Itruvone Nasal Spray Depolarizes Electrogram of Nasal Receptors and Increases Gamma Bandwidth of the Olfactory Bulb Electrogram 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 lifetime¹
- 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 trials⁴
- Adverse events often reduce adherence to antidepressants, hindering progress toward remission⁵
- Itruvone (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}
- Within milliseconds of intranasal (IN) administration at low microgram-level doses, itruvone 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 release⁶

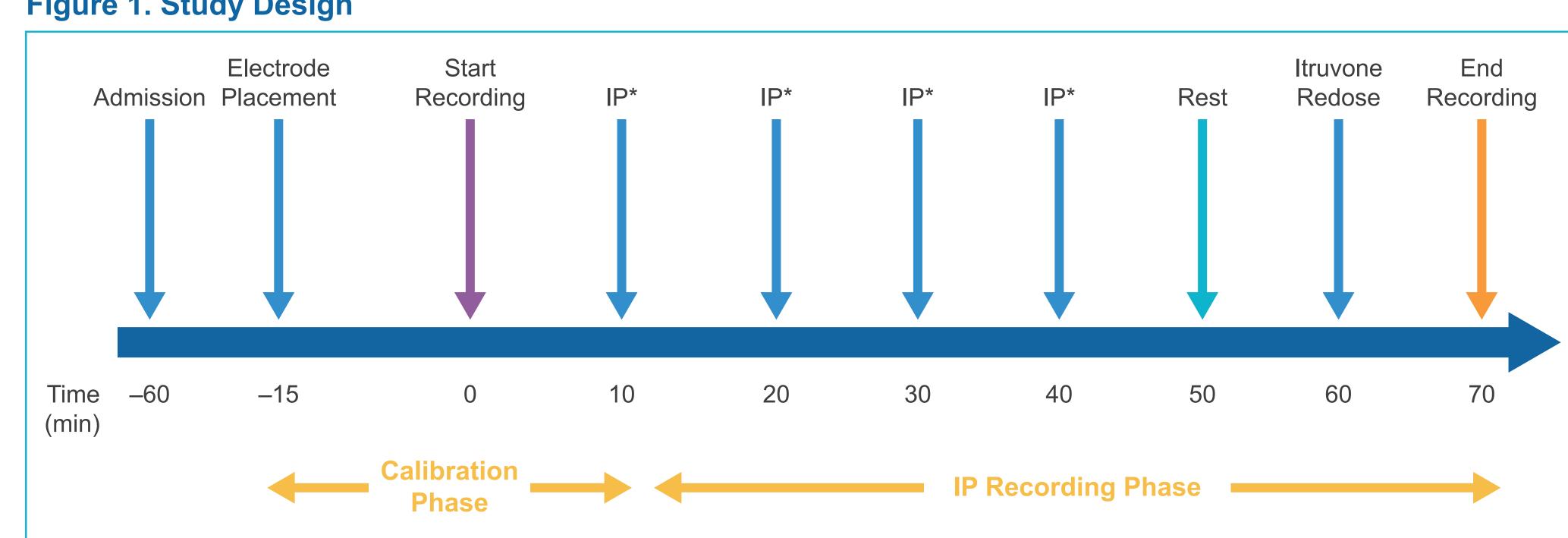
OBJECTIVE

- Primary: To compare the pharmacodynamic responses of IN placebo and itruvone 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 itruvone nasal spray (1.6 μg per 0.1 mL) and 2 IN doses of itruvone (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 who did not have olfactory dysfunction, as assessed using the quantitative Quick Olfactory Test
- The effect of placebo and single- (1.6 μg per 0.1 mL) and double-dose (1.6 μg per 0.1 mL × 2) itruvone 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 change vs placebo
- The order of IN administration was randomized, based on the initial stability of the electrogram recording, with 6–8 subjects receiving itruvone first and 6–8 subjects receiving placebo first during the single-dose phase
- The pharmacodynamic response of 1.6 μg × 2 itruvone (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
- 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
- y-band spectral power density was obtained using a fast Fourier transform

