ORIGINAL RESEARCH—FSD PHARMACOTHERAPY

Efficacy and Safety of Alprostadil Cream for the Treatment of Female Sexual Arousal Disorder: A Double-Blind, Placebo-Controlled Study in Chinese Population

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ABSTRACT

Introduction. To date, no approved medication is available for the treatment of female sexual arousal disorder (FSAD).

Aim. The purpose of this study was to evaluate the clinical efficacy and safety of a novel alprostadil topical cream for the treatment of FSAD.

Methods. This was a multicenter, randomized, double blind, placebo-controlled, parallel design dose-ranging study. Four hundred female patients with FSAD (22–62 years of age), after a 4-week nontreatment baseline period, were provided with 10 blinded doses of 500, 700, or 900 mcg alprostadil or a placebo cream to be applied to the clitoris and the G-spot in the vagina prior to vaginal intercourse.

Main Outcome Measures. The primary efficacy end point was the arousal success rate (equal number of the Yes responses to Question 3 of the Female Sexual Encounter Profile [FSEP] or number of the sexual encounters). Secondary endpoints included the Female Sexual Function Index (FSFI), Global Assessment Questionnaire, other FSEP question responses, and post-treatment changes in Female Sexual Distress Scale.

Results. A total of 374 FSAD patients completed the study. Primary efficacy analysis of the intent-to-treat (ITT) population showed a significant increase in arousal success rates with dose. Arousal success rates at the end of the total evaluation period were 33.1%, 46.3% ($P = 0.0161$), 43.5% ($P = 0.0400$), and 53.9% ($P = 0.0002$) in the *placebo*, 500, 700, and 900 mcg alprostadil groups, respectively. The changes of the FSFI score, relative to baseline were 14.7%, 20.7% ($P = 0.067$), 21.7% ($P = 0.035$), and 22.9% ($P = 0.002$) for the *placebo*, 500, 700, and 900 mcg treatment groups, respectively. The other secondary efficacy end point values showed a consistent trend in support of the primary efficacy results.

Conclusion. These results demonstrated that the application of topical alprostadil prior to vaginal intercourse significantly improved the sexual arousal rate of the subjects with FSAD. **Liao Q, Zhang M, Geng Li, Wang X, Song X, Xia P, Lu T, Lu M, and Liu V. Efficacy and safety of alprostadil cream for the treatment of female sexual arousal disorder: A double-blind, placebo-controlled study in Chinese population. J Sex Med 2008;5:1923–1931.**

Key Words. Alprostadil; Topical; Female; Arousal; Disorder; Trial

Introduction

The incidence of female sexual dysfunctions (FSD) may surpass the incidence of male sexual dysfunction [1–5]. However, the physiological and pathological mechanisms of FSD are yet to be fully understood. The FSD has been categorized into four specific disorders: desire, arousal, orgasmic, and sexual pain. Evidence from clinical case studies and epidemiology studies demonstrates that these disorders can overlap and may be interdependent [6].

Female sexual arousal disorder (FSAD) is the persistent or recurrent inability to attain, or to maintain, sufficient sexual excitement causing personal distress. It may be expressed as a lack of subjective excitement or a lack of genital lubrication/swelling or other somatic responses as defined by the Sexual Function Health Council of the American Foundation for Urologic Disease (AFUD Consensus Panel) [6]. FSAD is one form of FSD and is associated with the excitement phase of sexual response [6]. This definition provides a well-defined, broadly accepted diagnostic framework and classification for FSD in comparison to the World Health Organization International Classifications of Diseases-10 (ICD-10) and Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) of the American Psychiatric Association [6]. Recently, considerable changes in the definition of FSAD were added based on the observation that subjective arousal does not always correlate strongly with genital congestion. This resulted in a subdivision of FSAD into subjective, genital, and combined categories [7].

