Neurocrine Epilepsy Clinical Program Overview

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Table of Contents

Review of Epilepsy

EE-CSWS

Clinical Trial Overview: CSWS2010

SCN8A-DEE

Clinical Trial Overview: DEE2012

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Review of Epilepsy & Developmental and Epileptic Encephalopathies (DEEs)

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Epilepsy is a Neurological Disorder Characterized by Unpredictable Seizures

A seizure is a sudden surge of electrical activity in the brain caused by chemical changes occurring in nerve cells leading to an imbalance between excitatory and inhibitory activity[1,2]

Epilepsy is defined as:

At least two unprovoked seizures occurring greater than 24 hours apart[1]

OR

One unprovoked seizure and a probability of unprovoked seizure recurrence occurring over the next 10 years, not caused by some known medical condition[1]

Epilepsy occurs on a spectrum with a wide range of presentations, etiologies, and outlooks that can vary from person-to-person[2]

1. Fisher RS, et al. ILAE Official Report: A Practice Clinical Definition of Epilepsy. *Epilepsia*. 2014;55(4):475-82. | 2. Epilepsy Foundation. What is Epilepsy. Available online at https://www.epilepsy.com/learn/about-epilepsy-basics/what-epilepsy. Accessed November 16, 2021.

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Classification of Epilepsy[1]

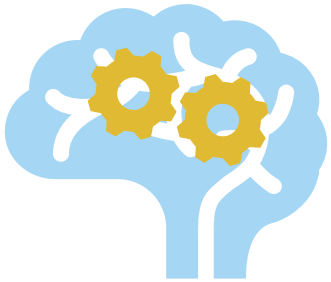
Epilepsies are classified by seizure type based on:

Location

Where did the seizure begin in the brain?

+

Awareness



What is the level of awareness during the seizure?

+

Other

Are there other distinguishing features?

Determining etiology can optimize classification, inform treatment decisions, and aid in syndrome diagnosis

1. Scheffer IE, Berkovic S, Capovilla, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):512-21.

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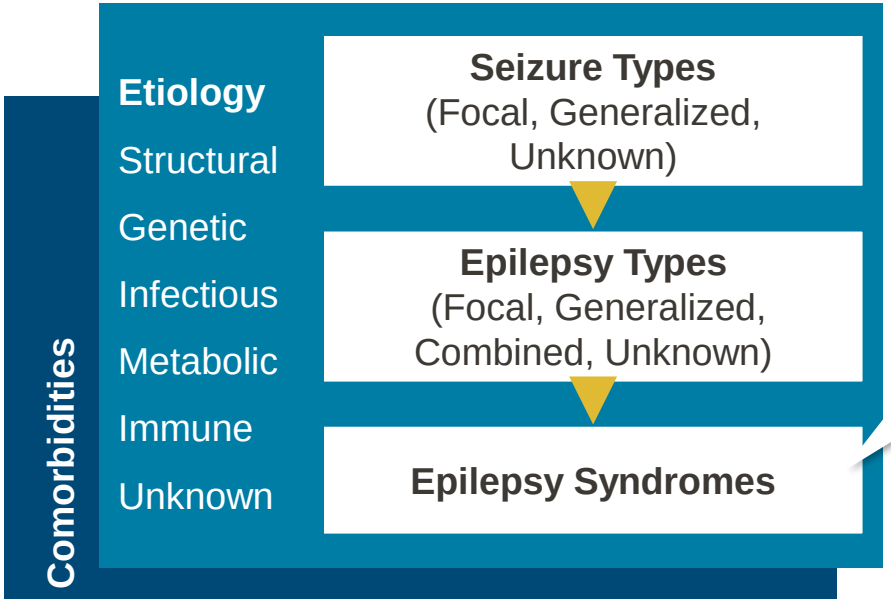
Framework for the Classification of Epilepsies[1]

The ILAE Classification of the Epilepsies is a multilevel system for classifying epilepsy in different clinical environments



An **epilepsy syndrome** is defined by a group of features that typically occur together, such as:

- Seizure types/triggers
- EEG patterns/imaging features
- Genetic mutations
- Comorbidities
- Age of onset/remission
- Treatment implications

View ILAE Classification of Seizures

Most identified single gene mutations resulting in epilepsy are ion channel mutations

EEG, electroencephalogram; ILAE, International League Against Epilepsy

1. Scheffer IE, Berkovic S, Capovilla, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):512-21.

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Developmental and Epileptic Encephalopathies (DEEs)*

DEEs are severe epilepsy syndromes in which epileptic activity contributes to pronounced cognitive and behavioral impairments or delays[1,2]

Common Features of DEEs[1-3]

- Multiple seizure types
- Genetic mutation(s)
- EEG paroxysmal activity
- Developmental regression or arrest at seizure onset
- Pharmacoresistance
- Behavioral disturbances
- Progressive psychomotor dysfunction

Many DEEs are early-onset (neonatal, infancy, childhood) and have a genetic or acquired etiology[1]

DEE patients typically have intractable seizures and neurological deficits that can be unremitting, resulting in early death[1]

**It is suggested that the term "developmental and epileptic encephalopathy" be used where appropriate: developmental encephalopathy where there is just developmental impairment without frequent epileptic activity; epileptic encephalopathy where there is no preexisting developmental delay; and developmental and epileptic encephalopathy where both factors play a role.[2]*

EEG, electroencephalogram

1. Panayiotopoulos CP. The Epilepsies: Seizures, Syndromes and Management. Oxfordshire (UK): Bladon Medical Publishing; 2005. Available at Panayiotopoulos: https://www.ncbi.nlm.nih.gov/books/NBK2611/#ch7.s2 | 2. Scheffer IE, Berkovic S, Capovilla, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):512-21. | 3. Berg, et al. Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005–2009. 2010;51(4):676-85.

