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RANDOMIZED, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF BENZOCAINE WIPES IN SUBJECTS WITH PREMATURE EJACULATION

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ABSTRACT

Aim

This study investigated the efficacy and safety of benzocaine wipes (PREBOOST) applied to the penis prior to intercourse for the treatment of men with premature ejaculation.

Materials and methods

The study utilized the local anesthetic benzocaine, in the form of wipes, for topical application to the glans penis prior to sexual intercourse. The design included three phases: screening and baseline, blinded randomized controlled, and an open-label phase with crossover of the placebo group to open-label active treatment. The two co-primary efficacy measures were the intravaginal ejaculatory latency time (IELT) measured by stopwatch, and the patient-reported outcome measured by the Index of Premature Ejaculation (IPE). Additional efficacy evaluation included a responder analysis using a predetermined 120s improvement in IELT as a responder threshold. Safety evaluation included patient-reported events along with a physical examination.

Results
The treatment phase showed a statistically significant increase from the baseline, in the treatment group (mean 165s) compared with the placebo group (mean 110s), P<0.007. After the second month of use, the treatment group had a mean IELT of 329.70s (±21.37 SE) in comparison to the placebo group which had a mean IELT of 110.10s (±9.90 SE) (P=0.001). The open-label phase showed further increase in IELT in the treatment group and a statistically significant increase in IELT in the placebo/crossover group. Using the IPE, the men in the treatment group reported significantly higher sexual satisfaction (P=0.047) and greater improvement in distress (P=0.020) with a trend toward improvement in the ejaculatory control domain scores (P=0.093). The responder analysis showed a statistically significant response to the use of benzocaine versus placebo, attesting an IELT increase that was clinically meaningful. Benzocaine wipes were well tolerated by subjects and partners.

Conclusion
This randomized, placebo controlled clinical trial with crossover design showed that benzocaine wipes applied topically to the penis prior to sexual intercourse had a statistically significant prolongation of time to ejaculation, a clinically meaningful benefit, in the treatment of premature ejaculation. Furthermore, benzocaine wipes were well tolerated by the subjects and no evidence of transference to their female partners.

Key Words: *premature ejaculation, benzocaine, PREBOOST, placebo-controlled, wipes, sexual satisfaction*

INTRODUCTION

Premature ejaculation (PE) is the most common form of sexual dysfunction in men.[1] It has been defined in several different ways, but the most widely accepted is the Diagnostic & Statistical Manual of Mental Disorders[2] (DSM-IV) definition:

> A persistent or recurrent ejaculation with minimal sexual stimulation before, upon or shortly after penetration and before the patient wishes it. The clinician must take into account factors that affect duration of the excitement phase, such as age, novelty of the sexual partner or stimulation, and frequency of sexual activity. The disturbance causes marked distress or interpersonal difficulty.

Most studies evaluating treatments for PE include intravaginal ejaculatory latency time (IELT) as a central element in the definition of PE.[3] It has been estimated that PE affects 30–40% of the male population,[4] but is paradoxically a condition for which they are least likely to seek help.

Behavioral therapy has been commonly used to treat PE, though with limited success and most post-therapy benefits are lost within 3 years of treatment.[5] Systemic treatments have included adrenergic antagonists,[6] gamma-amino butyric acid (GABA), and selective serotonin reuptake inhibitors (SSRIs).[7, 8,9,10] Success with these agents has been variable and is associated with side effects.

Men with PE may exhibit abnormal autonomic reflex pathways for the ejaculatory process. These include lower vibratory threshold to ejaculation, shorter bulb cavernous latency time, and higher bulb cavernous evoked potentials.[11,12,13] Reducing this heightened sensitivity of the glans with topical anesthetics might therefore be a way of improving IELT, without adversely affecting the sensation of ejaculation.

PREBOOST wipes contain the active ingredient benzocaine 4%. Single dose consists of use of

one wipe applied to the glans and shaft of penis, left to dry, before intercourse.

Prior experience with the use of PREBOOST suggested that one wipe of PREBOOST applied evenly to the surface of the glans penis resulted in a meaningful prolongation of IELT. The aim of this study was to evaluate the clinical efficacy of PREBOOST in the treatment of PE through a randomized, placebo-controlled trial. In addition, open-label efficacy and safety data would be collected to further prove the efficacy and tolerability of PREBOOST in the indication of treatment of PE.

