CLINICAL INVESTIGATION PLAN

TITLE: A multi-centre, randomised, open-label, home use, parallel group, clinical investigation of topically-applied MED3000 gel and oral tadalafil (5 mg) tablets for the treatment of erectile dysfunction (ED) over a 24 week period

SPONSORS REF. NUMBER: FM71

VERSION AND DATE: 7.0 dated 02Mar2022

PHASE: Pivotal

DEVICE: MED3000

REVISION HISTORY:

Version 1.0	New clinical investigation plan prepared to form the basis of pre-submission discussions with the US Food and Drugs Administration (CDRH) only. This version was not formally submitted for approval by any Regulatory Authority nor Ethics Committee.
Version 2.0	FM71 clinical investigation plan revised to include US Food and Drug Administration (CDRH) recommendations on the design of the proposed clinical investigation. This version was not formally submitted for approval by any Regulatory Authority nor Ethics Committee.
Version 3.0	The age of eligibility has been increased from 18 to 22 years of age which is in accordance with the US Food and Drug Administration (CDRH) definition of an adult population.
Version 4.0	• Section 21 updated to include AE expectedness review as part of the FMD Medical Advisor's assessment. • Corrected addresses in section 5. • Changed the term "Unexpected Serious Adverse Device Effect" to "Unanticipated Serious Adverse Device Effect" throughout. • Inclusion of an AE category of "expectedness". • Clarification on how AEs from female partners will be collected. • Section 14.9 updated stating that the number of intercourse attempts during treatment will be estimated using the number of completed onset of action questionnaires.

Version 5.0	• The volume of blood drawn from each patient during the investigation has been corrected from 50 mL to 150 mL (Section 13.1)
Version 6.0 (US Only)	• Section 12.1 updated to include text that patients will be expected to complete IIEF and SEAR questionnaires using a tablet device.
Version 7.0	• Deletion of text *"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 investigation product?'"* in section 13.11. As per the preceding sentence in section 13.11.1, the PI assesses the relatedness of AEs to investigation treatment as related, probably related, possibly related or unrelated, and this is what is captured in the eCRF. • Sections 6, 11, and 14.8.3 updated to include an exploratory objective, namely the comparison in onset of action times between patients receiving MED3000 and tadalafil, assessed whilst on treatment during the 24-week treatment period, as detailed in the Statistical Analysis Plan (V1.0 dated 02 Sep 2021) which was finalised before first patient enrolled. • Sections 6 , 11 and 14.5 updated with a clarification on the statistical analysis if randomisation/treatment errors occur, as detailed in the Statistical Analysis Plan (V1.0 dated 02 Sep 2021). In the case of randomisation/treatment errors, patients will be analysed according to treatment initially received at randomisation.

1. CLINICAL INVESTIGATION PLAN APPROVAL SIGNATURES

Version 7.0, dated 02 Mar 2022

Investigator's Agreement:

I have read this FMD Clinical Investigation Plan No. FM71

A multi-centre, randomised, open-label, home use, parallel group, clinical investigation of topically-applied MED3000 gel and oral tadalafil (5 mg) tablets for the treatment of erectile dysfunction (ED) over a 24 week period

I have fully discussed the objectives of this clinical Investigation and the contents of this Clinical Investigation Plan (CIP) with FMD (the Sponsor).

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

I agree to conduct this investigation according to this CIP and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the investigation in accordance with the EN ISO 14155:2020 standard on Good Clinical Practice (GCP) and with the applicable regulatory requirements.

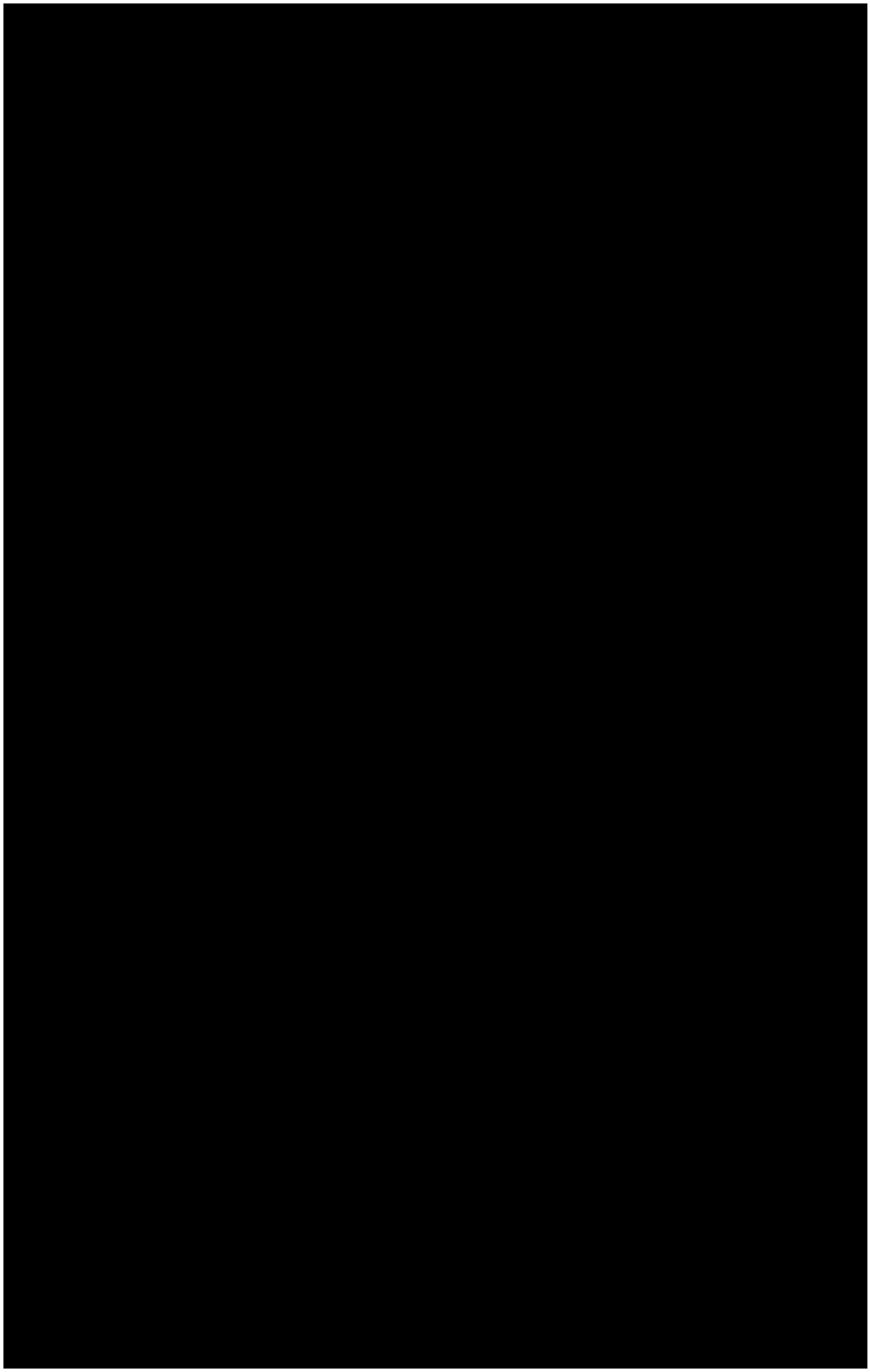
I understand that FMD may decide to suspend or prematurely terminate the clinical investigation at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the investigation I will communicate my intention immediately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

Principal Investigator:

Printed Name: _____ _____

Signature: _____ **Date:** _____

2. INVESTIGATION PERSONNEL



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4. LIST OF ABBREVIATIONS AND ACRONYMS

Abbreviation	Explanation
ABPI	Association of the British Pharmaceutical Industry
ACE	Angiotensin Converting Enzyme
ADE	Adverse Device Effect
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate Aminotransferase
AUA	American Urological Association
BMI	Body Mass Index
BP	Blood Pressure
CD	Compact Disc
CDRH	Center for Devices and Radiological Health
cGMP	Cyclic Guanosine Monophosphate
CIP	Clinical Investigation Plan
CIR	Clinical Investigation Report
CK	Creatine Kinase
CRO	Clinical Research Organisation
CRP	C-reactive Protein
CTCAE	Common Terminology Criteria for Adverse Events
CVD	Cardiovascular Disease
EC(s)	Ethics Committee(s)
ECG(s)	Electrocardiogram(s)
eCRF	electronic Case Report Form
ED	Erectile Dysfunction
EF	Erectile Function
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FMD	Futura Medical Developments Ltd
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GGT	γ-Glutamyl Transpeptidase

GP	General Practitioner
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
IP	Inorganic Phosphate
IRB(s)	Institutional Review Board(s)
IUD	Intrauterine Device
IUS	Intrauterine System
IWRS	Interactive Web Response System
LDH	Lactate Dehydrogenase
LS	Least-Squares
MCID	Minimal Clinically Important Difference
MedDRA	Medical Dictionary for Regulatory Activities
NAION	Non-arteritic Anterior Ischaemic Optic Neuropathy
NF	National Formulary
NHS	National Health Service
NIH	National Institutes of Health
NSAID	Non-Steroidal Anti-Inflammatory Drug
OPC	Objective Performance Criteria
OTC	Over the Counter
PDE-5	Phosphodiesterase type 5
PGE1	Prostaglandin E1
Ph.Eur	Pharmacopoeia Europaea
PI	Principal Investigator
PRO	Patient-reported Outcome
PT	Preferred Term

QA	Quality Assurance
QC	Quality Control
QoL	Quality of Life
QP	Qualified Person
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SEAR	Self-Esteem And Relationship
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP	Standard Operating Procedure
T½	Half-life
TEAE	Treatment-emergent adverse event
TMF	Trial Master File
ULN	Upper Limit of Normal
US	United States
USADE	Unanticipated Serious Adverse Device Effect
USP	United States Pharmacopeia
v/v	Volume per volume
w/w	Weight in weight

5. SPONSOR, COORDINATING INVESTIGATOR, PRINCIPAL INVESTIGATORS AND INVESTIGATIONAL SITE(S)

SPONSOR

[redacted]

COORDINATING INVESTIGATOR

[redacted]

PRINCIPAL INVESTIGATORS, AND INVESTIGATION SITES:

Details of the Principal Investigators (PIs) and sites involved in this investigation will be maintained in a separate tracker.

CENTRAL LABORATORY:

[redacted]

CLINICAL REASEARCH ORGANISATION

[redacted]

European Union Legal Representative

[redacted]

6. SYNOPSIS OF THE CLINICAL INVESTIGATION

Clinical Investigation Ref: FM71	**Investigational Device:** MED3000 gel

Investigation Title: A multi-centre, randomised, open-label, home use, parallel group, clinical investigation of topically-applied MED3000 gel and oral tadalafil (5 mg) tablets for the treatment of erectile dysfunction (ED) over a 24 week period

Sites: Approximately 24 investigation sites in countries that may include Poland, Slovakia, Georgia and Bulgaria, and 1 site in the United States (US).

[redacted]

Duration of Investigation: It is planned that each patient (and his female partner) will participate in the investigation for up to 30 weeks. This includes a screening period of up to 5 weeks, a 24-week treatment period, and a 1-week follow-up period.

Objectives: This clinical investigation is intended to assess the effectiveness and safety of MED3000 gel over a 24-week treatment period in male patients clinically diagnosed with ED.

Primary Effectiveness Objective:

- To demonstrate an improvement compared to baseline of the erectile function (EF) domain of the International Index for Erectile Function (IIEF) in patients randomised to MED3000, assessed at 24 weeks post-randomisation by rejecting the null hypothesis that the mean change from baseline is less than or equal to zero.
- To observe a mean change from baseline of the IIEF-EF in patients randomised to MED3000, assessed at 24 weeks post-randomisation, greater than or equal to the minimal clinically important difference (MCID) of 4, as published by Rosen et al 2011 [43].

The endpoint for the primary effectiveness objective is the EF domain of the IIEF, assessed at 24 weeks post-randomisation.

The primary objective will be assessed according to the outcomes in all randomised patients at 24 weeks attributed to the initially received treatment [45]. Treatment discontinuation reasons considered to be adversely related to randomised treatment (for example, lack of effectiveness or related adverse events [AEs]) are considered as attributable and will be treated as an unfavourable outcome; while a hypothetical estimand strategy, that is, as if the patient carried on treatment, will be used for intercurrent events not considered to be related to randomised treatment (for example lost to follow-up or unrelated AEs).

Secondary Effectiveness Objectives:

- To demonstrate a speed of onset of action from the application of MED3000 gel to the time when the patient notices their erection starting. Specifically, the objective is to provide evidence that the mean percentage of MED3000 uses per patient that result in the patient noticing their erection starting within a certain period of time is greater than 30%, assessed whilst on treatment during the 24-week treatment period.
- To demonstrate a speed of onset of action from the application of MED3000 gel to the time when the patient is able to have penetrative sex. Specifically, the objective is to provide evidence that the mean percentage of MED3000 uses per patient that result in the ability to have penetrative sex within a certain period of time is greater than 30%, assessed whilst on treatment during the 24-week treatment period.

Only on-treatment assessments made up to the time of treatment discontinuation will be used. Time from application of MED3000 gel will be assessed at 5 minutes, 10 minutes and 15 minutes.

