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Τμήμα Ιατρικής

Πρόγραμμα Μεταπτυχιακών Σπουδών (ΠΜΣ)
«Μεθοδολογία Βιοϊατρικής Έρευνας, Βιοστατιστική και Κλινική Βιοπληροφορική»

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Μπουχαλάκης Αθανάσιος

Έτος Υποβολής 2021.

Για την εκπόνηση της διπλωματικής εργασίας ο τίτλος είναι ο εξής:

Tadalafil 5mg plus Mirabegron 25mg Vs Tadalafil 5mg plus Placebo for the Treatment of Erectile Dysfunction and mild LUTS: a Randomized Clinical Trial

Ταδαλαφίλη 5mg και Μιραμπεγκρόνη 25mg Vs Ταδαλαφίλης 5mg και Εικονικής Θεραπείας για την Θεραπεία της Στυτικής Δυσλειτουργίας: μια Τυχαιοποιημένη Κλινική Μελέτη

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12/08/2026 22:46:39 EEST - 216.73.217.112

Table of Contents

Institutional Repository - Library & Information Centre - University of Thessaly
12/08/2026 22:46:39 EEST - 216.73.217.112

Institutional Repository - Library & Information Centre - University of Thessaly
12/08/2026 22:46:39 EEST - 216.73.217.112

Περίληψη

Υπόβαθρο

Η στυτική δυσλειτουργία αποτελεί ένα σημαντικό πρόβλημα της δημόσιας υγείας, το οποίο επηρεάζει μεταξύ άλλων και ανθρώπους οι οποίοι πάσχουν από συμπτώματα του κατώτερου ουροποιητικού συστήματος. Η στύση επιτυγχάνεται μέσω της χαλάρωσης των λείων μυϊκών ινών των σηραγγωδών σωμάτων του πέους. Οι αναστολείς της 5-φωσφοδιεστάρης αποτελούν την κύρια θεραπεία. Ωστόσο υπάρχουν μελέτες οι οποίες υποδεικνύουν ότι οι β3 αγωνιστές όπως η Μιραμπεγκρόνη μπορούν να επιτύχουν αντίστοιχο αποτέλεσμα μέσω διαφορετικής οδού, προτείνοντας την ανάγκη περαιτέρω έρευνας. Υπάρχουν ήδη ορισμένες μελέτες όπου ερευνούν την δράση της Μιραμπεγκρόνης στην στυτική δυσλειτουργία, καμία όμως που να εξετάζει την συνδυασμένη δράση της μαζί με έναν αναστολέα 5-φωσφοδιεστεράσης.

Μέθοδοι

Η επί του παρόντος μελέτη, αποτελεί μία προοπτική τυχαιοποιημένη, παράλληλων γκρουπ, διπλή τυφλή μελέτη. Η πειραματική θεραπεία αποτελείται από Ταδαλαφίλη και Μιραμπεγκρόνη και το γκρουπ ελέγχου από Ταδαλαφίλη και εικονική θεραπεία. Η διάρκεια θα είναι 6 μήνες, όπου το κάθε υποκείμενο θα παραστεί σε 4 επισκέψεις, 1 ελέγχου και 3 επιπλέον. Ενενήντα-πέντε ασθενείς θα προσφέρουν επαρκή ισχύ και θα διαχωριστούν σε 2 γκρουπ μέσω μιας διαδικασίας τυχαιοποίησης. Το κυρίως αντικείμενο θα είναι η αλλαγή στο IIEF-ED σκορ για την στυτική δυσλειτουργία. Δευτερεύον στόχος θα είναι η αλλαγή στο IPSS σκορ για τα συμπτώματα του κατώτερου ουροποιητικού. Αξιολογήσεις θα πραγματοποιηθούν πριν την θεραπεία, πριν την τυχαιοποίηση καθώς και κατά την διάρκεια της θεραπείας.

Συζήτηση

Τα αποτελέσματα της μελέτης θα είναι σημαντικά διότι δεν έχουν διεξαχθεί άλλες μελέτες που να αφορούν τον συνδυασμό των συγκεκριμένων ουσιών. Θέματα όπως η πιθανή επίδραση της Μιραμπεγκρόνης στην στυτική δυσλειτουργία, ή το πλεονέκτημα της σε συνδυασμό με την Ταδαλαφίλη και η ανάγκη για μελλοντική έρευνα θα συζητηθούν.

