PLETHORA SOLUTIONS LTD

CLINICAL STUDY PROTOCOL

A PILOT MULTICENTER, RANDOMIZED, DOUBLE-BLIND STUDY COMPARING THE PROPORTION OF RESPONDERS TO PSD502 AND TO PLACEBO USING THE PEBEQ™ IN SUBJECTS WITH PREMATURE EJACULATION

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PROTOCOL SYNOPSIS

Title of the Study: A Pilot Multicenter, Randomized, Double-Blind Study Comparing the Proportion of Responders to PSD502 and to Placebo Using the PEBEQ™ in Subjects With Premature Ejaculation
Coordinating Investigator: Dr. Jed Kaminetsky, 215 Lexington Avenue, 20th and 21st Floor, New York, NY 10016, United States of America
Study Center(s): Up to 30 centers in the United States of America will take part.
Study Population: Male subjects with lifelong premature ejaculation (PE) according to the International Society for Sexual Medicine (ISSM) definition, aged 18 and over, who are at least moderately bothered by their PE, as measured by the Premature Ejaculation Bothersome Evaluation Questionnaire (PEBEQ™) Item 3 (event-specific bother).
Planned Date of First Subject Enrolled: Quarter 4, 2018 **Planned Date of Last Subject Completed:** Quarter 1, 2020
Objectives: **PRIMARY OBJECTIVE** Determine if the PSD502 group has a greater proportion of successful subjects on the PEBEQ Item 3 (event-specific bother) than does the placebo group, where success is defined for each subject as having a mean response over the 4-week treatment period at least 1 point better than the subject's mean response over the 4-week baseline period. **SECONDARY OBJECTIVES** Determine the psychometric properties of PEBEQ Item 3 (event-specific bother). In particular, the consistency in scoring of the PEBEQ Item 3 (event-specific bother) with the Patient Global Impression of Severity (PGI-S), Patient Global Impression of Change (PGI-C), Patient Global Impression of Change-Bother (PGI-C-Bother), Independent Ejaculation Quickness Item (IEQI) and Independent Numeric Response Scale (NRS) Bother Item and its responsiveness to change and derivation of meaningful change (anchor-based and other methods) will be evaluated. Other psychometric properties including reliability (test-retest reproducibility) and validity will also be evaluated. Determine if the PSD502 group has a greater median score in the PGI-C and the PGI-C-Bother than does the placebo group. Determine if the PSD502 group has a greater mean increase in the intravaginal ejaculatory latency time (IELT), the PGI-S, the Index of Premature Ejaculation© (IPE) Domain Scores, the Independent NRS Bother Item, and the IEQI than does the placebo group over the course of the study. Evaluate safety and tolerability of PSD502 in subjects with PE and in their sexual partners.

EXPLORATORY OBJECTIVES

Determine if each of the PEBEQ multi-item scores are improved more in the PSD502 group than in the placebo group.

Other analyses suggested by the data.

Methodology:

This is a pilot, multicenter, randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy of PSD502 applied to the glans penis on bother-related symptoms secondary to PE. Additionally, psychometric evaluation of PEBEQ Item 3 (event-specific bother) will be investigated.

Subjects and their sexual partners will attend a Screening Visit (Visit 1) at which they will provide written informed consent. Subjects will be asked to complete a Subject Contact Form that collects the subject's preferred contact information for Plethora's selected vendor for qualitative interviews and the subjects will be screened for eligibility. The subject will be asked to answer a screening question on how bothered they are because of the quickness of their ejaculation on an 11-point NRS scale to confirm that they are bothered and will also be asked to complete the International Index of Erectile Function 5 (IIEF-5) questionnaire in order for the Investigator to assess erectile function. Screening will involve collection of demographic information, medical history (including history of PE), medication history, physical examination including visual examination of the glans penis, heart rate (HR), blood pressure (BP), 12-lead electrocardiogram (ECG) and blood sample collection (for hematology and biochemistry). As part of the screening procedures to confirm the subject's eligibility, the subject's sexual partner will undergo a urine pregnancy test at Visit 1. This result must be negative in order for the subject to participate in the study. Subjects that pass the initial screening assessments will then undergo a baseline evaluation period of 4 weeks during which they are required to have at least three sexual encounters. They will be provided with a stopwatch to measure IELT, a diary card in which to record adverse events (AEs), concomitant medications, date and time of sexual intercourse, PEBEQ responses, PGI-S, Independent NRS bother item, IEQI and IELT data after each encounter. They will also receive an electronic date and time stamper to document the time at which they record details for each sexual encounter in the diary card. Subjects will be instructed to start timing at vaginal penetration, stop timing at the start of ejaculation and that the diary must be completed immediately after the encounter if possible or within 12 hours of the encounter.

