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BHV-7000, A Novel, Selective Kv7.2/7.3 Potassium Channel Activator, Demonstrates Dose-Dependent Pharmacodynamic Effects on EEG Parameters in Healthy Adults

Jason Lerner, MD[1]; Bharat Awsare, MD[1]; Heather Sevinsky, MD[1]; Eric Ashbrenner, MS[1]; Randall Killingsworth, BA[1]; Racheal Kendrick, PharmD[2]; Emiel Vereycken, MS[3]; Nigel Colenbier, PhD[3]; Caroline Neuray, MD[3]; Pieter van Mierlo, PhD[3]; Jeremy Slater, MD[4]; David Wyatt, MD[5]; Irfan Qureshi, MD[1]; Steven Dworetzky, PhD[1]; Michael Bozik, MD[1]

[1]Biohaven Pharmaceuticals, New Haven, CT, USA; [2]Certara Inc., Princeton, NJ, USA; [3]Epilog, Clouds of Care, Ghent, Belgium; [4]Stratus, Irving, TX, USA; [5]Syneos Health, Quebec, Canada

INTRODUCTION

- BHV-7000 is a novel, small molecule, selective activator of Kv7.2/7.3 potassium channels,[1,2] a clinically validated target in epilepsy[3]
- In preclinical studies, BHV-7000 showed minimal $GABA_A$ receptor activation and exhibited potent anti-seizure efficacy in the maximal electroshock seizure model without negatively impacting neurobehavior or motor function[1,2]
- Ezogabine and other molecules in this class have been dose limited by adverse events (AEs) typical of anti-seizure medications, including somnolence[4-6]
- In phase 1 studies, BHV-7000 was safe and well tolerated at single doses up to 100 mg and multiple doses up to 120 mg daily without dose-limiting AEs[7]

OBJECTIVE

- Assess the pharmacodynamic (PD) effects of single doses of BHV-7000 on electroencephalogram (EEG) spectral power in healthy adults

METHODS

- A phase 1, open-label clinical trial was conducted in healthy adult males and females aged 18-55 years
- Subjects received single oral doses of BHV-7000 10, 25, and 50 mg (standard formulation) on days 1, 5, and 9 in a randomized sequence
  - Baseline was assessed on day -1, when no dose was given
- All subjects underwent sequential EEG recordings with the international 10-20 electrode setup at days -1, 1, 5, and 9
  - EEG measurements, collected by Stratus (Irving, TX), included a 5-min period of resting state with eyes open and 5 min of resting state with eyes closed at baseline, predose, 1 h, 2 h, 3 h, 4 h, and 6 h post drug intake. Data reported in this analysis are with eyes open
- Epilog (Ghent, Belgium) performed quantitative spectral analysis (**Box 1**; using Fast Fourier Transformation [FFT]) of all EEG recordings to assess PD effects over time
- Plasma concentrations of BHV-7000 were quantified at corresponding time points with EEG

