Antidepressant Ituruvone Nasal Spray Depolarizes Nasal Chemosensory Receptors followed by Increased Gamma Power Spectral Density of the Olfactory Bulb in Healthy Subjects

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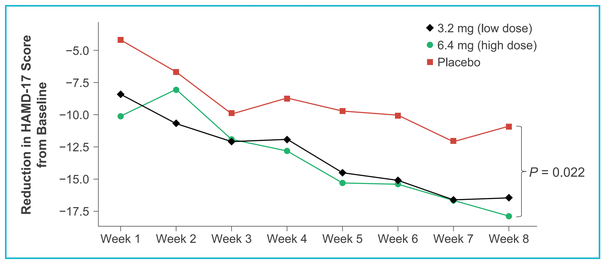
INTRODUCTION

- Major depressive disorder (MDD) is a severe, often long-lasting condition affecting an estimated 2%–21% of people globally over their lifetime[1]
- Previous meta-analyses of tricyclic antidepressants, selective serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors show that only 38%–49% of patients with moderate to severe MDD achieve remission[2,3]
  - Remission rates are likely even lower in real-world treatment settings outside of clinical trials[4]
  - Adverse events often reduce adherence to antidepressants, hindering progress toward remission[5]
- Ituruvone (PH10, pregn-4-en-20-yne-3-one) nasal spray is a nonsystemic, rapid-onset, investigational pherine in phase 2 development for MDD[6,7]
  - In a phase 2a study of patients with MDD (N = 30), ituruvone 6.4 µg produced rapid-onset and sustained antidepressant effects with minimal side effects (**Figure 1**)[8]

Figure 1. Hamilton Depression Rating Scale (HAM-D-17) Score Reduction from Baseline



- Within milliseconds of intranasal (IN) administration at low microgram-level doses, ituruvone activates specific receptors on peripheral chemosensory neurons in the nasal mucosa that regulate olfactory-amygdala neural circuits to increase limbic-hypothalamic sympathetic nervous system activity, inducing rapid antidepressant effects and increased norepinephrine release[6]

OBJECTIVE

- **Primary:** To compare the pharmacodynamic responses of IN placebo and ituruvone on the electrogram of nasal receptors (EGNR) and the olfactory bulb electrogram (EBG) in healthy adult subjects
- **Secondary:** To compare the pharmacodynamic response of single IN dose ituruvone nasal spray (1.6 µg per 0.1 mL) and 2 IN doses of ituruvone (2 sprays of 1.6 µg per 0.1 mL) administered consecutively

METHODS

- This was a single-center, randomized, single-blind, placebo-controlled phase 1 study in healthy male and female volunteers aged 18–60 years (**Table 1**) who did not have olfactory dysfunction, as assessed using the quantitative Quick Olfactory Test

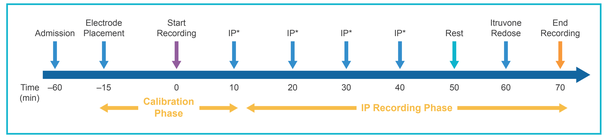
Table 1. Baseline Characteristics

Characteristic	Female Subjects (n=6)	Male Subjects (n=6)	Overall (N=12)
Age (years)			
Mean (SD)	38.5 (7.5)	43.3 (8.0)	40.9 (7.8)
Body mass index (kg/m²)			
Mean (SD)	32.8 (14.4)	26.4 (2.7)	29.6 (10.4)
Race, n (%)			
White	2 (33.3)	3 (50.0)	5 (41.7)
Black or African American	1 (16.7)	0 (0)	1 (8.3)
Asian	3 (50.0)	2 (33.3)	5 (41.7)
Multiple	0 (0)	1 (16.7)	1 (8.3)
Ethnicity, n (%)			
Hispanic or Latino	1 (16.7)	1 (16.7)	2 (16.7)
Not Hispanic or Latino	5 (83.3)	5 (83.3)	10 (83.3)

kg, kilogram; m², square meter; SD, standard deviation.