Λεξεις κλειδια : Ταδαλαφίλη, Μιραμπεγκρόνη, Στυτική Δυσλειτουργία, Συμπτώματα Κατώτερου Ουροποιητικού, Β3 αγωνιστές, Αναστολείς Φωσφοδιεστεράσης

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12/08/2026 22:46:39 EEST - 216.73.217.112

Abstract

Background

Erectile Dysfunction (ED) is a significant public health problem, affecting among other people with Lower Urinary Tract Symptoms (LUTS). Penile erection is achieved through relaxation of corpus cavernosum smooth muscles. Phosphodiesterase-5 inhibitor (PDE 5i) is the main treatment used. However, there are studies indicating that B3 agonists such as Mirabegron can achieve similar results through different pathway and suggest further research. There are few studies investigating the effect of Mirabegron on ED and none with primary objective the combined effect of a PDF 5 inhibitor and Mirabegron in men with ED and LUTS.

Methods

This clinical trial is a prospective, two-arm, parallel-group, randomized, placebo-controlled. The experimental treatment is Tadalafil and Mirabegron and control is Tadalafil and Placebo. The duration is 6 months, where each subject will go through 1 screening and 3 more visits. The subjects needed to provide enoughpower are ninety-five and an adaptive randomization procedure will allocate them to two groups. The primary outcome is change in the IIEF-ED score for (ED). The secondary will be the change in the IPSS score for (LUTS). Assessments will be conducted at pre-treatment, pre-double blinding, and mid-treatment.

Discussion

The study results will be significant because no other studies have been conducted regarding this combination of medication. Issues such as the possible effect of Mirabegron on ED, or the advantage of the combined Treatment with Mirabegron and Tadalafil and future research needed will be discussed.

Key Words : Tadalafil, Mirabegron, Erectile Dysfunction, B3 agonist, PDF-5i, LUTS

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12/08/2026 22:46:39 EEST - 216.73.217.112

1. INTRODUCTION

1.1 Background

Erectile dysfunction is a very common problem in men, especially when lower urinary track symptoms (LUTS) coexist. The severity of LUTS is associated with the erectile dysfunction (ED) and men should be checked for ED when presenting with LUTS and vice-versa. Thus, the treatment of LUTS can in some scale improve the erectile function. (Song et al., 2021)

Penile erection is achieved through corpus cavernosum smooth muscles relaxation. For this to be achieved many mediators contribute, but the main is nitric oxide (NO) when it is released either from nitrergic nerves or endothelial cells and make concentration related binds to soluble guanylyl cyclase (sGC) to increase its main mediator, cyclic guanosine monophosphate (cGMP). {(Andersson, 2011, (Rajfer et al., 1992)}. The procedure is stopped by phosphodiesterase-5 (PDE 5) which is allosteric activated by the concentration of cGMP to stop its action. (Ahmed, Geethakumari and Biswas, 2021)

For that reason, PDE 5 inhibitors are considered as the main efficient and safe per-os treatment for erectile dysfunction. They are also used for the treatment of LUTS. (EAU guidelines 2021). However, there are people who don't response and, in these cases, LUTS often are present.

B3 agonists and especially mirabegron are proven to be beneficial for men with LUTS when the storage symptoms prevail and can be used not only as a combined therapy but also as a monotherapy. (EAU guidelines 2021, (Sebastianelli et al., 2017).

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12/08/2026 22:46:39 EEST - 216.73.217.112

Moreover, there are also b3 receptors in corpus cavernosum, localized especially in smooth muscle cell. The activation of a specific b3 agonist (BRL 37344) caused the relaxation of these muscles by inhibition of the RhoA-Rho-associated protein kinase (ROCK) pathway. The cGMP pathway is involved but act independently of NO-pathway. That can offer a possible alternative treatment for erectile dysfunction. (Cirino et al., 2003)

There are also some researchers that make suggestions after in vitro experiments, that mirabegron, a b3 agonist had an effect on human penile tissue and caused relaxation on the smooth muscle. The same happened in rats in vivo and in vitro. The fact that PDF 5 cause relaxation through the NO road caused by the wave of cGPM and mirabegron is independent from it, opens a place for such clinical trials. (Gur et al., 2016). Another study showed that mirabegron intracavernosum injection can help ED in rats when other factors as diabetes reduces the effect of PDF5 and suggest further clinical trial with the combination of PDE 5 and mirabegron. (Yilmaz-Oral et al., 2019). Based on the results of another study, mirabegron can help improve the relaxation of corpus cavernosum in vitro and the erectile function in rats in vino independent from b1,2,3 receptors activation. (de Oliveira et al., 2019)

1.2 Study Rationale

There are no studies that compare Mirabegron with a PDE-5 inhibitor and a PDE-5 inhibitor with placebo in men with mild LUTS and ED with primary objective the ED. In this scope, aim of this study is to test whether the combination of mirabegron 25 mg and Tadalafil 5 mg is superior to Tadalafil and Placebo in terms of ED.