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Epileptic Encephalopathy with Continuous Spike and Wave During Sleep (EE-CSWS)

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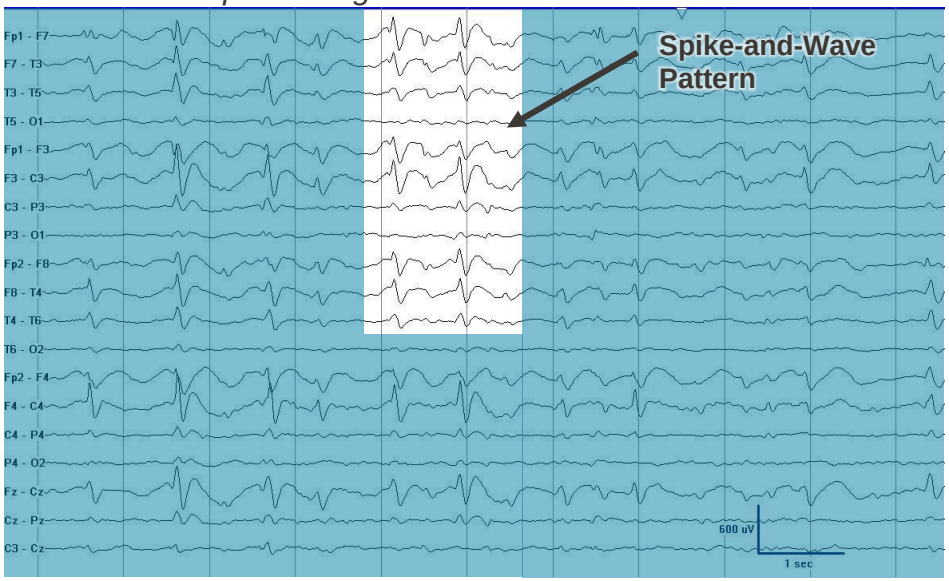
Epileptic Encephalopathy with Continuous Spike and Wave During Sleep (EE-CSWS)

EE-CSWS is a rare childhood-onset epilepsy syndrome characterized by an electrical status epilepticus during sleep (ESES) EEG pattern, seizures, and cognitive regression[1]

EEG of child experiencing CSWS



ESES manifests as **diffuse spike and wave discharges** that **appear continuous or nearly continuous** during the non-rapid eye movement (**NREM**) phase of sleep (CSWS)[1,2]

EE-CSWS patients can also experience seizures while awake, with increasing frequency over time[1]

Image courtesy of The Epilepsy Foundation

EEG, electroencephalogram

1. Samanta D, Al Khalili Y. Electrical Status Epilepticus In Sleep. StatPearls [Internet]. Available from https://www.ncbi.nlm.nih.gov/books/NBK553167/. Accessed November 16, 2021. | 2. Gencpinar P, Dundar NO, Tekgu H. Electrical status epilepticus in sleep (ESES)/continuous spikes and waves during slow sleep (CSWS) syndrome in children: An electroclinical evaluation according to the EEG patterns. Epilepsy & Behavior. 2016;61:107-11

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EE-CSWS Clinical Features[1-3]

Dormant Stage

- **Ages: Birth to Onset**
- No seizures; EEG generally not performed
- Normal to moderately abnormal baseline development

Prodromal Stage

- **Ages: 2 – 4 years**
- Seizures typically infrequent & mild; EEG pattern of infrequent spikes and waves
- ≥2 seizure types seen in only 20% of patients

Acute Stage

- **Ages: 5 – 12 years**
- Marked increase in frequency and types of seizures and definitive ESES EEG
- Severe neurocognitive global regression (peaks at age 5-6)

Residual Stage

- **Ages: Puberty**
- Gradual disappearance of seizures and progressive normalization of EEG
- Mild to moderate improvement in cognition; developmental delays often remain

EEG, electroencephalogram; ESES, electrical status epilepticus during sleep

1. Sanchez Fernandez I, Chapman KE, Peters JM, et al. Continuous Spikes and Waves during Sleep: Electroclinical Presentation and Suggestions for Management. Epilepsy Res Treat. 2013;2013:583531. | 2. Samanta D, Al Khalili Y. Electrical Status Epilepticus In Sleep. StatPearls [Internet]. Available from https://www.ncbi.nlm.nih.gov/books/NBK553167/. Accessed November 16, 2021. | 3. De Giorgis V, et al. Neurobehavioral consequences of continuous spike and waves during slow sleep (CSWS) in a pediatric population: A pattern of developmental hindrance. Epilepsy & Behavior. 2017;74:1-9.