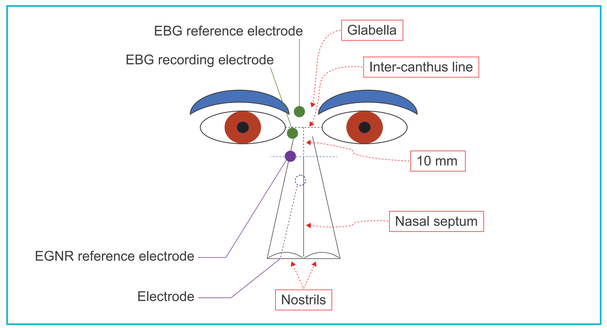
- The effects of placebo and single- (1.6 µg per 0.1 mL) and double-dose (1.6 µg per 0.1 mL × 2) ituruvone on the EGNR and the gamma (γ) band spectral power density of the EBG recording were compared using a within-group paired Student's t-test for differences in mean vs placebo
- The order of IN administration was randomized, based on the initial stability of the electrogram recording, with 6–8 subjects receiving ituruvone first and 6–8 subjects receiving placebo first during the single-dose phase (**Figure 2**)
- The pharmacodynamic response of 1.6 µg × 2 ituruvone (2 consecutive doses of 1.6 µg) was measured to assess a possible cumulative effect on the EGNR and the EBG
- A conventional, nonpolarizable silver electrode (0.5-mm diameter coated with conductive gel) positioned on the surface of the nasal chemosensory mucosa was used to record the EGNR (**Figure 3**)
  - Recordings were amplified using a DC-coupled low-noise preamplifier (MP160, Biopac Systems) and continuously collected on a computer for offline processing and analysis
- The EBG was recorded using electroencephalogram electrodes attached to the skin adjacent to the internal eye canthus using conductive paste
  - γ-band power spectral density (PSD) was obtained using a fast Fourier transform

Figure 2. Study Design



*IP can be either placebo or ituruvone based on random assignment of order.
IP, investigational product; min, minutes.

Figure 3. Positioning of EGNR and EBG Recording Electrodes

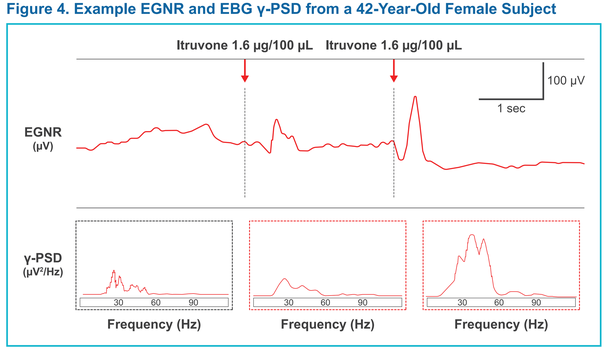


EBG, olfactory bulb electrogram; EGNR, electrogram of nasal receptors.

RESULTS

- Ituruvone led to dose-dependent activation of the EGNR, followed by activation of γ-PSD of the EBG (**Figure 4**)

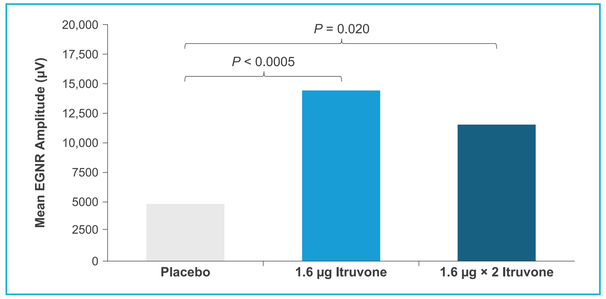
Figure 4. Example EGNR and EBG γ-PSD from a 42-Year-Old Female Subject



EBG, olfactory bulb electrogram; EGNR, electrogram of nasal receptors; Hz, Hertz; PSD, power spectral density; sec, second; µg, microgram; µV, microvolt.