MATERIAL AND METHODS

Study medication

Test Product, Dose and Administration: PREBOOST wipes contain benzocaine 4%; inactive ingredients include purified water, ethyl alcohol (SDA 40B), and propylene glycol. A single dose consisted of one wipe applied to the glans and shaft of the penis, allowing to dry before intercourse (see Figure 1). Placebo Dose and Administration: Placebo wipes included the inactive ingredients only and were used according to the same instructions as the test product.

FIG. 1 PreBoost is a nonprescription wipe with the active ingredient of the local anesthetic benzocaine that is packaged in a sealed individual packs.

Study objective and justification of study design

The primary objective of this study was to investigate the efficacy of benzocaine wipes in the treatment of PE. Although IELT is an objective measure of ejaculatory function, it does not address the impact of therapy on patients' well-being and confidence in their sexual performance, which are important markers of treatment benefit. Therefore, if IELT is used as a sole efficacy measure, it may not fully characterize the treatment benefit to the patient. For this reason, in this study, a patient-reported outcome (PRO) known as the Index of Premature Ejaculation (IPE) was used in conjunction with IELT to evaluate efficacy. Althof et al. developed and validated the final 10-point questionnaire and the relationship of the three major domains (control, distress, and sexual satisfaction) in over 900 men with PE and over 400 normal subjects.[14] All three domains were well correlated with IELT. Thus, the combination of the objective measure of ejaculatory latency with the PRO of IPE should be able to provide efficacy data which are representative of clinical benefit to the patient. The design of blinded, randomized, placebo-controlled, parallel group phase is a classic method to investigate efficacy. The open-label phase afforded the study of crossover of the placebo group to active treatment.

Study design

This was a single-center, randomized, placebo-controlled clinical trial. Subjects were randomized to placebo or benzocaine wipes in a 1:2 ratio. Subjects attended a Screening Visit (visit 1) at which they were provided written informed consent and were screened for eligibility. Screening involved collection of demographic information,

medical history (including history of PE), and medication history, and physical examination including examination of the glans penis, heart rate, and blood pressure. The subjects were also asked to complete the IPE questionnaire, Premature Ejaculation Profile (PEP) 16, and IIEF5. Subjects who met the initial screening assessments underwent a baseline evaluation period of 28 days in which they were required to have at least four sexual encounters, separated by an interval of at least 24 h and use a stopwatch to time IELT. The IELT of each sexual encounter was to be recorded on the diary card. The stopwatch was used to time IELT so that clock started the time penetration began and stopped at the start of ejaculation.

Upon completion of the baseline evaluation period, the subjects returned to the clinic for Visit 2. During this visit, AE and concomitant medication information were collected and the subject had their glans penis examined. In addition, subjects were asked to complete a baseline IPE questionnaire and PEP, and were asked to rate the quality of their orgasm using a 5-point scale. Those subjects who had a baseline IELT average of ≤2 min of at least four sexual encounters and suitable responses to the PEP were eligible to continue in the study and receive study medication (benzocaine or placebo) for the 1 month placebo-controlled treatment phase.

If a subject was eligible, he was randomized to either benzocaine or placebo and was given sufficient study medication until the next month clinic visit. The subject was instructed on how to use the wipe and instructed to use it as desired often in the following month but to leave at least 24 h between sexual encounters using the wipes. During each sexual encounter where the study medication was used, the subject timed his IELT the same way that they had during the baseline period with a stopwatch. The subject also documented efficacy and tolerability data in the diary card.

At Visit 3, the diary card and any unused study medications were collected, AEs and concomitant medications inquiries were made, and the subjects were asked to complete the IPE questionnaire and PEP.

At Visit 3 the subjects were invited to continue in the open-label phase. If the subject agreed to participate in the open-label phase, he was dispensed sufficient benzocaine for approximately 28 days of sexual encounters along with a new diary card. The subject could use the study medication as desired up to a maximum of one wipe within a 24 h period.

The subjects were also asked to rate the quality of their orgasms when using the study medication using a 5-point scale and rate the study medication in answer to the question "What was your opinion of the study medication?" using the scale: poor, fair, good or excellent. At this last visit of the placebo-controlled phase, the subjects will also be asked to give a global rating of their distress, control, and satisfaction versus Baseline on a 4-point scale of "no change/worse," "small improvement," "moderate improvement," and "large improvement."