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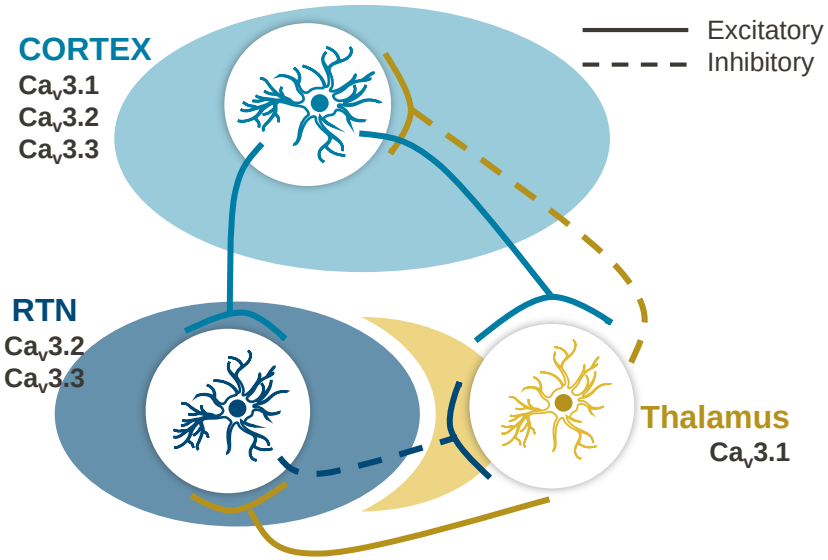
The Thalamic Oscillatory Circuit Contributes to Rhythms Associated With Sleep[1]

The reticular thalamic nucleus (RTN), thalamic relay neurons, and neocortical pyramidal cells form a circuit integral to the formation of sleep[2]

The Thalamic Oscillatory Circuit



T-type calcium channels (Ca_v) allow for low-threshold depolarization of neurons which contributes to the generation of synchronized oscillations within the circut[2]

View Ca_v Family

Ca_v, voltage-gated calcium ion channel; EEG, electroencephalogram; ESES electrical status epilepticus during sleep; RTN, reticular thalamic neurons

1. Fogerson PM, et al. Tapping the brakes: cellular and synaptic mechanisms that regulate thalamic oscillations. *Neuron*. 2016;92(4):687-704. | 2. Samanta D, Al Khalili Y. Electrical Status Epilepticus In Sleep. StatPearls [Internet]. Available from https://www.ncbi.nlm.nih.gov/books/NBK553167/. Accessed November 16, 2021. | 3. Chen Y, Parker WD, Wang K. The role of T-type calcium channel genes in absence seizures. Front. Neurol. 2014;5:45.

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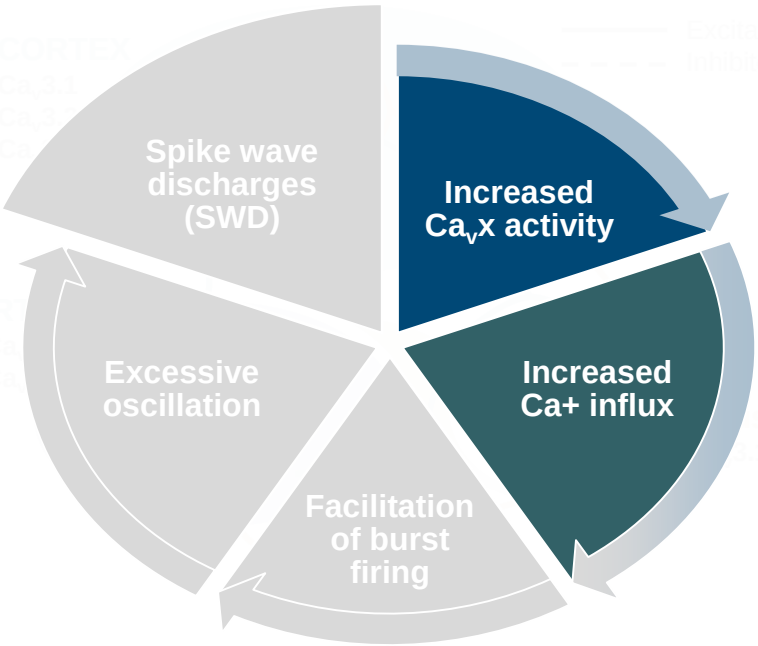
ESES EEG is Correlated with Abnormal Thalamic Oscillatory Circuit Activity[1]

ESES is due to probable interplay between inhibitory GABAergic reticular thalamic neurons and excitatory glutaminergic dorsal thalamic neurons[1]

The Thalamic Oscillatory Circuit



Inhibition of the calcium influx can forestall burst firing and in turn, SWDs

Ca_V, voltage-gated calcium ion channel; EEG, electroencephalogram; ESES electrical status epilepticus during sleep; RTN, reticular thalamic neurons

1. Fogerson PM, et al. Tapping the brakes: cellular and synaptic mechanisms that regulate thalamic oscillations. *Neuron*. 2016;92(4):687-704. | 2. Samanta D, Al Khalili Y. Electrical Status Epilepticus In Sleep. StatPearls [Internet]. Available from https://www.ncbi.nlm.nih.gov/books/NBK553167/. Accessed September 23, 2021. | 3. Chen Y, Parker WD, Wang K. The role of T-type calcium channel genes in absence seizures. Front. Neurol. 2014;5:45.