- Compared with placebo, both 1.6 µg and 1.6 µg × 2 doses of ituruvone increased EGNR amplitude (**Figure 5**)

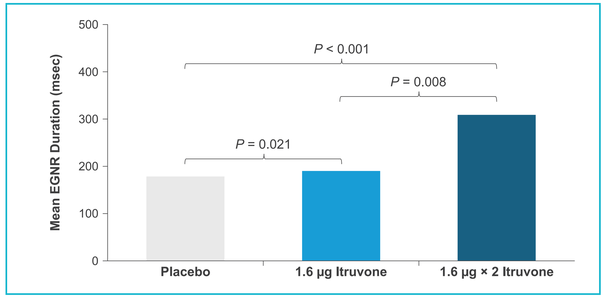
Figure 5. Mean EGNR Amplitude During Placebo, Single- and Double-Dose IN Administrations of Ituruvone



P-value from paired Student's *t*-test comparing within-group placebo and ituruvone responses.
EGNR, electrogram of nasal receptors; IN, intranasal; µg, microgram; µV, microvolt.

- Compared with placebo, both 1.6 µg and 1.6 µg × 2 doses of ituruvone increased EGNR duration (**Figure 6**)
- EGNR duration also increased significantly with double-dose administration when compared with single-dose administration

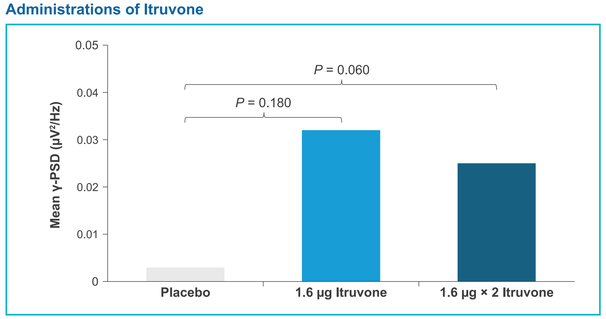
Figure 6. Mean EGNR Duration During Placebo, Single- and Double-Dose IN Administrations of Ituruvone



P-value from paired Student's t-test comparing within-group placebo and ituruvone responses.
EGNR, electrogram of nasal receptors; IN, intranasal; µg, microgram; msec, millisecond.

- Compared with placebo, both 1.6 µg and 1.6 µg × 2 doses of ituruvone numerically increased EBG γ-PSD (**Figure 7**)

Figure 7. Mean EBG γ-PSD During Placebo, Single- and Double-Dose IN Administrations of Ituruvone



P-value from paired Student's t-test comparing within-group placebo and ituruvone responses.
EBG, olfactory bulb electrogram; Hz, Hertz; IN, intranasal; PSD, power spectral density; µg, microgram; µV, microvolt.

SAFETY

- Overall, 1 (8.3%) subject reported having treatment-emergent adverse events (TEAEs) that were mild in severity and were deemed not related to the study drug by the investigators
  - The reported TEAEs included dizziness (8.3%) and initial insomnia (8.3%)
- No serious TEAEs were reported, and none led to study discontinuation
- Tolerability was similar for single- and double-dose ituruvone and placebo

LIMITATIONS

- Due to small sample size and crossover design, the data should be interpreted with caution
- The use of EBG recording is novel, and technical improvements are expected to help reduce variability in future studies

CONCLUSIONS

- For the first time, the results show a similarity between the magnitude of ituruvone-induced EGNR and a rapid increase (latency = 2.4 msec) in EBG γ-PSD
- The increase in amplitude and duration of the EGNR-induced single- and double-dose ituruvone indicates that both doses lead to substantial recruitment of chemosensory receptors, with a suggestion that higher doses may increase the duration of ituruvone's effects
- The positive signal for increased activation of the EBG recordings with both 1.6 µg and 1.6 µg × 2 doses of ituruvone supports the use of EBG γ-PSD going forward as a physiologic marker for activation of olfactory-limbic amygdala neurocircuits
- With the additional validation of target engagement in the present study, the therapeutic potential of ituruvone will be further tested in a planned phase 2b clinical study in patients with MDD

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Disclosures

Louis Monti, Danajane Katz, Ester Salmán, Weiping Zhang, Ross A. Baker, and **Rita Hanover** are employees of and owners of stock or stock options in Vistagen Therapeutics, Inc.