[redacted]

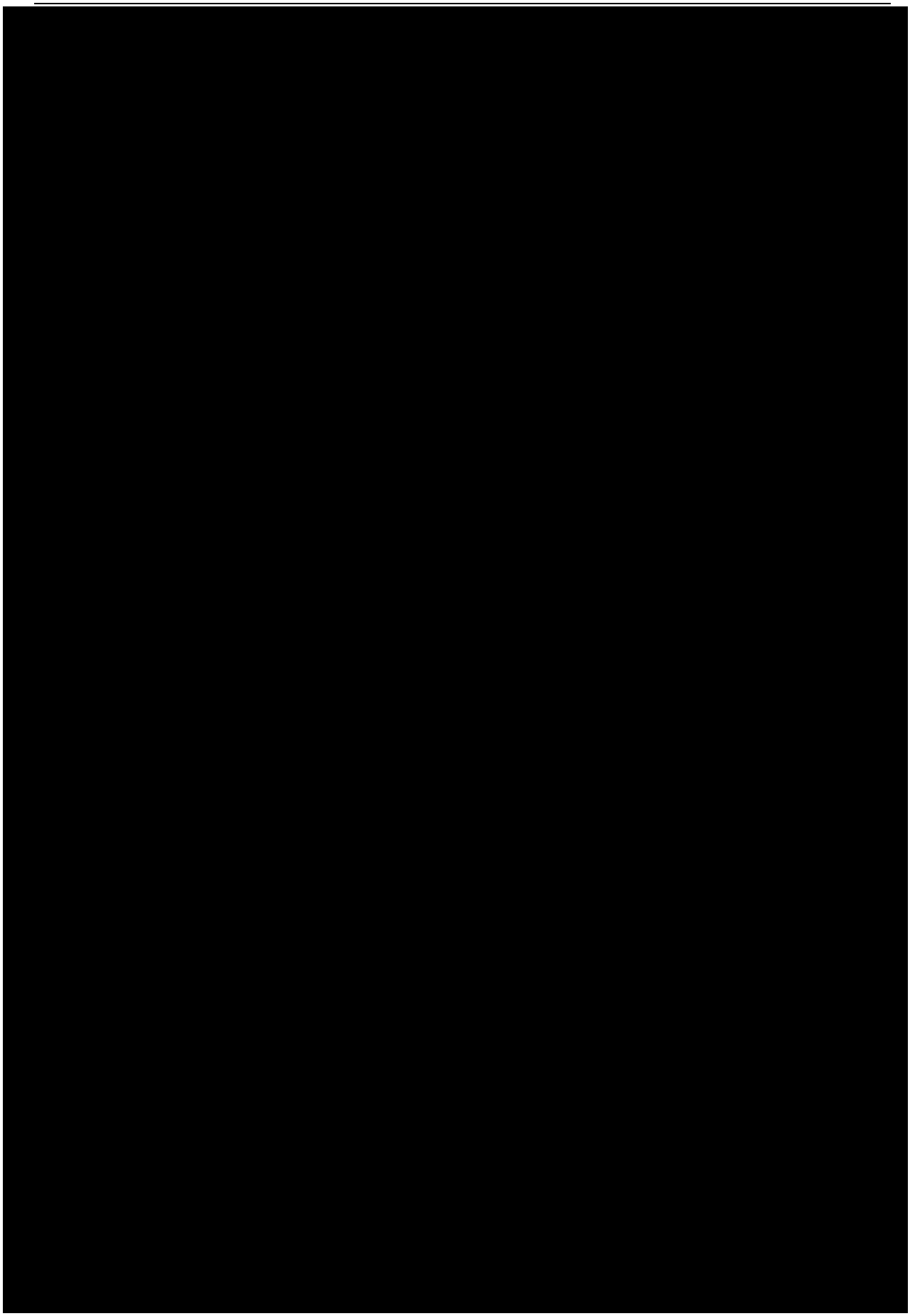
[redacted]

Safety Objectives:

The safety objectives are to evaluate the safety of MED3000 and tadalafil using occurrence and severity of treatment-emergent adverse events (TEAEs) and standard physical and laboratory assessments. Safety will be evaluated using a "while on treatment" strategy.

Investigation Design:

[redacted]



[redacted]

Statistical Methods:

[redacted]

Effectiveness Analyses:

[redacted]

Safety Analyses:

[redacted]

7. IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATION DEVICE

7.1 Description of the Medication/Device

The clinical investigational device is MED3000, a gel formulation currently under development by Futura Medical Developments Ltd (FMD) as a topical treatment for erectile dysfunction (ED). MED3000 will be provided to patients in tubes, each tube containing 800 mg of MED3000 gel. Each tube will contain sufficient gel to apply a single dose (approximately 300 mg) of MED3000 at each application.

Tadalafil (5 mg) tablets will also be used in this clinical investigation. The medication will be packaged in boxes; each box containing twelve 5 mg tablets.

Neither investigational product will be administered using a specific dosing frequency regimen. Instead, they should be administered on an 'as needed' basis (i.e. the investigational product is taken prior to a sexual intercourse attempt).

Details of the manufacturer:

[redacted]

Name/Number of model to permit full identification:

Not applicable.

Device traceability:

MED3000 gel will be supplied to the sites in single-dose tubes contained within an outer carton (i.e. each carton contains 4 tubes). Both carton and tubes will display details of the investigational device's batch number and unique kit identification number.

Tadalafil (5 mg) tablets will be provided to patients in boxes; each box containing 12 tablets. All boxes will be labelled with a unique kit identification number.

Traceability of dispensed and returned investigational product (i.e. MED3000 gel and tadalafil [5 mg] tablets) will be managed using a combination of Interactive Web Response System (IWRS) and site maintained dispensing/return logs.

Intended use:

The intended use of MED3000 gel is for the treatment of ED in adult males. The clinical investigation will be conducted in patients with ED in both the United States (US) and Europe to demonstrate the performance over a 24-week period. The US site will recruit African-Americans exclusively to ensure patient ethnic diversity and associated comorbidities.

Patients with hypogonadism, prostatectomy and uncontrolled or severe diabetes will be specifically excluded from the clinical investigation (see Section 12.3.1 Inclusion and exclusion criteria). The rationale for this exclusion is based on the fact that these groups respond poorly to all current treatments for ED, including PDE5 inhibitors, and there is no evidence to suggest MED3000 will overcome this unresponsiveness.

Product labelling will reflect the absence of data in these groups. The proposed indication for use of MED3000 will be for the treatment of ED in adult males and include an appropriate caveat excluding relevant comorbidities.

Details of the device components:

[redacted]

Table 1 MED3000 Qualitative Formula

[redacted]

Summary of required training: The device is applied to the glans penis immediately prior to sexual intercourse. Training will be provided by the site staff using a model phallus to demonstrate how the patient or partner applies the medication. Further training may be provided to the participants as required. Previous studies have assessed that MED3000 is a safe product with an extremely favourable safety profile.

Description of specific medical procedures: This product is intended for home use. No specific medical or interventional procedures are necessary.

Investigator's Brochure: Details of previously conducted clinical and non-clinical studies can be found in the MED3000 investigator's brochure (IB).

8. JUSTIFICATION OF THE DESIGN OF THE CLINICAL INVESTIGATION

8.1 Introduction

ED is the consistent or recurrent inability to attain and/or maintain a penile erection sufficient for satisfactory sexual performance. Although not seen as life-threatening, ED is closely associated with a number of physical conditions and may affect psychosocial health [1].

ED is a highly prevalent condition. The pivotal Massachusetts Male Aging Study estimated that as many as 52% of men aged 40 years or over have some degree of ED (combined prevalence of minimal, moderate and complete ED) [2]. More than 150 million men worldwide are thought to be affected by ED, and ED is projected to impact in excess of 320 million men worldwide by 2025 [3, 4].

Factors that might contribute to this increasing prevalence include the ageing of the world's population, as well as dietary changes, health behaviours and an emerging diabetes pandemic [3, 4].

ED can affect all age groups; however, the frequency of ED clearly increases with age [2]. As an example, men aged 60–69 years of age experience more than four times the level of ED compared with men in the 40–49 year age group [3]. Nevertheless, ED is increasingly affecting men younger than 40 years with the prevalence of ED in young men estimated to be as high as 30% [5]. The burden of ED among differing racial and ethnic groups is uncertain and under studied. While one study suggested that Asian and black men are less likely to have severe ED compared with white men, another suggested an increased risk in black and Hispanic men, and a third found no effect of race/ethnicity on ED [6, 7, 8]. Smith *et al*. (2009) suggests that the effects of race or ethnicity may depend on a complex interaction between socioeconomic, demographic, cultural and lifestyle characteristics [6].

The degree of severity of ED is highly variable among men, but is often described as mild, moderate or severe. The International Index for Erectile Function (IIEF), a widely used, multidimensional, self-report instrument for the assessment of ED, is commonly used for diagnostic evaluation of ED severity. The IIEF consists of 15 questions divided into five domains of sexual function: erectile function (EF), orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction. An evaluation of severity is based on the EF domain, classified into five categories based on the score achieved: no ED, mild ED, mild to moderate, moderate, and severe [9]. The IIEF is discussed further in Justification of Clinical Endpoints of the Clinical Investigation Plan (CIP) (Section 9).

There are many potential causes of ED. These can be psychological, organic or of mixed aetiology [10].

The pathophysiology of ED is complex and may be anatomical, vascular, neuronal, hormonal, traumatic or drug-induced, among others. ED is often attributable to organic causes such as altered blood flow to and from the penis possibly owing to damage to the arteries, endothelium or smooth muscle. Damage can be the result of a chronic condition, with an increased risk particularly evident in men with cardiovascular diseases (CVD) such as hypertension, heart disease and diabetes [4]. Indeed, the underlying risk factors associated with ED (e.g. age, sedentary lifestyle, obesity, smoking, metabolic syndrome) are common to CVD in general, and the pathophysiologies of ED and CVD are thought to share several similarities, including atherosclerosis, endothelial dysfunction, structural vascular damage and subclinical inflammation [1, 10, 11, 12].

ED is also common in men with other conditions such as depression, spinal cord injury, chronic kidney disease, those undergoing cancer treatment and following prostatectomy [4]. Common medications, such as antihypertensives, non-steroidal anti-inflammatory drugs (NSAIDs) and antacids, may also be linked to ED [11, 13]. Furthermore, ED has been associated with the use of less common medications, such as psychotropic drugs (e.g. antidepressants, atypical antipsychotics and benzodiazepines) [13, 14].

Situational or psychosocial factors may also play a causative role and can be complex and multidimensional. Situational/psychosocial causes can be related to performance anxiety, psychological distress (e.g. depression, general anxiety, post-traumatic stress disorder) or relationship problems, as well as age-related reductions in libido or chronic sexual intimacy disorders [5]. High levels of performance anxiety may worsen or maintain ED which can cause a vicious cycle of anxieties and stress leading to impaired sexual arousal and sexual avoidance [1, 5, 12].

The genetic aspects of ED are not well studied or completely understood. Multiple genetic variants potentially associated with ED have been identified, but few have been consistently replicated across ED models [15].

In summary, ED is a common but complex condition with a multifaceted aetiology that is still not fully understood.

8.2 Impact of Erectile Dysfunction

ED is a chronic condition affecting male sexual function and has a significant health economic impact worldwide [16, 17, 18].

On an individual level, ED can be a major factor contributing to an unsatisfactory sexual life, may impact physical and psychosocial health and can negatively affect a man's quality of life (QoL), including his mental health (including causing anxiety and depression), his relationship and his general wellbeing [1, 2, 19]. There is a wealth of evidence suggesting ED has a detrimental effect of many aspects of QoL for both men and their partners, and that treatment can help [20]. Nevertheless, despite the availability of treatments, many men avoid seeking medical help for the condition, which only adds to the problem [1].

ED is a serious public health problem and is costly to both the individual men who suffer from ED and also healthcare systems, with the largest costs attributable to diagnosis and treatment [17]. Between 1997 and 2000, the costs to the UK National Health Service (NHS) increased from £29.4 to £73.8 million. In 2000, most NHS costs came from specialist and general practitioner (GP) consultations, sildenafil prescriptions and psychosexual therapy. The authors thought the increased costs were mainly owing to a three-fold increase in the number of men presenting to GPs with ED, many of whom were then referred for specialist consultations [21]. Of note, minimal research has been carried out to assess the costs of modern therapeutic approaches to ED, and many studies are dated [18]. The economic landscape for ED treatment is changing and costs to healthcare systems have increased owing to ageing populations, increasing ED prevalence accompanied by more severe comorbidities and increased demand for treatment [18].

In light of this, a correct diagnosis of ED and its comorbidities, as well as a better understanding of the causes and treatments of ED should not only improve QoL, sexual and general health, but also reduce the burden of ED on societies [4]. Furthermore, because of the strong link between ED and CVD (and other conditions), ED could potentially act as a marker for various other disorders, helping to cut healthcare costs in these areas as well.

8.3 Management of Erectile Dysfunction

There are a number of published evidence-based and multidisciplinary expert consensus-based guidelines for the management of ED [1, 10, 12, 19, 22, 23]. The goal of ED treatment is to restore or enhance sexual function and to improve the individual and his partner's physical health and QoL while minimising adverse events (AEs) and diagnosis- and treatment-associated burden [22].

The management of ED usually follows a stepwise progression.

Following a thorough medical/sexual history, physical examination and appropriate laboratory testing (e.g. fasting serum glucose and/or glycated haemoglobin, lipid profile, morning total testosterone), the first-line approach for the treatment of ED is often lifestyle changes (e.g. changes

in diet and increased physical activity) and modifications to risk factors (e.g. smoking cessation, alcohol/drug intake, blood pressure [BP] treatment).

If the ED is thought to be associated with an underlying medical condition, all of the guidelines recommended that this should be managed accordingly as a first step of treatment. Most men will however be treated with therapeutic options that are not cause-specific. Lifestyle modifications are usually followed by (or used concurrently with) first-line oral pharmacotherapy with a selective phosphodiesterase type 5 (PDE-5) inhibitor such as sildenafil (sold under the brand name Viagra® [Pfizer Inc], among others), tadalafil (sold under the brand name Cialis® [Eli Lilly and Company], among others), vardenafil (sold under the brand name Levitra® [Bayer Healthcare, GlaxoSmithKline, Schering-Plough], among others) and avanafil (sold under the brand names Stendra®/Spedra® [Vivus Inc, Mitsubishi Tanabe, Menarini]).

The enzyme PDE-5 is found in relatively high concentrations in the blood vessels of the corpus cavernosum, or erectile body, of the penis. PDE-5 inhibitors obstruct the PDE-5 enzyme from breaking down cyclic guanosine monophosphate (cGMP) in the cavernosal tissue, the accumulation of which acts to increase arterial blood flow which causes smooth muscle relaxation in the corpora cavernosa, vasodilation and consequent penile erection [2, 19, 22].

Although PDE-5 inhibitors are widely used in ED and their side-effects have been well documented, all PDE-5 drugs are contraindicated in men taking nitrates in any form (such as glyceryl trinitrate [GTN], isosorbide dinitrate and isosorbide mononitrate) for CVD; e.g. for angina or heart failure. In addition, dose adjustments may be required in certain populations; for example, older men, those with hepatic or renal impairments and those taking certain medications [1]. As oral drugs, PDE-5 inhibitors are commonly associated with systemic AEs such as headache, flushing and dyspepsia, which although often mild in intensity can contribute to significant treatment dropouts [20, 24, 25]. Furthermore, PDE-5 inhibitors are associated with treatment failure in a sizeable proportion of users, and compliance with treatment has been shown to decrease over time [26, 27]. One estimate suggests oral therapies are effective in about 75% of users, but almost 50% of men discontinue PDE-5 inhibitor treatment within one year [1, 28]. This is discussed further in the next section (Section 8.4).