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There are Currently no Guidelines or Approved Treatments for EE-CSWS

Primary treatment goals:[1]

Suppression of EEG Abnormalities +/- **Improved Seizure Control** → **Improved Cognitive Function**

Current treatment consists of traditional AESs, benzodiazepines, corticosteroids, epilepsy surgery, and other non-pharmacological therapies[3]

Most Common AESs:
Valproate
Levetiracetam
Ethosuximide

———

Some AESs such as phenytoin, phenobarbital, and carbamazepine can **worsen seizure control**[3]

Effects of Analyzed Treatments on Cognition and EEG in Patients with ESES/CSWS[1,2]

Treatment	N	Any Improvement	Cognitive Improvement
Conventional AESs	310	34%	32%
BZDs	107	59%	45%
Corticosteroids	100	75%	70%
Surgery*	30	93%	83%
Other	38	58%	71%

*Only indicated for a subset of EE-CSWS patients

CSWS, continuous spike and wave during sleep; EEG, electroencephalography; ESES, electrical status epilepticus in sleep; AES, antiepileptic drug; BZD, benzodiazepine

1. Sanchez Fernandez I, Chapman K, Peters JM, et al. Treatment for continuous spikes and waves during sleep (CSWS): Survey on treatment choices in North America. Epilepsia. 2014;55(7):1099-108. | 2. Kotagal P. Current Status of Treatments for Children with Electrical Status in Slow-Wave Sleep (ESES/CSWS). Epilepsy Curr. 2017;17(4):214-16. | 3. Samanta D, Al Khalili Y. Electrical Status Epilepticus In Sleep. StatPearls [Internet]. Available from https://www.ncbi.nlm.nih.gov/books/NBK553167/. Accessed November 16, 2021.

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NBI-827104: An Investigational Treatment for Epileptic Encephalopathy with Continuous Spike and Wave During Sleep (EE-CSWS)

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NBI-827104 and CSWS2010

NBI-827104 is an investigational product and not approved for use by the FDA

NBI-827104[1-3]	
Putative MOA	Selective T-type calcium channel blocker
Clinical Phase	Phase 2
Indication Sought	Epileptic Encephalopathy with Continuous Spike and Wave During Sleep (EE-CSWS) in pediatric patients
Anticipated Population	~7,000 people in the United States
Administration	Oral
Expected Timing	Estimated study completion Q2 2022

FDA, US Food and Drug Administration; MOA, mechanism of action.

1. Data on file, Neurocrine Biosciences, Inc. **2.** Clinicaltrials.gov. https://www.clinicaltrials.gov/ct2/show/NCT04625101?term=NBI-827104&draw=2&rank=2. Accessed November 16, 2021. **3.** Chipaux M et al. *Epilepsia.* 2016;57(5):757-769.

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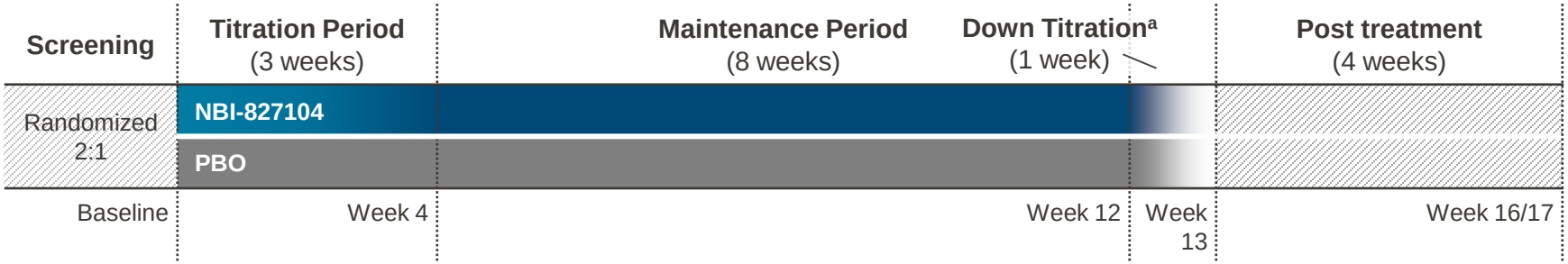
CSWS2010: Study Design[1,2]

CSWS2010 is a Phase 2, double-blind, placebo-controlled study to assess the efficacy, safety, tolerability, and pharmacokinetics of NBI-827104 in pediatric patients for the treatment of epileptic encephalopathy with continuous spike-and-wave during sleep (EE-CSWS)

Study Timeline



[a]The dose during the down titration period will be 1 dose level lower than the last dose the subject received during the maintenance period. Subjects who are receiving dose level 1 at Week 12 will not receive study drug during the down titration period.