Upon completion of the baseline period, subjects will return to the clinic for Visit 2. The diary card will be reviewed, and AE and concomitant medication information will be collected. Those subjects who have a baseline IELT of $\leq$1 minute for all sexual encounters, where each encounter is separated by at least 24 hours and who indicate a level of Bother on Item 3 of the PEBEQ of either "moderately", "quite a bit" or "extremely" on all encounters during the baseline period will be eligible to continue in the study and receive study medication for 4 weeks. Subjects will complete a baseline IPE questionnaire and also have their glans penis visually examined.

If the subject is eligible, he will be stratified into one of two groups, according to whether or not he is circumcised. The subject will be randomized within each stratification group to either PSD502 or placebo (1:1) and will be given sufficient study medication to last until the next clinic visit as well as a new diary card. The subject must be willing to use the study spray for all sexual encounters. The subject will be instructed on how to use the spray and instructed to use it in the next 4 weeks, at least once per week and to leave at least 24 hours between each sexual encounter. For each sexual encounter, the subject will time his IELT using a stopwatch. The subject will record the date and time of sexual intercourse, PEBEQ responses, PGI-S, Independent NRS bother item, IEQI, number of sprays used and IELT data in the diary card. The subject will document efficacy and tolerability data in a diary card and will use the date and time stamper to document the time at which they record details for each sexual encounter. The diary must be completed immediately after the encounter if possible or within 12 hours of the encounter.

At Visit 3, Final Evaluation Visit, the diary card, date and time stamper and any previously dispensed medication will be collected, AE and concomitant medication enquiries will be made and the subject will be asked to complete an IPE questionnaire. The subjects will undergo safety evaluations as for the Screening Visit (Visit 1), including examination of the glans penis. At this last visit, subjects will be asked to provide a PGI-C in the quickness of their ejaculation and will be asked to answer "Was this a meaningful or important change for you?" All subjects will also be asked to complete a PGI-C-Bother and will be asked if the change was meaningful or important.

Subjects who do not prematurely discontinue from the study will participate in the telephone exit interview. The interviewer at Plethora's selected vendor for qualitative interviews will work with the subject and the study site before and at the Final Evaluation Visit to arrange for the interview to take place on the day of the Final Evaluation Visit once all assessments have been performed. If this is not possible, it will be scheduled with the subject to be conducted as soon as possible after the visit, up to a maximum of 10 days following the Final Evaluation Visit. The subject will be asked to describe the change in ejaculation time they experienced during their participation in the study, how meaningful the change was for them and exactly what made the change meaningful. Subjects will be asked to identify the smallest amount of positive change that they would find to be a meaningful treatment benefit and describe the change as a descriptive narratively and as a rating.

The subject's sexual partner will maintain a diary of changes in health that will be used to record AE information throughout the study. If a partner does experience any AEs, the Investigator will contact her by telephone to obtain full details. The partner will send the completed diaries to the study center by post, or in an envelope handed to the subject.

Number of Subjects: Sufficient subjects will be screened to ensure that 100 subjects are randomized into the study, 50 per arm.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria: A subject will be considered suitable for the study if he fulfills all of the following criteria:

1. Willing and able to provide written informed consent.
2. Male and aged 18 years and over.
3. Diagnosed with PE according to the ISSM definition, that is, he ejaculates always or nearly always prior to or within about one minute of vaginal penetration; and is unable to delay ejaculation on all or nearly all vaginal penetrations; and experiences negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy.
4. Subject has lifelong PE from the first sexual experience.
5. Subject must be in a stable heterosexual and monogamous relationship of at least 3 months' duration with this partner.
6. Subject has at least documented 3 sexual encounters, each separated by an interval of at least 24 hours, in the baseline period.[i]
7. IELT ≤1 minute in all sexual encounters in the baseline period.
8. The subject's partner must provide written informed consent, be aged 18 years or over and willing to comply with the study procedures.
9. Subject indicates a level of Bother on Item 3 of the PEBEQ of either "moderately", "quite a bit" or "extremely" on all encounters during the baseline period.
10. Subject registers a level of "bother" at a score of 4 or greater on an 11-point NRS scale at Screening to ensure that subjects not bothered by their quickness of ejaculation are not entered into the baseline period.