Figure 1. Study Design



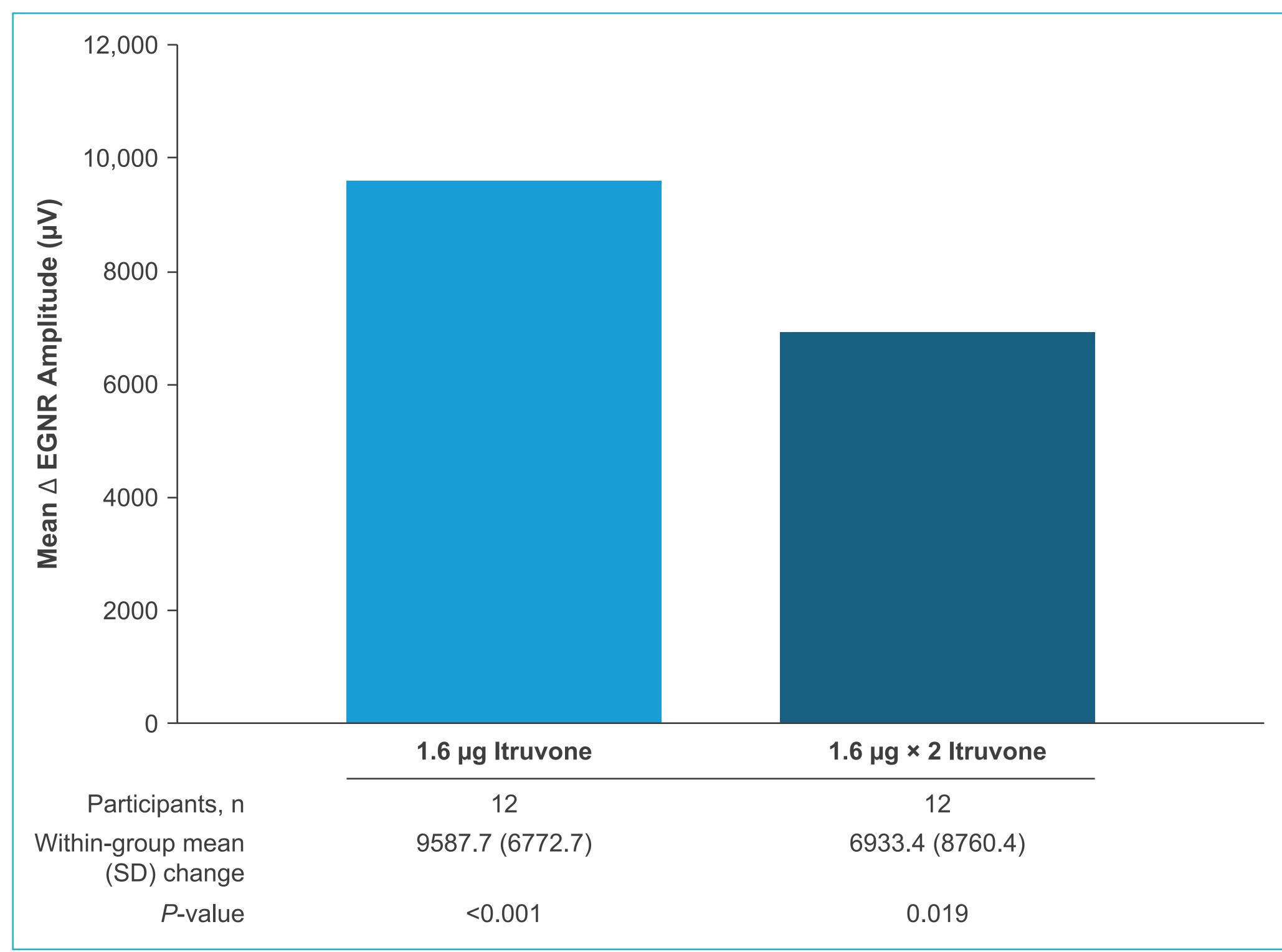
^{*}IP can be either placebo or itruvone based on random assignment of order. IP, investigational product; min, minutes.

RESULTS

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)