Cardiovascular risk factors have been shown to correlate with complaints of vaginal and clitoral dysfunction [8–12]. Thus, it can be hypothesized that FSAD may be amenable to treatment with vasodilators, which are commonly used to improve cardiovascular function through the relaxation of vascular smooth muscle, producing dilatation of peripheral arteries and veins. A few studies on the effect of orally administered phentolamine [13–14] (an alpha adrenergic antagonist and a vasodilator) and sildenafil citrate (PDE5 inhibitor and vasodilator), showed significant positive results in women with FSAD [15]. However, no decisive conclusions could be drawn due to the use of various efficacy measuring instruments or enrollment of different patient populations, e.g., the aforementioned sildenafil study [15] was done in spontaneously or surgically postmenopausal women with FSAD. Primary end points were questions 2 (increased genital sensation during intercourse or stimulation) and 4 (increased satisfaction with intercourse and/or foreplay) from the Female Intervention Efficacy Index. Topical application of alprostadil (PGE_1) to the clitoris resulted in a doubling of the peak systolic velocity of the clitoral artery and labial and clitoral engorgement [16]. These changes were accompanied by a "pleasant" sensation of warmth. The results provided preliminary evidence for the investigators to further explore the therapeutic effects of PGE_1 on women's sexual arousal responses.

Recently, neurophysiological mechanism of FSAD was explored for the cerebral activation patterns using functional magnetic resonance imaging (fMRI) [17] and subjective arousal responses during visual sexual stimulation after application of a single dose of alprostadil cream to the clitoris and G-spot [18]. The results suggest that the left superior frontal gyrus and right anterior frontal lobe are the activation areas associated with the alprostadil cream administration in sexual arousal response. The arousal effect of the alprostadil cream was sexual stimulation dependent. It is postulated that alprostadil acts on the genital chemoreceptors, and facilitates sexual related nerve reflexes and further enhances regional brain activation that involve sexual response or behavior. The consequences of regional brain activation, facilitated or enhanced by genital alprostadil application, could be used for treating FSAD. More studies are needed to further elucidate the mechanism of alprostadil action.

PGE_1 has been used successfully as an injectable therapy [19], as an intraurethral pellet [20] and an intrameatal cream for the treatment of male erectile dysfunction [21]. Vulvar area application of an alprostadil cream that is formulated with a proprietary skin permeation enhancer, has demonstrated positive effects on patients' subjective arousal with a dose range from 500 mcg to 1500 mcg PGE_1 in studies in premenopausal women with FSAD [22–23]. More recently, it has been reported that a topical solution was successful for the treatment of FSAD with 400 mcg dose of PGE_1 [24]. These studies have shown the alprostadil cream to be safe and well-tolerated when administered to both healthy and FSAD female subjects. The evidence supports that it is possible to pharmacologically improve symptoms of women with FSAD.

The current study was conducted to evaluate the efficacy and safety of a novel cream with a delivered dose of 125 mg, 175 mg, and 225 mg equivalent to 500, 700, and 900 mcg of 0.4%

alprostadil with a novel skin permeation enhancer compared to a placebo cream in women with FSAD under conditions of home use in conjunction with sexual intercourse in China.

Aim

The purpose of this study was to evaluate the clinical efficacy and safety of a novel alprostadil topical cream in dosages (placebo 500 mcg, 700 mcg, and 900 mcg alprostadil) for the treatment of FSAD.

Methods

This was a multicenter, randomized, double-blind, parallel design, and placebo-controlled study. Four medical centers in Beijing, China participated in the study. The study was approved by an Institutional Review Board at each site and was conducted in accordance with Good Clinical Practice and the International Conference on Harmonization guidelines and the ethical principles of the Declaration of Helsinki. All patients signed the written informed consent before participating in the study.