Study Details

- ~24 male and female adolescent patients will be enrolled, randomized 2:1 study drug:placebo
  - The first six patients will form the sentinel cohort; analyzed for safety, tolerability and pharmacokinetic data through Week 6
  - The main cohort, composed of the remaining 18 participants, will then be enrolled based on the sentinel cohort's response

1. Clinicaltrials.gov. Accessed November 16, 2021. https://clinicaltrials.gov/ct2/show/NCT04625101?term=neurocrine&draw=2&rank=2 | 2. Data on file. Neurocrine Biosciences.

 The use of NBI-827104 for the treatment of EE-CSWS is investigational and not approved by the FDA

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CSWS2010 Key Inclusion/Exclusion Criteria[1,2]

Key Inclusion Criteria

- Male or female, aged 4 to 12 years at time of screening
- Diagnosis of EE-CSWS confirmed by the Diagnosis Confirmation Panel (DCP)
- Stable dosage at time of intake of >1 and ≤ 3 anti-seizure medications (ASMs) excluding systemic corticosteroids, from 4 weeks prior to screening and anticipated to be stable from screening until end of study (EOS)
- Treatment other than ASMs (excluding systemic corticosteroids) must be at a stable dosage from 2 weeks prior to screening and anticipated to be stable from screening until EOS

Key Exclusion Criteria

- Lennox-Gastaut syndrome, Doose syndrome (epilepsy with myoclonic-atonic seizures), or Dravet syndrome
- Presence of a relevant psychiatric disease interfering with cognitive functioning or a relevant neurological disorder other than EE-CSWS
- Body weight <10 kg at randomization
- Mild to severe renal impairment
- Taking cannabinoids excluding Epidiolex®/Epidyolex® within 30 days of screening or use of systemic corticosteroids ≤ 8 weeks prior to screening

1. Clinicaltrials.gov. Accessed November 16, 2021. https://clinicaltrials.gov/ct2/show/NCT04625101?term=neurocrine&draw=2&rank=2 | 2. Data on file. Neurocrine Biosciences.

The use of NBI-827104 for the treatment of EE-CSWS is investigational and not approved by the FDA

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CSWS2010 Assessments[1,2]

Primary Efficacy Endpoint

- Ratio of spike-wave index (SWI) during the first hour of nonrapid eye movement (NREM) sleep based on centralized overnight video-EEG reading [Time Frame: Baseline to Week 6]

Secondary Objectives

- Ratio of SWI during first hour of NREM sleep, based on centralized evaluation. [Time Frame: Baseline to Week 12]
- Caregiver Global Impression of Change (GI-C) and Clinical Global Impression of Change (CGI-C) scores. [Time Frame: Week 6 and Week 12]
- Clinical Global Impression of Severity (CGI-S) scores. [Time Frame: Baseline to the end of Week 6 and Week 12]

Safety Endpoints

- AEs, clinical laboratory tests, vital signs, physical examinations, 12-lead ECG, Columbia-Suicide Severity Rating Scale (Children's Version), ophthalmological examinations

AEs, adverse events; ECG electrocardiogram; EEG, electroencephalography; EECSWS, Epileptic Encephalopathy with Continuous Spike-and-Wave During Sleep

1. Clinicaltrials.gov. Accessed November 16, 2021. https://clinicaltrials.gov/ct2/show/NCT04625101?term=neurocrine&draw=2&rank=2 | 2. Data on file

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SCN8A Developmental and Epileptic Encephalopathy (SCN8A-DEE)

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SCN8A Developmental and Epileptic Encephalopathy (SCN8A-DEE)

SCN8A-DEE is a rare and severe childhood-onset epilepsy syndrome associated with a gain of function mutation in the SCN8A gene[1,2]

Severe cognitive and motor impairments develop over disease progression, which is highly variable in its presentation and prognosis[1-3]

Seizure onset in first 18 months of life (mean age 4 months)[1]

Patients experience multiple seizure types and developmental delays[1]

Seizure frequencies range from hundreds per day to fewer than one per month[1]

Overall mortality estimated at **5.38%** based on a global cross-sectional review[3]

Patients with SCN8A-DEE have a high risk of sudden unexpected death in epilepsy (SUDEP) (~1.6% of published cases)[3]

1. Hammer 2016, SCN8A-Related Epilepsy with Encephalopathy http://www.ncbi.nlm.nih.gov/books/nbk379665/ | 2. Gertler TS, Carvill GL. SCN8A: When Neurons Are So Excited, They Just Can't Hide It. *Epilepsy Currents*. 2019;19(4):269-271. | 3. Johannesen KM, Gardella E, Scheffer I, et al. Early Mortality in SCN8A-related Epilepsies. *Epilepsy Research*. 2018;143:79-81

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SCN8A-DEE Clinical Presentation[1,2]