PDE-5 inhibitors have to be taken sufficiently in advance of sexual intercourse because they are associated with a delayed speed of onset, leading to a lack of spontaneity. The different oral PDE-5 inhibitors take different times to reach maximal plasma concentrations and thus have an onset of effect ranging from 15 minutes to up to 1 hour, and peak circulating drug concentrations are typically attained only 1–2 hours following administration [19, 22]. Add to this their relatively long-half life, meaning effects last beyond the usual duration of sexual intercourse. Furthermore, the absorption of sildenafil can be delayed by food ingestion, and absorption of vardenafil and avanafil can be delayed by a high fat meal [19, 22].

The British Society for Sexual Medicine mention the recent European Union (EU) approval of an over the counter (OTC) formulation of sildenafil (Viagra Connect® 50 mg; approved in November 2017 for commencement of sales in 2018) in their 2017 guidelines on the management of ED [1]. However, as the guidelines were published before Viagra Connect® went on general sale, it has not yet been incorporated into the treatment model.

In general, PDE-5 inhibitors have a good benefit-risk profile but are associated with a number of issues that reduce the ratio and contribute to an unmet need in the therapy area.

For PDE-5 inhibitor non-responders, or in men who are not satisfied with PDE-5 inhibitors, stepwise progression from oral agents to other therapies occurs as needed. Other second- and third-line treatment options include vacuum erection devices, intracavernosal injections (e.g. alprostadil, papaverine), intraurethral suppositories (e.g. alprostadil) and penile prosthesis implantations. Second/third-line therapies can be used alone or in combination with PDE-5 inhibitors. However, these treatments are frequently associated with AEs such as local pain, fibrosis and priapism (a persistent and painful erection) and can lead to poor compliance owing to their invasive nature. In light of this, the benefit-risk profile of these second-line therapies is quite poor related to their generally unacceptable safety risks. Newer treatments include low-intensity extracorporeal shock wave therapy, intracavernosal stem cell therapy and platelet-rich plasma therapy; however, these treatments should be considered experimental as they are still undergoing testing and further studies are required to establish effectiveness.

Owing to their less invasive route of administration and ease of use, topical therapies approved for other indications have recently been explored as alternative candidates for the treatment of ED.

Alprostadil, a synthetic analogue of prostaglandin E_1 (PGE1), has been marketed for many years as an intracavernosal injection and a urethral stick for the treatment of ED. Alprostadil cream (Vitaros®/Virirec®), PGE1 combined with a skin permeation enhancing drug delivery system, has been developed for the treatment of ED, although clinical data are limited [1, 19]. Alprostadil cream is not approved for use in the US. Administered at a dose of 300 µg inserted into the urethra, topically-applied alprostadil has shown to be safe and effective (increased penile blood flow, improved erections, increased successful intercourse attempts) versus baseline and placebo in a broad range of men with mild to severe ED [26, 29]. Side effects tend to be mild to moderate, transient and localised, including genital pain, burning, tenderness and erythema; but have been seen in up to 78% of patients [30]. Owing to its low systemic absorption, systemic AEs are usually rare or absent. Furthermore, the effectiveness and safety of topical alprostadil has been demonstrated for up to 9 months in an open-label study in 1,161 men [26, 31].

There are little long-term safety data for alprostadil cream, and no published comparisons with other treatments [26, 32]. Furthermore, alprostadil cream should not be used in combination with oral PDE-5 inhibitors because an additive increased cardiovascular risk cannot be excluded [32].

In summary, there are a number of treatment options available to men with ED. Most men will follow a structured treatment strategy that will depend on effectiveness, tolerability, invasiveness, cost and preference. As there is a continually expanding literature on ED, management strategies should evolve as our understanding of ED expands. Importantly, the American Urological Association (AUA) suggests a 'shared decision-making' approach is the cornerstone of the patient-centred management of ED, during which the man, in collaboration with his physician and in consultation with his partner when applicable, is enabled to fully consider all of the treatment options available to him and supported in the decision making process. The AUA believe the model should rely on concepts of autonomy and respect for the individual; i.e. every man who presents with ED is unique, and the most effective approach for a particular man is best determined by that man [22].

8.4 Potential of MED3000 in the Market for Erectile Dysfunction

The aim of MED3000 is to target a large potential patient population with a clear unmet need.

The ED market is well-established with sales of ED treatments worth 5.6 billion US dollars in 2018 [33]. Tadalafil (Cialis®) is the current market leader; however, brand and generic markets for ED medications are changing allowing patients and providers more flexibility in prescribing and in their treatment decisions and enabling tailoring to patient preference and needs. For example, sildenafil and tadalafil are both now available as generic medications: Pfizer's patent on sildenafil expired in 2013, and the patent for tadalafil expired in most markets in 2017. Previously only available via doctor's prescription, the ED market is also changing with the EU approval of OTC pharmaceutical products such as Viagra Connect®.

Existing treatments have significant limitations. There are four main issues with the current treatment landscape: AEs, drug interactions, slow onset of action and treatment failure.

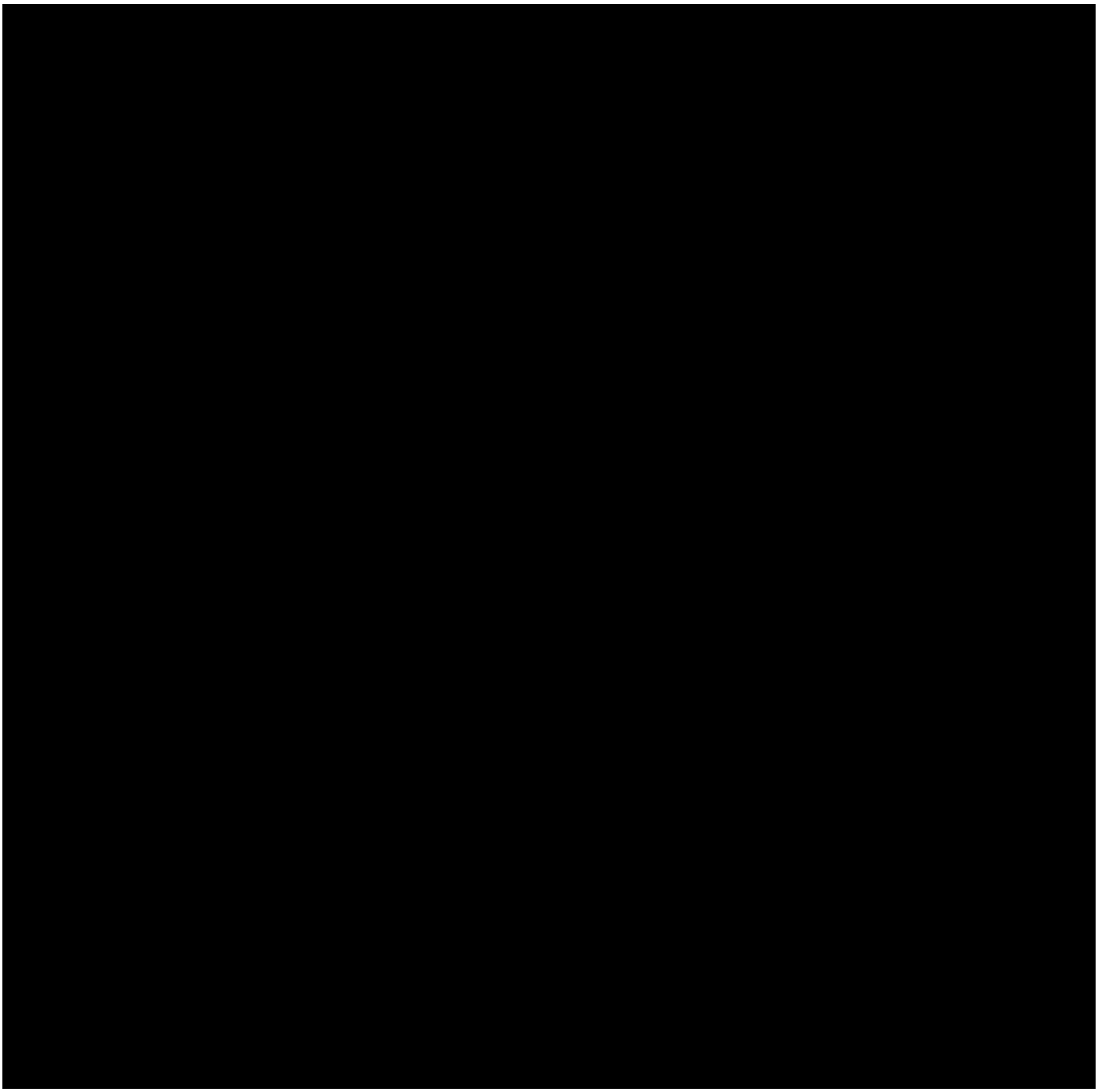
Oral PDE-5 inhibitors may be the cornerstone of modern ED therapy, but do not meet the needs of many men and their partners. Firstly, there is a subset of ED sufferers who are not able to be prescribed any of the PDE-5 inhibitors owing to contraindications with other medications taken by them for comorbid conditions. PDE-5 inhibitors are contraindicated in men who are taking any form of organic nitrates or nitrate-containing compounds, both regularly or intermittently; e.g. in patients who have stable angina or heart failure. Both PDE-5 inhibitors and nitrates are vasodilators, and when taken together their additive and synergistic effects may cause an augmented hypotensive response, potentially leading to unpredictable reductions in BP [34]. According to recent independent market research commissioned by Futura Medical, this group represents at least 10% of ED patients [data on file: market research from Cello Health Consulting amongst physicians carried out in the US, France and Germany and commissioned by Futura Medical in 2017]. Interactions have also been reported in men taking concomitant antihypertensives or alpha blockers, and drugs inhibiting the P450 cytochrome pathway [26, 35, 36]. Secondly, in a significant proportion of men this class of drugs is associated with treatment failure; and thirdly, compliance with PDE-5 inhibitors has been shown to decrease over time [26, 27]. In 2016, a review and meta-analysis of 22 clinical trials, including more than 162,000 ED patients, found that the mean discontinuation rate was 4% per month, equivalent to almost 50% after 1 year. The main reasons for discontinuation were partner-related problems and lack of effectiveness [28]. On top of this, many second- and third-line therapies and devices have issues with side effects and invasiveness.

Access to therapies is also important. Despite the availability of treatments, many men do not seek medical help for the condition [1]. Futura Medical's market research indicates that only 15–30% of men with ED consult a doctor [data on file]. Apart from some limited products, existing treatments for ED require a prescription from a doctor, and there has been little innovation in the ED space in recent years.

User satisfaction is also an issue: the currently available ED treatments do not always reflect a patient's preference. According to Futura Medical's independent market research, 68% of ED patients are not fully satisfied with their treatment, citing concerns which include barriers to spontaneity and intimacy, insufficient effectiveness and side effects [data on file]. Doctors expect that within just one year of treatment initiation, 25% of all ED patients will have discontinued their therapy [data on file]. ED affects the patient's emotions and relationships, and an ideal ED treatment should address more than the ability to have and maintain an erection. The delayed speed of onset associated with PDE-5 inhibitor use is a major barrier to spontaneity and intimacy, which are important considerations in the treatment of ED. In contrast, application of a topical treatment that relies on thermodynamic activity, and the cooling-warming action on the skin, may lead to an enhanced effect and is an attractive proposition [37]. The market research showed that 72% of doctors considered that helping to restore spontaneity and intimacy in the relationship

would be very appealing to their patients and would be a key driver of initiation or switch to MED3000.

In summary, although there is a large, established ED market, it is changing and there are also clear and significant unmet needs. There remains a strong unmet need for an effective, fast-acting and non-invasive local therapy that is easy to administer and well-tolerated with a low risk of systemic AEs; i.e. with a more favourable benefit-risk balance than the majority of currently available treatments. Any therapy matching this profile would make a prime candidate for OTC availability. Futura Medical suggest that a topical treatment such as MED3000 gel could offer an alternative to oral medications and represents a potential new treatment option for men contraindicated to oral PDE-5 inhibitors, for those who find the side-effects associated with PDE-5 inhibitors (or other second- or third-line therapies) unacceptable and for those who have – due to dissatisfaction with PDE-5 inhibitor treatment regimens – discontinued use of those products.



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9. JUSTIFICATION OF CLINICAL ENDPOINTS

9.1 International Index for Erectile Function (IIEF) questionnaire

The IIEF was developed and validated in 1996–1997 as part of the sildenafil clinical study program and in 1999, the IIEF was recommended by the first International Consultation on Erectile Dysfunction as the primary effectiveness endpoint of choice for clinical studies in ED [9, 39]. After years of use, the IIEF is considered the gold standard self-report questionnaire for measuring EF.

The IIEF has been validated, is widely used in numerous countries, and has demonstrated specificity for detecting treatment-related changes in EF [40]. The IIEF consists of 15 questions divided into five domains of sexual function: EF (6 questions), orgasmic function (2 questions), sexual desire, (2 questions), intercourse satisfaction (3 questions) and overall satisfaction (2 questions). A score of 0 to 5 is awarded to each of the 15 questions [39]. Higher scores indicate better sexual function. The IIEF-EF, a subset of the IIEF measuring EF, is commonly used as the primary endpoint in clinical trials and comprises Questions 1–5 and 15 of the IIEF.

The questionnaire is completed by a patient's recollection of the effects that his erection problems have had on his sex life over the previous 4 weeks.

9.2 Onset of Action (Erection) Questions

The purpose of the estimation of the time of onset is to provide useful clinical guidance to both patients and healthcare professionals. An accessible presentation of the time of onset is the mean percentage of uses, per patient, that led to the onset of an erection and result in the ability to have penetrative sex within a stated timeframe.

The Onset of Action (Erection) and Erection Hardness questionnaire was used in the FM57 study. This patient-reported outcome (PRO) instrument was designed to capture details of various time-related events associated with sexual intercourse, including the time that the patient and partner noticed the onset of an erection after the application of the MED3000 gel and when the patient and partner were able to have penetrative sexual intercourse. An abbreviated version of this instrument will be used in this clinical investigation to determine how rapidly each treatment type (i.e. MED3000 or tadalafil [5 mg]) becomes effective after dosing (i.e. the onset of an erection and the ability of the patient to have penetrative intercourse).

In this clinical investigation, the Onset of Action (Erection) questionnaire is completed by patients after the first intercourse attempt after each administration of the investigational product (i.e. MED3000 gel or tadalafil [5 mg]).

The onset of action assessments using this questionnaire do not require the use of a stopwatch to time events as the questions have a time component included. A study investigating the earliest time within 30 minutes to erectogenic effect of tadalafil 10 mg and 20 mg [41], suggested that a limitation of stopwatch studies in general is the potential lack of clinical application. It is therefore concluded that using a stopwatch in this clinical investigation could have a potentially detrimental effect on the sexual experience which could, in turn, influence the IIEF scores (i.e. the Primary Objective) reported by the patients.

9.3 Self-Esteem And Relationship (SEAR) questionnaire

The Self-Esteem And Relationship (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 [42].