To be eligible for the study, patients were required to be between 21 and 65 years of age, in a stable monogamous relationship, with FSAD as defined according to the AFUD Consensus Panel [6] for at least the previous 6 months but to have experienced sexual arousal and/or orgasm during vaginal intercourse for at least 5 years. They were required to have a score of ≥40 on the FSDS, a scored ≤8 and ≤7 in the Covi Anxiety and Raskin Depression scales, correspondingly. The Covi Anxiety and Raskin Depression scales each have three questions regarding "To what extent does the patient evidence anxiety or depression in verbal report, behavior, and somatic complaints?" The severity scores vary from a range of 1 (not at all) to 4 (very much) and were used for the enrollment criteria only. In addition, the partner was required to be "Not Impotent" or "Minimally Impotent," which was defined as "Always" or "Usually" able to get and keep an erection sufficient for sexual intercourse" on the "Single Question Assessment of Erectile Dysfunction" as determined by the patient [25].

A total of 400 eligible patients were enrolled and randomly assigned to one of the four groups (100 patients per group) for the entire study, to receive a total of 10 identical premeasured doses (i.e., five doses for each treatment period of 4 weeks with the same alprostadil dose) of either the placebo, 500 mcg, 700 mcg, or 900 mcg alprostadil cream during 8 weeks of active treatment after a 4-week nontreatment baseline period. This 12-week study required four clinic visits.

The study medication was a white cream containing 0 mcg, 500 mcg, 700 mcg, or 900 mcg of alprostadil and a novel skin permeation enhancer. The patients were required to apply 10 doses of study medication in an "at-home" setting prior to sexual intercourse during the 8 weeks of active treatment. Each premeasured dose was double-blinded and individually packaged and labeled in a plastic dispenser. The patient was instructed to wash her hands and vulva, remove the cap from the tip of the dispenser, expel the cream onto a fingertip and equally spread the cream over the clitoris and the vaginal anterior G-spot (at ~5 cm deep, 1/3 middle passage of the vagina). The entire dose was to be applied as directed by a physician approximately 5–30 minutes prior to attempting intercourse. After application of the cream, the patient was to engage in foreplay to facilitate the action of the medication. She was also instructed to attempt vaginal intercourse five times between visits 2 and 3, and five times between visits 3 and 4. Efficacy was assessed by patient diary (Female Sexual Encounter Profile [FSEP]), patient questionnaire (Female Sexual Function Index [FSFI]) [26], patient distress scale (Female Sexual Distress Scale [FSDS]) [27], and a global assessment questionnaire (GAQ). FSEP includes 6 questions with either a Yes or No choice, or a check box, regarding the sexual environment, genital stimulation or intercourse, arousal satisfaction, lubrication, orgasm, and arousal level. FSFI includes 19 questions (Q), which were divided into 6 domains: desire (Q1. frequency, Q2. level); arousal (Q3. frequency, Q4. level, Q5. confidence, Q6. satisfaction); lubrication (Q7. frequency, Q8. difficulty, Q9. frequency of maintaining, Q10. difficulty in maintaining); orgasm (Q11. frequency, Q12. difficulty, Q13. satisfaction); global satisfaction (Q14. with amount of closeness with partner, Q15. with sexual relationship, Q16. with overall sex life); and pain (Q17. frequency during vaginal penetration, Q18. frequency following vaginal penetration, Q19. level during or following vaginal penetration). All of the questions have a score range of 0–5, except Q1, Q2, and Q14 with a range of 1–5. The psychometric evaluation of reliability and validity of FSFI were well established [25–28]. FSFI has been widely used for assessing sexual function in women. Recently, FSFI scores were

proposed to be used to establish the diagnostic cut-off scores for potential classification of women's sexual dysfunction [29]. FSDS includes 20 questions with a frequency score of 0 (never) to 4 (always) to measure the stress levels from various aspects.

Main Outcome Measures

The primary efficacy end point was the change in arousal success rate (baseline versus treatment period), defined as the number of successes (patient satisfaction with sexual arousal during sexual activity as indicated by a "Yes" response to diary question #3 of the FSEP ("Were you satisfied with your arousal [excitement] during this sexual encounter") divided by the number of sexual encounters. Secondary efficacy criteria included the changes in the FSDS scores (baseline versus final visit), scores reported in the FSFI, scores reported in the FSEP (baseline versus final visit), and scores reported in the GAQ.