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12/08/2026 22:46:39 EEST - 216.73.217.112

In this study we compare the effect of Mirabegron and Tadalafil in men with ED and mild LUTS, predominantly storage symptoms, against Tadalafil and Placebo. The classification between voiding and storage symptoms will be based on I-PSS voiding-to-storage sub-score ratio (IPSS-V/S) where score <1 is safe indicator of bladder related problems instead of obstructive. (Liao and Kuo, 2014). The ED will be assessed with the IIEF-EF scores with scores between 12-21 indicating mild to moderate ED.

There will be two arms, one with Tadalafil and Placebo and one with Mirabegron and Tadalafil. The groups will receive the treatment for a total of 6 months.

2. STUDY OBJECTIVES

2.1 Primary Objective

- To compare the efficacy of Tadalafil 5mg plus Mirabegron 25mg vs. Tadalafil plus Placebo for the treatment of erectile function based on the IIEF-ED score in patients with mild LUTS.

2.2 Secondary Objectives

- To compare the efficacy of Tadalafil 5mg plus Mirabegron 25mg vs. Tadalafil plus Placebo for the treatment LUTS (mostly storage symptoms) based on the IPSS score.
- To compare the safety of Tadalafil 5mg plus Mirabegron 25mg vs. Tadalafil plus Placebo for the treatment of erectile function in patients with mild LUTS.

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12/08/2026 22:46:39 EEST - 216.73.217.112

3. INVESTIGATIONAL PLAN

3.1 General Schema of The Study

This study is a Phase III, single-centre, randomized, parallel-group study and aims to assess the therapeutic possibilities of the combination of Mirabegron and Tadalafil, in men with ED who suffer also from storage type LUTS. The acting of PDE-5 inhibitor, Tadalafil 5mgl, in combination with Mirabegron administered once daily, will be compared to the effect of tadalafil 5mg and Placebo administered once daily. Men may be considered for entry to the study if they are at least 18 years of age, have storage type LUTS based on the I-PSS voiding-to-storage sub-score ratio (IPSS-V/S) and ED based on the IIEF-ED score. The duration of the study will be 6 months and the patients will have to make a total of 4 visits (baseline,1 month,2 months and 6 months) with the choice of out of schedule visits after communication with the investigator.

3.2 Randomization/ Allocation Concealment/Blinding

Randomization: This is a randomized, double-blind, placebo-controlled, parallel-group study. All suitable subjects at screening are assigned to tadalafil 5mg and placebo. All eligible patients will be randomized to one of 2 groups with an equal allocation ratio (1:1). The coordinating team of the study will generate the randomization sequence using a computer.

Group A: tadalafil 5mg and placebo once daily

Group B: tadalafil 5mg and mirabegron once daily.

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12/08/2026 22:46:39 EEST - 216.73.217.112

Allocation Concealment: Treatment allocation will be communicated by the coordinating centre to the investigators via a web-based registration system to ensure allocation concealment and minimize bias.

Blinding: Study medication will be blister packaged in order to avoid recognition of mirabegron and placebo. After the second visit the randomization is double-blind. The aforementioned process will ensure the double-blind character of the study as the participants, the clinicians/data collectors will be unaware of the treatments the participants receive.

3.3 Study Population

3.3.1 Inclusion Criteria

- Presence of mild to moderate ED (IIEF EF domain score 17-21) or moderate ED (IIEF EF domain score 11-16)
- Men sexually motivated with stable sexual partner

3.3.2 Exclusion Criteria

- Men with Peyronie's disease.
- Patients with contraindication to receive mirabegron (High PVR).
- Psychiatric disorders.
- Previous pelvic surgery or trauma
- Men with prostatic adenocarcinoma
- concurrent ED therapy
- History of penile surgery

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12/08/2026 22:46:39 EEST - 216.73.217.112

4. STUDY PROCEDURES

4.1 Visit 1(screening phase)

At Visit 1, the patient will sign the informed consent document (ICD) before any protocol-specific procedure is performed. Written informed consent for this study will be obtained from all patients by the investigator or his/her designee. Eligible patients will enter a 4-week period following Visit 1 taking only tadalafil 5mg and placebo. During this period, the patient will be required to make at least three or four sexual intercourse attempts to figure out the baseline of each patient.