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.

9.4 Objective Performance Criteria and Clinically Meaningful Differences

Objective performance criteria (OPC) are standardised numerical target values derived from historical data taken from clinical studies and/or registries that may be useful for the review and comparison of safety or effectiveness endpoints in novel trials. OPC serve as additional evidence for the effectiveness of MED3000.

In 2011 Rosen *et al*. published a paper titled 'Minimally clinically important differences in the erectile function domain of the International Index of Erectile Function scale' [43]. In this paper, the EF domain of the IIEF questionnaire were questions 1 to 5, inclusive, and question 15. The study used anchor-based minimal clinically important differences (MCIDs) estimated using data from 17 randomised, double-blind, placebo-controlled, parallel-group clinical trials of the PDE-5 inhibitor tadalafil (Cialis®) for 3,345 men with ED who received treatment for 12 weeks (meta-analysis). The overall MCID for IIEF-EF change from baseline was established as 4. MCIDs for IIEF-EF changes from baseline were also established for different ED severities as follows: mild, 2; moderate, 5; and severe, 7. These 'Rosen' criteria have now been widely accepted and used for responder definitions by academia and leading experts in the field of ED, and are cited by the US FDA in a recent strategic review as an acceptable PRO.

9.5 Safety Assessments

Safety will be evaluated throughout the investigation, whilst patients are on treatment, using standard assessments including physical examinations and visual examination of the penis, vital signs (BP, heart rate [HR], body temperature), standard clinical laboratory safety tests (haematology, biochemistry, urinalysis), 12-lead electrocardiograms (ECGs) and monitoring of AEs and concomitant medications with paper diaries (any AEs experienced by the partner will be captured at site visits [Visits 1, 2 and 8] or in the paper diaries. If information is missing from the paper diaries then the site should make every effort to obtain the required information).

9.6 Patient Population

All patients who meet the eligibility criteria may be enrolled in this investigation, irrespective of their ED severity (i.e. mild, moderate or severe). However, limits will be imposed on the number of patients recruited into each severity cohort (i.e. mild, moderate or severe) to ensure that these are broadly similar to that in PDE-5 studies and the Massachusetts Aging Study [2]. It is anticipated that enrolled patients in this clinical investigation will be ethnically diverse as sites will be located in both the US and Europe. The US site will enrol African-American patients exclusively to ensure that a representative population of this ethnic group are included in the clinical investigation.

A publication by Fisher *et al.* (2016) stated that the overwhelming majority of clinical trials involving patients with ED required the enrolment of patients in a heterosexual relationship for a minimum of 3 months [44]. As the majority of ED studies involve heterosexual patients, an exclusively heterosexual population will be enrolled in this clinical investigation.

10. BENEFITS AND RISKS OF THE DEVICE, CLINICAL PROCEDURES AND INVESTIGATION

MED3000 is being developed for the treatment of ED and as such, the anticipated clinical benefits for patients receiving treatment with MED3000 are improvements in EF with consequent improvements in QoL for themselves and their partners.

[redacted]

The risks associated with participation in the investigation are directly related to the two products involved, namely MED3000 and tadalafil 5 mg. The safety profile of MED3000 is listed above. The safety profile of tadalafil 5 mg is well established and tadalafil 5 mg is the lowest approved on demand dose in the US. In common with other PDE-5 inhibitors, tadalafil is a well-tolerated medicine. The most commonly reported adverse reactions in patients taking tadalafil for the treatment of ED are headache, dyspepsia, back pain and myalgia, in which the incidences increase with increasing dose of tadalafil. The adverse reactions reported are transient, and generally mild or moderate. As a 5 mg dose of tadalafil will be used in this clinical investigation, risks associated with participation are therefore mild and will further be mitigated by careful and regular monitoring by clinical investigators of any potential AEs throughout the investigation.

The rationale for the benefit-risk ratio for both products is based on their individual safety profiles and clinical effectiveness. In the case of MED3000 this has been established in developmental clinical trials. In the case of tadalafil this has been established by virtue of its status as an approved drug.

11. OBJECTIVES AND HYPOTHESES OF THE CLINICAL INVESTIGATION

This clinical investigation is intended to assess the effectiveness and safety of MED3000 gel over a 24-week period in male patients clinically diagnosed with ED.

Primary Effectiveness Objective:

- To demonstrate an improvement compared to baseline of the EF domain of the IIEF in patients randomised to MED3000, assessed at 24 weeks post-randomisation by rejecting the null hypothesis that the mean change from baseline is less than or equal to zero.

- To observe a mean change from baseline of the IIEF-EF in patients randomised to MED3000, assessed at 24 weeks post-randomisation, greater than or equal to the MCID of 4, as published by Rosen et al 2011 [43]).

The endpoint for the primary effectiveness objective is the EF domain of the IIEF, assessed at 24 weeks post-randomisation.

The primary objective will be assessed according to the outcomes in all randomised patients at 24 weeks attributed to the initially received treatment [45]. Treatment discontinuation reasons considered to be adversely related to randomised treatment (for example, lack of effectiveness or related AEs) are considered as attributable and will be treated as an unfavourable outcome; while a hypothetical estimand strategy, that is, as if the patient carried on treatment, will be used for intercurrent events not considered to be related to randomised treatment (for example lost to follow-up or unrelated AEs).

Secondary Effectiveness Objectives:

The secondary effectiveness objectives are:

- To demonstrate a speed of onset of action from the application of MED3000 gel to the time when the patient notices their erection starting. Specifically, the objective is to provide evidence that the mean percentage of MED3000 uses per patient that result in the patient noticing their erection starting within a certain period of time is greater than 30%, assessed whilst on treatment during the 24-week treatment period.

- To demonstrate a speed of onset of action from the application of MED3000 gel to the time when the patient is able to have penetrative sex. Specifically, the objective is to provide evidence that the mean percentage of MED3000 uses per patient that result in the ability to have penetrative sex within a certain period of time is greater than 30%, assessed whilst on treatment during the 24-week treatment period.

Only on-treatment assessments made up to the time of treatment discontinuation will be used. Time from application of MED3000 gel will be assessed at 5 minutes, 10 minutes and 15 minutes.

The endpoints for the secondary effectiveness objectives are:

- The percentage of times that a patient indicates that they began to notice their erection starting within 5 minutes (10 minutes, 15 minutes) out of the total number of intercourse attempts made using the product during the 24 week treatment period post-randomisation.

- The percentage of times that a patient indicates that they were able to have penetrative sex within 5 minutes (10 minutes, 15 minutes) out of the total number of intercourse attempts made using the product during the 24 week treatment period post-randomisation.

The justification for the definitions is a clinically accepted and published precedent. The objective is based on the results from a study which assessed the effectiveness of avanafil within approximately 15 minutes after dosing in men with ED [46]. This study observed a mean of 29.1% for the per subject percentage of sexual attempts in which men were able to have penetrative sexual intercourse within 15 minutes of using avanafil (200 mg). Subjects were encouraged to attempt intercourse approximately 15 minutes after dosing and made use of a stopwatch. This study allowed the following text to be included on the avanafil on the prescribing information, “The starting dose is 100 mg taken as early as approximately 15 minutes before sexual activity”.

A study investigating the earliest time within 30 minutes to erectogenic effect of tadalafil 10 mg and 20 mg [41], suggested that a limitation of stopwatch studies in general is the potential lack of clinical application.

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Safety Objectives:

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12. DESIGN OF THE CLINICAL INVESTIGATION

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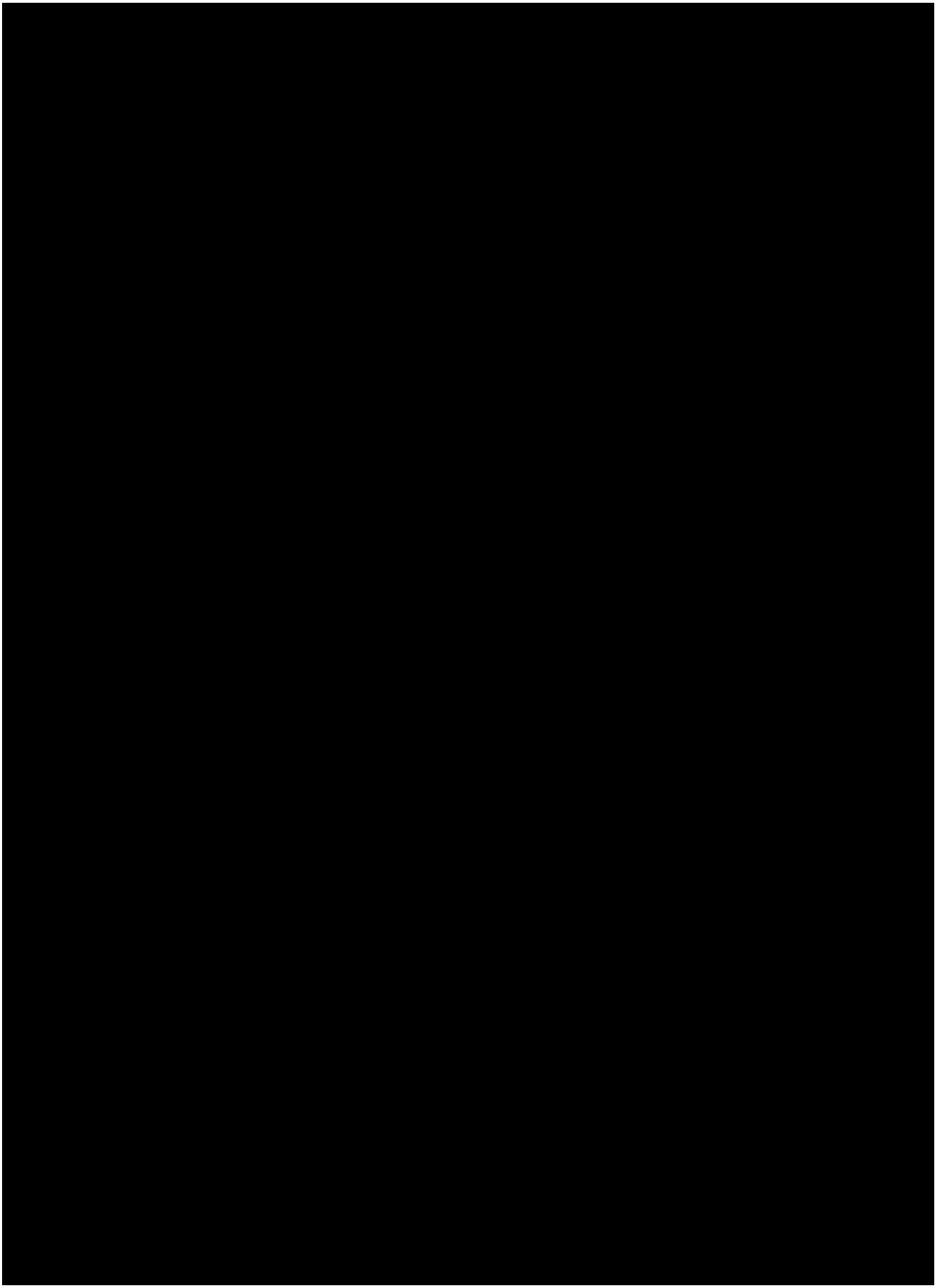
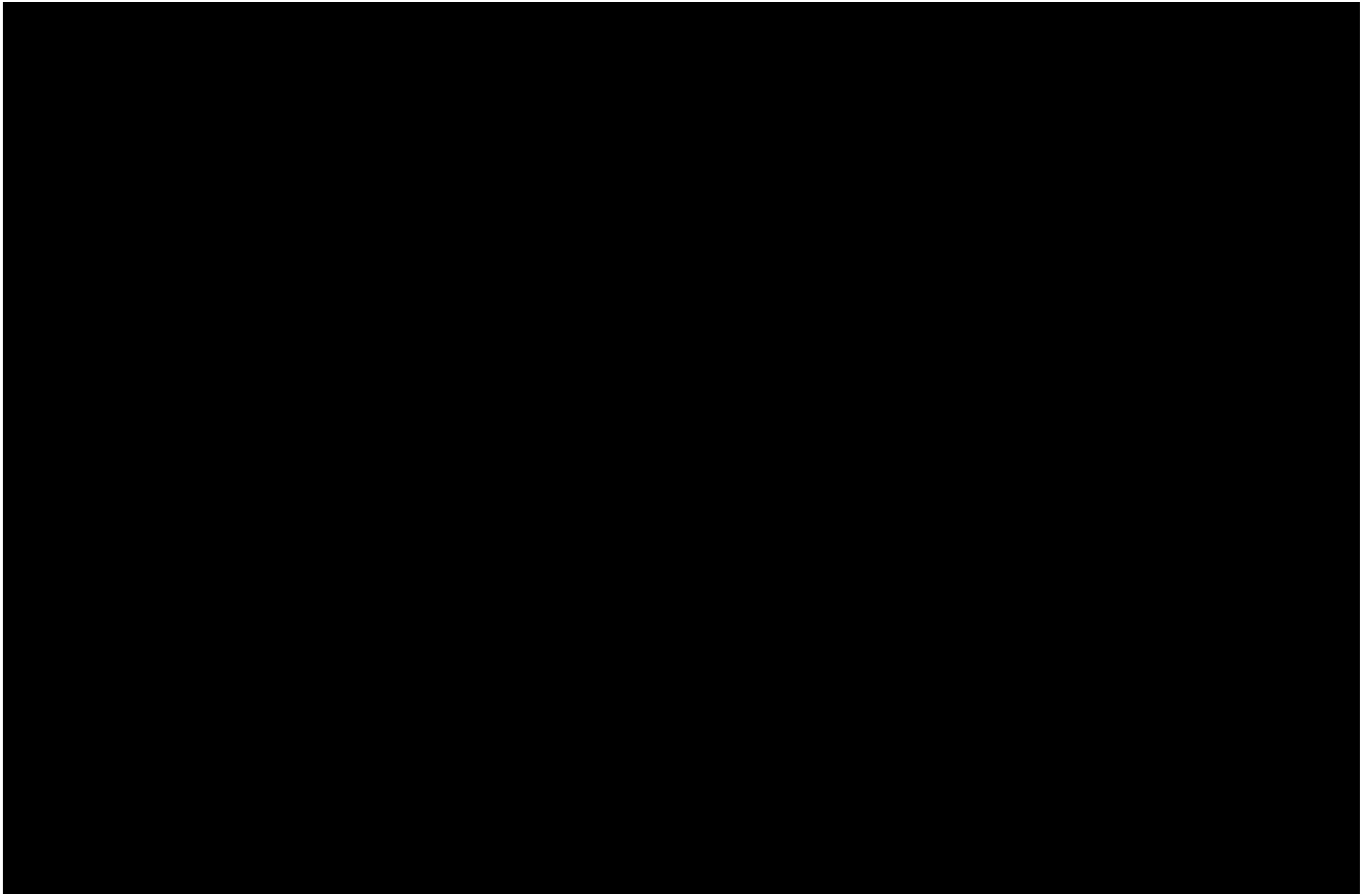




