, relationship to treatment, time to onset (following the last dose of IMP prior to AE start date) and duration (offset).

Listings will be presented for SAEs and AEs leading to withdrawal.

14.7 Sample Size

A sample size of n = 250 per group (total N = 1000) provides 90% study power to reject the null hypotheses for all three primary endpoints when comparing a MED2005 dose to placebo, using a Bonferroni corrected type I error, adjusting for three dose versus placebo comparisons. The sample size calculations were performed using EAST 6.4 in the continuous endpoint two-sample multiple comparisons multiple endpoints platform using the assumptions described below.

It is assumed that MED2005 is slightly better than alprostadil [33]. For the higher two doses alprostadil saw an improvement compared to placebo for IIEF-EF of 3.2 and 3.1 (least squares [LS] mean changes), giving an average of 3.15, for SEP Question 2 of 9.6 and 11.3 (LS mean changes), giving an average of 10.65, and for SEP Question 3 of 13.4 and 8.7 (LS mean changes), giving an average of 11.05. In Study FM53 there was a better improvement in SEP Question 3 than SEP Question 2 so the sample size assumptions take this into account. PDE 5's also appear to find SEP Question 2 more difficult to improve compared to placebo than SEP Question 3. Compared with the alprostadil results therefore it is assumed that the difference of MED2005 minus placebo for IIEF-EF is 3.2, for SEP Question 2 is 11.5 and for SEP Question 3 is 12.

Estimates of standard deviations are based on FM53 and published results from other ED treatments and are assumed to be 5.6, 33 and 33 for IIEF-EF, SEP Question 2 and Question 3, respectively [33, 34]. The differences between MED2005 and placebo for each endpoint are assumed to follow a multivariate normal distribution with the following correlation matrix, based on observed data from study FM53.

	IIEF-EF	**SEP Question 2**	**SEP Question 3**
IIEF-EF	1	0.5	0.5
SEP Question 2	0.5	1	0.6
SEP Question 3	0.5	0.6	1

For the open-label extension phase it is planned to recruit a total of 450 male subjects in order to meet ICH requirements.

15. DATA MANAGEMENT

The data management process is described below and subject to change after finalisation of the study roles and responsibilities which will be described in detail in the Data Handling Plan (DHP).

The CRO's Data Management department will be responsible for developing and maintaining the DHP; setting-up and validating the clinical study database; programming validation checks; entering data into the clinical study database; reviewing data for accuracy, completeness and consistency between the eCRFs and the database; and verifying adherence to the clinical pharmacology study protocol and the DHP. The study database will be built using appropriate software based on the eCRF design. Data entry will be performed using a double independent data entry method with second pass verification.

Clinical laboratory safety data will be loaded into the database as an electronic data transfer file according to the validated transfer specification document. Clinical data queries will be

generated and resolved according to the DHP. Clinical data queries will be resolved with the assistance of CRO and site clinical staff.

The study will involve two database locks. For the data up to and including Visit 6, after all clinical data queries are resolved, the final error rate is confirmed and QC checks are considered acceptable, the database will be locked. The same process will apply at the end of the open-label extension phase. Standard SAS® datasets will be generated from the final study database ready for the analyses. A complete audit trail of all corrections will be available for inspection.

AEs, diagnoses from Medical History and procedures from Surgical History will be classified according to the current version of MedDRA (Version 20.1 or higher). Previous and Concomitant Medications will be coded using the current version of the WHODrug dictionary (Version 1 March 2017 or higher). SAEs in the clinical database will be reconciled with the safety database.

15.1 Case Report Forms

eCRFs, paper diaries (for the collection of AEs and concomitant medications) and ePRO devices will be used to record the data in the study.

The Study Monitor will check data at the monitoring visits to the study sites. The PI will ensure that the data in the eCRFs are accurate, complete and legible.

Any missing, impossible (inconsistent with human life) or inconsistent recordings in the eCRFs will be referred back to the PI and documented for each individual subject before clean file status is declared.

