A Phase 2A Clinical Study to Investigate the Efficacy, Safety, and Tolerability of PH80 for the Acute Management of Menopausal Vasomotor Symptoms (Hot Flashes) in Women

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INTRODUCTION

- Vasomotor symptoms (ie, hot flashes and night sweats) affect up to 80% of women as they transition from early perimenopause to postmenopause[1] and are associated with negative impacts on quality of life[2,3]
  - Past research indicates that women experience vasomotor symptoms for a median duration of 7.4 years,[4] but this estimate varies by race and ethnic group
- Currently available US FDA-approved treatments for vasomotor symptoms include hormonal treatments (estrogen with or without progesterone) and non-hormonal treatments (low-dose paroxetine [SSRI] and fezolinetant [NK3 receptor antagonist])[5,6]
- Despite the intensity and duration of symptoms, a considerable proportion of women experiencing menopause do not consult a health care professional for medical care[7] due to safety concerns with hormonal therapies; fewer still receive prescription treatment[8]
- PH80 is a non-hormonal synthetic neuroactive pherine delivered via nasal spray that engages nasal chemosensory receptors in the same manner as naturally occurring chemosignals[9]
- In vitro pharmacology studies suggest that PH80 produces a nongenomic effect, resulting in stimulation of a slow calcium conductance and dose-dependent increase in intracellular calcium (Ca2+) concentration via its actions on human nasal chemosensory cells[10]
  - Following activation of nasal chemosensory cells by PH80, modulation of limbic-hypothalamic brain areas results in pharmacologic and behavioral effects, including decreased body temperature, decreased electrodermal activity, decreased skeletal muscle tone (relaxation), decreased nervousness and anxiety, and increased positive mood[10]
- Another synthetic neuroactive pherine nasal spray, fasedienol (PH94B), has shown efficacy and good tolerability in phase 2[11,12] and phase 3 studies for the acute treatment of social anxiety disorder (see Lappalainen et al and Liebowitz et al posters presented at this meeting)

OBJECTIVES

- This proof-of-principle study evaluated the efficacy of PH80 for the acute management of menopausal vasomotor symptoms
- A secondary objective was to evaluate the safety and tolerability of PH80 when used for acute management of menopausal vasomotor symptoms

METHODS

Study Design

- Written informed consent was obtained from all patients prior to any performed screening procedures
- This double-blind, placebo-controlled, phase 2A study randomized women with frequent vasomotor symptoms (ie, ≥8 per day) to PH80 or placebo in a 1:1 ratio
- At the screening visit (visit 1), informed consent, study eligibility, baseline demographics, and clinical laboratory assessments were obtained
  - Patients received a diary to record their baseline daily hot flash experience over the next 7 days (including the number, severity, disruption in function (bother), and sweating experienced during hot flashes); other menopausal symptoms, spontaneous vaginal bleeding, and compliance with treatment were also recorded
- At visit 2, hot flash diaries were reviewed, and clinical evaluations were conducted; based on these safety and efficacy findings, the investigator decided whether the patient should continue in the study
  - Patients eligible to continue in the study were randomized to treatment with PH80 or placebo, which was taken up to 4 times per day (with a fifth dose available at night if awakened by hot flashes) as needed for the next 4 weeks
  - Patients filled out hot flash diaries and returned for weekly visits (weeks 2–5, 4 weeks in total) during which evaluation of the nasal passages, arterial blood pressure, therapeutic effects, and side effects were assessed
- Visit 6 was the final visit; completed diaries were returned and the investigator clinically evaluated each patient for efficacy and adverse events
  - Patients were instructed to contact the clinic for any adverse events occurring within 2 weeks of the final visit

Study Treatments

- PH80 nasal spray was formulated for intranasal administration (Aptar metered spray pump VP7/50); placebo was formulated in the same manner but did not contain PH80
  - Each actuation of PH80 nasal spray provided 0.8 µg of PH80; each dose of PH80 provided 3.2 µg of PH80 (2 sprays or 1.6 µg in each nostril)

Study Participants

Inclusion Criteria

1. Menopausal women aged 45–60 years
2. Last natural menstrual period completed at least 60 days before screening
3. ≥ 8 hot flashes per day on average for 1 week, or ~56/week during 2 weeks
4. Moderate to severe hot flashes that interfere with functioning