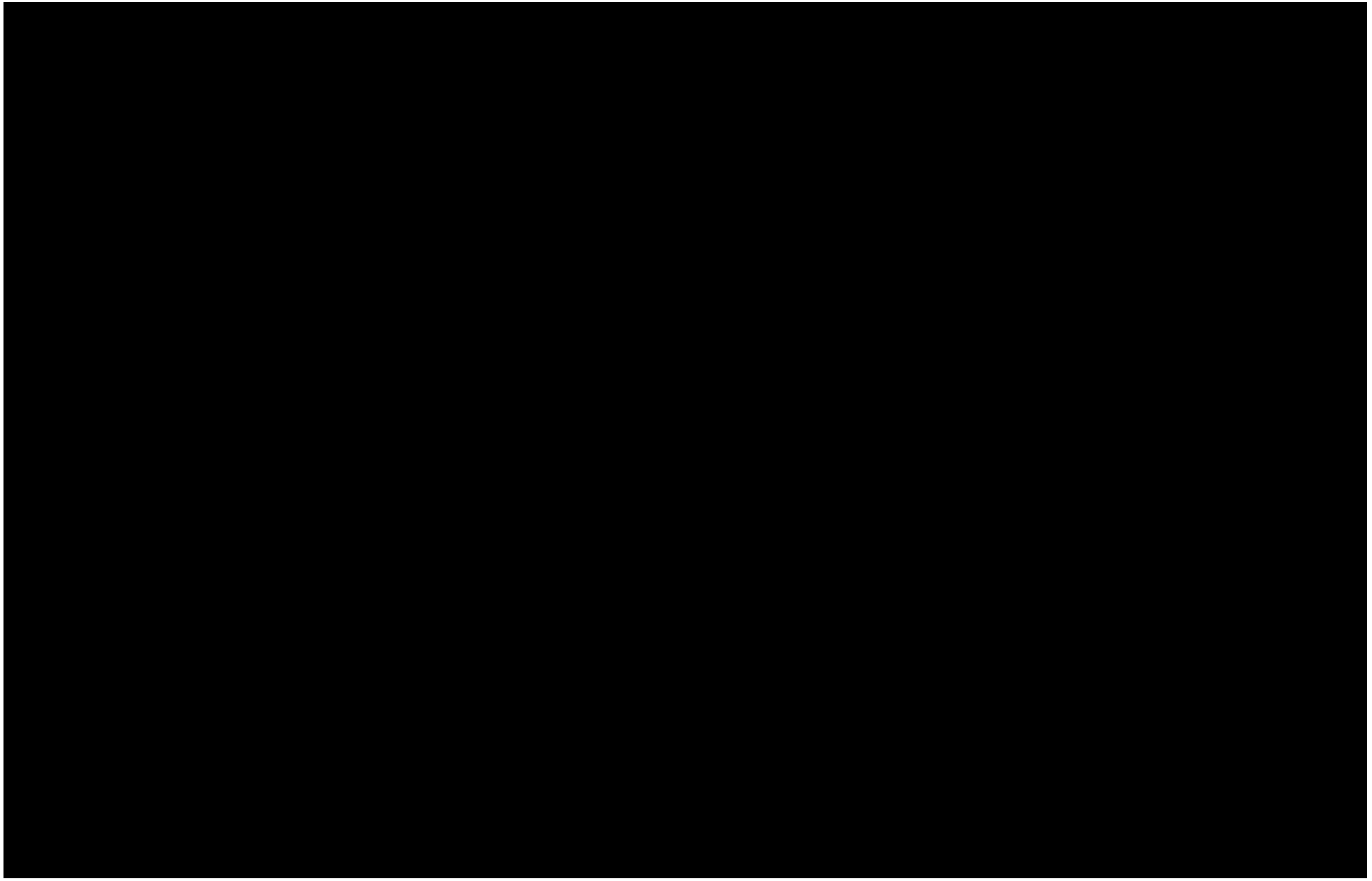
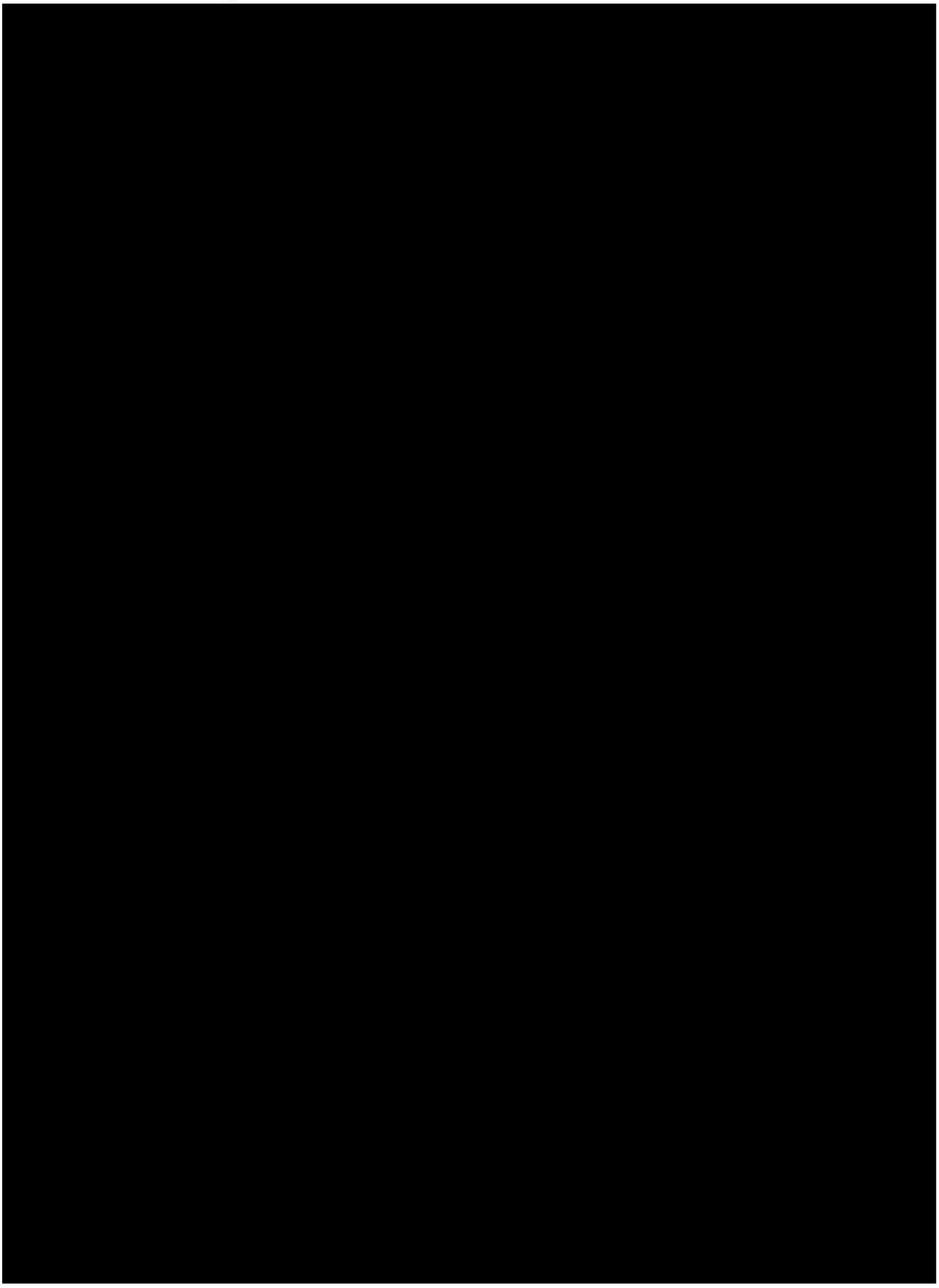


Table 3 Schedule of Questionnaires

12.2 Investigational Device and Control



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12.3 Patients

Ethnicity and FM71:

Patients will be recruited from across Europe and in the US. The latter group will specifically focus on American Afro-Caribbeans for two reasons. First, to guarantee that a selection of Afro-Caribbean patients are included in the investigation. Second, because Afro-Caribbean ethnicity has a relatively higher prevalence of diabetes and CVD, which can frequently be associated with obesity, this can impact the severity of ED.

The US population also includes Hispanics and Asians who may not be represented in the cohort of European patients. However, these ethnicities do not have a similarly high prevalence for these comorbidities. The prevalence of hypertension among Mexicans, for instance, is lower than the prevalence of hypertension in the general American population [57]. In the same publication The American Heart Association advised that there was "a remarkable lack of consistent information regarding the prevalence of hypertension among US Hispanics".

The American Heart Association has also stated that Asian Americans (Asian Indian, Chinese, Filipino, Japanese, Korean and Vietnamese) comprise a widespread ethnic group which has differing patterns of disease tendencies within its many sub-groups. However, aggregated as a single group they are at lower risk of CVD [58].

The comparability of European and American populations within this context is further supported by the reliability and robustness of the IIEF as a measure of ED when used in different geographic populations or etiologic sub-groups. Baseline and post treatment IIEF scores were "almost identical" in the first European and US studies [9].

In addition, a literature review (data on file) shows that the results reported on studies in the US were similar to those reported in the rest of the world thereby confirming that for the purposes of

studying the effectiveness and safety of treatments of ED, the US population is comparable with Europe.

12.3.1 Inclusion and Exclusion Criteria

MED3000 is being developed to treat ED. In this clinical investigation, patients with mild, moderate and severe ED will be enrolled. The severity (i.e. mild, moderate or severe) of the patients' ED at baseline (i.e. Visit 2) will be determined using the IIEF questionnaire. Additionally, prior to randomisation, all patients must meet the eligibility criteria as detailed below.

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

1. Patient is a male aged between 22 and 70 years inclusive, at screening
2. Confirmed clinical diagnosis of ED for more than 3 months according to the National Institutes of Health (NIH) Consensus Statement ('the inability to achieve or maintain penile erection sufficient for satisfactory sexual performance at least once')
3. Patient 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. Patient has been involved in a continuous heterosexual relationship for at least 6 months prior to screening
5. Documented written informed consent from both patient and his female partner
6. If the male patient's female partner is of childbearing potential from the time of first sexual intercourse attempt during the screening period until the last administration of investigational treatment, then the couple must have been using a medically acceptable form of contraception for at least 3 months prior to entering the clinical investigation, and agree to continue such use for at least 1 month after the last administration of MED3000 or tadalafil (5 mg)

   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 investigation:

   - 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.

As an additional precaution against pregnancy, the date of the Last Menstrual Period (LMP) of the female partner will be recorded in the CRF before proceeding with the investigation. Any history of irregularity of periods will also be recorded.

Patients who are or wish to become pregnant will not be included in the investigation.

7. Patient and his female partner are capable of understanding and complying with the requirements of the CIP and must have signed the informed consent form (ICF) prior to participation in any investigation-related procedures
8. Low IIEF-EF scores (≤ 25) at the end of the screening period (i.e. Visit 2)

Exclusion Criteria: Patients are prohibited from participating in the investigation 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 patient unfit to take part in the investigation
2. Patient 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 patient's ability to complete the investigation or precludes the patient's participation in the investigation

   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 tadalafil; therefore, the PI must consider this carefully and include patients 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 investigation
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. Patients taking two or more anti-hypertensives for the treatment of BP
10. Hypersensitivity to any of the excipients
11. Concomitant treatment with sildenafil citrate, vardenafil and other PDE-5 inhibitors
12. Patients taking alpha blockers, guanylate cyclase stimulators, such as riociguat, doxazocin, any form of organic nitrate
13. Patients 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. Patients who have loss of vision in one eye because of non-arteritic anterior ischaemic optic neuropathy (NAION)
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. Patients with nursing partners, known pregnant partners or with partners who wish to become pregnant during the course of the investigation
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 patient will be excluded from the investigation). In the instance that a patient is using medication which may give a positive result, exclusion will be at the PI's discretion
26. Patient has recent (last 12 months) clinical evidence of alcoholism or drug abuse
27. Patient 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. Patients unwilling to cease use of vacuum devices, intracavernosal injections, PDE-5s or other non-clinical investigation therapies for ED for the entire course of the investigation
30. Unwillingness of the patient 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. Patients or their partners who are illiterate or are unable to understand the language in which the questionnaires are available
34. Patient has received any investigational product during the 90 days prior to dosing for this investigation
35. Patient or his partner cannot communicate reliably with the PI
36. Patients with severe premature ejaculation (little or no control of ejaculation at the time of penetration)

12.4 Post-Investigation Restrictions

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

- Blood donation will not be allowed at any time during the investigation and up to 3 months (90 days) after completion of the investigation
- Male patients should not donate sperm and their female partners should not donate egg(s) from the time of the first administration of investigational product until 3 months after the last administration of investigational product

12.5 Withdrawal of Patients

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

Reasons for withdrawing a patient from the investigation can include:

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

Although a low dropout rate is anticipated in this clinical investigation, investigation sites should make every effort (in accordance with the CRO's agreed standard operating procedures [SOPs] on follow-up) to encourage withdrawn patients (and their partners) to the site to undertake all required assessments.

Various strategies will be employed throughout the clinical investigation to promote the retention of patients in the clinical investigation without compromising patients' rights as stated in the Declaration of Helsinki.

12.5.1 Criteria for Withdrawal from Investigational Product

Patients (and their female partners) may be withdrawn from the investigational product at any time.

A PI will withdraw a patient from the investigational product at any time for any of the following reasons:

- If a patient experiences a serious or intolerable AE, that prevents them from continuing
- If a patient incurs a significant CIP 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 patient's health is compromised by remaining in the clinical investigation or the patient is not sufficiently cooperative

12.5.2 Procedures for Patient Withdrawal

Patients who withdraw from the investigation (and their female partners) should always be asked about the specific reason(s) for withdrawal, the presence of any AEs and any concomitant medication that the patient (and/or partner) may be taking. Investigation-related AEs will be monitored closely and provided with the appropriate medical care and follow-up as necessary.

