Compassionate Use of Kv7.2/7.3 Potassium Channel Activator Opakalim (BHV-7000) in a Child With KCNQ2 Developmental and Epileptic Encephalopathy

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RATIONALE

- KCNQ2-developmental and epileptic encephalopathy (DEE) is a severe neonatal-onset epilepsy syndrome. Most Kv7.2 pathogenic variants are associated with loss-of-function of the Kv7.2/7.3 channel with decreased channel opening.[1]
- Opakalim (BHV-7000) is a 3rd generation, selective activator of the Kv7.2/7.3 channel that has previously demonstrated the ability to restore channel function near wild type levels (i.e., current density and activation $V_{1/2}$) across 50 different pathogenic *KCNQ2* variants.[2]
- Opakalim is in late-stage clinical development for epilepsy and neuropsychiatric disorders and was rationally designed to differentiate from other Kv7 activators, including on safety and tolerability.
- CASE HISTORY:
  - 9-year-old boy with KCNQ2-DEE, heterozygous for a Kv7.2 G281E pathogenic variant.
  - Initial presentation with Ohtahara syndrome.
  - Ongoing drug-resistant epilepsy: multiple daily brief tonic seizures at baseline, despite treatment with multiple ASMs including a 1st generation potassium channel activator.
  - He has had episodes of status epilepticus, severe dystonia and irritability with prior attempts to wean the 1st generation potassium channel activator.

METHODS

- The patient was initiated on Opakalim by compassionate use IND, via gastrostomy tube.
- Medication levels, vision assessments, EKG and seizure diaries were documented >3 months before initiation.
- Initial test dose of 1 mg as an oral suspension confirmed exposures and was used to identify the titration scheme, target maintenance dose and frequency of Opakalim.
- Inpatient cross titration from a 1st generation potassium channel activator to Opakalim over 10 days.
- Pharmacokinetic modelling and simulation were used to determine and confirm optimal maintenance dosing.
- Maintenance Opakalim dose of 15 mg QID (suspension) by gastrostomy tube results in estimated daily AUC comparable to that achieved with 75 mg ER QD under evaluation for the treatment of focal epilepsy.
- Outcome measures:
  - **Primary:** Seizure count by Diary, safety by tracking treatment-related adverse events
  - **Secondary:** EEG, Clinical Global Impression of Change
  - **Exploratory:** CDKL5 Clinical Severity Assessment[3] (developed for a similarly severe genetic developmental and epileptic encephalopathy)

Table 1. Schedule of Assessments

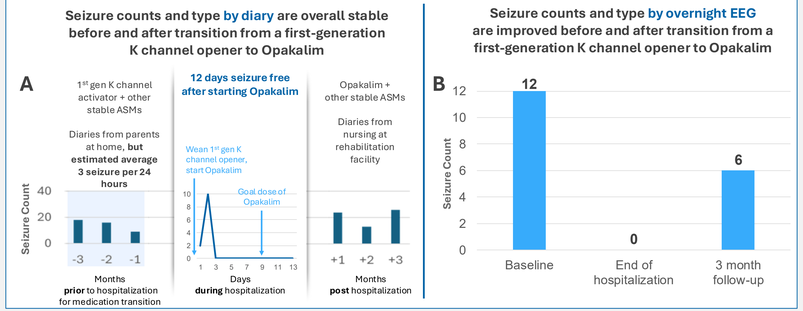
Type of surveillance	Pre-Opakalim	Test dose of Opakalim, in hospital	In hospital during change-over	In hospital after change-over	Ongoing surveillance
Serum/plasma samples	ASM levels	PK on Opakalim	PK at each dose level of Opakalim		ASM levels Q6 months in the first year then at least annually Opakalim levels Q6 months and serial PK as needed
Urinary	Average daily diaper use		Bladder ultrasound at baseline	NA	Notify PI if diaper count decreases by 50% or low urinary output
Ophthalmologic	Dilated indirect fundoscopy + visual acuity				Dilated indirect fundoscopy with visual acuity testing, Q6 months
Cardiac			ECG with QTcF calculation	ECG with QTcF calculation	ECG with QTcF calculation annually and as needed per GCP
Routine medical monitoring	At least annual neurology and primary care visits		Baseline medical and neurologic examination	Medical and neurologic examination	Neurology visits at 3 +/- 1 month, 6 +/- 1 month, 12 +/- 1 month then annually. Primary care visits at least annually.
Seizure frequency	Seizure diary ≥3 months		Maintain accurate seizure diary	Maintain accurate seizure diary	Maintain seizure diary for 6 months, then at least 1 month per year; Video-EEG as needed
EEG			Overnight video EEG	Overnight video EEG	Routine EEG at 3-6 months of treatment