During visit 4 end of trial and end of open-label phase, the subject returned to the clinic. At this visit, AE's and concomitant medications enquiries were made, IPE and PEP were completed, and IELT diaries were collected. In addition, any unused study medications were collected. The subject underwent safety assessments, had his glans penis examined, and rated the study medication in answer to the question "What was your opinion of the study medication?" using the scale: poor, fair, good or excellent.

Inclusion criteria

A subject was considered suitable for the study if he fulfilled all of the following criteria:

1. Willing and able to provide written informed consent (subject and partner).

2. Male aged 18 years and over.
3. Diagnosed with PE according to DSM IV criteria.
4. Response to Baseline PEP17 as follows:
   a. Perceived control over ejaculation of "Poor" or "Very poor."
   b. Satisfaction with sexual intercourse of "Poor" or "Very poor."
   c. Personal distress related to ejaculation of "Quite a bit" or "Extremely" or "Moderate."
   d. Interpersonal difficulty related to ejaculation of "Quite a bit" or "Extremely" or "Moderate."
5. Subject had to be in a stable heterosexual and monogamous relationship of at least 3 months duration.
6. Subject had at least four documented sexual encounters in the screening period.
7. Average IELT ≤2 min in at least four of the sexual encounters in the screening period.

Exclusion criteria

A subject who met any of the following criteria was excluded from the study:

1. Subject had received an investigational drug within 30 days of screening.
2. Subject had erectile dysfunction, defined as an IIEF5 score of ≤18, unless the low score is entirely related to PE symptoms in the opinion of the Investigator.
3. Subject had a physical or psychological condition that would prevent him from undertaking the study procedures, including, but not limited to, the following: 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. Subjects taking tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), or SSRIs, for indications other than PE, where the dose had been changed within 28 days of screening and it was planned that the dose would change during the placebo-controlled treatment period.
5. Subject had received any treatment for PE, for example, antidepressant therapy, local anesthetic spray, intracavernosal injection, or psychotherapy within 28 days of screening. A 4-week washout was allowed to qualify for the study.
6. Subject had a current history of alcohol or drug abuse, in the opinion of the Investigator.
7. Subject was unlikely to understand or was unable to comply with study procedures, for whatever reason.
8. Subject or partner had known drug sensitivity to amide-type local anesthetics.
9. Subjects with pregnant partners.
10. Subject with partners of child-bearing potential and not using appropriate contraception method, for example, hormonal contraception or intrauterine device (IUD) or condoms, should not alter this during the course of the trial.
11. Subjects and their partners with known inborn defects such as glucose-6-phosphodiesterase deficiency, hemoglobin-M-disease, NADH-methemoglobin reductase (diaphorase 1) deficiency, and pyruvate-kinase deficiency.

Outcome measures

There were two co-primary efficacy outcome measures, the objective IELT as measured by the stopwatch method, and the PRO IPE.

RESULTS

Based upon this single-site study, an analysis of the 21 men who were randomized

(17 treatment, 9 placebo) and had complete follow-up data was conducted.

Results of IELT

Compared with baseline, the treatment group showed a statistically significant increase in IELT during the randomized placebo-controlled phase, and further significant increase during the open-label phase (see Figure 2).

Compared with baseline, the placebo group showed no significant change in IELT during the randomized placebo-controlled phase, but did not have a statistically significant increase in IELT with the crossover to the open-label phase (see Figure 3).

At the end of the first month of treatment, the treatment group experienced a mean IELT of 164.80 s (±11.40 SE) in comparison to the placebo group which had a mean IELT of 110.10 s (±9.90 SE) (P=0.007) (see Table 1). After the second month of use, the treatment group had a mean IELT of 329.70 s (±21.37 SE) in comparison to the placebo group which had a mean IELT of 110.10 (±9.90 SE) (P=0.001) (see Table 2).

An ad hoc responder analysis was performed to investigate and reconfirm the efficacy of benzocaine in the treatment of PE. This evaluation included a responder analysis using a 120 s improvement in IELT as a responder threshold. A greater proportion of men in the treatment group after 1 and 2 months achieved IELT of at least 2 min versus placebo (76%, 88.0% vs. 33.3%, respectively). In a responder's analysis, using a Fisher's exact test this difference was significant with a P-value equal to 0.046. Based upon an IELT of greater than 2 min, 88% of the men on treatment were no longer considered to have PE (see Table 3).