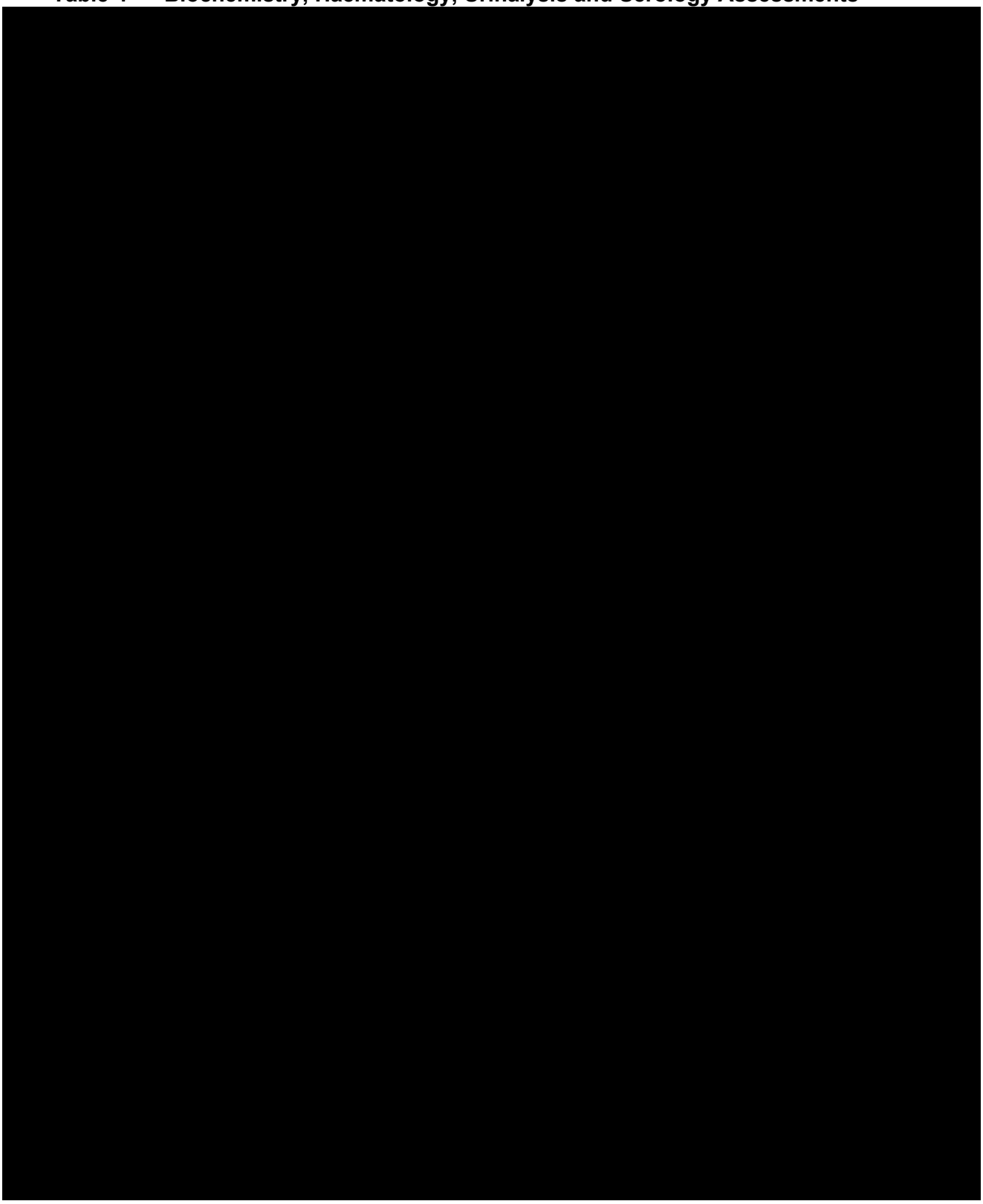
A patient will be enrolled into the investigation at Day 1 (i.e. the start of the screening period), having satisfied all of the eligibility. After completing the run-in period (Visit 2), the patient's eligibility will be reassessed, and the IIEF-EF scores evaluated. If the patient satisfies the eligibility criteria and scores ≤ 25 on the IIEF-EF questionnaire, they will be randomised into the investigation and a treatment type (i.e. MED3000 gel or tadalafil [5 mg] tablets) assigned. The investigation is expected to have a duration of 9 months (i.e. first patient first visit until last patient last visit) with each patient being on the investigation for up to 30 weeks (including the screening period and follow-up visit).

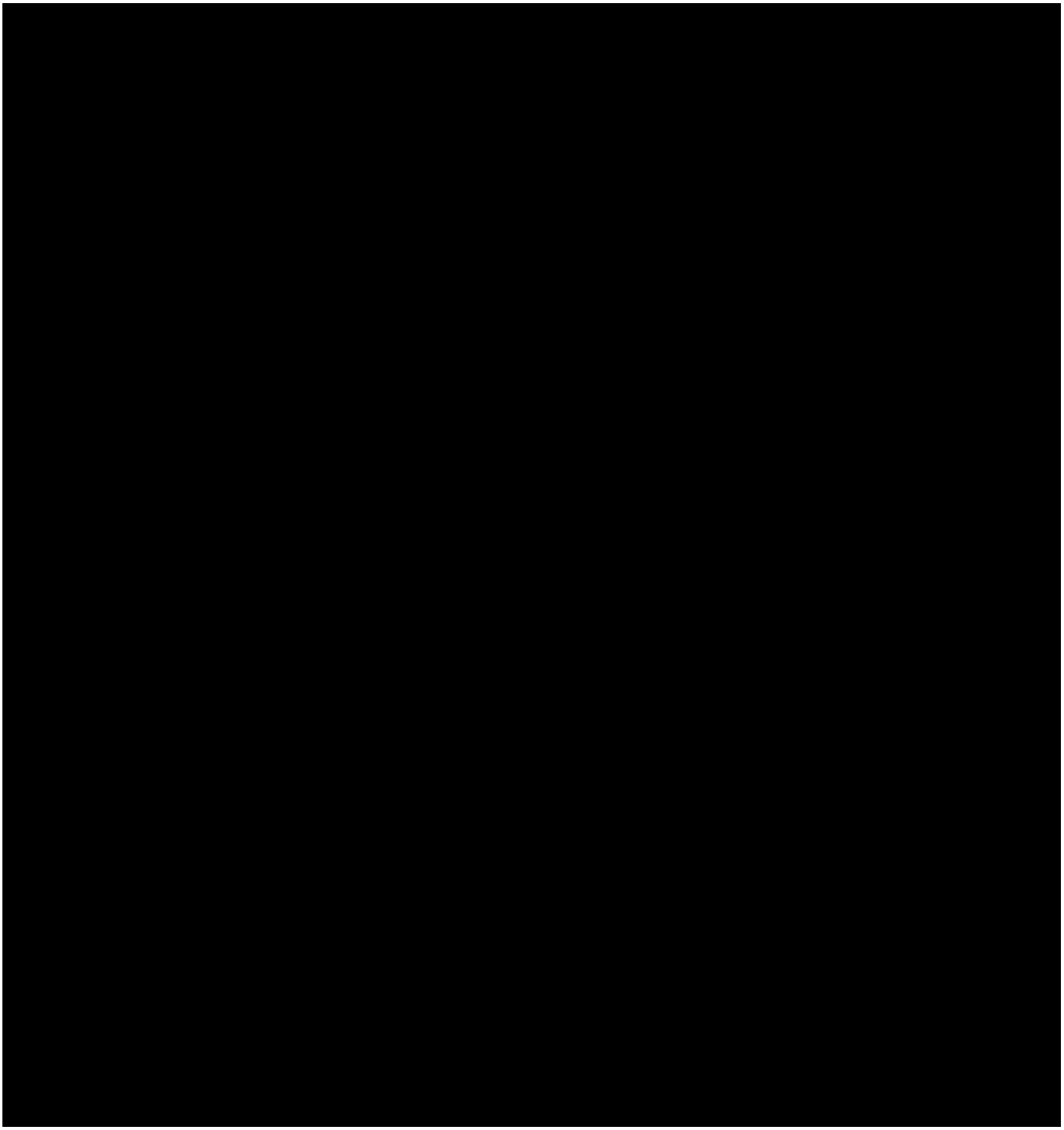
One hundred randomised patients (50 patients on each treatment arm) with ED are required in this investigation. The recruitment period is expected to be approximately 2 months. If the female partner is of childbearing potential then the couple must use a medically acceptable form of contraception for at least 3 months prior to entering the clinical investigation and continue to use it for at least 1 month after the last dose of the investigational product. A list of acceptable contraception is provided in inclusion criterion 6. Patients whose partners are pregnant or breast feeding will be excluded from this investigation.

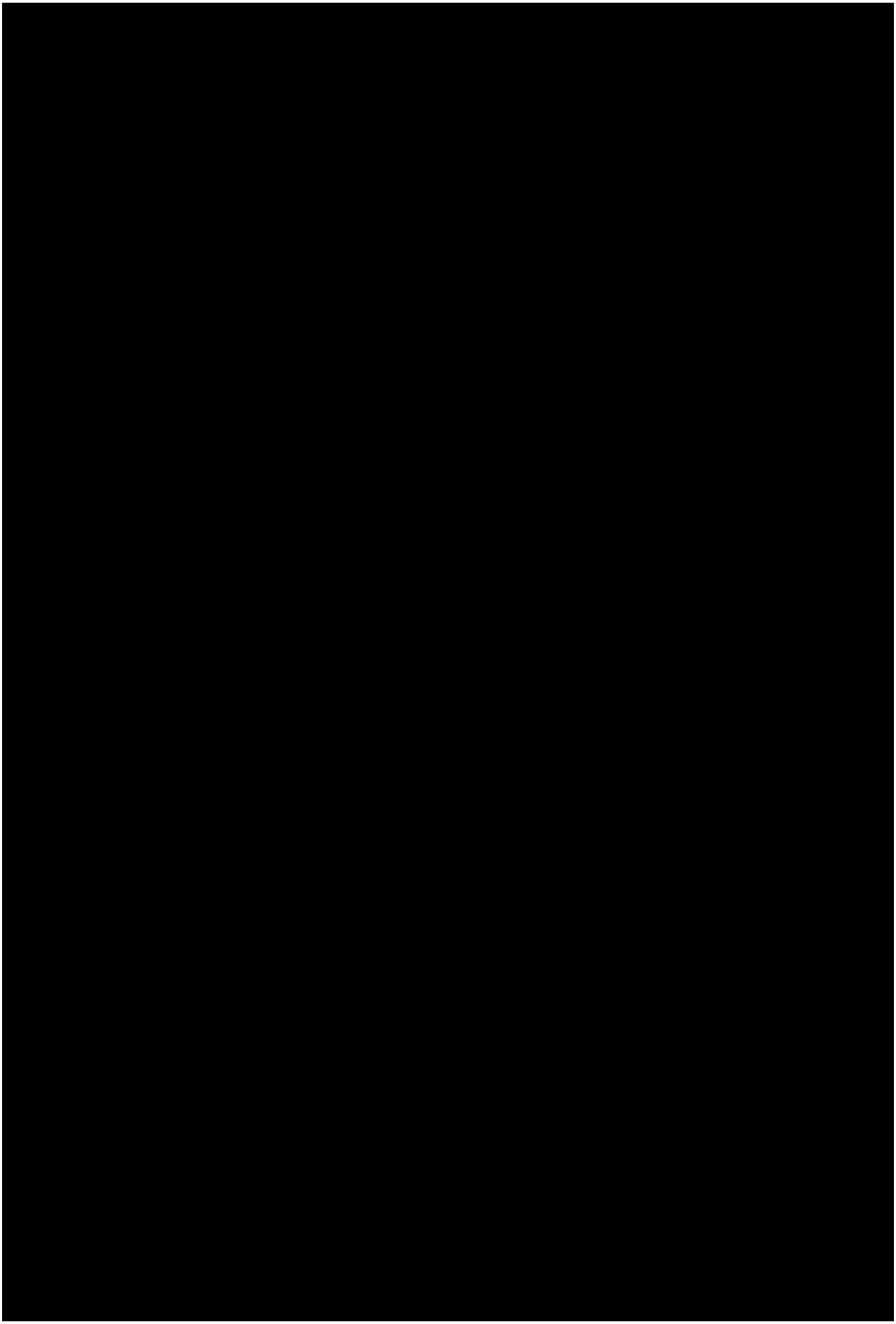
13. PROCEDURES

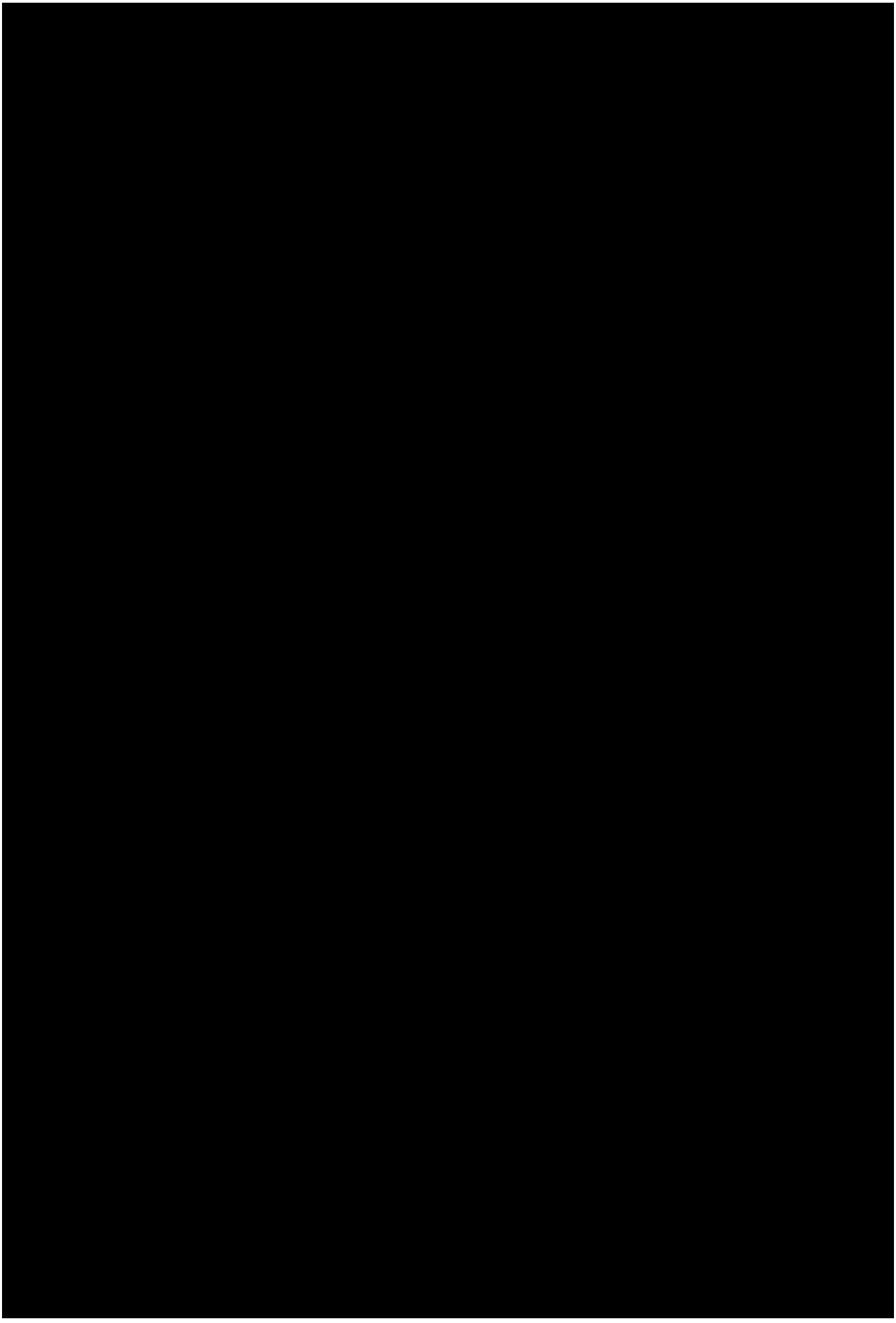
This list of activities can be found in the Schedule of Events table (Table 2).

