PH80 Nasal Spray Effects on Brain and Autonomic Activity: A Novel, Investigational, Rapid-Onset, Non-Hormonal Treatment for Vasomotor Symptoms Due to Menopause

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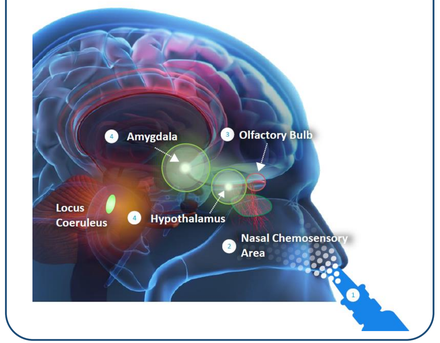
Introduction

- Vasomotor symptoms (VMS) due to menopause, including hot flashes and night sweats,[1,2] can have a negative impact on women's overall quality of life and mental health[3-6]
- Pherines are a novel class of odorless, tasteless, non-hormonal, nasal chemosensory receptor agonists that are under investigation by Vistagen as intranasal drug candidates for multiple psychiatric and women's health indications[7]
  - Pherines rapidly and selectively bind to receptors in human nasal chemosensory neurons (NCNs), activating olfactory bulb-to-brain neurocircuits
  - Activating receptors in NCNs avoids systemic absorption and brain uptake to achieve therapeutic effects with a favorable safety profile
- PH80 is a pherine that is administered as a nasal spray with a proposed mechanism of action to treat VMS due to menopause via its rapid agonist effect on NCN receptors, activating microcircuits (glomeruli) in the mood and thermoregulatory neurocircuits of the olfactory-limbic and amygdala-hypothalamic networks, and the autonomic nervous system (**Figure 1**)[7]
- In an exploratory, phase 2a study, PH80 nasal spray reduced hot flash frequency, severity, bother, and sweating for up to 4 weeks, with a tolerability profile similar to that with placebo, in menopausal women having moderate to severe hot flashes[8]

Figure 1. PH80's proposed mechanism of action to treat VMS due to menopause is via its rapid activation of NCNs to the olfactory bulb and then the limbic amygdala and hypothalamic neurocircuits[7]



Objectives

To characterize the effects of PH80 on

- The electrogram of the nasal chemosensory epithelium of the upper medial nasal septum
- Physiologic markers in healthy volunteers

Methods

Study 1: Effect of PH80 on the electrogram of nasal chemosensory epithelium

- Single-blind, crossover study in 8 healthy, female volunteers of reproductive age (20-45 years) who were assessed on day 11 of the menstrual cycle (±2 days), to minimize the influence of cyclic endocrine changes
- PH80 was administered intranasally using a commercially available, metered-spray pump delivering 50-µL sprays
- Ascending quantities of PH80 were administered (0.0 [control], 0.014, 0.072, 0.144, 1.44, and 7.2 µg) at 15-minute intervals for a total dose of 8.87 µg

Study 2: Effect of PH80 on nasal chemosensory epithelium

- Single-blind, crossover study in 20 healthy, volunteers (10 women, 10 men)
- PH80 was administered locally to the surface of the nasal chemosensory epithelium in 1-second, vapor pulses delivering 150 pg/pulse of PH80 or vehicle (propylene glycol 10%) at 5-minute intervals

In both studies

- Local electrograms (transepithelial electrical potential) were recorded from the nasal chemosensory epithelium (EGNR) using an electrode positioned in contact with the surface chemosensory epithelium of the upper medial nasal septum
- Physiologic markers evaluated were respiratory rate (RR), heart rate (HR), electrodermal activity (EDA), electromyogram (EMG), body temperature (study 2 only), and cortical electroencephalograms (EEG) recorded from the frontal cortex (CzA1) and the temporal cortex (T3 A1)
- All physiological recordings were amplified, digitized, monitored, and computer stored for off-line processing and statistical analysis

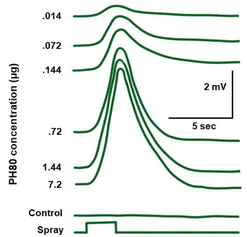
Results

Electrograms of the nasal chemosensory epithelium

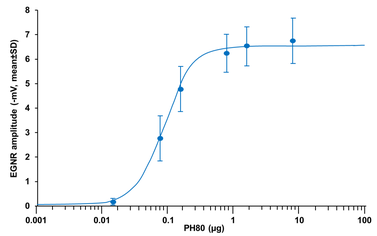
- PH80 nasal spray increased the amplitude and duration of the EGNR in a dose-dependent manner, and decreased EGNR latency (**Figure 2A**)
- The EC_{50} for PH80 was 0.087 µg and the Hill coefficient 1.89 (**Figure 2B**)