Clinical Features		
Seizure	▪ Focal clonic seizures evolving to a bilateral convulsive seizure ▪ Afebrile generalized tonic clonic seizures ▪ Seizure clusters	▪ Tonic seizures ▪ Infantile spasms ▪ Myoclonic seizures ▪ Generally treatment resistant
Psychomotor	▪ Marked slowing or arrest in development	▪ Ataxia and sudden loss of mobility
Cognitive	▪ Mild to severe intellectual disability ▪ Limited or absent speech	▪ Autistic features
Movement	▪ Hypotonia ▪ Dystonia ▪ Choreoathetosis	▪ Ataxia ▪ Spasticity
Imaging	▪ EEG abnormalities with progressive background deterioration	▪ Brain MRI abnormalities (cerebral atrophy and corpus callosum hypoplasia)
Other Complications	▪ Progressive visual impairment leading to cortical blindness ▪ Spontaneous bone fractures	▪ Gastrointestinal disorders ▪ Startle and sleep problems

EEG, electroencephalography; MRI, magnetic resonance imaging

1. Hammer 2016, SCN8A-Related Epilepsy with Encephalopathy http://www.ncbi.nlm.nih.gov/books/nbk379665/ | 2. Gertler TS, Carvill GL. SCN8A: When Neurons Are So Excited, They Just Can't Hide It. *Epilepsy Currents. 2019*;19(4):269-271

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There Are No Published Treatment Guidelines For SCN8A-DEE[1,2]

The following evaluations are recommended:[1]

- Neurological examinations (EEG, MRI)
- Cognitive and behavioral evaluation
- ECG to assess for cardiac arrhythmias (may increase SUDEP risk)
- Genetic consultation

AES selection is often influenced by concurrent disease states[1-3]

-

Many agents have off-target effects, require high doses (leading to additional side effects) and/or may exacerbate symptoms

Commonly Used Treatment Options[1,2]

Non-selective Na channel blockers	Other ASMs*	Non-ASMs
Phenytoin	Clobazam	Corticosteroids
Valproic acid	Phenobarbital	Immunoglobulins
Carbamazepine		VNS
Lacosamide		Ketogenic diet
Lamotrigine		Cannabinoids
Rufinamide		
Oxcarbazepine		

*Levetiracetam has been reported to worsen symptoms in patients with SCN8A-DEE

ASM, anti-seizure medication(s); DEE, developmental and epileptic encephalopathy; ECG, electrocardiogram; EEG, electroencephalography; MRI, magnetic resonance imaging; SUDEP, sudden unexpected death in epilepsy; VNS, vagal nerve stimulation

1. Hammer 2016, SCN8A-Related Epilepsy with Encephalopathy http://www.ncbi.nlm.nih.gov/books/nbk379665/ | 2. Gardella e, Moller RS. Phenotypic and genetic spectrum of SCN8A-related disorders, treatment options, and outcomes. 2019;60(S3):S77-85. | 3. Meisler MH, Helman G, Hammer MF, et al. SCN8A encephalopathy: Research progress and prospects. *Epilepsia*. 2016;57(7):1027-35.

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$Na_v1.6$ and the SCN8A Gene

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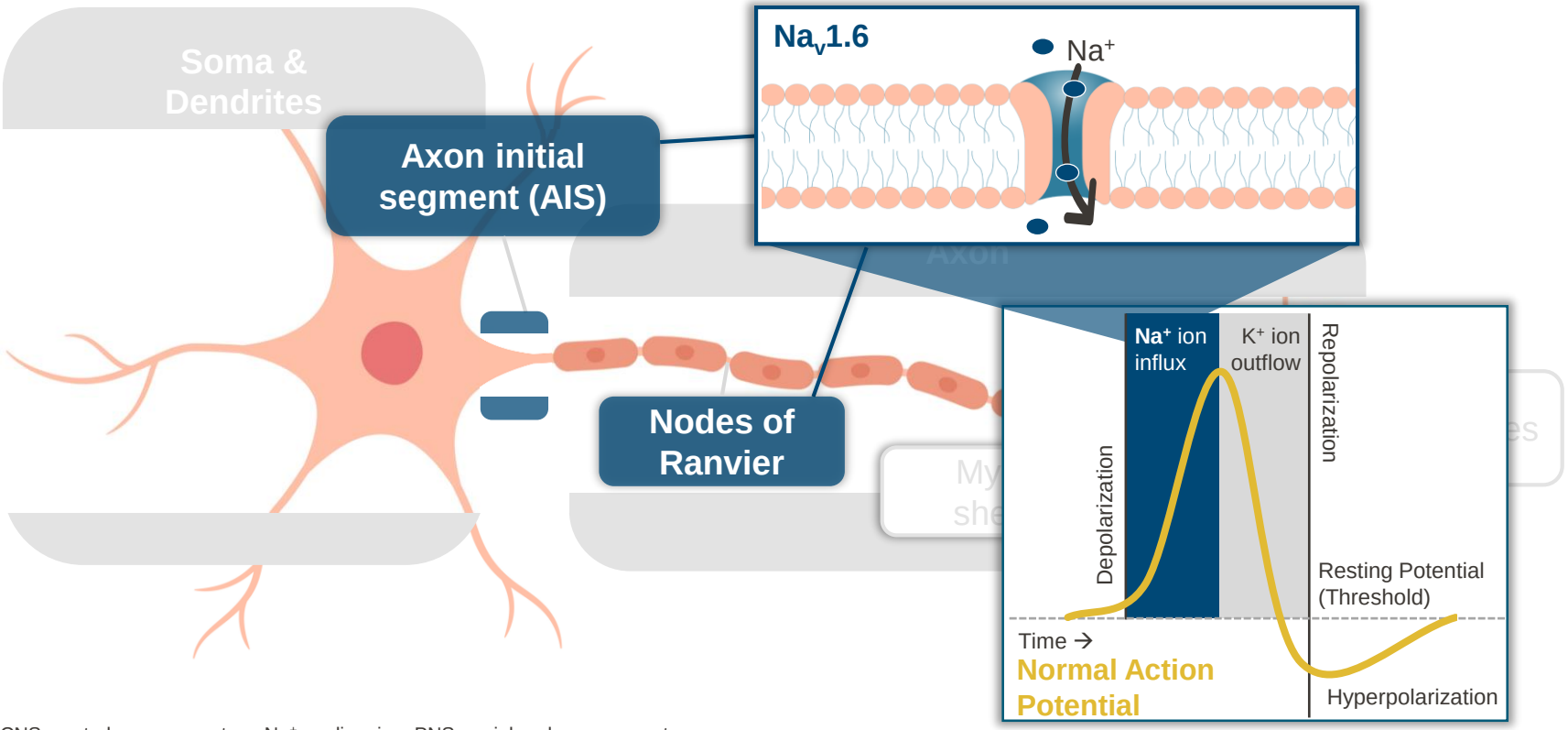
The Sodium Voltage-Gated Channel Type 1.6 ($Na_v1.6$)