Exclusion Criteria

- History, presence, or suspicion of estrogen-dependent neoplasia
- Malignancy, or treatment of malignancy, within the previous 2 years
- History of endocrinopathies, nasal pathology, or nasal trauma
- Use of therapy for hot flashes within the past 2 months
- History of cerebrovascular accident, stroke, or transient ischemic attack
- Active or recent arterial thromboembolic disease or history of venous thromboembolism
- Presence of major depressive disorder, bipolar disorder, psychotic disorder, or generalized anxiety disorder requiring therapy or SSRI therapy within last 2 months
- Persistent elevated blood pressure
- Any medical condition/disease or concomitant medication that could place the subject at undue risk or could confound study results
- Positive urine screen for substance abuse

Study Outcomes

- The primary endpoint assessed the effect of PH80 vs placebo on the number, severity, disruption in function (bother), and sweating of hot flashes
- Secondary endpoints included:
  - Clinical Global Impression of Improvement (CGI-I) and Patient Global Impression of Change (PGI-C); each ranked on a scale of 1 "very much improved" to 7 "very much worse"
- Other endpoints included:
  - Spontaneous vaginal bleeding
  - Adverse event number, type, and severity

Statistical Analysis

- For the primary efficacy analysis, differences in hot flash number, severity, disruption in function (bother), and sweating scores between baseline and subsequent visits over the course of the study were compared for PH80 and placebo using the Student's t-test

RESULTS

- Of 40 patients who were randomized, 36 (PH80, n=18; placebo, n=18) completed the study
- At baseline, demographics were similar between treatment groups (**Table 1**)

Table 1. Patient demographics

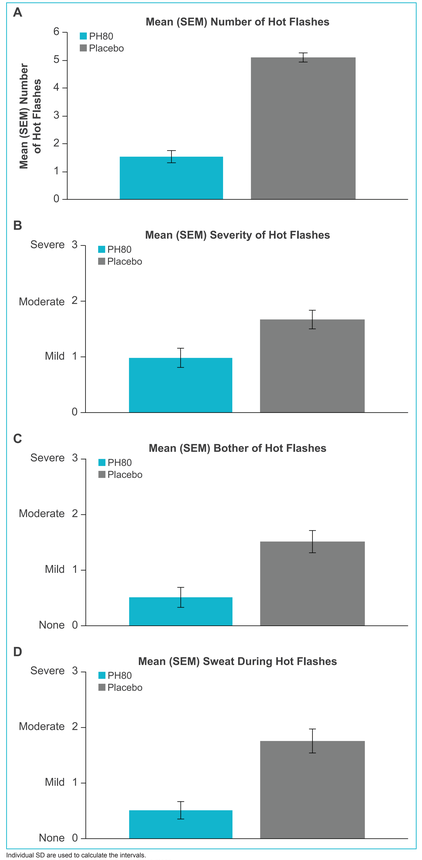
Demographics	PH80 (n=18)	Placebo (n=18)
Age, years	52.4 (4.6)	53.5 (3.8)
Body weight, kg	65.8 (8.7)	63.9 (6.2)
Height, m	1.50 (0.02)	1.50 (0.04)
Body mass index, kg/m²	29.12 (4.08)	28.44 (3.24)
Years since menopause began	3.3 (1.5)	3.6 (1.7)
Smoker, n	11	9
Education: primary/secondary/ university, n	6/12/2	6/10/4
Baseline daily hot flashes	8 (0.8)	8 (0.7)

Data are mean (SD) unless otherwise noted. 4 screened subjects that abandoned the study before treatment began are included in the demographics
SD, standard deviation.

