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A Modern Design for a Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Efficacy and Safety of BHV-7000 in Idiopathic Generalized Epilepsy With Generalized Tonic–Clonic Seizures

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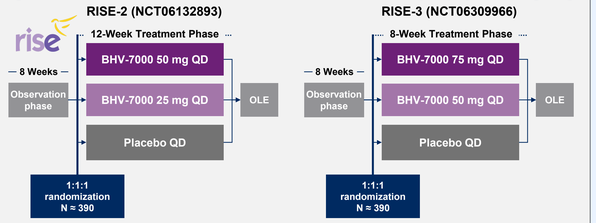
INTRODUCTION

- BHV-7000 is a small molecule, selective activator of the Kv7.2/7.3 voltage-gated potassium channel and is in late-stage clinical development for focal epilepsy (**Figure 1**) and generalized epilepsy, as well as neuropsychiatric disorders
- In preclinical studies, BHV-7000 exhibited potent antiseizure efficacy in the maximal electroshock seizure model with a wide protective index[1]
- BHV-7000 was safe and well tolerated in phase 1 studies, without central nervous system adverse effects, such as somnolence, that are typical of antiseizure medications (ASMs)[2]
- The pharmacodynamic activity of BHV-7000 in the brain of healthy adults was demonstrated in a phase 1 study by dose-dependent increases in electroencephalogram spectral power[3]
- Epilepsy studies have traditionally been double-blind, placebo-controlled, change-from-baseline endpoint studies, and participants receiving placebo for a fixed treatment duration remain at risk for continued seizures, injury, and sudden unexpected death in epilepsy (SUDEP)[4]
  - In 2011, Ryvlin et al published a meta-analysis of 112 randomized trials and reported that rates of definite or probable SUDEP were significantly higher in participants on placebo than those on efficacious ASMs[5]
- We designed a clinical trial of BHV-7000 that reduces these risks in idiopathic generalized epilepsy (IGE) with generalized tonic–clonic (GTC) seizures by utilizing a time-to-event (TTE) endpoint[4,6]

Figure 1. Two Phase 2/3 Studies of BHV-7000 in Focal Epilepsy Are Ongoing



DESIGN	Multicenter, randomized, double-blind, placebo-controlled trials
POPULATION	Participants aged 18-75 years with refractory focal epilepsy
KEY ENTRY CRITERION	Average of ≥ 4 observable focal seizures per 28 days
PRIMARY ENDPOINT	Change in seizure frequency
KEY SECONDARY ENDPOINTS	50% responder rate, freedom from seizures, safety and tolerability

OLE, open-label extension; QD, once daily.

OBJECTIVE

- To describe the design of the SHINE phase 2/3 study of BHV-7000 in IGE (NCT06425159)

