PH80 Nasal Spray for Acute Management of the Symptoms of Premenstrual Dysphoric Disorder: Results from a Phase 2a Study

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INTRODUCTION

- Women of reproductive age suffering from premenstrual dysphoric disorder (PMDD) develop symptoms during the late luteal phase of the menstrual cycle that are associated with clinically significant distress, interference with work, school, social activities, and relationships
  - PMDD diagnostic criteria require the presence of at least 5 symptoms, with at least 1 of the following: marked affective lability, irritability/anger, depressed mood, and anxiety/tension
  - One or more of the following symptoms are also required for diagnosis, including anhedonia, poor concentration, lethargy/lack of energy, marked change in appetite, hypersomnia/insomnia, feeling out of control or overwhelmed, and physical symptoms (breast tenderness, joint/muscle pain, or a sensation of feeling bloated or gaining weight)[1]
- PMDD affects 3% to 9% of menstruating women[2]
- Moderate to severe PMDD negatively impacts psychological and physical functioning, reduces quality of life, increases health care costs, and has been linked to perinatal/postpartum depression and suicidality[3-9]
- PMDD treatments are often limited by side effects, reducing adherence[10,11]
- Pherines are a new class of neuroactive molecules, formulated as nasal sprays, with an innovative proposed mechanism of action involving chemosensory neurons in the nasal passages that impact fundamental neural circuits in the brain without the need for systemic absorption or binding to central nervous system neurons
  - PH80 is an investigational pherine compound that is hypothesized to exert mood stabilizing effects via rapid stimulation of receptors in nasal chemosensory neurons that directly regulate olfactory/hypothalamic and olfactory/amygdala neural circuits
- Data presented here are the results from a phase 2a study of the effect of PH80 on women diagnosed with PMDD according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (*DSM*-IV) criteria

OBJECTIVE

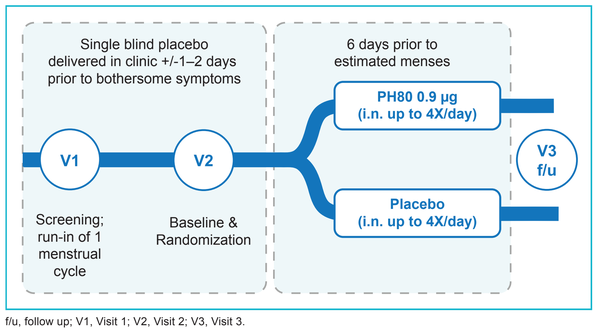
- Primary: to conduct a proof-of-principle evaluation of the efficacy of PH80 nasal spray for acute management of premenstrual symptoms in adult women who regularly experience PMDD
- Secondary: to evaluate the safety and tolerability of PH80 when used for acute management of PMDD symptoms

METHODS

Study Design and Treatment

- Single-center, randomized, double-blind, placebo-controlled phase 2a study conducted at the Hospital Ángeles Mocel, Mexico City, Mexico (**Figure 1**)

Figure 1. Study Design



f/u, follow up; V1, Visit 1; V2, Visit 2; V3, Visit 3.

- Females aged 18 to 40 years with ≥1-year history of *DSM*-IV–defined PMDD were enrolled
- During a 3- to 5-week screening period, patients who presented to the clinic for bothersome PMDD symptoms (defined as "affected functioning") were recruited
- After study eligibility criteria and PMDD symptom presence were confirmed at Visit 1, patients received single-blind placebo; those with no acute improvement were eligible for randomization
- Randomized patients presented for Visit 2 when PMDD symptoms were bothersome during the second cycle after entry
  - PH80 0.9 µg or placebo was administered; PMDD symptoms were evaluated 30 and 60 minutes later
  - Patients were then supplied with their assigned double-blind treatment for self-administration up to 4 times a day (PH80 0.9 µg/dose or matching placebo) for up to 6 consecutive days before the estimated menses onset in that cycle
- On the first day of menses in the second cycle, a follow-up visit (Visit 3) occurred

Patients

Table 1. Key Inclusion/Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Nonpregnant, nonbreastfeeding females 18–40 years of age with regular menstrual cycles between 22–35 days (inclusive) in length	Presence of any acute or chronic medical condition that is considered clinically significant
Patients who reported at least a 1-year history of experiencing PMDD • Premenstrual PMTS score was ≥10 during the first day of treatment • Postmenstrual PMTS score was <10 during menstrual cycle following the first visit • Swelling, bloating, and/or breast tenderness for at ≥2 days during the qualifying menstrual cycle during the Run-In Phase; post-menstrual mean PMTS score for all physical symptoms is <2 during both qualifying menstrual cycles during the Run-In Phase • No clinically significant comorbid psychiatric disorder(s)	Current diagnosis; or history within 1 year prior of another mood, anxiety, or eating disorder; or of a major psychiatric disorder Current or past history of malignancy History of nasal trauma or pathology Patients who used psychotropic medication within 14 days or SSRIs within 2 months of study entry Positive urine drug screen
Patients with clinically healthy nasal passages, as verified by clinical nasal examination	

PMDD, premenstrual dysphoric disorder; PMTS, Premenstrual Tension Scale; SSRI, selective serotonin reuptake inhibitors.