16. SPONSOR AND INVESTIGATOR RESPONSIBILITIES

This study will be conducted in accordance with current applicable regulations, ICH, EU Directive 2001/20/EC and local ethical and legal requirements.

16.1 Sponsor Responsibilities

16.1.1 GCP Compliance

FMD and any third party to whom aspects of the study management or monitoring have been delegated will undertake their roles for this study in compliance with all applicable regulations and ICH GCP Guidelines.

FMD assigns the ICH compliance statement for the study to the CRO and ensures that the CRO complies with ICH GCP through a program of oversight activities including, but not limited to, review of project meeting minutes, attending initiation visits, and review of monitoring reports, etc.

Visits to the sites will be conducted to inspect study data, subject medical records and eCRFs in accordance with current GCP and the respective local and national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by Regulatory Authorities.

16.1.2 Regulatory Approval

FMD will ensure that local Regulatory Authority requirements are met before the start of the study. FMD (or a nominated delegate) will be responsible for the preparation, submission and

confirmation of receipt of any Regulatory Authority approvals required prior to study commencement.

16.1.3 Indemnity/liability and Insurance

FMD will adhere to the recommendations of the Association of British Pharmaceutical Industry (ABPI) Guidelines. A copy of the indemnity document will be supplied to the CRO before study initiation.

FMD will ensure that suitable insurance cover is in place prior to the start of the study. An insurance certificate will be supplied to the sites.

16.1.4 Protocol Management

All protocols and amendments will be prepared by FMD and/or the CRO. If it becomes necessary to issue a protocol amendment during the course of the study, FMD will notify the CRO and collect documented Investigator Agreements to the amendment.

16.1.5 End of Study Notification

FMD (or a nominated delegate) will submit an end of study notification to the Competent Regulatory Authority of the Member State within 90 days of the end of the study, in accordance with EU Directive 2001/20/EC and to the local Regulatory Authority according to applicable regulatory requirements. FMD will forward copies of the end of study notification documents to the CRO. The CRO or their delegate will be responsible for submitting these to the relevant EC within 90 days of the end of the study.

16.1.6 Submission of Summary of Clinical Trial Report to Competent Regulatory Authorities of Member States Concerned and ECs

FMD will provide a summary of the clinical trial report within 1 year of the end of the study to the Competent Regulatory Authority of the Member States concerned, as required by the regulatory requirement and to comply with the community guideline on GCP. FMD will provide the PI with a copy of the summary report to forward to the relevant EC.

16.2 Investigator Responsibilities

16.2.1 GCP Compliance

The PI will have been assigned by FMD to perform the study in accordance with ICH GCP Guidelines, EU Directive 2001/20/EC and the applicable regulatory requirements and local regulatory requirements.

It is the PI's responsibility to ensure that adequate time and appropriate resources are available at the individual study sites prior to commitment to participate in this study. The PI should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The PI will maintain a list of appropriately Qualified Persons (QPs) to whom the PI has delegated significant study-related tasks. Up-to-date copies of the *curriculum vitaes* for the PI, Co-Investigator(s) and essential study staff will be provided to FMD (or their delegate) before starting the study.

Agreement with the final clinical study report (CSR) will be documented by a dated signature of the PI, in compliance with Directive 75/318/EC, Directive 2001/83/EC and ICH E3 and local regulatory requirements.

16.2.2 Protocol Adherence and Investigator Agreement

The PI must adhere to the protocol as detailed in this document. The PI will be responsible for enrolling only those subjects who have met protocol eligibility criteria. The PI will be required to sign an Investigator Agreement to confirm acceptance and willingness for themselves and the Co-Investigator(s) to comply with the study protocol.

16.2.3 Documentation and Retention of Records

After completion of the study, all data and documents relating to the study will be kept in a secure and orderly manner by the CRO or their delegate in a secure file in an electronic or paper TMF. The data will be available for inspection by FMD or their representatives. Unless other union law requires archiving for a longer period, the Sponsor and the CRO shall archive the content of the TMF for at least 25 years after the end of the study. However, the medical files of subjects shall be archived in accordance with national law. The CRO or their delegate must contact FMD before destroying any study-related documentation and it is the responsibility of FMD to inform the investigative sites of when these documents can be destroyed.