Figure 2. Effect of PH80 on the EGNR

A) Representative EGNRs



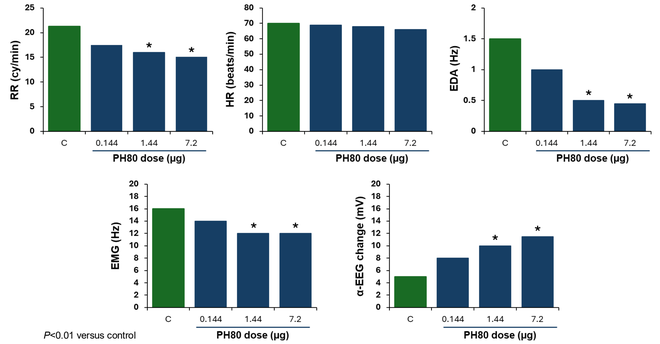
B) Agonist, dose-dependent effect of PH80 on EGNR amplitude



Physiologic markers

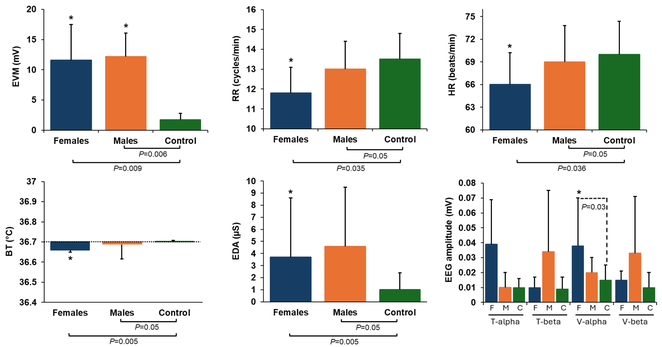
- Study 1: PH80 nasal spray (doses of 1.44 µg and 7.2 µg) significantly decreased RR, EDA, and EMG; and increased the alpha frequency band of the EEG (α-EEG) (**Figure 3**)
- Study 2: PH80 (150-pg vapor pulses) significantly reduced RR, HR, and body temperature in women only; numerically increased EDA versus control in men and women; and significantly increased α-EEG in the temporal and frontal cortices of women (**Figure 4**)
- Effects of PH80 on autonomic-nervous-system markers and EEG appeared with a latency of 500±130 milliseconds

Figure 3. Effects of PH80 on physiologic markers in healthy, women of reproductive age



P<0.01 versus control

Figure 4. Effects of PH80 on physiologic markers in healthy men and women



C; control; F, female; M, male; RR, respiratory rate; HR, heart rate; EDA, electrodermal activity, EMG, electromyogram; BT, body temperature; EEG, electroencephalogram

Safety

- Study 1: PH80 nasal spray was well tolerated, with no reported local, nasal irritation or mucosal disruption, or general adverse events; or treatment-related adverse events
- Study 2: No adverse events were reported immediately after PH80 administration, or within 24 hours after the study session

Key Takeaways

- PH80 depolarizes the EGNR in a concentration-dependent manner
- Rapid-onset effects of PH80 on physiologic markers were recorded after intranasal administration
- Results presented here support ongoing clinical development of PH80 for treating VMS due to menopause

Conclusions

- PH80 nasal spray induces significant, rapid-onset, agonist effects on NCNs that activate the limbic system and autonomic neurocircuits
- Effects of PH80 also support target engagement after intranasal administration of 1.44-µg to 7.2-µg doses
- No adverse events were reported in healthy subjects receiving a total dose of 8.87 µg administered over a period of 2 hours
- Collectively, the present results and previously reported phase 2 data[8] support ongoing clinical development of PH80 for the treatment of VMS due to menopause

References

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Disclosures

- LM and RAB are employees of and own stock or stock options in Vistagen Therapeutics, Inc (Vistagen) . RH is a consultant to Vistagen.
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See also Poster #P-124 on steroid receptor binding, in vivo effects, and pharmacokinetics