Assessments

- Efficacy Outcomes
  - Penn Daily Symptom Report (DSR)
    - A validated diary that lists 17 premenstrual symptoms: irritability/anger, mood swings, depression, anxiety/tension, feeling out of control, feeling worthless/guilty, decreased interest in usual activities, poor coordination, insomnia, difficulty concentrating/confusion, fatigue, aches, headache, cramps, breast tenderness, swelling/bloating, and food cravings/increased appetite
    - Each symptom was rated daily by the patient on a 5-point scale ranging from 0 (none) to 4 (severe)
  - Premenstrual Tension Scale (PMTS)
    - A 10-item investigator-rated scale assessing premenstrual symptoms: irritability/hostility, tension, efficiency, dysphoria, motor coordination, mental/cognitive functioning, eating habits, sexual drive and activity, physical symptoms, and social impairment
    - Each symptom was rated on a 5-point scale ranging from 0 (none) to 4 (severe) at study endpoint
  - Clinical Global Impression of Improvement (CGI-I)
    - Global improvement in PMDD symptoms was rated by the investigator on a 7-point scale from "very much improved" to "very much worse" before and after treatment with placebo or study medication
  - Patient Global Impression of Change (PGI-C) was rated on a 7-point scale from "very much improved" to "very much worse" and was assessed on the day of onset of menses of the menstrual cycle during Visit 2 and Visit 3 for the PMDD symptom improvement experienced during the preceding menstrual cycle
- Safety assessments: physical exam, vital signs, clinical laboratory, electrocardiograms (ECGs), adverse events (AEs), and vaginal bleeding

Statistics

- For the primary efficacy analysis, the difference between treatment groups for total DSR during the 6-day treatment period was compared with a student's T-test
- For the PMTS, the difference between total PMTS at Visit 2 and Visit 1 was compared across treatment groups using a student's T-test
- For the CGI-I and PGIC, the proportion of responders in each treatment group was compared using a nonparametric test for the difference between 2 proportions

RESULTS

Patient Disposition and Baseline Characteristics

- 82 females were screened, 61 met eligibility criteria, and were randomized to receive PH80 (n=33) or placebo (n=28) (**Table 2**)
  - Seven patients failed to return for Visit 2 and/or pick up study medication and 2 were lost to follow-up
  - Thus, 52 were treated with study medication (PH80, n=29; placebo, n=23); all enrolled patients completed the study

Table 2. Demographics and Baseline Patient Characteristics

Parameter	PH80 (n=33)	Placebo (n=28)
Age, mean (SD), years	31 (6)	33 (5)
Body weight, kg (SD)	69.4 (12.2)	68.5 (11.8)
BMI, mean (SD)	27.7 (2.1)	27.4 (2.2)
Menarche (age), mean (SD)	12 (2)	12 (1)
Cycle length (days), mean (SD)	28.5 (2.1)	28 (2)
Menses duration, days, mean (SD)	4.5 (0.9)	5 (1)
Pre-menstrual symptom history (years), mean (SD)	12 (7)	12 (8)
Baseline PMTS* score, mean (SD)	18.8 (5.5)	14.9 (4.5)
Smoker, n	11	13
Non-smoker, n	19	17
Ethnicity		
White Hispanic	24	20
Caucasian	6	4

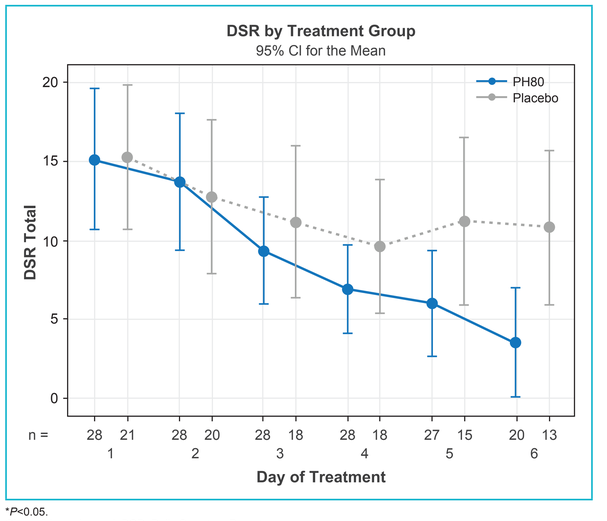
*PMTS (rated by patient).
BMI, body mass index; PMTS, Premenstrual Tension Scale; SD, standard deviation.