View Na_v Family

$Na_v1.6$ regulates sodium ion flow across multiple neuronal cell type membranes in the CNS and PNS[1-3]



CNS, central nervous system; Na^+, sodium ion; PNS, peripheral nervous system

1. Gardella E, Moller RS. Phenotypic and genetic spectrum of SCN8A-related disorders, treatment options, and outcomes. *Epilepsia*. 2019;60(S3): S77-85. | 2. Genetics Home Reference. SCN8A Gene. Available from https://ghr.nlm.nih.gov/gene/SCN8A#synonyms. Accessed July 20, 2021| 3. Wagon JL, Bunton-Stasyshyn RK, Meisler MH. Chapter 10 - Mutations of Sodium Channel SCN8A (Nav1.6) in Neurological Disease. In Perspectives in Translational Cell Biology. Edited by Geoffrey Pitt. Academic Press, 2016:239-64.

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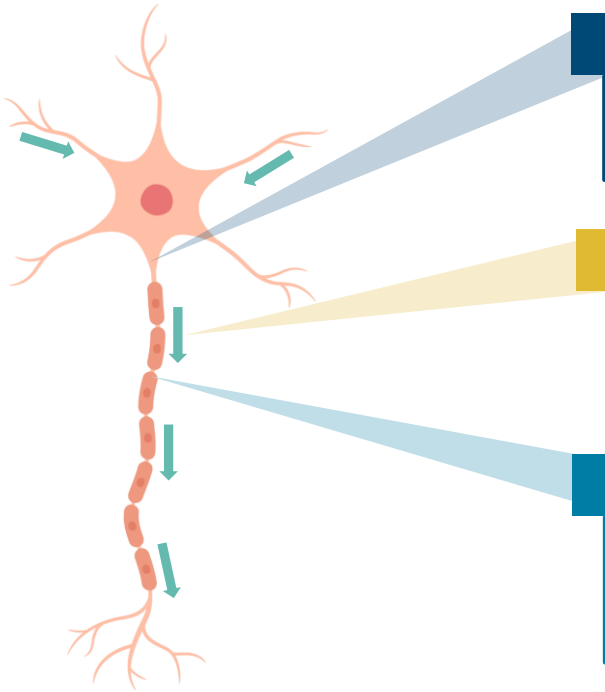
$Na_V1.6$ Has a Unique Expression Profile and Biophysical Properties[1-3]

$Na_V1.6$ is ubiquitously expressed in neurons throughout the CNS and PNS:[1,2]



Voltage dependent activation[1,2]

$Na_V1.6$ activates more hyperpolarized voltages than $Na_V1.1$ and 1.2 allowing for a lower threshold for AP generation

Persistent & resurgent current[1,2]

$Na_V1.6$ is found in neuronal cells in which persistent current is important for repetitive firing

Subcellular localization at AIS and nodes of Ranvier[1-3]

Nav1.6 channels are one of the most prominent isoforms expressed on excitatory neurons, and are the main component of the AIS and nodes of Ranvier

Nav1.6 is a favorable isoform for supporting high frequency, repetitive firing in the CNS and PNS[1]

AIS, axon initial segment; AP, action potential; CNS, central nervous system; PNS, peripheral nervous system

1. Pan Y, Cummings TR. Distinct functional alterations in SCN8A epilepsy mutant channels *J Physiol*. 2019;1-21. | 2. O'Brien JE, Meisler MH. Sodium channel SCN8A (Nav1.6): properties and de novo mutations in epileptic encephalopathy and intellectual disability. *Fgene*. 2013;4(213):1-9. | 3. Dumenieu M, Oule M, Kreutz MR, et al. The Segregated Expression of Voltage-Gated Potassium and Sodium Channels in Neuronal Membranes: Functional Implications and Regulatory Mechanisms. *Front. Cell. Meurosci.* 2017;11(15):1-19.