Box 1. Quantitative Spectral Analysis

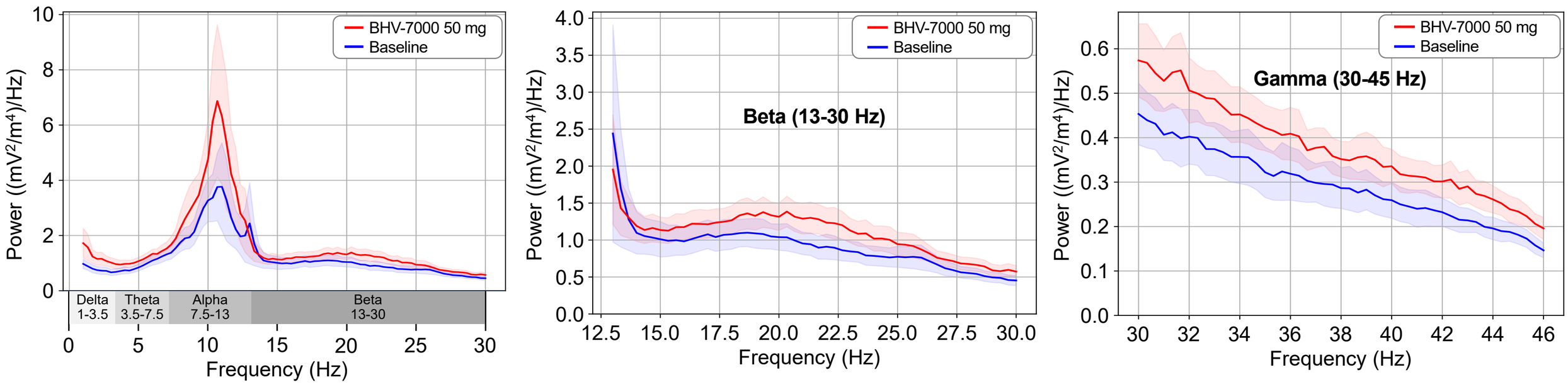
- Quantitative EEG (qEEG) is an advanced technique to quantify and analyze electrical activity of the brain in a standardized and objective manner, helping clinicians and researchers gain insights into brain function
- Spectral analysis is a fundamental method used in qEEG to quantify the power, spatial distribution, and peaks of rhythmic brain activity. Changes in spectral power have been linked to epileptogenesis and seizure prediction and detection in epilepsy and cognitive changes, awareness, and treatment efficacy in neurological disorders
- In this study, the EEGs were preprocessed to remove muscle and eye artifacts and environmental noise. Current source density analysis was applied to estimate the radial current flow at the scalp, leading to more spatially distinct and reference-free topographies
- FFT was applied to extract the spectrum in epochs of 3 seconds. From these, the peak frequency, power at peak, and the corresponding topography in the canonical frequency bands (delta [1-3.5 Hz], theta [3.5-7.5 Hz], alpha [7.5-13 Hz], beta[13-30 Hz], and gamma [30-100 Hz]) were derived

RESULTS

- Eleven healthy adult males and females were enrolled and received BHV-7000
- BHV-7000 increased alpha power in the resting-state EEG of healthy volunteers (**Figure 1**); this effect was also seen in the beta and gamma bands
  - A minimal effect was observed in delta and theta frequencies, which are frequencies associated with somnolence and sleep

Figure 1. Spectral Power in Resting-State EEGs: BHV-7000 Has Greatest Impact on Alpha; Minimal Impact on Delta and Theta