4.2 Visit 2 (double blinding)

At the second visit the subjects will be randomized into two groups 1:1,with the first group receiving 25 mg mirabegron and 5 mg tadalafil and the second group 5 mg tadalafil and placebo. The randomization will be double blind and neither the investigator nor the patient will know the schema that they receive. The subjects will be provided with medication for one month. They will have also a urine stick and a urine culture.

The IIEF-EF score and the IPSS score will be assessed.

4.3 Visit 3

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12/08/2026 22:46:39 EEST - 216.73.217.112

This visit is one month after the randomization. The IIEF-EF and the IPSS score will once again be assessed. In this visit there will be also a PVR check, and the subjects will be asked of any adverse effects that have any connection to the medication as the concomitant medication they receive. They will also have a urine stick and a urine culture.

4.4 Visit 4

This is the last visit, five months after the randomization. The IIEF-EF and the IPSS scores once again will be assessed and the patient will have to address any possible side effect related to the medication or the concomitant therapy. The overall compliance of the patient will be also assessed.

4.5 Follow up

If subject has ongoing adverse events at the previous visit the site should contact the subject 1 week after their last dose of medication to: Assess and record adverse events; Review concomitant medications and non-drug treatments.

4.6 Unscheduled Visits

The subjects have the right to make unscheduled visits after an appointment with the investigator in case they want to report an adverse event or if they want an extra evaluation that is related to the trial. They have to visit and report any signs of urine infection.

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12/08/2026 22:46:39 EEST - 216.73.217.112

4.7 Withdrawal

For administrative, safety or behavioral reasons the investigator may withdraw subjects from the study, or they may be withdrawn at their own request at any time. If a subject does not come back for a scheduled visit, efforts should be made for contact. In any case, efforts should be made to document subject outcome, if possible. The investigator should inquire about the reason of withdrawal, request the subject to return all unused investigational products, request the subject to return for a final visit, if applicable, and follow-up with the subject regarding any unsolved adverse events. If a subject withdraws from the study, and withdraws consent for disclosure of future information, no further evaluations should be made, and no further data should be collected. Any data may be retained and continue to be used if collected before such withdrawal of consent.

5. SCREENING AND MONITORING EVALUATION AND MEASUREMENTS

5.1 Medical Record Review

All the patients should provide a complete list of their medical history, drug they are receiving and their history of operations.

5.2 Physical Examination

A physical examination should be undertaken to check for possible gynecomastia, cryptorchidism, phimosis or peyronie disease.

5.3 Vital Signs

Vital signs such as blood pressure, pulse, temperature and BMI will be recorded.

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12/08/2026 22:46:39 EEST - 216.73.217.112

5.4 Laboratory Evaluations

A basic blood chemistry, hematologic exam, and urine exam will be recorded.

5.5 Other Evaluations, Measures

The neccesary IIEF-EF and IPSS scores will be assessed.

6. STATISTICAL CONSIDERATIONS

6.1 Statistical methods.

6.1.1 Efficacy analysis

A t-test for independent data will be used to test the difference between the means of the change of the IIEF score between the two groups, tadalafil 5 mg and placebo and tadalafil 5 mg and mirabegron 25mg at month 6 relative to baseline. The primary comparison will be the IIEF-EF score and the secondary will be the IPSS. Change from baseline in within each treatment and between treatment differences will be estimated by means and 95% confidence intervals. Treatment comparisons will be performed with 2-sided test at 5% significance level. If normality assumptions are violated, non-parametric methods will be used to test treatment difference. Descriptive statistics, including N, mean, median and standard deviation will be reported for baseline and change from baseline.

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12/08/2026 22:46:39 EEST - 216.73.217.112

6.1.2 Safety analysis

The safety analysis set will include all subjects who take at least one dose of study drug. Safety analysis will be based on safety analysis set.

6.2 Sample Size and Power

To define the sample size of our study we should set the proportion of patients that will be improved (in both ED and LUTS) with the use of the combination of tadalafil and mirabegron. The comparison of proportion of patients that improved tadalafil and mirabegron vs tadalafil and Placebo was examined using a x2 - test with a threshold P-value of P=0.05. The expected response using tadalafil was 40% {taken from the literature (Roehrborn et al., 2016)}. A difference of at least Δ=20% in response was considered as clinically important and the probability that the difference will be detected as statistically significant was set equal to 80%. The population needed is 97, thus 59 people in each group, if we suspect a drop-out ratio of 20 percent.