METHODS

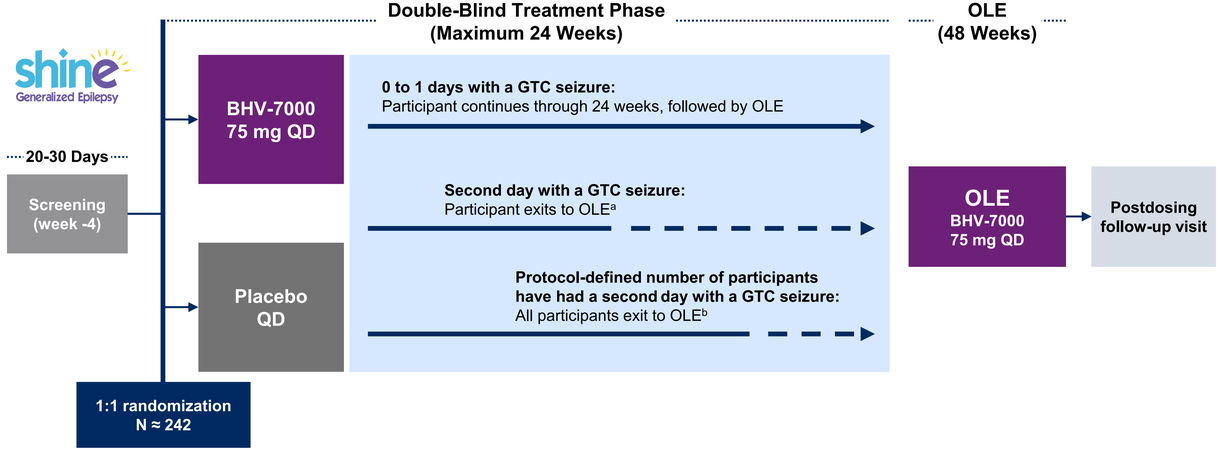
- SHINE is a phase 2/3 randomized, double-blind, placebo-controlled study with an open-label extension (OLE) to evaluate the efficacy, safety, and tolerability of BHV-7000 as adjunctive therapy in people with IGE with GTC seizures
- Eligibility criteria are shown in the **Table**
- Approximately 242 participants will be randomized 1:1 to BHV-7000 75 mg or placebo once daily and treated for up to 24 weeks (**Figure 2**)
- The primary endpoint is the time to the second day with a GTC seizure during the 24-week double-blind treatment period
  - Participants will end double-blind treatment early if/when they have the protocol-defined seizure event of a second day with a GTC seizure and may enter the optional OLE phase
- Secondary endpoints include the percentage of participants with freedom from GTC seizures during the 24-week double-blind phase estimated using Kaplan-Meier methods, and safety and tolerability
- The study is currently enrolling, with plans to include patients across multiple countries (**Figure 3**)

Table. Key Inclusion and Exclusion Criteria

Inclusion criteria
Aged 18-75 years at time of consent
Diagnosis of IGE (2017 ILAE Classification) ≥ 6 months prior to the screening visit and based on Epilepsy Adjudication criteria
Current treatment with 1 to 3 ASMs as part of no more than 4 epilepsy treatments in total
Meets the 2009 ILAE definition of drug-resistant epilepsy (failure of adequate trials of 2 tolerated and appropriately chosen ASMs to achieve sustained seizure freedom)[6]
Exclusion criteria
History of status epilepticus[a] within 6 months prior to screening visit that is not consistent with the participant's habitual seizure

[a]Convulsive status epilepticus for > 5 minutes or focal status epilepticus with impaired consciousness for > 10 minutes.
ASM, antiseizure medication; IGE, idiopathic generalized epilepsy; ILAE, International League Against Epilepsy.

Figure 2. Phase 2/3 Study Design of BHV-7000 in IGE With GTC Seizures



[a]A participant will discontinue the double-blind treatment phase if/when they have the protocol-defined event, a second day with a GTC seizure.
[b]The study is expected to be fully powered after a protocol-defined number of participants experience a second day with a GTC seizure, at which time the double-blind phase will be closed.
GTC, generalized tonic–clonic; IGE, idiopathic generalized epilepsy; OLE, open-label extension; QD, once daily.

Figure 3. Global Enrollment Planned

SHINE will enroll participants in the United States and globally

Approximately half of the participants will come from the United States and half from other countries.

CONCLUSIONS

- SHINE is an innovative registrational study in IGE with the selective Kv7 activator BHV-7000
- SHINE has an efficient, patient-centric design utilizing a TTE endpoint that decreases time on placebo, potentially reducing the risk of exposure to additional seizures, injury, and SUDEP

Please scan the QR code for more information on the ongoing clinical trials with BHV-7000

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DISCLOSURES: JL, DS, MB, VS, CJ, LD, NK, VC, and **IQ** are employed by and/or hold stock/stock options in Biohaven Pharmaceuticals. **MD** was employed by and received stock/stock options in Biohaven Pharmaceuticals. **WK** is a paid consultant for Biohaven Pharmaceuticals and a member of the data monitoring committee for Biohaven's trials. **JF** is a consultant for Biohaven Pharmaceuticals through the Epilepsy Study Consortium and has received travel reimbursement.

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