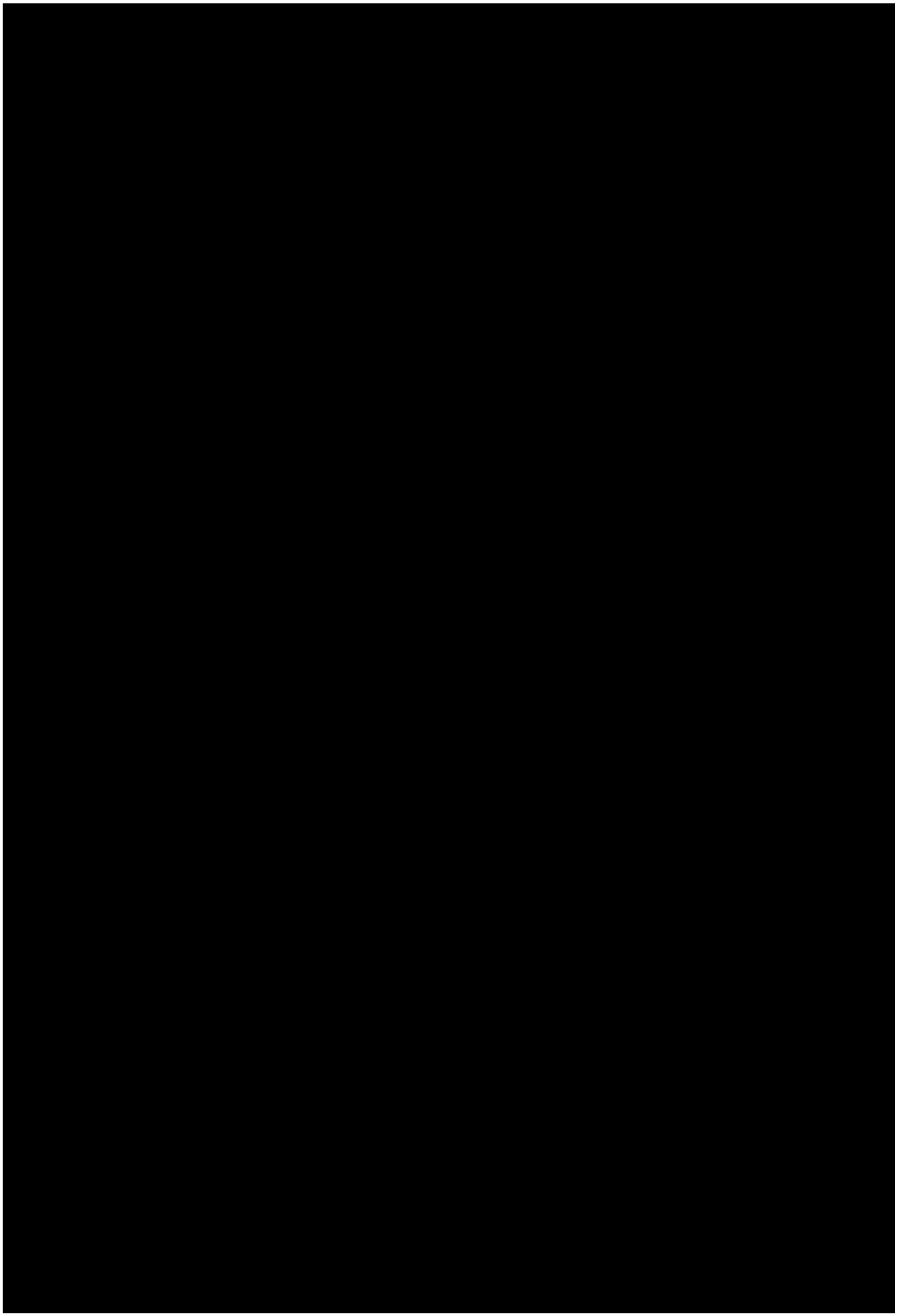
Table 4 Biochemistry, Haematology, Urinalysis and Serology Assessments











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13.11.2 Concomitant Medication

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13.13 Monitoring

Details of the monitoring arrangements are specified in the investigation-specific Monitoring Plan.

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

FMD will ensure that the CRO complies with GCP through a program of oversight activities including, but not limited to, review of project meeting minutes, review of site initiation visit reports, and review of monitoring reports, etc.

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

14. STATISTICAL DESIGN AND ANALYSIS

14.1 General

Methodology for summary and statistical analyses of the data collected in this investigation is described here. Further details of the proposed statistical analysis will be documented in a statistical analysis plan (SAP), which will be written following completion of the CIP and prior to randomisation of any patient into the trial. The SAP may modify what is outlined in the CIP where appropriate; however, any major modifications of the primary and secondary definitions or their analyses will also be reflected in a CIP amendment. Any deviations from the planned statistical analyses post-SAP finalisation will be detailed in the investigation report.

This investigation plan includes the two treatment groups MED3000 and tadalafil. The primary and secondary effectiveness objectives will be assessed by testing hypotheses that only use the results from the MED3000 treatment group, that is, by considering this single arm only. Other analyses will primarily be descriptive and will consist of both within and between treatment group summaries.

In general, safety and effectiveness variables will be presented by means of descriptive statistics and figures, as appropriate, by treatment group and by time point, where 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 patients and percentages, with percentages based on the number of non-missing values. For ordered categorical variables, cumulative percentages may also be presented. Two-sided, 95% confidence intervals will be presented as part of the descriptive statistics. Summaries will be based on observed data. In addition, multiple imputation will be used to produce summaries whilst taking into account treatment discontinuations and other missing data.

Data will be pooled across all sites. Descriptive statistics will be produced for sub-groups according to baseline ED severity and according to country.

There will be no planned interim analyses. Analyses will be conducted once all patients have completed the investigation and the database has been locked.

14.2 Test of Hypotheses

[redacted]

[redacted]

14.3 Sample Size and Power

A total sample size of 100 patients (50 per arm) is deemed appropriate for this investigation.

[redacted]

14.4 Randomisation

Patients will be randomised to receive MED3000 gel or tadalafil (5 mg) tablets using a 1:1 allocation ratio. Randomisation will be stratified based on the patients baseline ED severity scores (from the end of the screening period); mild (IIEF-EF domain score of 17–25), moderate (IIEF-EF domain score of 11–16) or severe (IIEF-EF domain score ≤ 10). Stratified recruitment will be used, with the aim to randomise and treat approximately 40, 36 and 24 mild, moderate and severe ED patients respectively. The plan is to randomise and treat 20 African Americans from the US site.

Cohort recruitment will be managed using an IWRS.

14.5 Analysis Sets

[redacted]

14.6 Demographic and Baseline Measurements

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

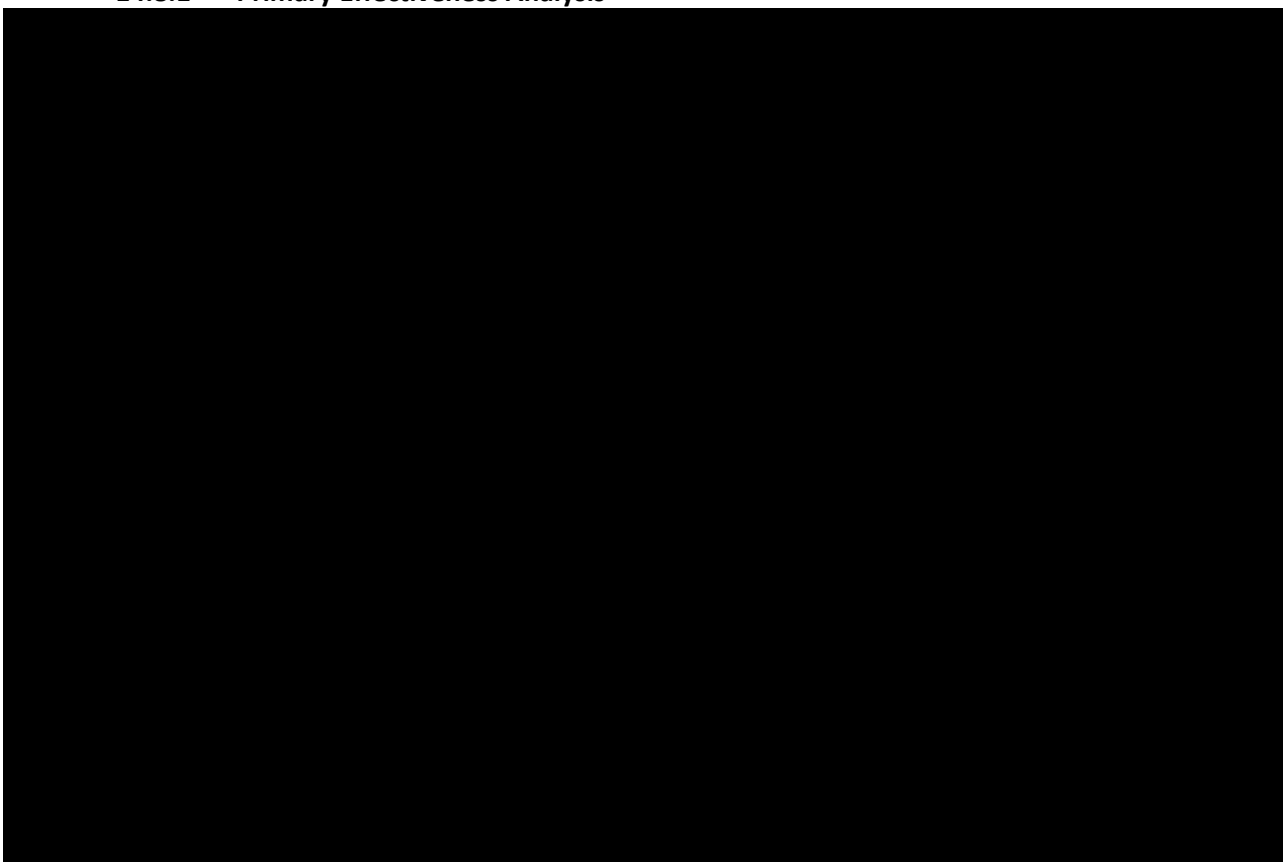
Assessments made at screening and at baseline will be summarised overall and for each treatment group. These assessments will include demographic and other relevant baseline characteristics (such as medical history, physical examination and the assessments made during the screening period). There will be no formal comparison of baseline data via statistical hypothesis testing as this is not appropriate methodology.

14.7 Prior and Concomitant Medication

Prior and concomitant medication will be summarised overall and by treatment group.

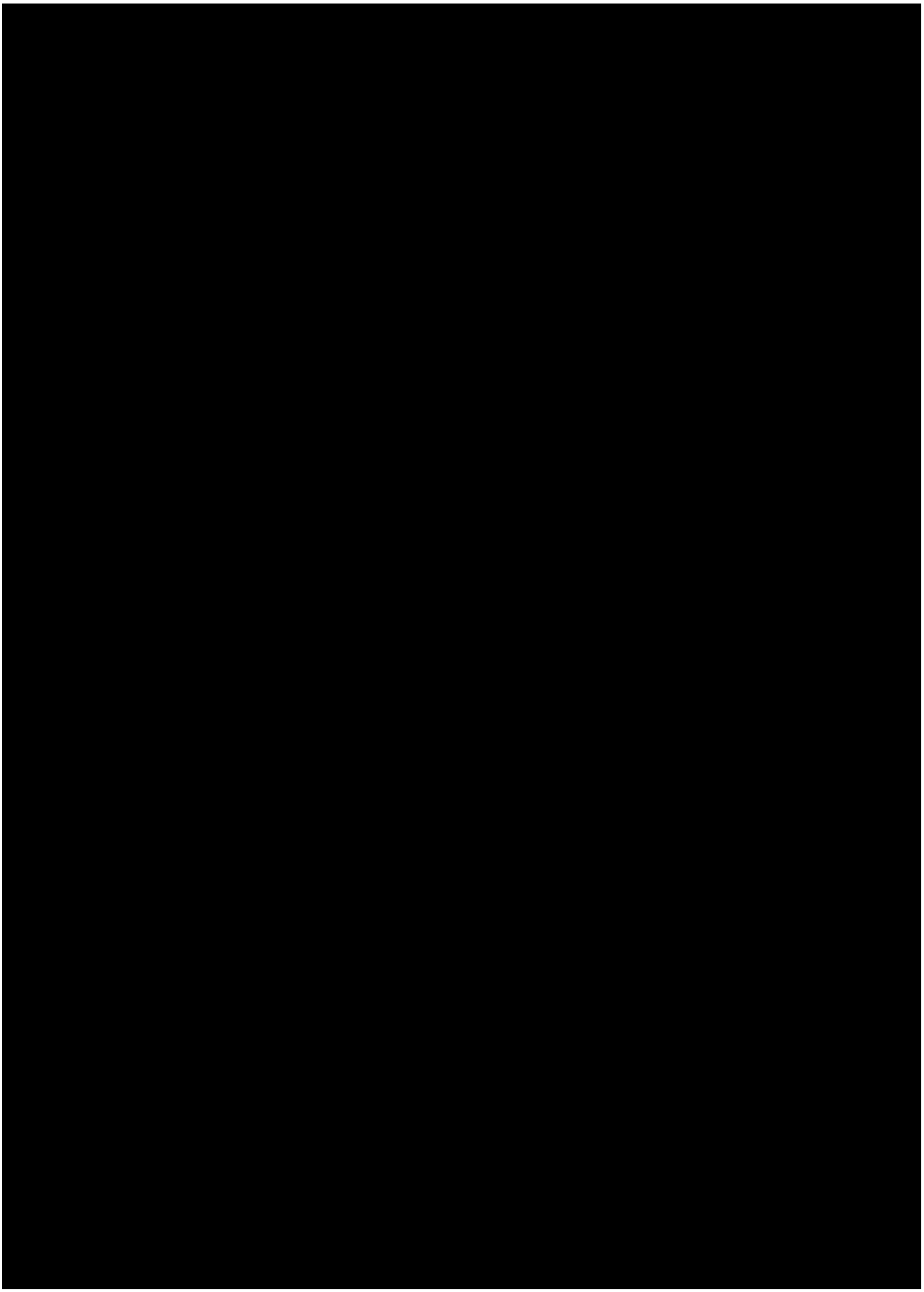
14.8 Effectiveness Evaluation

14.8.1 Primary Effectiveness Analysis



14.8.2 Secondary Effectiveness Analysis

14.8.3 Exploratory Effectiveness Objectives



[redacted]

14.9 Safety Analysis

[redacted]

[redacted]

15. DATA MANAGEMENT

A fully validated eCRF will be used to capture all required clinical investigation data throughout the Investigation. Paper diaries will be used to collect AEs and concomitant medication, as well as responses to the onset of action questions.