Patient satisfaction was assessed utilizing the IPE which can be analyzed based upon domain scores. After 1 month of use, the men in the treatment group reported significantly higher sexual satisfaction (P=0.047) and greater improvement in distress relating to intercourse (P=0.020) with a trend toward improvement in the ejaculatory control domain scores (P=0.093) (see Figures 4 and 5). The reported patient satisfaction corresponded directly with the improved quantitated IELT reported above.

All adverse events reported during the study were recorded. The treatment was well tolerated and no transference was reported. Two men in the treatment group reported adverse events. One had a mild headache and back pain which resolved and the second had a mild irritation on the penis which likewise resolved. One man in the placebo group reported a worsening hernia

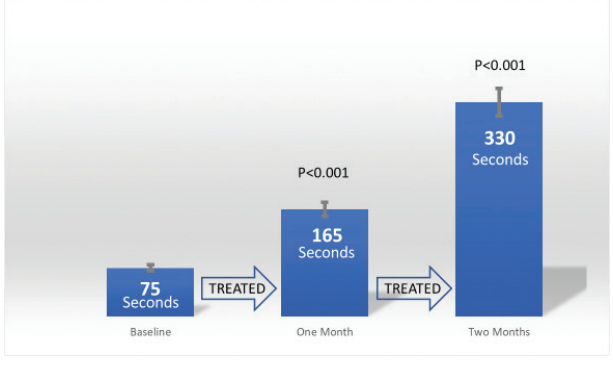

FIG. 2 Mean Intravaginal Ejaculatory Latency Time (IELT) as measured by the stopwatch method in the treatment group (n=17).

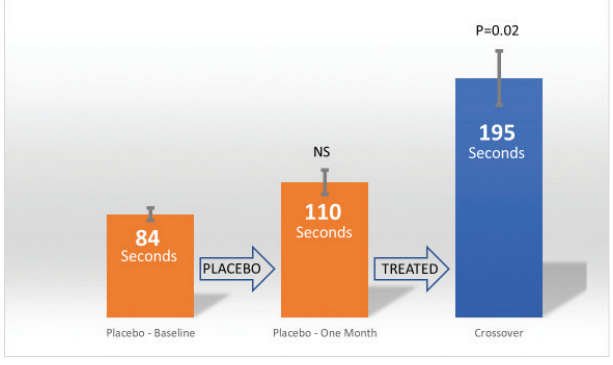

FIG. 3 Mean Intravaginal Ejaculatory Latency Time (IELT) as measured by the stopwatch method in the placebo/crossover group (n=9).

TABLE 1 Change at 1 month of Intravaginal Ejaculatory Latency Time (IELT) as Measured by the Stopwatch Method in the Treatment and the Placebo Group

Change in Duration Between Treatment and Placebo Month 1							
Group	**Enrolles Size**	**Sample Size**	**Mean (seconds)**	**Std Error**	**Std. Dev.**	**[95% Conf. Interval]**	
Treatment	17	86	164.80	11.40	106.00	142.09	187.56
Placebo	9	50	110.10	9.90	70.00	90.21	129.99
Combined	26	136	144.70	8.40	97.70	128.10	161.30
Difference			54.7	16.80		21.50	87.90

Ha: dlff > 0: Pr(T > t) = 0.007

TABLE 2 Change at 2 months of Intravaginal Ejaculatory Latency Time (IELT) as Measured by the Stopwatch Method in the Treatment and the Placebo Group

Change in Duration Between Treatment and Placebo Month 2							
Group	**Enrollees Size**	**Sample Size**	**Mean (seconds)**	**Std Error**	**Std. Dev,**	**(95% Conf. Interval]**	
Treatment	17	94	329.70	21.37	207.20	287.26	372.14
Placebo	9	50	110.10	9.90	70.00	90.21	129.99
Difference			219.6	23.55		172.99	266.21

Ha: diff > 0: Pr(T > t) = 0.001

TABLE 3 Responder Analysis with Comparisons of Responder Groups to Treatment and Placebo Groups

	30 day assessment (randomized, placebo controlled phase)		**P**
	>120 s (responsder)	**≤120 s (nonresponsder)**	
Preboost treatment group	13	4	
Control placebo group	3	6	0.046