Safety assessment was determined by the monitoring of adverse events, changes in vital signs, clinical laboratory tests, physical examinations, and ECGs.

Demographic and baseline characteristics for the ITT population were summarized. Continuous variables were summarized using description statistics (N, mean, median, standard deviation [SD], minimum and maximum), and categorical variables were summarized by frequency distribution.

The arousal success rates for the baseline selection period (4 weeks without treatment) and treatment periods (8 weeks treatment per protocol) were recorded, calculated, and statistically described. ITT cohort was used for the study data analysis, that is, all patients who are exposed to at least three doses of study medication. The data from the last visit were used for endpoint analysis if the patient did not complete the study.

Per-protocol populations were analyzed as supportive for the ITT analysis. The Wilcoxon test was used to determine the differences between groups. The second treatment period was the principal evaluation period. Last observation carried forward (LOCF) analysis, that is, missing efficacy values, was imputed by the LOCF method. Baseline value was not carried forward.

All secondary efficacy variables were analyzed and compared among treatment groups and vs. placebo.

All patients who applied at least one dose were included in the safety analyses. Incidences of treatment-induced adverse events were summarized by preferred term, relationship to study drug, and intensity.

Results

Demographics and Other Baseline Characteristics

A total of 93.5% of the patients completed the study with an early discontinuation rate of 6.5% mainly due to lost to follow-up. The ITT population included 374 patients comprising 268 non-menopausal and 106 post-menopausal patients. The mean age was 45.0 years with a range of 22–62 years of age. There were no statistically significant differences among the groups in their baseline characteristics (Table 1).

There was no significant difference between groups in medical history, the Raskin and Covi score assessment, the FSDS (day 0) and FSFI (day 0). The following efficacy and safety end points were analyzed with the total ITT population due to the limited post-menopausal patient population and the original intention of the trial design.

Efficacy End Points

The arousal rate for the treatment period of all four groups was significantly higher as compared to baseline. In the entire treatment period, the *P* values of the three treatment groups vs. the placebo group were all less than 0.05 (double-sided). The difference between the three drug groups (500 mcg, 700 mcg, and 900 mcg) and placebo group was significant (Table 2). At the end of the entire treatment period, the primary efficacy was further improved up to 22.63%, 36.67%, 34.01%, and 44.29%, respectively ($P = 0.0224$, $P = 0.0.0358$, and $P = 0.0002$ vs. placebo).

The FSFI total score changes of the last (the second 4-week, 5-dose) treatment period vs. baseline were 14.68, 20.71, 21.69, and 22.89 (placebo, 500 mcg, 700 mcg, and 900 mcg). The analysis of the covariance of the changes illustrated that the differences of score changes vs. baseline among the four groups were significant if the center and baseline effects were removed.

The differences between drug groups and the placebo group were analyzed by the same analysis of covariance (Table 3). The difference between the 500 mcg group and the placebo group was not significant. The difference between the 700 mcg or 900 mcg group and the placebo group was significant ($P = 0.035$ and $P = 0.002$, respectively). Significantly higher mean scores pertaining to sat-

Table 1 Demographic and other baseline characteristics (intent-to-treat patients)