The eCRF will have controlled access (e.g. password protection) to ensure the privacy of the patient's and partner's information, whilst maintaining data integrity. The clinical database used will be CFR 21 part 11 compliant.

The Monitor will check data at monitoring visits to the investigational sites. Additionally, the Monitor will have secure access to the clinical database to allow remote monitoring where necessary. The PI will ensure that the data in the eCRFs are accurate, complete, legible and consistent with that recorded in the source documents.

Throughout the investigation, the Data Manager or designee will review the data entered into the eCRF, requesting clarification where necessary. A full audit trail will be maintained within the clinical database to capture all changes made to the data entered in the eCRF.

All reported AEs will be coded using the most current version of the MedDRA dictionary. Likewise, all concomitant medication will be coded using the most current version of the WHODrug dictionary. Listings of the coded AEs and concomitant medication will be reviewed by the Sponsor's Medical Advisor prior to the database lock.

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 patient before clean file status is declared.

All data queries raised by Data Management or the Monitor will be addressed by the site prior to database lock. Once all outstanding points requiring data clarification have been addressed, the Data Manager or designee will notify the Sponsor and request to lock the clinical database. Only when permission has been given by the Sponsor may the database be locked. No formal statistical analysis of the captured clinical investigation data will be performed until the database has been locked.

A copy of the collected clinical investigation data will be provided to the Sponsor in a Compact Disc (CD) media format at the end of the clinical investigation. This will be stored in a suitable archiving facility.

Each site will also receive all eCRF data, pertinent to that site, in a CD media format. All such CDs will be stored along with all site-related clinical investigation documentation.

All clinical investigation related data will be stored for a minimum of 10 years.

16. AMENDMENTS TO THE CIP

If it becomes necessary to issue an amendment during the course of the investigation, the amendment will be developed by FMD and/or the CRO in consultation with the Coordinating Investigator and the Biostatistician as necessary.

FMD will notify the CRO and collect documented Investigator Agreements to the amendment. No amendments to the CIP may be implemented until the Regulatory Authorities and ECs (as appropriate) provide a favourable opinion in writing or the necessary review timeframe has elapsed.

17. DEVIATIONS FROM THE CIP

Emergencies excepting, under no circumstances will prospective deviations (waivers) from the approved CIP and subsequent amendments be permitted. Any changes to the CIP should be covered by an amendment which will be approved by the necessary Regulatory Authorities and ECs as necessary.

The Sponsor will be notified of all major deviations from the CIP within 24 hours of their discovery. All deviations that are identified during the course of the investigation, be they major or minor in severity, will be recorded on a CIP deviations tracking log. This log will be reviewed by the Sponsor periodically for risk and trend evaluation purposes, and corrective and preventative action taken as necessary.

18. DEVICE ACCOUNTABILITY

The PI, trained delegate or pharmacy staff (as applicable) is responsible for the correct storage of the investigational product according to the manufacturer's recommendations (see current version of the IB or SmPC as applicable). The investigational products made available for this clinical investigation must be used in accordance with the CIP and must only be handled by the pharmacist or other site authorised personnel. The pharmacy staff must maintain complete and accurate records, showing the receipt and disposition of all supplies of the investigational product. These records must include a master record which lists the date of receipt of all investigational products (i.e. MED3000 or tadalafil [5 mg]) and the quantities received, and a dispensing record which includes all quantities dispensed, the patient numbers to whom the medication was dispensed, the date of each dispensing and the identification of the dispenser. Patients will be expected to return all dispensed investigational product (used and unused) to the site to allow full reconciliation to be undertaken.

No investigational products will be destroyed until full reconciliation has been performed nor without prior written confirmation from the Sponsor. The CRO will be responsible for coordinating the destruction of any unused or returned 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.

19. STATEMENTS OF COMPLIANCE

This clinical investigation will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki, the requirements of GCP, and all necessary regional or national regulatory and ethical legislation.

The clinical investigation may not commence in a particular country or region until all required approvals have been provided, in writing, by the appropriate Regulatory Authority and ECs or Institutional Review Boards (IRBs) or the required review timeframe has elapsed, as necessary. Any additional requirements imposed by the IRB/EC or the Regulatory Authority as a condition of approval must also be followed.

FMD will ensure that local Regulatory Authority requirements are met, if required, before the start of the clinical investigation. FMD (or a nominated delegate) will be responsible for the preparation, submission and confirmation of receipt of any Regulatory Authority approvals required prior to clinical investigation commencement.

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

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

The Sponsor will ensure that suitable insurance cover is in place prior to the start of the investigation. The Sponsor will adhere to the recommendations of the Association of the British Pharmaceutical Industry (ABPI) guidelines and all other requirements of insurance in the countries where the clinical investigation will be conducted.

This investigation is being sponsored by Futura Medical Developments Limited (FMD). Before a site can begin any investigation related activity a fully executed clinical trial agreement is in place between FMD and each site.

20. INFORMED CONSENT PROCESS

It is the responsibility of the PI or suitable qualified designee (e.g. sub-investigators) to obtain written informed consent from all patients and their female partners at Visit 1 before any investigation related procedures are undertaken. All consent documentation must be in accordance with applicable regulations and GCP. Each patient and his partner is required to sign the patient and partner ICF after they have both read the written patient information and received an explanation of what the investigation involves. This can include, but is not limited to: the objectives, potential benefits and risks, inconveniences and the patient's/partner's rights and responsibilities. Signed consent forms must remain on file and must be available for verification by Investigation Monitors at any time. A signed original copy of the informed consent documentation (ICF or Patient Information and ICF, as applicable) must be given to the patient and his partner or the patient'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 investigation. Additionally, if the EC required modification of the sample Patient Information and ICF documents provided by the Sponsor, the documentation supporting this requirement must be provided to the Sponsor.

It is not anticipated that there will be any circumstances whereby a patient or his female partner will not be able to provide their informed consent in this investigation.

21. ADVERSE EVENTS, ADVERSE DEVICE EFFECTS, AND DEVICE DEFICIENCIES

21.1 Definitions

Adverse Event (AE): Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in patients and their partners whether or not related to the investigational medical device or the control used in the investigation.

Adverse Device Effect (ADE): An AE related to the use of the investigational medical device. This definition includes:

- AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device (malfunction is the failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the CIP)

- Any event resulting from use error or from intentional misuse of the investigational medical device (use error is user action or lack of user action while using the medical device that leads to a different result than that intended by the manufacturer or expected by the user)

Serious Adverse Event (SAE): An AE that leads to any of the following:

- Death
- A serious deterioration in the health of the patient or the patient's partner by one or more of the following:
    - A life-threatening illness or injury, or
    - A permanent impairment of a body structure or a body function including chronic diseases, or
    - In-patient or prolongation of hospitalisation, or
    - Medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or body function
- Foetal distress, foetal death, a congenital abnormality, or birth defect including physical or mental impairment

Note: In this investigation, planned hospitalisation for a pre-existing condition, or procedure required by the CIP without serious deterioration in health, is not considered an SAE.

Serious Adverse Device Effect (SADE): An ADE which results in any of the consequences as characterised in an SAE.

Serious Health Threat: Signal from any AE or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in patients, users or other persons, and that requires prompt remedial action for other patients, users or other persons. A device deficiency is the inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance.

Unanticipated Serious Adverse Device Effect (USADE): A SADE which by its nature, incidence, severity or outcome has not been identified in the current risk assessment. In some regions, this may be referred to as an Unanticipated Adverse Device Effect.

AEs/ADEs will be collected from the signing of the ICF at screening (Visit 1) until the end of the investigation. Any AEs that are unresolved at the patient's last AE assessment during the investigation (i.e. at the patient's final investigation 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 patient and/or their female partner with ongoing AE(s)/SAE(s) at the end of the investigation, if judged necessary.

All AEs/ADEs will be recorded in the patient's paper diary and entered into the eCRF after review by the PI or suitable qualified designee (e.g. sub-investigators) at the next investigation visit. The details to be recorded are:

- The date of the AE/ADE onset and its resolution
- Treatment (if any)

- Seriousness
- Relationship to the investigational device or control and the related procedure

Any SAE/SADE/USADE will be notified by the PI to the Medical Device Vigilance Service Provider and Medical Monitor designated by the Sponsor within 24 hours by email or fax. Contact details for the Medical Device Vigilance Service Provider are included in the Medical Device Vigilance manual.

Assessment of relationship and seriousness will be made by the site Physician (see Section 13.11.1). The FMD Medical Advisor will not be able to downgrade the opinion of the site Physician with regards to the relationship or seriousness. Assessment of expectedness of all AEs will be conducted by the FMD Medical Advisor with reference to the 'Reference Safety Information' section of the IB.

Occurrence of SAEs/SADE/USADEs will be notified to the Regulatory Authority and/or the IRB/ECs by the Medical Device Vigilance Service Provider or their delegate within the requisite timeframes for the countries where the clinical investigation is being conducted.

SAEs/SADE/USADEs must be recorded and reported whether or not the PI considers the SAE/SADE/USADEs to be related to the investigational device or the control.

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

A Data Monitoring Committee will not be established for this clinical investigation.

22. VULNERABLE POPULATION

This investigation will involve adult male patients (i.e. 22 to 70 years of age) who are not vulnerable.

23. SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION

The Sponsor may take the decision to prematurely terminate the investigation at any time and for whatever reason; such a decision will be communicated to all PIs participating in the investigation.

As this is an open-label investigation, unblinding of treatment allocation will not be necessary if the investigation is suspended or terminated.

If the investigation is terminated, all ongoing patients will be invited to attend the Follow-up Visit and undertake the assessments scheduled for that visit.

24. PUBLICATION POLICY

Details of the clinical investigation will be registered on a publicly accessible database (e.g. clinicaltrials.gov). Upon completion of the investigation and publication of the Clinical Investigation Report (CIR). FMD will provide a summary of the CIR within 1 year of the end of the investigation 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.

The results of the investigation will be made available publicly. This is expected to occur up to 6 months after the publication of the CIR.

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

25. INVESTIGATOR RESPONSIBILITIES

25.1 GCP Compliance

The PI will have been assigned by FMD to perform the investigation in accordance with the EN ISO 14155:2020 GCP standard, the ethical principles that have their origin in the Declaration of Helsinki, EU Directive 2001/20/EC and all other applicable regulatory and ethical requirements.

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

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

Agreement with the final CIR will be documented by a dated signature of the Coordinating Investigator and local regulatory requirements.

25.2 CIP Adherence and Investigator Agreement

The PI must adhere to the CIP as detailed in this document. The PI will be responsible for enrolling only those patients who have met CIP 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 CIP.

25.3 Documentation and Retention of Records

After completion of the investigation, all data and documents relating to the investigation 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 10 years after the end of the investigation. However, the medical files of patients shall be archived in accordance with national law. The CRO or their delegate must contact FMD before destroying any investigation-related documentation and it is the responsibility of FMD to inform the investigative sites of when these documents can be destroyed.

26. CONFIDENTIALITY

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

After patients have consented to take part in the investigation, their medical records and the data collected during the investigation 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 investigation to proceed.

Patients will be known by a unique patient number. The results of this investigation containing the unique patient 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 investigation. The purpose of any such transfer would be to support regulatory submissions made by FMD in such countries.

27. 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 investigation may be carried out by regulatory agencies. Such audits/inspections can occur at any time during or after completion of the investigation. 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.

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29. APPENDICES

29.1 APPENDIX 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

29.2 APPENDIX 2 SEAR Questionnaire

Self-Esteem And Relationship (SEAR) Questionnaire

INSTRUCTIONS: Please think about **the past 4 weeks** when responding to the following statements.

Please check ☒ one box for each statement.

1. I felt relaxed about initiating sex with my partner.

- ☐ 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

2. I felt confident that during sex my erection would last long enough.

- ☐ 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

3. I was satisfied with my sexual performance.

- ☐ 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

Self-Esteem and Relationship Questionnaire
Version 2: 20FEB02 PPG Mens/Womens Health Team

Self-Esteem And Relationship (SEAR) Questionnaire – Continued

INSTRUCTIONS: Please think about **the past 4 weeks** when responding to the following statements.

Please check ☒ one box for each statement.

4. I felt that sex could be spontaneous.

- ☐ 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

5. I was likely to initiate sex.

- ☐ 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

6. I felt confident about performing sexually.

- ☐ 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

Self-Esteem And Relationship (SEAR) Questionnaire – Continued

INSTRUCTIONS: Please think about **the past 4 weeks** when responding to the following statements.

Please check ☒ one box for each statement.

7. I was satisfied with our sex life.

- ☐ 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

8. My partner was unhappy with the quality of our sexual relations.

- ☐ 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

9. I had good self-esteem.

- ☐ 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

Self-Esteem And Relationship (SEAR) Questionnaire – Continued

INSTRUCTIONS: Please think about **the past 4 weeks** when responding to the following statements.

Please check ☒ one box for each statement.

10. I felt like a whole man.

- ☐ 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

11. I was inclined to feel that I am a failure.

- ☐ 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

12. I felt confident.

- ☐ 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

Self-Esteem And Relationship (SEAR) Questionnaire – Continued

INSTRUCTIONS: Please think about **the past 4 weeks** when responding to the following statements.

Please check ☒ one box for each statement.

13. My partner was satisfied with our relationship in general.

- ☐ 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

14. I was satisfied with our relationship in general.

- ☐ 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

29.3 APPENDIX 3 Onset of Action Questions