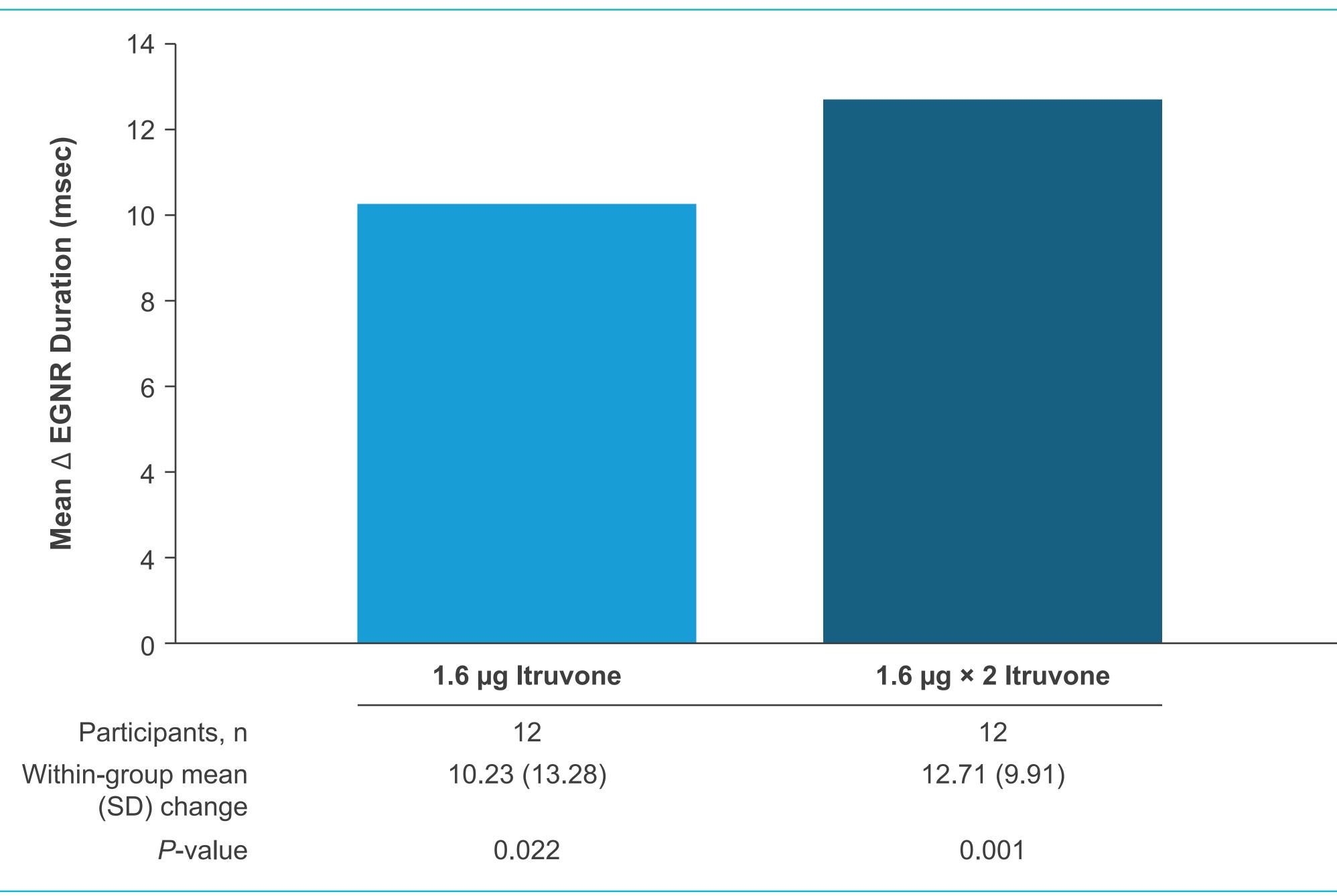
Figure 2. Within-Group Mean Difference From Placebo in EGNR Amplitude During Single-Dose and Double-Dose IN Administration of Itruvone



P-value from paired Student's t-test comparing within-group placebo and itruvone response. Delta (Δ), change in; EGNR, electrogram of nasal receptors; SD, standard deviation; μ g, microgram; μ V, microvolt.

• Compared with placebo, both 1.6 μg and 1.6 μg × 2 doses of itruvone increased EGNR amplitude