Exclusion Criteria: A subject, or his sexual partner where stated, who fulfills any of the following criteria will be excluded from the study:

1. Subject, or his sexual partner, has received an investigational (unapproved) drug within 30 days of Screening.
2. Subject has erectile dysfunction, defined as an IIEF-5 score of ≤21, unless the low score is entirely related to PE symptoms in the opinion of the Investigator.
3. The subject, or his sexual partner, has a physical or psychological condition that would prevent them from undertaking the study procedures, including, but not limited to, the following:

[i] The requirement for each documented encounter in the baseline period to be at least 24 hours after any previous encounter is applicable to <u>all</u> documented encounters in the baseline period, not just the first 3.

- Urological disease (e.g., prostatitis, urinary tract infection) or genitourinary surgery within 8 weeks of Screening
- Ongoing significant psychiatric disorder (e.g., bipolar disease, depression / anxiety disorder or schizophrenia) not controlled by medication.

4. Subject has safety testing abnormalities at the Screening Visit, in particular liver function tests or anemia, that are indicative of a medical condition that would preclude further participation in the opinion of the Investigator.
5. Subjects taking tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs) or selective serotonin reuptake inhibitors (SSRIs), for indications other than PE, where the dose has been changed within 4 weeks of Screening or it is planned that the dose will change during the treatment period.
6. Subject has received any treatment for PE e.g., anti-depressant therapy, local anesthetic spray, eutectic mixture of local anesthetics (EMLA®) cream, intra-cavernosal injection, tramadol or psychotherapy within 4 weeks of Screening.
7. Subject, or his sexual partner, has a current history of alcohol or drug abuse, in the opinion of the Investigator.
8. The subject, or his sexual partner, is unlikely to understand or be able to comply with study procedures, for whatever reasons.
9. Subject, or his sexual partner, has known drug sensitivity to amide-type local anesthetics.
10. Subjects with pregnant partners.
11. Subject with sexual partners of child-bearing potential and not using appropriate contraception (hormonal contraception or intra-uterine device [IUD]).
12. Subject, or his sexual partner, has a history of glucose-6-phosphate dehydrogenase (G-6-PD) deficiency or currently using medications that would increase susceptibility to methemoglobinemia (e.g., anti-malarial agents) or has congenital or acquired methemoglobinemia, or is at risk of industrial exposure to agents causing methemoglobinemia.
13. Subject, or his sexual partner, uses Class I (e.g., mexiletine, tocainide) or III (e.g., amiodarone, sotalol) anti-arrhythmic drugs, or cimetidine, beta blockers or local anesthetics.
14. Subject has received PSD502 in a clinical study or has received Fortacin® within 1 year of Screening.

Test Product, Dose and Administration: PSD502 is a metered dose cutaneous spray containing a eutectic-like mixture of the active ingredients lidocaine and prilocaine, and a propellant (norflurane), which also serves as a solvent. Each actuation (spray) contains 7.5 mg lidocaine and 2.5 mg prilocaine. A single dose consists of 3 sprays applied to the glans penis for a total dose of 22.5 mg lidocaine and 7.5 mg prilocaine.

PSD502 spray will be administered topically to cover the glans penis (one spray per region of the glans), approximately 5 minutes prior to sexual intercourse. Subjects must leave at least 24 hours between sexual encounters during the treatment period and refrain from activity leading to ejaculation for ≥24 hours prior to each use of the spray.

Study spray will be administered at least once per week during the 4 week treatment period.

Duration of Treatment: 4 weeks double-blind.

Reference Product, Dose and Mode of Administration: Placebo metered dose spray, identical in appearance to the PSD502 spray, containing the same propellant (norflurane) but does not contain the actives prilocaine or lidocaine, instead it contains PEG600 and Povidone, which are both listed on the US Food and Drug Administration (FDA) Inactive Ingredients Database.

The placebo spray will be administered in the same manner as the PSD502 spray.