Primary Efficacy

- PH80 induced a significant reduction in the mean daily number of hot flashes between baseline through the end of treatment (**Figure 1A**)
  - In patients treated with PH80, the mean number of daily hot flashes decreased from a baseline of 7.69 to 1.54 at the end of 4 weeks of treatment; in patients taking placebo, the mean number of hot flashes decreased from 7.97 at baseline to 5.11 after 4 weeks of treatment
  - The mean (standard error of the mean [SEM]) number of sprays self-administered per week decreased significantly over the treatment period for PH80, from 3.1 (0.7) at week 1 to 2.0 (0.6) at week 4, but not for placebo (3.1 [0.9] at weeks 1 and 4)
    - PH80 was self-administered significantly less frequently than placebo during treatment weeks 3 (P=.02 vs placebo) and 4 (P=.03 vs placebo)
    - The mean (SEM) number of sprays self-administered over the entire treatment period trended lower for PH80 vs placebo (2.5 [0.9] vs 3.1 [0.2]), but the difference did not reach statistical significance (P=.07)
  - The mean number of hot flashes increased during follow-up after PH80 treatment was suspended
- PH80 treatment also significantly improved the severity, disruption in function (bother), and sweating scores associated with hot flashes through the end of treatment (P<.001) vs placebo; see **Figure 1B-D** for week 4 treatment effects

Figure 1. Effect of 3.2 µg PH80 nasal spray compared with placebo nasal spray (as needed up to 5 times daily) on mean daily A) number, B) severity, C) disruption in function (bother), and D) sweating associated with hot flashes at treatment week 4

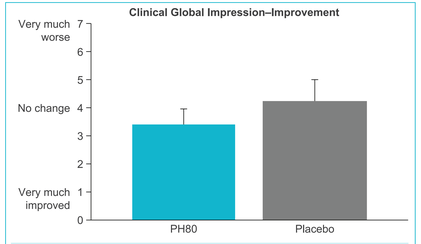


Individual SD are used to calculate the intervals.
SD, standard deviation; SEM, standard error of the mean.

Secondary Efficacy

- At the study endpoint, CGI-I scores improved to a greater extent with PH80 than with placebo, but the effect did not reach statistical significance (P=.093) (**Figure 2**)

Figure 2. Effect of 3.2 µg PH80 (as needed up 5 times daily) on Clinical Global Impression-Improvement in menopausal women (N=36)

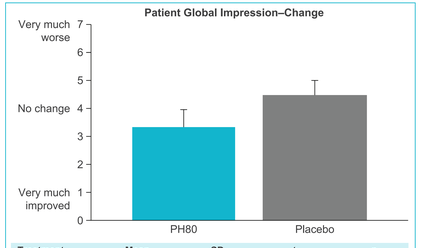


Treatment	Mean	SD	t	p
Placebo	4.23	1.7	1.73	.093
PH80	3.39	1.2		

SD, standard deviation.

- PGI-C scores significantly improved at study endpoint for those treated with PH80 (PGI-C=3.308) vs placebo (PGI-C=4.462; P=.013) (**Figure 3**)

Figure 3. Effect of 3.2 µg PH80 (as needed up 5 times daily) on Clinical Global Impression-Improvement in menopausal women (N=36)



Treatment	Mean	SD	t	p
Placebo	4.46	1.1	2.61	.013
PH80	3.31	1.4		

SD, standard deviation.

Other Endpoints

- There were no reports of vaginal bleeding or vaginal spotting during the study treatment period in the PH80 and placebo groups
- PH80 was well tolerated; no patients discontinued due to adverse events. The number of patients reporting adverse events and the number of adverse events reported decreased after treatment with PH80 (**Table 2**)
- Headache was the most common adverse event noted, occurring in 2 patients treated with PH80 and 5 patients treated with placebo
  - There were no reported serious adverse events

Table 2. Adverse events before and after receiving study medication

	PH80 (n=18)		Placebo (n=18)	
	Pre-dose	Post-dose	Pre-dose	Post-dose
Number (%) of patients reporting				
0 events	0	9 (50)	0	0
1 event	4 (22)	7 (39)	5 (28)	8 (44)
2 events	8 (45)	2 (11)	7 (39)	7 (39)
≥ 3 events	6 (33)	0	6 (33)	3 (17)
Number of events reported	29	14	30	33
Events related to study medication	0	1	0	10
Serious adverse events	0	0	0	0

LIMITATIONS

- The study is limited by its small sample size

CONCLUSIONS

- The significant reduction in menopausal symptoms and improved function induced by PH80 in women with vasomotor symptoms compared with placebo provide a strong signal for continued development of PH80 for the treatment of hot flashes
- The safety data further suggest that, if approved, PH80 will provide a substantial safety benefit over presently available agents

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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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