ASM = anti-seizure medication; **ECG** = electrocardiogram; **EEG** = electroencephalogram; **GCP** = Good Clinical Practice; **N/A** = not applicable; **PI** = Principal Investigator; **PK** = pharmacokinetics; **QTcF** = heart rate corrected QT interval using Fridericia's correction formula

RESULTS

Figure 1. Seizure Frequency and Counts Before and After Transition to Opakalim

A: Generalized tonic and tonic-clonic seizure frequency per month by diaries, 3 months prior to and 3 months post the month including 2-week hospitalization for transition to Opakalim (BHV-7000), reaching goal dose of 15mg Q6 hours. **Differences in documentation at home vs rehabilitation may account for differences in counts, overall stable seizure frequency and type. Spike of seizures during hospitalization occurred with wean of 1st generation K channel opener then seizures resolved. B:** Generalized tonic and tonic-clonic seizure count (≥3 seconds) on overnight EEG at baseline before medication transition (15 hours), at goal dose of Opakalim at the end of the medication transition (12 hours) and at 3 months follow-up on Opakalim goal dose (15 hours).



Overall disease severity is stable before and after transition to Opakalim

Figure 2. CDKL5 Clinician Severity Assessment, Clinician Report[3]

Scores range from 0-100. A Score of 100 indicates greatest clinical severity. Baseline evaluations recorded at time of test dose (hospitalization).

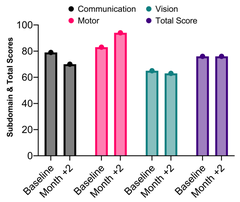


Figure 3. CDKL5 Clinician Severity Assessment, Caregiver Questionnaire[3]

Scores range from 0-100. A Score of 100 indicates greatest clinical severity. Baseline evaluations recorded at time of test dose (hospitalization).

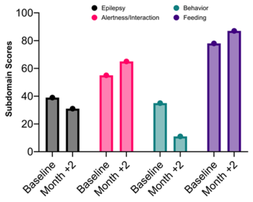
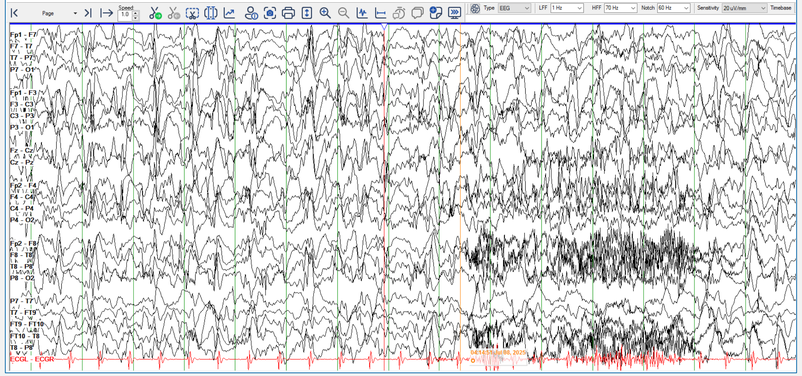


Figure 4. Baseline EEG Background and Tonic Seizure

Baseline EEG background demonstrating frequent multifocal and generalized epileptiform activity, generalized slowing, and a typical brief tonic seizure. There was no change in the EEG background at the end of the admission after medication cross-titration or at 3-month follow-up.



Safety & Efficacy of Opakalim:

- **NO status epilepticus**
  - Severe seizure exacerbation/status epilepticus x2 in the past with slight lowering of the dose of the 1st generation K channel opener.
- **NO irritability or sedation**
- **NO treatment emergent adverse events**

CONCLUSIONS AND ACKNOWLEDGEMENTS

Opakalim demonstrates early tolerability and initial improvement in seizures followed by return to baseline seizure frequency. There is stability of seizures and overall clinical severity compared to prior treatment with another potassium channel activator despite a history of severe exacerbation, irritability and dystonia with attempts to wean. Follow-up evaluations will determine additional changes in EEG
or clinical status **Funding:** Biohaven Pharmaceuticals

REFERENCES:

1. Miceli F, Soldovieri MV, Weckhuysen S, Cooper E, Taglialatela M. KCNQ2-Related Disorders. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993 [cited 2025]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK32534/
2. Vanoye CG, Desai RR, Dworetzky S, George AL. Functional effects of the M-current activator BHV-7000 on 50 epilepsy-associated *KCNQ2* variants. Poster at AES December 6-10, 2024. Available from: https://biohaven.b-cdn.net/wp-content/uploads/AES-2024-poster-BHV-7000-effects-on-KCNQ2-variants.pdf
3. Saldaris JM, Jacoby P, Downs J, Marsh ED, Leonard H, Pestana-Knight E, et al. Psychometric evaluation of clinician- and caregiver-reported clinical severity assessments for individuals with CDKL5 deficiency disorder. Epilepsia [Internet]. [cited 2024]; n/a(n/a). Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/epi.18094