Criteria for Evaluation:

Efficacy:

The primary efficacy variable is the:

- Success on the PEBEQ Item 3 (event-specific bother), where success is defined as having a 1-point or greater improvement between the mean response over the treatment period and the mean response during the baseline period

The secondary efficacy variables are the:

- PGI-C
- PGI-S
- PGI-C-Bother
- IELT
- IEQI
- Change from baseline in the IPE Control, Distress and Satisfaction Domain Scores
- Independent NRS Bother Item

The exploratory efficacy variables are the:

- PEBEQ Multi-Item Event Specific Subscale Total

- PEBEQ Multi-Item General Subscale Total

Psychometric:

- PEBEQ Item 3 (event-specific bother)

Safety:

Safety variables include study drug exposure, the nature, incidence, relationship and severity of AEs and serious AEs (SAEs), incidence of and reasons for withdrawals, laboratory parameters, use of concomitant medications, vital signs, findings on physical examination, 12-lead ECG and visual examination of the penis.

Statistical Methods

Sample Size: In order to assess the proportion of subjects who achieve a 1-point or greater improvement over 4 weeks in the mean PEBEQ Item 3 (event-specific bother), 100 subjects will be randomized into this pilot study, 50 per arm (allowing for a 10% dropout rate). This sample size is sufficient to detect a difference of 30% in success rates when the placebo rate is 20%, with power 80% using a chi square test with a 5% Type I error rate.

In order to assess the psychometric properties of the PEBEQ Item 3 (event-specific bother), the 100 subjects will be used. This sample size is sufficient to provide estimates of meaningful change; in a validation study conducted on 56 males to test the psychometric performance of the full PEBEQ including the General and Event Specific subscales, the standard error associated with correlations of about 0.50 on a number of patient reported outcomes (PROs) was about 0.12. With a sample size of 100, the standard error is expected to decrease to around 0.05 to 0.08.

Randomization:

A randomization schedule assigning subjects to treatment will be defined for each site and stratified by circumcision status. Each schedule will be blocked, independently of the other schedules.

Analysis Populations:

All randomized subjects who receive at least one dose of a study drug and who have at least three observations of PEBEQ Item 3 (event-specific bother) in the baseline period and at least one in the treatment period will be included in the modified intent-to-treat (MITT) population.

To adequately assess the reliability and validity of the PEBEQ Item 3 (event-specific bother), all eligible subjects entering the baseline period who indicate a 4 or greater on the Screening 11-point NRS Scale to Assess Bother will be included in the analyses (psychometric population). The PEBEQ Item 3 (event-specific bother) analysis set will consist of all subjects with valid sexual event data completed between screening and randomization.

Safety variables will be evaluated on all subjects who are treated (safety population).

Efficacy Analysis:

The primary response variable is success on the PEBEQ Item 3 (event-specific bother), where success is defined *a priori* as having a 1-point or greater improvement between the mean response over the treatment period and the mean response during the baseline period. Success will be modelled using a generalized linear mixed effects model with treatment, circumcision status and baseline mean PEBEQ Item 3 (event-specific bother) score as fixed effects and site as a random effect. The null hypothesis of no treatment effect will be tested after adjustment for these other covariates.

PGI-C and PGI-C-Bother will be evaluated using a non-parametric test adjusted for site and, circumcision status.

A linear mixed effects analysis model will be used to evaluate treatment effect on IELT during the study. The fixed effects are period (baseline or treatment period), treatment, period-by-treatment interaction and circumcision status and the random effects are site and subject within site.

The same analysis will be conducted on PGI-S, Independent NRS bother item, and IEQI.

A linear mixed effects model will be used to evaluate treatment effect on the change from baseline in each of the IPE domains. The fixed effects are treatment, circumcision status and baseline, while site is the random effect.

Treatment effects will also be evaluated for each circumcision status.

A linear mixed effects model will be used to evaluate treatment effect on the two PEBEQ multi-item subscales during the study. The fixed effects are period (baseline or treatment period), treatment, period-by-treatment interaction and circumcision status and the random effects are site and subject within site.

Descriptive statistics will include sample size, number of missing observations, counts or mean values and standard deviations for discrete and continuous variables, respectively. Descriptive statistics will be provided for subgroup categories (treatment, site, circumcision status).