Parameter N	Placebo 97	500 mcg 91	700 mcg 91	900 mcg 95
Age in years, mean (range)	45.2 (22.3–61.9)	45.8 (22.3–61.9)	44.6 (26.4–60.4)	44.4 (23.6–62.1)
Height (cm), mean (range)	161.4 (150–173)	160.7 (148–170)	161.0 (140–175)	161.2 (150–173)
Weight (kg), mean (range)	60.6 (40–86)	59.0 (39–86)	59.8 (40–85)	59.4 (45–92)
Ethnicity (%)				
Han	89 (97.8%)	89 (97.8%)	86 (94.5%)	85 (89.5%)
Others	4 (4.1%)	2 (2.2%)	5 (5.5%)	10 (10.5%)
Baseline Scores of Raskin and Covi, Mean (+/–SD)				
Raskin depression score	3.55 (0.87)	3.31 (0.71)	3.51 (0.98)	3.38 (0.72)
Covi anxiety score	3.48 (0.96)	3.43 (0.98)	3.37 (0.86)	3.45 (0.87)
Baseline Scores of FSFI and FSDS, Mean (+/–SD)				
FSDS Total Score	50.84 ± 9.65	50.51 ± 8.72	51.88 ± 9.82	51.87 ± 9.70
FSFI	39.18 ± 11.50	36.80 ± 10.20	36.64 ± 11.16	38.66 ± 10.51
FSFI Desire Domain	3.96 (1.48)	4.04 (1.63)	3.74 (1.49)	3.91 (1.47)
FSFI Arousal Domain	7.47 (2.59)	6.96 (2.24)	6.73 (2.53)	7.02 (2.40)
FSFI Lubrication Domain	8.68 (3.70)	8.15 (3.21)	8.31 (3.10)	8.98 (3.60)
FSFI Orgasm Domain	5.58 (2.40)	5.12 (2.09)	4.92 (1.81)	5.02 (2.04)
FSFI Satisfaction Domain	6.87 (2.36)	6.59 (2.17)	6.60 (2.30)	6.88 (1.90)
FSFI Pain Domain	6.62 (2.95)	5.93 (2.76)	6.34 (2.91)	6.85 (3.00)

FSDS = Female Sexual Distress Scale; FSFI = Female Sexual Function Index.

isfaction with overall sexual life in the 700 mcg or 900 mcg alprostadil treatment groups vs. placebo group, were obtained.

Table 3 lists the six domains (desire, arousal, lubrication, orgasm, satisfaction, and pain). In comparison with the placebo group, significant changes in arousal, orgasm and satisfaction factors were observed in the treatment groups (500 mcg, 700 mcg, and 900 mcg). The results demonstrated that differences between the 900 mcg group and

Table 2 Primary efficacy end point: patient sexual arousal satisfaction rate (intent-to-treat)

Parameter N	Placebo 97	500 mcg 91	700 mcg 91	900 mcg 95
Screening period, Mean (SD)	10.50 (20.41)	9.65 (17.51)	9.45 (18.73)	9.63 (16.91)
Entire treatment period, Mean (SD)	33.12 (36.02)	46.32 (36.76)	43.46 (36.49)	53.92 (37.97)
P value[a]		0.0161	0.0400	0.0002
Entire treatment period—Screening period, Mean (SD)	22.63 (32.70)	36.67 (38.44)	34.01 (39.21)	44.29 (39.66)
P value*		0.0224	0.0358	0.0002

*Difference relative to placebo, from ANOVA.

Table 3 Secondary efficacy end point: female sexual function index score changes (visit 4 vs. baseline, intent-to-treat patients)

Parameter N	Placebo 97	500 mcg 91	700 mcg 91	900 mcg 95
Total, Mean (SD)	14.68 (20.36)	20.71 (17.91)	21.69 (17.95)	22.89 (19.77)
P value*		0.067	0.035	0.002
Desire domain, Mean (SD)	1.16 (2.26)	1.44 (2.04)	1.84 (2.27)	2.00 (2.08)
P value*		0.185	0.104	0.002
Arousal domain, Mean (SD)	2.40 (4.20)	4.02 (4.01)	4.36 (4.12)	4.92 (4.38)
P value*		0.012	0.010	0.001
Lubrication domain, Mean (SD)	3.98 (5.33)	5.01 (4.81)	5.06 (4.34)	5.46 (4.93)
P value*		0.271	0.236	0.009
Orgasm domain, Mean (SD)	1.83 (3.52)	3.13 (3.32)	3.18 (3.06)	3.89 (3.59)
P value*		0.021	0.030	0.000
Satisfaction domain, Mean (SD)	1.80 (3.81)	3.13 (3.09)	3.43 (2.97)	3.27 (3.08)
P value*		0.014	0.002	0.001
Pain domain, Mean (SD)	3.11 (4.42)	4.11 (3.70)	4.17 (4.12)	4.04 (4.39)
P value*		0.242	0.161	0.041

*Difference relative to placebo, from analysis of covariance method (the center and baseline effect was removed).