7. MEDICATION DESCRIPTION

7.1 Formulation and Packaging

Subjects will receive study medication (tadalafil 5mg and placebo) for the 4-week run-in period and then will be randomized to one of the 2 arms of the study (tadalafil 5m and placebo or tadalafil 5mg and mirabegron 25mg) per the randomization schedule. Mirabegron 25 mg and matching placebo have identical appearance. The tablets will be packaged according to applicable regulatory requirements. The tadalafil 5 mg and 25 mg mirabegron, as well as the placebo, dosage forms are tablets designed for oral administration. At Visit 1, subjects will be provided run-in study medication (tadalafil

Institutional Repository - Library & Information Centre - University of Thessaly
12/08/2026 22:46:39 EEST - 216.73.217.112

5mg placebo) for 4 weeks. The subject will take the two tablets daily as a single dose each morning. At Visit 2, subjects will be provided study medication for 4 weeks, according to the arm they are randomized to. The subject will take one tablet daily as a single dose each morning.

7.2 Administration

One tablet will be taken with a sufficient amount of water every day and swallowed whole. It should not be chewed, divided, or crushed. The study drug can be taken with or without food and should be taken in the morning. The subjects will take their first tablet of single blind medication at Visit 1 and their first tablet of double-blind medication at Visit 2 whilst at the investigator site.

7.3 Compliance

Subjects must be informed that compliance with taking medication as instructed is imperative. Subjects will return all medication blister packages to assess compliance at Visits 2 and 3. Any unused medication will be returned and collected by the study site at Visits 2 and 3 (or upon early termination). Dosing information and study medication compliance information will be entered into the case report form as required. Subjects who take 80% and no greater than 120% of their study medication are considered compliant. Subjects who are non-compliant may be discontinued. A designated monitor will perform inventory checks of all used and unused study medications at each monitoring visit.

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12/08/2026 22:46:39 EEST - 216.73.217.112

7.4 Drug Storage and Accountability

All drug supplies must be stored in accordance with manufacturer instructions. The normal hospital stocks must be stored separately from the study drug supplies. Until dispensed to the subjects, the investigator, or an approved representative (eg, pharmacist), will ensure that all investigational product is stored in a secured and locked area accessible only to authorized personnel, under recommended storage conditions and in accordance with applicable regulatory requirements. The investigator, or approved representative, will be responsible for recording the receipt, administration and return of all study medication, and for ensuring the supervision (via a hospital pharmacist where relevant) of the storage and allocation of the study medication. A complete inventory should be performed of the study medication upon its delivery to the site. Any discrepancies between what is documented on the drug shipment form and what is contained in the shipment should be noted. It is also the responsibility of the investigator, or approved representative, to ensure that the integrity of study medication will not be jeopardized prior to dispensing. Each individual subject blister package must be dispensed as provided with no further repackaging or labeling done at the site or by the subject. Clinical supply accountability should be strictly monitored. The investigator, or approved representative, must preserve adequate documentation of the receipt, use, loss, or other disposition of the investigational product(s). The investigational product must be identified by the accountability forms, including code or batch numbers, as well as account for its disposition on a subject by subject basis, including specific dates and quantities.

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12/08/2026 22:46:39 EEST - 216.73.217.112

8. SAFETY MANAGEMENT

8.1 Clinical Adverse Event

All the adverse events that are observed or volunteered no matter of treatment group or any suspected causal relationship to the investigational product(s) will be reported as described in the following sections. For all adverse events, the investigator must pursue and collect information sufficient both to establish the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate reporting. For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event.

8.2 Reporting

For serious adverse events, the reporting period begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to going through any study-related procedure and/or receiving investigational product, through and after 28 days of the last administration of the investigational product. Any serious adverse event occurring after the reporting period must be punctually reported if a causal relationship to investigational product is suspected.

8.3 Definition of Adverse Event

An adverse event is any unforeseen medical occurrence in a clinical investigation subject administered a product or medical device; the event does not necessarily need to have a causal relationship with the treatment or usage.

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12/08/2026 22:46:39 EEST - 216.73.217.112

8.4 Definition of Serious Adverse Event

A serious adverse event is any unforeseen medical occurrence at any dose that: Requires inpatient hospitalization or prolongation of existing hospitalization; Is life-threatening (immediate risk of death); Results in persistent or significant disability/incapacity; Results in death; etc.