16.3 Ethical Considerations

This protocol complies with the principles of the World Medical Assembly (Helsinki 1964) and subsequent amendments.

16.3.1 Informed Consent

It is the responsibility of the PI to obtain written informed consent from all subjects and their female partners to enter the study and also to obtain written informed consent from all subjects and their female partners to continue into the open-label extension phase. All consent documentation must be in accordance with applicable regulations and GCP. Each subject and his partner is required to sign the subject and partner ICF after they have both read the written subject information and received an explanation of what the study involves. This can include, but is not limited to: the objectives, potential benefits and risks, inconveniences and the subject's/partner's rights and responsibilities. Signed consent forms must remain on file and must be available for verification by Study Monitors at any time. A signed original copy of the informed consent documentation (ICF or Subject Information and ICF, as applicable) must be given to the subject and his partner or the subject's/partner's legally authorised representative.

The CRO will provide the Sponsor with a copy of the EC approved consent forms, and a copy of the EC written approval, prior to the start of the study. Additionally, if the EC required modification of the sample Subject Information and ICF documents provided by the Sponsor, the documentation supporting this requirement must be provided to the Sponsor.

16.3.2 Ethics Committee Approval

It is the responsibility of the CRO to submit this protocol, the informed consent documents (approved by FMD), relevant supporting information and all types of subject recruitment information to the relevant EC for review, and all must be approved prior to the start of subject screening. Advertisements must be approved by the EC prior to their use at the study site, if applicable. Prior to implementing changes in the study, FMD and the ECs must also approve any substantial amendments to the protocol and corresponding updates to the informed

consent documents. For non-substantial protocol amendments (that do not require EC approval) and subsequent updates of the informed consent documents, all changes will be done in agreement with FMD and the study sites.

The CRO is responsible for keeping the relevant EC apprised of the progress of the study and of any changes made to the protocol. FMD (or a nominated delegate) will keep the ECs informed of any serious and significant AEs.

16.4 Confidentiality

Data collected during this study may be used to support the development, registration or marketing of a medicinal product. FMD will control all data collected during the study, and will abide by the General Data Protection Regulation (GDPR) (EU) 2016/679 concerning the processing and use of subjects' personal data. For the purpose of GDPR, FMD will be the data controller.

After subjects have consented to take part in the study, their medical records and the data collected during the study will be reviewed by FMD and/or its representatives. These records and data may, in addition, be reviewed by the following: independent auditors who validate the data on behalf of FMD, national or local Regulatory Authorities, and the ECs which gave approval for this study to proceed.

Subjects will be known by a unique subject number. The results of this study containing the unique subject number and relevant medical information including ethnicity may be recorded and transferred to and used in other countries throughout the world, which may not afford the same level of protection that applies within the EU and countries participating this study. The purpose of any such transfer would be to support regulatory submissions made by FMD in such countries.

16.5 Publication Policy

If the Sponsor, CRO and CI agree that it is desirable to publish the results of this study; all parties will liaise in good faith to publish the results. The CRO/CI agree to obtain the Sponsor's prior written approval of such publications.

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18. APPENDIX 1

18.1 IIEF Questionnaire

INTERNATIONAL INDEX
OF ERECTILE FUNCTION
(IIEF)

Subject Questionnaire

These questions ask about the effects that your erection problems have had on your sex life over the last four weeks. Please try to answer the questions as honestly and as clearly as you are able. In answering the questions, the following definitions apply:

- sexual activity includes intercourse, caressing, foreplay & masturbation
- sexual intercourse is defined as sexual penetration of your partner
- sexual stimulation includes situation such as foreplay, erotic pictures etc.
- ejaculation is the ejection of semen from the penis (or the feeling of this)
- orgasm is the fulfilment or climax following sexual stimulation or intercourse