Psychometric Analysis:

The evaluation of test-retest reliability will be made using the intra-class correlation coefficient (ICC) using a two-way mixed effect model with absolute agreement for single measures. These analyses will be conducted using one pair of successive valid diary entries per subject where subject indicated no change from the PGI-S on the second sexual encounter. The primary analysis will use diary entries for sexual encounter 1 and sexual encounter 2. If the subject indicates having a change between sexual encounter 1 and sexual encounter 2, then that subject's diary entries for sexual encounter 2 and sexual encounter 3 will be used for the analysis; or if there is a change between 2 and 3, then diary entries for sexual encounter 3 and sexual encounter 4 will be used.

Convergent validity (demonstrating that different measures of the same concept substantially correlate when assessed concurrently) will be evaluated by examining

magnitude of correlations between the PEBEQ Item 3 (event-specific bother) and the Independent NRS bother item. Convergent validity would be supported when the PEBEQ Item 3 (event-specific bother) is substantially correlated (≥0.40).

Known-groups validity (the extent to which scores from a measure can discriminate between groups of participants that differ on a known relevant dimension, such as a measure/assessment of disease severity will be examined using an analysis of variance (ANOVA) model to ensure adequate variability in the bother grouping variables based on (1) IEQI, (2) PGI-S and (3) groups defined by the IELT ≤30 seconds, >30 seconds-≤1 minute, >1 minute-≤2 minutes, and >2 minutes).

Responsiveness to change of the PEBEQ Item 3 (event-specific bother) will be examined between the mean response over the treatment period and the mean response during the baseline period. Effect size estimate of change ([Mean $_{\text{treatment period}}$ – Mean $_{\text{baseline}}$] ÷ standard deviation (SD) $_{\text{baseline}}$), standardized response mean ([Mean $_{\text{treatment period}}$ - Mean $_{\text{baseline}}$] ÷ SD $_{\text{change}}$), standardized mean change difference ([Mean change $_{\text{PSD502}}$ - Mean change $_{\text{placebo}}$] ÷ SD $_{\text{baseline pooled}}$), and Guyatt's statistic ([Mean $_{\text{improved/worsened group in treatment period}}$ - Mean $_{\text{improved/worsened group at baseline}}$] ÷ SD $_{\text{change in stable group}}$) will be used in the evaluation of responsiveness. For each type of effect size, a larger absolute value always indicates a stronger effect. Cohen (1988) defines effect sizes as: small (0.20), medium (0.50) and large (0.80).

Anchor-based assessments of change will also be evaluated. Differences in the PGI-S and IELT will be used to define subjects as responders (decrease in severity at end of study versus those that did not change or worsened at end of study) and descriptively compared to changes in PEBEQ Item 3 (event-specific bother). Similar analyses will be performed with PGI-S replaced with the other anchor scales.

To evaluate the consistency of effects across the entire distribution, a cumulative distribution plot (based on the cumulative distribution function [CDF]) will be generated showing the change from baseline by cumulative percent of subjects. This distribution curve will reveal the extent to which overall results are driven by outliers who improve or worsen more than others.

Safety Analysis:

Safety data will be summarized and descriptive statistics applied as appropriate.

Missing Data:

No individual PEBEQ Item 3 (event-specific bother) data will be imputed.

For each subject, the mean of PEBEQ Item 3 (event-specific bother) responses observed during the baseline period will serve as the baseline period score. In order to continue in the study, the subject must have at least three (3) observations of PEBEQ Item 3 (event-specific bother) in the baseline period. Similarly, the mean of PEBEQ Item 3 (event-specific bother) responses observed during the treatment period will serve as the treatment period score. At least one (1) treatment period PEBEQ Item 3 (event-specific bother) response is required. Subjects who do not have a treatment response for PEBEQ

Item 3 (event-specific bother) will be dropped from all efficacy analyses and psychometric analyses concerning the responsiveness to change and meaningful change. The treatment period score must be at least 1 unit larger than the baseline period score for that subject to be considered a "success".

If a missing IELT for an individual encounter occurs due to anteportal ejaculation (ejaculation happening before penetration), the IELT for that encounter will be set to 0 seconds. If a missing IELT for an individual encounter occurs due to the non-ejaculation (penetration achieved but no ejaculation occurring), the IELT for that encounter will be set to the maximum achieved for that subject.

No safety data will be imputed.