9. QUALITY CONTROL AND ASSURANCE

During study conduct, periodic monitoring visits will be conducted to ensure that the protocol and GCPs are being followed. The monitors may examine source documents to validate that the recorded data on CRFs is accurate. The investigator and institution will allow monitors and appropriate regulatory authorities direct access to source documents to perform this verification. The study site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and/or to quality assurance audits performed by monitors, and/or to inspection by appropriate regulatory authorities.

10. DATA HANDLING AND RECORD KEEPING

10.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term Case Report Form (CRF) should be referred to either an electronic data record or a paper form or both, depending on the data collection method used in this study. A CRF is compulsory and should be completed for each subject included. The completed original CRFs should not be made available in any form to third parties, except for authorized representatives or appropriate regulatory

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12/08/2026 22:46:39 EEST - 216.73.217.112

authorities. The investigator has supreme responsibility for the collection and reporting of all clinical, safety and laboratory data entering the CRFs and the collection of other data forms (source documents) and certifying that they are accurate, authentic / original, ascribable, complete, legible, timely (contemporaneous), enduring and available when required. The investigator or an authorized staff member must sign the CRFs to attest that the data on the CRFs is true and valid. Any adjustments made to recordings in the CRFs, must be dated, and explained with signed source documents and should not put in doubt the original entry.

10.2. Record Retention

For the evaluations and/or audits to be enabled from regulatory authorities, the investigator complies with keeping records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, source documents, safety reporting forms, and records of treatment disposition. The records should be preserved by the investigator according to ICH, local regulations, or as specified in the Clinical Study Agreement. Authorities should be informed if for any reason the investigator is no longer available to retain study records for the period needed (e.g. retirement, relocation).

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12/08/2026 22:46:39 EEST - 216.73.217.112

11. ETHICS

11.1 Institutional Review Board (IRB) / Independent Ethics Committee (IEC)

The investigator is responsible for the approval of the study protocol and its amendments, informed consent forms, and other relevant documents, from the IRB/IEC. All correspondence with the IRB/IEC should be reserved in the Investigator File. The only situation in which an amendment may be launched prior to IRB/IEC confirmation is where the change is required to eliminate assumed immediate risks to the subjects.

11.2 Ethical Conduct of the Study

The study will be directed in agreement with legal and regulatory requirements, as well as the principles proposed in, Guidelines for Good Clinical Practice (International Conference on Harmonization 1996), the Declaration of Helsinki (World Medical Association 1996 and 2008) and in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002). Additionally, the study will be conducted in accordance with the protocol, laws applicable to the local regulatory requirements and the International Conference on Harmonisation guideline on Good Clinical Practice.

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13. APPENDIX

Over the past six months:

1	How do you rate your **confidence** that you could get and keep an erection?	Very low	Low	Moderate	High	Very high
		1	2	3	4	5
2	When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	Almost never/never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always/always
		1	2	3	4	5
3	During sexual intercourse, **how often** were you able to maintain your erection after you had penetrated (entered) your partner?	Almost never/never	A few times (much less than half the time)	Sometimes (about half the time)	Most time (much more than half the time)	Almost always/always
		1	2	3	4	5
4	During sexual intercourse, **how difficult** was it to maintain your erection to completion of intercourse?	Extremely difficult	Very difficult	Difficult	Slightly difficult	Not difficult
		1	2	3	4	5
5	When you attempted sexual intercourse, how often was it satisfactory for you?	Almost never/never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always/always
		1	2	3	4	5

[a] The IIEF-5 score is the sum of the ordinal responses to the five items; thus, the score can range from 5 to 25

Table 1. The IIEF Score

International Prostatic Symptom Score						
	Not at all	Less than 1 in 5 times	Less than half the times	About half the times	More than half the times	Almost always
How often have you had the sensation of not emptying your bladder?	0	1	2	3	4	5
How often have you had to urinate less than every two hours?	0	1	2	3	4	5
How often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
How often have you found it difficult to postpone urination?	0	1	2	3	4	5
How often have you had a weak urinary stream?	0	1	2	3	4	5
How often have you had to strain to start urination?	0	1	2	3	4	5
	None	1 time	2 times	3 times	4 times	5 times
How many times did you typically get up at night to urinate?	0	1	2	3	4	5

Table 2. IPSS Score

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