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	Over the past 4 weeks:	*Please check **one** box only*
☐ Q1	How often were you able to get an erection during sexual activity?	0 No sexual activity 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q2	When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	0 No sexual activity 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q3	When you attempted intercourse, how often were you able to penetrate (enter) your partner?	0 Did not attempt intercourse 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q4	During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	0 Did not attempt intercourse 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q5	During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	0 Did not attempt intercourse 1 Extremely difficult 2 Very difficult 3 Difficult 4 Slightly difficult 5 Not difficult

☐ Q6	How many times have you attempted sexual intercourse?	0 No attempts 1 One to two attempts 2 Three to four attempts 3 Five to six attempts 4 Seven to ten attempts 5 Eleven or more attempts
☐ Q7	When you attempted sexual intercourse, how often was it satisfactory for you?	0 Did not attempt intercourse 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q8	How much have you enjoyed sexual intercourse?	0 No intercourse 1 No enjoyment at all 2 Not very enjoyable 3 Fairly enjoyable 4 Highly enjoyable 5 Very highly enjoyable
☐ Q9	When you had sexual stimulation or intercourse, how often did you ejaculate?	0 No sexual stimulation or intercourse 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q10	When you had sexual stimulation or intercourse, how often did you have the feeling of orgasm or climax?	1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q11	How often have you felt sexual desire?	1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q12	How would you rate your level of sexual desire?	1 Very low or none at all 2 Low 3 Moderate 4 High 5 Very high
☐ Q13	How satisfied have you been with your overall sex life?	1 Very dissatisfied 2 Moderately dissatisfied 3 Equally satisfied & dissatisfied 4 Moderately satisfied 5 Very satisfied
☐ Q14	How satisfied have you been with your sexual relationship with your partner?	1 Very dissatisfied 2 Moderately dissatisfied 3 Equally satisfied & dissatisfied 4 Moderately satisfied 5 Very satisfied
☐ Q15	How do you rate your confidence that you could get and keep an erection?	1 Very low 2 Low 3 Moderate 4 High 5 Very high

18.2 SEP Questionnaire

Male Version

1. Sexual Encounter Profile Diary question number 1:

'Were you able to achieve at least some erection (some enlargement of the penis)?'

2. Sexual Encounter Profile Diary question number 2:

'Were you able insert your penis into your partner's vagina?'

3. Sexual Encounter Profile Diary question number 3:

'Did your erection last long enough for you to have successful intercourse?'

4. Sexual Encounter Profile Diary question number 4:

'Were you satisfied with the hardness of your erection?'

5. Sexual Encounter Profile Diary question number 5:

'Were you satisfied overall with this sexual experience?'

Female Version

1. Sexual Encounter Profile Diary question number 1:

'Was your partner able to achieve at least some erection (some enlargement of the penis)?'

2. Sexual Encounter Profile Diary question number 2:

'Was your partner able to insert his penis into your vagina?'

3. Sexual Encounter Profile Diary question number 3:

'Did your partner's erection last long enough for you to have successful intercourse?'

4. Sexual Encounter Profile Diary question number 4:

'Were you satisfied with the hardness of your partner's erection?'

5. Sexual Encounter Profile Diary question number 5:

'Were you satisfied overall with this sexual experience?'

18.3 SEAR Questionnaire

Male and Female Version

SEAR domains (subscales)	SEAR items (for women/men)
Sexual relationship domain	1. I felt relaxed about initiating sex with my partner.
	2. I felt confident that during sex my arousal/erection would last long enough.
	3. I was satisfied with my sexual performance.
	4. I felt that sex could be spontaneous.
	5. I was likely to initiate sex.
	6. I felt confident about performing sexually.
	7. I was satisfied with our sex life.
	8. My partner was unhappy with the quality of our sexual relations.
Confidence domain (Self-esteem subscale)	9. I had good self-esteem.
	10. I felt like a whole woman/man.
	11. I was inclined to feel that I am a failure.
	12. I felt confident.
Confidence domain (Overall relationship subscale)	13. My partner was satisfied with our relationship in general.
	14. I was satisfied with our relationship in general.