Spectrum at Broadband Max Response: BHV-7000 50 mg vs Baseline

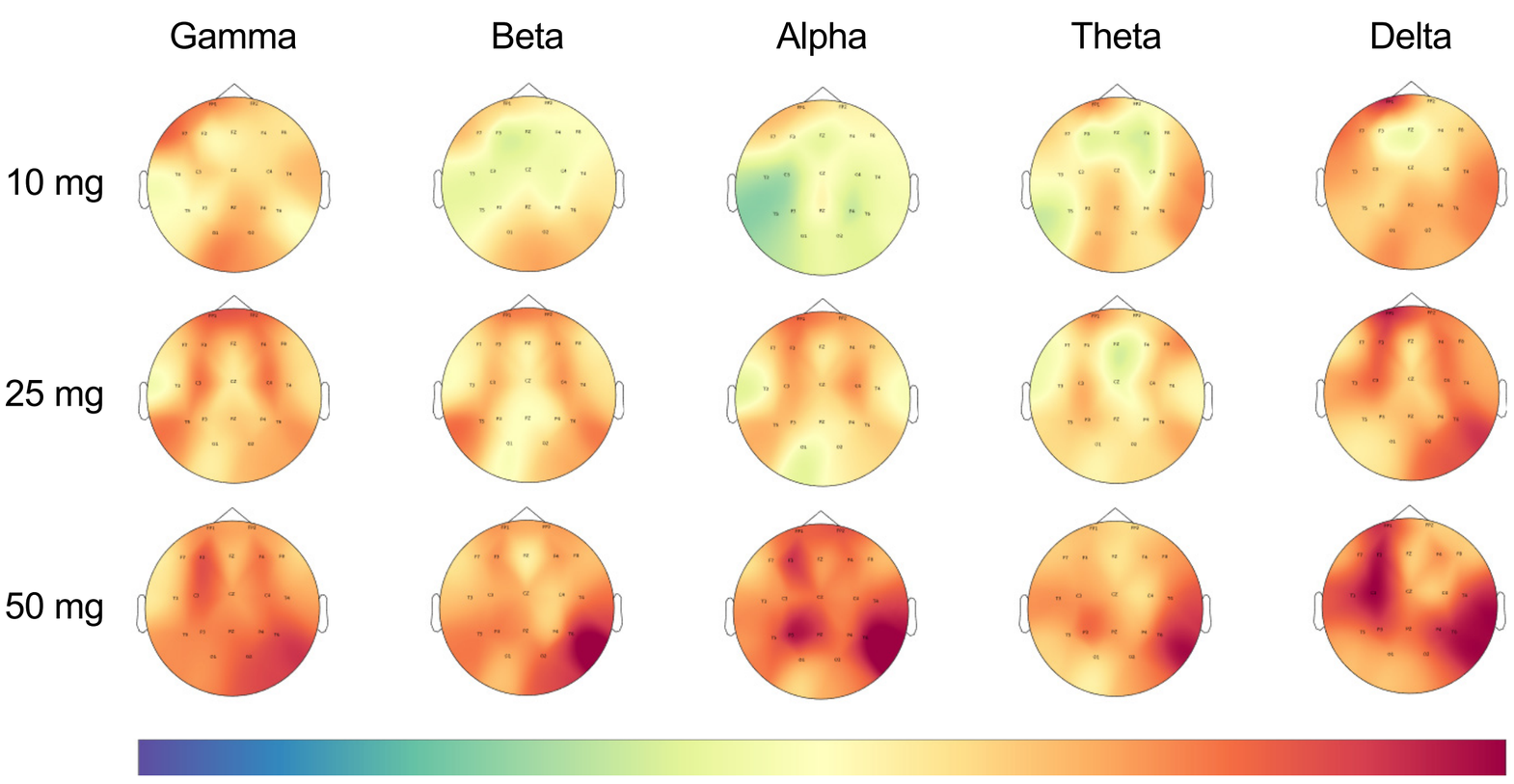


Changes in spectral power of various frequencies at baseline (day -1; blue) and BHV-7000 50-mg dose (red). Shading represents the standard error of measurement.

- Dose-dependent increases in spectral power were observed (**Figure 2**); relative increases in spectral power were observed across all frequency bands demonstrating central nervous system (CNS) target engagement
- BHV-7000 was well tolerated at all doses tested; increases in spectral power were not accompanied by CNS AEs

Figure 2. BHV-7000 Shows Dose-Dependent Increases in EEG Spectral Power

Relative Power Change Postdose: BHV-7000 – Baseline



CONCLUSIONS

- PD activity of BHV-7000 in the brain of healthy adults was demonstrated in this study by dose-dependent increases in EEG spectral power across all canonical frequency bands
  - Unlike prior reports where EEG effects of a Kv7.2/7.3 activator showed the greatest power increase in the delta frequency band,[8] the highest spectral power increases with BHV-7000 were seen in alpha, beta, and gamma frequency bands
- PD activity of BHV-7000 in the brain of healthy adults was demonstrated in this study by dose-dependent increases in EEG spectral power across all canonical frequency bands
- Although changes in spectral power were observed across all frequency bands with BHV-7000, the reduced impact on slower frequencies (delta and theta) is consistent with the low incidence of CNS AEs seen in BHV-7000 phase 1 studies
- These results support continued development of BHV-7000 for epilepsy and its potential to deliver anti-seizure efficacy without dose-limiting AEs and to have informed dose selection, with an extended-release tablet for a phase 2/3 study

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DISCLOSURES: JL, **BA**, **HS**, **EA**, **RKi**, **IQ**, **SD**, and **MB** are employed by and hold stock/stock options in Biohaven Pharmaceuticals. **RKe** has nothing to disclose. **EV**, **NC**, **CN**, and **PvM** are employed by Clouds of Care. **CN** and **PvM** hold stock/stock options in Clouds of Care. **JS** is employed by Stratus. **DW** is employed by Syneos Health.

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