Pain Symptom Cluster Analysis From the Daily Symptom Report in a Phase 2a Study of PH80 for the Treatment of Premenstrual Dysphoric Disorder (PMDD)

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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 and 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
- In a phase 2a study, it was previously shown that PH80 administration in women diagnosed with PMDD, according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV), led to overall improvement in Penn Daily Symptom Report (DSR) scores vs placebo[12]
- The data presented here represent an exploratory, post-hoc subanalysis of the Penn DSR, focusing on the pain cluster score, which includes headache, aches, and cramps[13]

OBJECTIVE

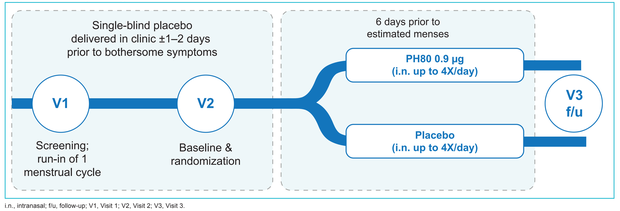
- Exploratory post-hoc subanalysis of the effects of PH80 administration on pain symptoms, assessing changes in headache, aches, and cramps using the DSR pain cluster score

METHODS

Study Design and Treatment

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

Figure 1. Study Design



i.n., intranasal; 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 (**Table 1**)
- During a 3- to 5-week screening period, patients who presented to the clinic for bothersome PMDD symptoms (defined as "affected functioning") were recruited
  - The Premenstrual Tension Syndrome scale was used for screening
- 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 intranasally; PMDD symptoms were evaluated 30 and 60 minutes later
  - Patients were then supplied with their assigned double-blind treatment for intranasal 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 was 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 ≥2 days during the qualifying menstrual cycle during the run-in phase; post-menstrual mean PMTS score for all physical symptoms was <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
Patients with clinically healthy nasal passages, as verified by clinical nasal examination	Positive urine drug screen

PMDD, premenstrual dysphoric disorder; PMTS, Premenstrual Tension Syndrome; SSRI, selective serotonin reuptake inhibitor.

Assessments

- Efficacy Outcomes
  - Penn DSR
    - A validated diary listing 17 premenstrual symptoms was used, and the DSR pain cluster (headaches, aches, and cramps) was analyzed from the recorded symptoms
    - Each symptom was rated daily by the patient on a 5-point scale ranging from 0 (no symptoms at all) up to 4 (very severe)
- Safety assessments: physical exam, vital signs, clinical laboratory, electrocardiograms (ECGs), adverse events (AEs), and vaginal bleeding

Statistics

- The overall pain cluster score and individual symptom ratings were compared post-hoc using two-sided T-tests, without adjustments for multiplicity or within-patient variance; means for each group were plotted for each reported day, and no imputation was made for missing data

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
  - A total of 49 patients provided at least 1 post-treatment assessment and were included in the pain efficacy analysis

Table 2. Demographics and Baseline Patient Characteristics

Parameter	PH80 (n=33)	Placebo (n=28)
Age in years, mean (SD)	31 (6)	33 (5)
Body weight in kg, mean (SD)	69.4 (12.2)	68.5 (11.8)
BMI in kg/m², mean (SD)	27.7 (2.1)	27.4 (2.2)
Menarche age in years, mean (SD)	12 (2)	12 (1)
Cycle length in days, mean (SD)	28.5 (2.1)	28 (2)
Menses duration in days, mean (SD)	4.5 (0.9)	5 (1)
Pre-menstrual symptom history in years, mean (SD)	12 (7)	12 (8)
Ethnicity, n		
White Hispanic	24	20
Caucasian	6	4