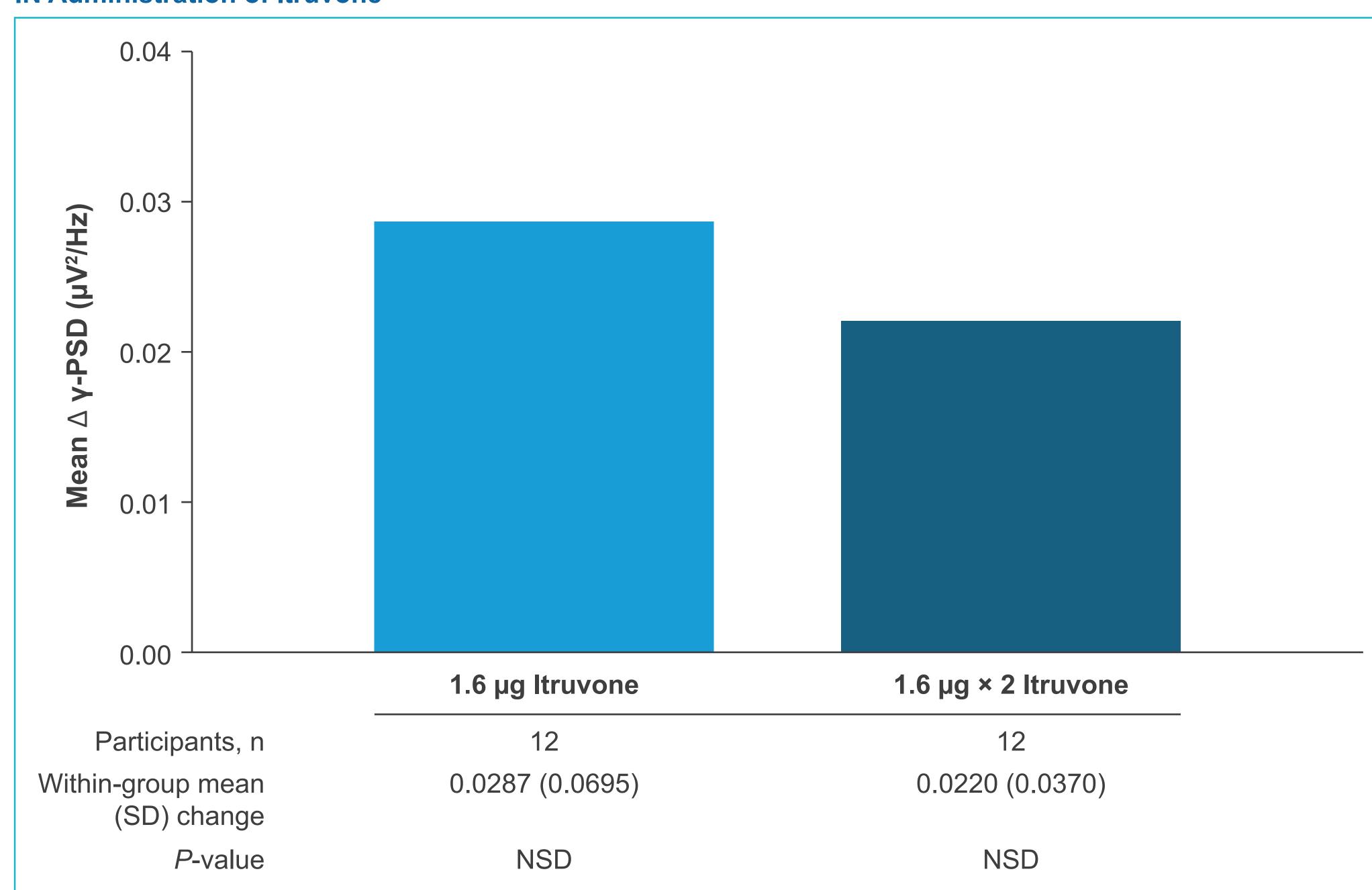
Figure 3. Within-Group Mean Difference From Placebo in EGNR Duration During Single- and Double-Dose IN Administration of Itruvone



alue from paired Student's t-test comparing within-group placebo and itruvone response.

• Compared with placebo, both 1.6 μg and 1.6 μg × 2 doses of itruvone increased EGNR duration

Figure 4. Within-Group Mean Difference From Placebo in EBG γ-PSD at Single- and Double-Dose IN Administration of Itruvone



P-value from paired Student's t-test companing within-group placebo and itruvone response.

Delta (Δ), change in; EBG, olfactory bulb electrogram; Hz, Hertz; PSD, power spectral density; NSD, no significant difference; SD, standard deviation; μg, microgram; μV, microvolt.

Compared with placebo, both 1.6 µg and 1.6 µg × 2 doses of itruvone numerically increased EBG γ-PSD

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

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

DISCUSSION/CONCLUSIONS

- For the first time, the results show a similarity between the magnitude of itruvone-induced EGNR and a rapid increase (latency = 2.4 msec) in EBG γ-PSD
- The increase in amplitude and duration of the EGNR-induced singleand double-dose itruvone suggests that both doses lead to substantial recruitment of chemosensory receptors
- The positive signal for increased activation of the EBG recordings with both
 1.6 μg and 1.6 μg × 2 doses of itruvone 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 itruvone 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.