Table 4 Secondary efficacy end point: female sexual distress scale (visit 4 vs. baseline)

Parameter	Placebo	500 mcg	700 mcg	900 mcg
N	97	91	91	95
Mean change (SD) in FSDS total score	–17.60 (18.81)	–20.27 (18.79)	–21.98 (18.49)	–25.97 (17.95)
P value*		0.332	0.140	0.002

*Difference relative to placebo, from analysis of covariance method.

the placebo group were significant in all of the FSFI domains (Table 3).

The results based on the analysis of covariance illustrated that the difference in score change of FSDS between the four groups was significant. The difference between the placebo group and the 500 mcg or 700 mcg groups was not significant. The difference between the placebo group and the 900 mcg group was significant (Table 4).

Patient satisfaction as measured by the Global Assessment Questionnaire is presented in Table 5. All three doses showed significant patient satisfaction compared to placebo. An obvious improvement in the other secondary efficacy parameters, e.g., FSEP Question 4, 5 and 6, was also observed during the study, which was consistent with the primary efficacy outcome (Table 2).

These results demonstrate that the 900 mcg novel alprostadil significantly improved the sexual arousal rate of FSAD women. The efficacy of the 900 mcg group was better than the 700 mcg and 500 mcg groups. The results of FSFI and FSDS analysis as well as other secondary efficacy parameters showed a similar trend in supporting the primary efficacy outcome of the novel alprostadil cream groups.

Table 5 Secondary efficacy end point: global assessment questionnaire

Parameter	Placebo	500 mcg	700 mcg	900 mcg
N	94	90	89	92
Improved	48.94%	64.44%	64.04%	66.30%
Not improved	51.06%	35.56%	35.96%	33.70%
P value*		0.0339	0.0395	0.0166

*Difference relative to placebo, from Chi-square (χ^2) test.

Safety

Of the 400 randomized patients, 387 subjects who used at least one dose of the study medication were included in the safety evaluations. The most frequently reported adverse events were in the genital area (burning, itching, swelling, irritation, or soreness). The incidence of urogenital events was lowest in the placebo group. In the active treatment groups, the incidence of urogenital events was similar in the 500 mcg and 700 mcg groups, but slightly higher in the 900 mcg group.

Most of the adverse events reported in the placebo, 500 mcg, 700 mcg, and 900 mcg groups were mild or moderate in intensity, and transient (Table 6). No serious adverse events were reported. A total of 28 patients discontinued from the study before completion. The major reason was failure to follow-up. Five patients withdrew from the study because of adverse events: two in the 700 mcg group and three in the 900 mcg group.

Discussion and Conclusion

The study results demonstrate that alprostadil cream improves the sexual arousal success rates

Table 6 Overall summary of AE: AE occurring in ≥3% of patients per group

Parameter	Placebo patient (%)	500 mcg patient (%)	700 mcg patient (%)	900 mcg patient (%)
Patients with at least one AE	20 (20%)	24 (24%)	26 (26%)	36 (36%)
Dermatological vulva itching, rash, allergic	1 (1.0%)	2 (2.0%)	3 (3.0%)	2 (2.0%)
Gastroenteric system	0	3 (3.0%)	1 (1.0%)	2 (2.0%)
Respiratory system	4 (4.0%)	0	3 (3.0%)	5 (5.0%)
Female urogenital system	14 (14.0%)	22 (22.0%)	18 (18.0%)	31 (31.0%)
Local dryness and pain	4 (4.0%)	0	0	2 (1.0%)
Local pain	3 (3.0%)	6 (6.0%)	4 (4.0%)	5 (5.0%)
Pudendal sting	1 (1.0%)	0	1 (1.0%)	3 (3.0%)
Pudendal swell/pain	0	2 (2.0%)	7 (7.0%)	9 (9.0%)
Local dryness, acerbity	3 (3.0%)	0	1 (1.0%)	1 (1.0%)
Local burning	3 (3.0%)	12 (12.0%)	8 (8.0%)	17 (17.0%)
Patient discontinuation due to AEs	0	0	2	3

