PH80 Nasal Spray for Treatment of Vasomotor Symptoms (Hot Flashes) Associated with Menopause: a Phase 2 Randomized, Controlled Study

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INTRODUCTION

- Vasomotor symptoms (VMS), including hot flashes and night sweats, occur in 75% of menopausal women and 40% of women in perimenopause[1]
  - These symptoms persist, with a median duration of 7.4 years,[2] and are associated with negative impacts on quality of life[3-5]
- Hormonal treatments, estrogen with or without progesterone, and nonhormonal treatments, such as low-dose paroxetine (selective serotonin reuptake inhibitors [SSRI]) and fezolinetant (NK3 receptor antagonist) are the US FDA-approved treatments for VMS[6,7]
- Many women experiencing menopause do not consult a health care professional for medical care due to safety concerns about taking hormonal therapies;[5] fewer still receive prescription treatment[8]
- PH80 is a nonhormonal synthetic neuroactive pherine delivered via nasal spray that engages specific 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 concentration after binding to 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 electrodermal activity, decreased skeletal muscle tone (relaxation), decreased nervousness and anxiety, and increased positive mood

OBJECTIVE

- To evaluate the efficacy, safety, and tolerability of daily treatment of PH80 vs placebo over 4 weeks on VMS in menopausal women

METHODS

Study Design

- Written informed consent was obtained from all patients prior to any 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
- This single-site study was conducted at Hospital Ángeles Mocel in Mexico City
- 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
- At visit 2, hot flash diaries were reviewed, and clinical evaluations (physical exam, vital signs, electrocardiogram) were conducted; based on these findings, the investigator reviewed whether the patient should continue in the study based on inclusion/exclusion criteria
  - 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 daily hot flash diaries for each week (ie, weeks 2–5; 4 weeks in total) with the same assessments as at screening; clinical evaluation of the nasal passages, arterial blood pressure, therapeutic effects, and side effects were collected
- 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

- Menopausal women aged 45 to 60 years
- Last natural menstrual period completed at least 60 days before screening
- ≥8 hot flashes per day on average for 1 week, or ~56/week for 2 weeks
- 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 the 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 (bothersome symptoms), and sweating related to 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, and sweating scores between baseline and subsequent visits over the course of the study were compared for PH80 and placebo using a two-tailed 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

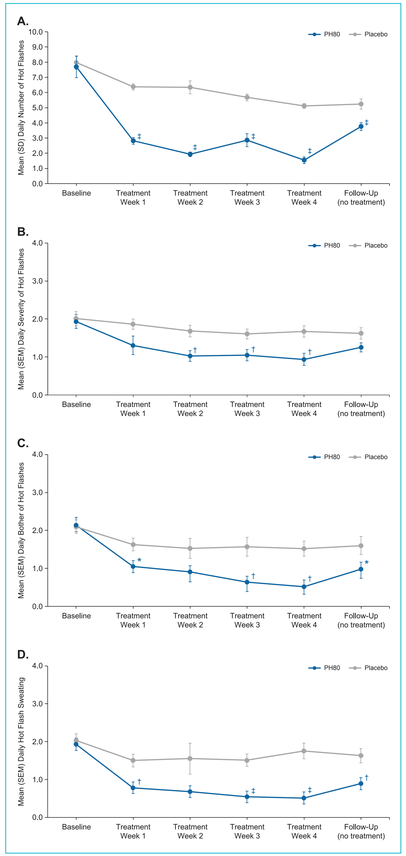
Demographics	PH80 (n=18)	Placebo (n=18)
Age, years	52.4 (4.6)	53.5 (3.8)
Body weight, kg	65.8 (8.7)	63.9 (6.2)
Height, m	1.50 (0.02)	1.50 (0.04)
Body mass index, kg/m²	29.12 (4.08)	28.44 (3.24)
Years since menopause began	3.3 (1.5)	3.6 (1.7)
Smoker, n	11	9
Education: primary/secondary/ university, n	6/12/2	6/10/4
Baseline daily hot flashes	7.7 (0.7)	8 (0.5)

Data are mean (SD) unless otherwise noted.
SD, standard deviation.

Primary Efficacy

- For the objective measure of mean daily number of hot flashes, PH80 induced a significant reduction between baseline and the end of the first week of treatment (P<.001); hot flash number continued to decrease significantly through the end of treatment (P<.001 for each week) with PH80 (**Figure 1A**)
  - In patients treated with PH80, the mean number of daily hot flashes decreased from a baseline of 7.7 to 1.5 at the end of 4 weeks of treatment, a reduction of 80%; and increased substantially to 3.8 in the follow-up week with no treatment; in patients taking placebo, the mean number of hot flashes decreased from 8.0 at baseline to 5.1 after 4 weeks of treatment, a reduction of 36%; and 3.2 in the follow-up week with no treatment
  - The mean (standard deviation [SD]) 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)
- For the subjective measures of severity, disruption in function (bother), and sweating, PH80 treatment also significantly improved all three by week 4 end of treatment. At the end of the first week of treatment, PH80 significantly improved disruption in function and sweating (P<.05 and P<.01, respectively), and at the end of week 2 of treatment for severity (P<.01) (**Figure 1B–D**)

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) functional impairment (bother), and D) hot flash sweating during 4 weeks of treatment

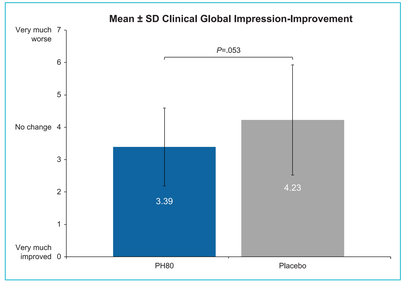


*P<.05; †P<.01; ‡P<.001 vs placebo.
SD, standard deviation; SEM, standard error of the mean.

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=.053) (**Figure 2**)

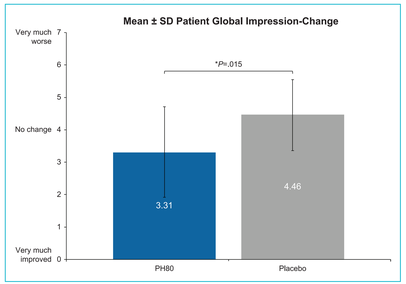
Figure 2. Effect of 3.2 µg PH80 (as needed up to 5 times daily) on Clinical Global Impression-Improvement in menopausal women (N=36)



Note: SD is reported for numerical data to illustrate variability due to small standard error of the mean.
SD, standard deviation.

- PGI-C scores significantly improved at study endpoint for those treated with PH80 (PGI-C=3.31) vs placebo (PGI-C=4.46; P=.015) (**Figure 3**)

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



Note: SD is reported for numerical data to illustrate variability due to small standard error of the mean.
*P=.05 vs placebo.
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

LIMITATIONS

- The study is limited by its small sample size

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

CONCLUSIONS

- The significant reduction in menopausal symptoms and improved function induced by PH80 in women with hot flashes as early as 1 week compared with placebo provide a strong signal for continued development of PH80 for the treatment of hot flashes
- Most importantly, PH80 reduced the number of mean daily hot flashes (an objective measure) by 80% vs 36% for placebo, suggesting that subjects had a strong, positive physiologic response to treatment
- The safety data further suggest that, if approved, PH80 will provide a substantial safety benefit over presently available agents

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Disclosures

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

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