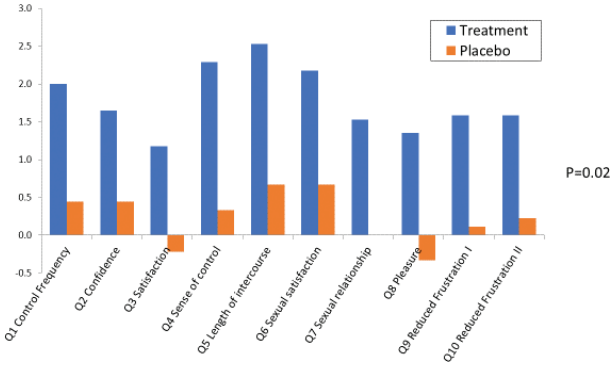

FIG. 4 Change in scores of Index of Premature Ejaculation (IPE), treatment versus placebo.

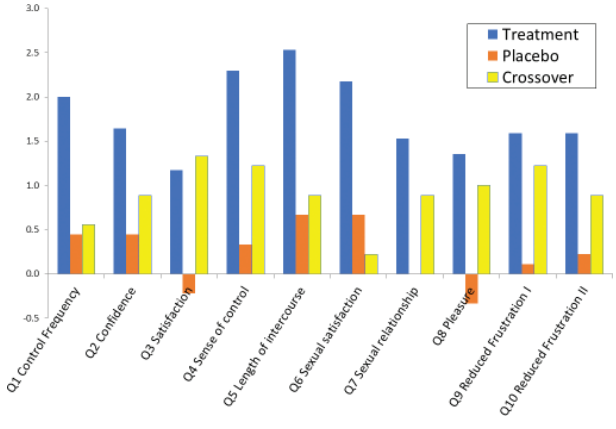

FIG. 5 Change in scores of Index of Premature Ejaculation (IPE), treatment versus placebo/crossover.

which resolved. No clinical evidence of transference of benzocaine from partner to partner was reported.

DISCUSSION

To our knowledge, this is the first blinded, placebo-controlled study of a topical treatment for men with PE. Based upon a placebo-controlled, randomized design, this study provides evidence of efficacy of benzocaine wipes topical therapy for PE using an appropriate design in all aspects of clinical research. First, the screening/baseline phase assured a population representative of PE with proper inclusion and exclusion criteria. Second, the blinded, randomized, placebo-controlled, parallel group phase afforded the investigation of the efficacy eliminating bias. Third, the open-label phase gave the opportunity to study the effect of crossover of the placebo group to the treatment. Fourth, the choice of two co-primary efficacy measures ascertained both the statistical significance of efficacy and the clinical meaningfulness of the treatment. IELT provided objective data using the stopwatch method. The IPE provides a patient-reported outcome corroborating the IELT results. Finally, the responder analysis gave additional insight into the efficacy and its magnitude. The good tolerability of benzocaine wipes as a topical therapy is not unexpected.

The limitations of this study include the single site and the small number of subjects. However, the fact that efficacy was proven with a relatively small number of subjects may be an attestation to the efficacy of benzocaine wipes in the treatment of PE.

Topical therapy of PE plays a substantial role in the overall treatment of PE. It provides a quick on-demand treatment that is efficacious and well tolerated. Furthermore, it avoids the side effects of systemic therapies. Benzocaine wipes (PREBOOST™) have a statistically significant and clinically meaningful efficacy and are well tolerated.

CONCLUSION

This randomized, placebo-controlled clinical trial with crossover design showed that benzocaine wipes applied topically to the penis prior to sexual intercourse had a statistically significant efficacy and a clinically meaningful benefit in the treatment of PE. Furthermore, benzocaine wipes were well tolerated by the subjects and no transference of benzocaine was reported by their female partners.

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AUTHORS' CONTRIBUTION

Ridwan Shabsigh was responsible for the conceptualization of the study, data analysis, writing, and editing of the manuscript. Michael Perelman and Allison Grant reviewed and edited the manuscript. Robert Getzenberg contributed towards the writing, editing, and statistical analysis of the manuscript. Jed Kaminetsky functioned as the principal investigator of the clinical trial and participated in reviewing and editing of the manuscript.

CONFLICT OF INTEREST

Ridwan Shabsigh and Michael Perelman are nonpaid scientific consultants to the sponsor Veru Inc. Robert Getzenberg is a paid scientific consultant to the sponsor Veru Inc.

Allison Grant is a nonpaid research assistant.

Jed Kaminetsky: paid principal investigator of the clinical trial.

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