AE = adverse effects.

and FSFI score as well as other secondary efficacy end point values in patients with FSAD. The most effective dosage was the 900 mcg alprostadil cream as evidenced in Tables 2–5. The current study results provide further support for the previous studies [22–23] that alprostadil cream could be used as a potential medication for FSAD. The vessal dilation mechanism of alprostadil was well established. It has also been demonstrated that topical application of alprostadil to the clitoris resulted in a doubling of the peak systolic velocity of the clitoral artery and labial and clitoral engorgement [16]. However, the genital congestion effect of alprostadil alone seems insufficient to explain the current study efficacy outcome [7]. It has been reported that alprostadil could have peripheral and/or central actions to influence the neurotransmission or reflex [30–32]. In consideration of the recent report that topical application of alprostadil cream to the clitoris and G-spot did change the pattern of cerebral activation using fMRI [18], we postulate that alprostadil not only acts through local vascular dilation, but also on the chemoreceptors, and facilitates sexual related nerve reflexes and further enhances the sexual response. This could also partially explain why vasodilation induced by alprostadil cream was effective at increasing subjective reports of sexual satisfaction while the vasodilation induced by Sildenafil or others did not. Further studies to explore the effects of alprostadil on local nervous terminals, e.g., sensitivity or threshold could be helpful to elucidate the mechanism, correlate its pharmacologic effects and clinical efficacies.

It should be noted that the current study design was not specified to distinguish the subcategories of FSAD. Significant patients in the subjective sexual arousal disorder category could be enrolled in the study. Psychological factor of intention to be treated (expectation) may influence the sexual performance or the outcome of sexual encounter of this subjective category of FSAD patients. This assumption was evidenced by the significantly improved efficacy outcomes in the placebo groups. Recently, another study reported on the subjective sexual response in premenopausal women with sexual arousal disorder [33]. A new valid and reliable research tool to evaluate physiological, emotional, and cognitive aspects of subjective sexual arousal and desire was developed [34]. It could be interesting to further explore the effectiveness of the study medications in the treatment of subcategories of FSAD patients and use the newly developed tool in future trials.

In all four treatment groups, most of the adverse events were mild to moderate in intensity and were well tolerated. The most frequently reported adverse events were irritation signs or symptoms at the application site. The incidence of urogenital events was lowest in the placebo group and slightly higher in the 900 mcg alprostadil group. No serious adverse events were reported. For the patients who reported adverse effects, they were more frequently reported at the beginning of the study suggesting a better tolerability for an extended treatment period.

The efficacy and safety data of the novel alprostadil cream in comparison with placebo demonstrate for the first time, a successful topical treatment for patients with FSAD. The improvement of the arousal success rate reached 44% for the entire treatment period in the 900 mcg group and was statistically significant compared to placebo at 23%.

The primary efficacy results were further supported by all of the secondary efficacy endpoint results where both improved sexual satisfaction (FSFI) and overall treatment satisfaction (GAQ scores) were markedly and statistically higher than placebo. The efficacy and safety profiles of the patients in the active drug groups support a successful novel alprostadil treatment for FSAD.

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Conflict of Interest: Drs. Q. Liao, M. Zhang, L. Geng, X. Wang, X. Song, P. Xia, and T. Lu, were investigators in this trial and were paid by NexMed for their services. Dr. M. Lu was, and Ms. V. Liu is, a full time NexMed employee.

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