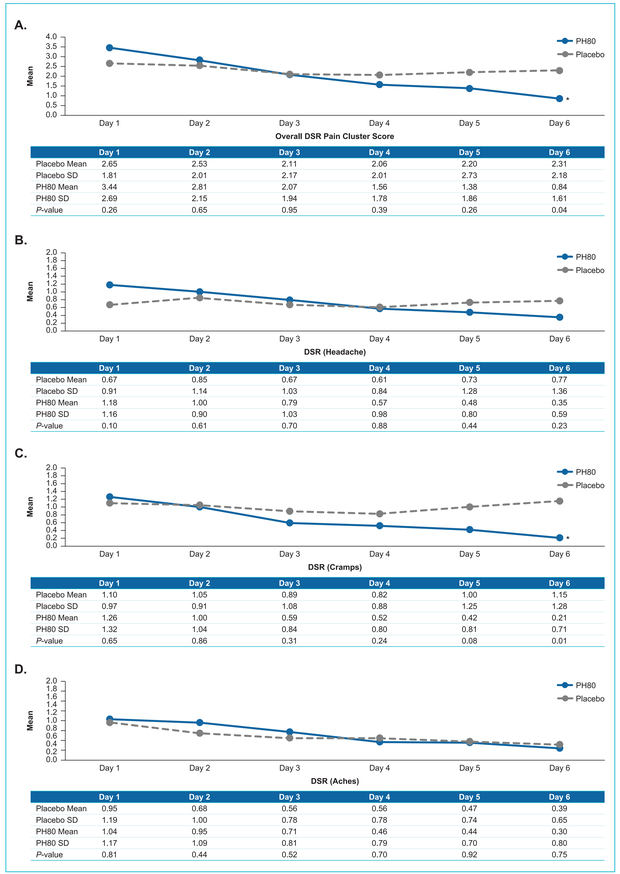
BMI, body mass index; SD, standard deviation.

- There were no significant differences in baseline characteristics between groups

EFFICACY

Penn DSR Scores

Figure 2. DSR Pain Cluster Scores for (A) Overall, (B) Headaches, (C) Cramps, and (D) Aches



A. Overall DSR Pain Cluster Score

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Placebo Mean	2.65	2.53	2.11	2.06	2.20	2.31
Placebo SD	1.81	2.01	2.17	2.01	2.73	2.18
PH80 Mean	3.44	2.81	2.07	1.56	1.38	0.84
PH80 SD	2.69	2.15	1.94	1.78	1.86	1.61
P-value	0.26	0.65	0.95	0.39	0.26	0.04

B. DSR (Headache)

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Placebo Mean	0.67	0.85	0.67	0.61	0.73	0.77
Placebo SD	0.91	1.14	1.03	0.84	1.28	1.36
PH80 Mean	1.18	1.00	0.79	0.57	0.48	0.35
PH80 SD	1.16	0.90	1.03	0.98	0.80	0.59
P-value	0.10	0.61	0.70	0.88	0.44	0.23

C. DSR (Cramps)

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Placebo Mean	1.10	1.05	0.89	0.82	1.00	1.15
Placebo SD	0.97	0.91	1.08	0.88	1.25	1.28
PH80 Mean	1.26	1.00	0.59	0.52	0.42	0.21
PH80 SD	1.32	1.04	0.84	0.80	0.81	0.71
P-value	0.65	0.86	0.31	0.24	0.08	0.01

D. DSR (Aches)

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Placebo Mean	0.85	0.68	0.56	0.56	0.47	0.39
Placebo SD	1.19	1.00	0.78	0.78	0.74	0.65
PH80 Mean	1.04	0.95	0.71	0.46	0.44	0.30
PH80 SD	1.17	1.09	0.81	0.79	0.70	0.80
P-value	0.81	0.44	0.52	0.70	0.92	0.75

*Indicates significant difference between groups (*P*<0.05).
DSR, Daily Symptom Report; SD, standard deviation.

- At Day 6, PH80 (n=19) demonstrated statistically significant improvement over placebo (n=13) on the overall pain cluster score (0.84 for PH80 vs 2.3 for placebo; *P*=0.036) (**Figure 2A**)
- At Day 6, PH80 (n=19) demonstrated statistically significant improvement over placebo (n=13) on the cramps line item (0.21 for PH80 vs 1.15 for placebo; *P*=0.01) (**Figure 2C**), whereas the individual items headache (**Figure 2B**) and aches (**Figure 2D**) were not different

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

LIMITATIONS

- This phase 2a study was exploratory and conducted at a single site with a small sample size
- The data should be interpreted cautiously, as the exploratory post-hoc subanalysis was conducted to help inform future development of PH80 and did not take into account within-patient variability or correct for multiplicity

CONCLUSIONS

- In addition to previously reported benefits on overall symptoms of PMDD, hormone-free PH80 nasal spray also showed beneficial effects on PMDD pain symptoms, particularly on cramps
  - PH80 decreases autonomic system activity; thus, we hypothesize that the reduction in PMDD-related cramps and pain may be partly due to relaxation of the myometrium from decreased vasopressin and partly due to vasodilation because of decreased central norepinephrine
- Side effects are a key consideration for patients with PMDD in choosing treatment in clinical practice and in trials. Notably, the placebo group had a higher rate of AEs than the PH80 group, with few AEs being attributed to the 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.

RH contributed to the study design, interpretation of results, and medical writing.

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Disclosures

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

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