Response options
Almost always/always.
Most times (much more than half the time).
Sometimes (about half the time).
A few times (much less than half the time).
Almost never/never.
Scoring
All questions except questions 8 and 11 were scored as 1=almost never/never, 2=a few times (much less than half the time), 3=sometimes (about half the time), 4=most times (much more than half the time), and 5=almost always/always. Questions 8 and 11 were reverse scored, with 5=almost never/never, 4=a few times (much less than half the time), 3=sometimes (about half the time), 2=most times (much more than half the time), and 1=almost always/always. Thus, a higher score signified a more favorable response for all 14 items.
Domain (Sexual Relationship, items 1–8; Confidence, items 9–14), subscale (Self-Esteem, items 9–12; Overall Relationship, items 13 and 14), and total scores (items 1–14) were computed by summing their respective items. Each domain score, subscale score, and overall (total) score was transformed onto a 0–100 scale: transformed score=100 × [(actual raw score−lowest possible raw score)/possible raw score range]. Higher scores indicated a more favorable response (0=least favorable, 100=most favorable).

18.4 GAQ

Male Version

1. GAQ question number 1:

'Has the treatment you have been taking improved your erectile function?'

2. GAQ question number 2:

'If yes, has the treatment improved your ability to engage in sexual activity?'

Female Version

1. GAQ question number 1:

'Has the treatment you have been taking improved your partner's erectile function?'

2. GAQ question number 2:

'If yes, has the treatment improved his ability to engage in sexual activity?'

18.5 PGI Scales

PGI-S (Severity) Scale

Please choose the response below that best describes the severity of your erectile dysfunction over the past 4 weeks.

1. None.
2. Mild.
3. Moderate.
4. Severe.
5. Very severe.

PGI-C (Change) Scale

Please choose the response below that best describes the overall change in your erectile dysfunction since you started using the study treatment.

1. Very much better.
2. Moderately better.
3. A little better.
4. No change.
5. A little worse.
6. Moderately worse.
7. Very much worse.

18.6 Onset and Duration of Action (Erection) and Erection Hardness Questions

Male and Female Version

1. After application of the gel, when did you (and your partner) begin to notice your erection starting?

Please note: subjective measures of time will be used for all the following questions:

- Almost immediately.
- Under 5 minutes.
- Between 5 and 10 minutes.
- Between 10 and 20 minutes.
- Between 20 and 30 minutes.
- Between 30 minutes and 1 hour.
- Over 1 hour.
- Not at all.

2. After application of the gel, when were you (and your partner) able to have penetrative sex?

- Almost immediately.
- Under 5 minutes.
- Between 5 and 10 minutes.
- Between 10 and 20 minutes.
- Between 20 and 30 minutes.
- Between 30 minutes and 1 hour.
- Over 1 hour.
- Not at all.

3. From the time you began to notice your (your partner's) erection starting, how long did it last (estimated minutes)?

- Under 5 minutes.
- Between 5 and 10 minutes.
- Between 10 and 20 minutes.
- Between 20 and 30 minutes.
- Between 30 minutes and 1 hour.
- Over 1 hour.
- Not at all.

4. How would you rate the hardness of your (your partner's) erection during your sexual encounter?

0 No enlargement

1 Penis was larger, but not hard

2 Penis was hard, but not hard enough for penetration

3 Penis was hard enough for penetration, but not completely hard

4 Penis was completely hard and fully rigid

18.7 Questions on Usage and Application

1. Who applied the gel most of the time? You/Your partner
2. Did you/your partner find the tube easy to use? Yes/No
3. Did you/your partner find the gel easy to apply? Yes/No
4. Would you have preferred to use a different applicator such as a pad? Yes/No
5. Did you incorporate the application of the gel as part of your foreplay? Yes/No
6. Did you like using the gel? Liked a lot/Mostly liked/Neither liked or disliked/Disliked/Disliked a lot.