- There were no significant differences in baseline characteristics between groups

EFFICACY

Penn DSR scores

Figure 2. Penn DSR Score During the Treatment Period



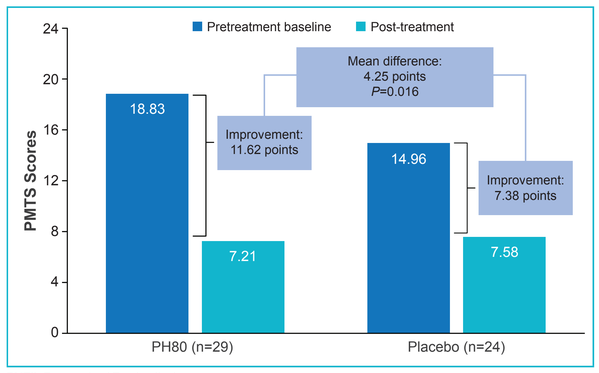
*P<0.05.
CI, confidence interval; DSR, Daily Symptom Report.

- Penn DSR scores (**Figure 2**) diverged between PH80 and placebo on Day 3, with PH80 treatment providing significant symptom severity reduction compared with placebo on Day 6 (P<0.05)

PMTS scores

- At baseline, mean (standard deviation [SD]) PMTS scores were 18.83 (5.52) for PH80 and 14.96 (4.53) for placebo; the mean difference between baseline PH80 and placebo values was significant (P=0.007)
- At endpoint, mean baseline PMTS scores improved by 11.62 (4.84) with PH80 and 7.38 (7.00) points with placebo; the mean (SD) PMTS improvement score difference between PH80 and placebo was 4.25, significantly favoring PH80 (P=0.016) (**Figure 3**)

Figure 3. PMTS Scores: Pretreatment vs Post-treatment



PMTS, Premenstrual Tension Scale.

CGI-I

- CGI-I response rates (ie, "very much" or "much" improved) were similar between PH80 (75.9%) and placebo (76.9%)

PGI-C

- PGI-C response rates (ie, "very much" or "much" improved) were also similar for PH80 (75.9%) and placebo (65.2%)

SAFETY

Adverse Events

- AEs occurred more frequently with placebo than with PH80 treatment (PH80: n=14/30 [47%] vs placebo, n=16/24 [67%], respectively)
  - Overall, most AEs were mild (n=29 [63%]; PH80, n=15 [62%]; placebo, n=14 [64%]) or moderate (n=12, [26%]; PH80, n=6 [25%]; placebo, n=6 [27%]) in severity; severe AEs (n=5 [9%]) were noted in 3 (13%) patients taking PH80 and 2 (9%) taking placebo
  - Two of 24 (8%) AEs with PH80 and 3 of 22 (14%) AEs with placebo were considered related to study drug
- Headache was the only AE that occurred in >1 patient in either group (PH80, n=2 [7%]; placebo, n=4 [17%])

Other Safety Measures

- No clinically significant physical exam, vital sign, clinical laboratory, or ECG changes were noted
- No increased vaginal bleeding was observed

CONCLUSIONS

- PH80 treatment provided significant acute improvement of moderate to severe PMDD symptoms and was well tolerated
  - Efficacy results as reported by patients in the Penn DSR showed a clear benefit of PH80 vs placebo; differences in baseline PMTS scores make interpretation of the improvement observed less clear
  - High placebo response rates as measured by CGI-I responders and PGI-C responders reinforce the need for controlling placebo response in studies of PMDD
- The results show management of AEs is also an important consideration for patients with PMDD, in either clinical practice or clinical trials, as the placebo AE rate was higher than that for PH80 and few AEs were considered to be related to study drug

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Key Contributors

LM contributed to the study design and execution, data interpretation, and medical writing. **RAB** contributed to the data analysis, critical input, and medical writing. **ES** contributed to the review and organization of the clinical data, interpretation of the results, and medical writing. **RH** contributed to the study design, interpretation of results, and medical writing.

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Disclosures

Louis Monti, Ross A. Baker, Ester Salman, and **Rita Hanover** are employees and owners of stock or stock options in Vistagen Therapeutics, Inc.

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