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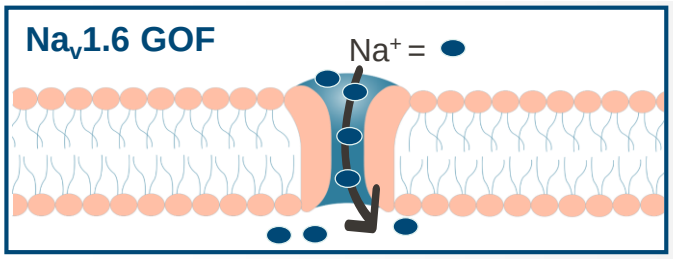
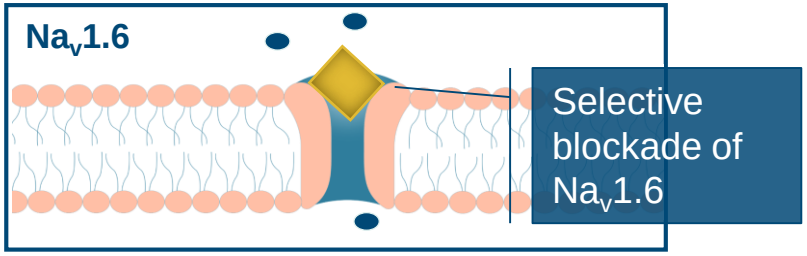
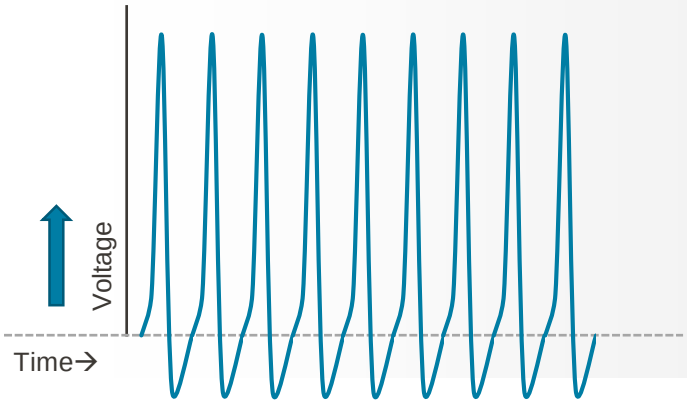
SCN8A Gain of Function (GoF) Mutations Can Result in Elevated $Na_v1.6$ Activity[1]

Elevated $Na_v1.6$ activity is associated with neuronal hyperexcitability and seizures[1-3]

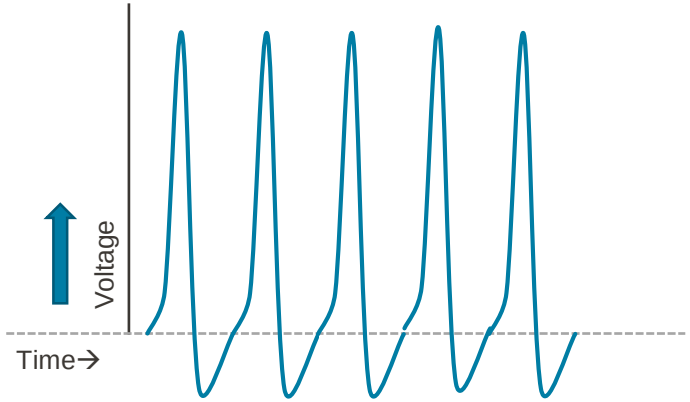




Increased repetitive AP firing



Decreased repetitive AP firing



AP, action potential; Na^+, sodium ion

1. Gardella E, Moller RS. Phenotypic and genetic spectrum of SCN8A-related disorders, treatment options, and outcomes. *Epilepsia*. 2019;60(S3): S77-85. | 2. O'Brien JE, Meisler MH. Sodium channel SCN8A (Nav1.6): properties and de novo mutations in epileptic encephalopathy and intellectual disability. *Front. Genet*. 2013;4(213):1-9. | 3. Pan Y, Cummins TR. Distinct Functional Alterations in SCN8A Epilepsy Mutant Channels. *J of Physio.* 2019;598(2):381-401.

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NBI-921352: An Investigational Treatment for SCN8A Developmental and Epileptic Encephalopathy

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NBI-921352 and DEE2012

NBI-921352 is an investigational product and not approved for use by the FDA

NBI-921352[1-3]	
Putative MOA	Novel and selective $Na_v1.6$ sodium channel inhibitor
Clinical Phase	Phase 2
Indication Sought	Seizures associated with SCN8A-DEE in pediatric patients
Anticipated Population	SCN8A-DEE is estimated to cause less than 5,000 cases of epilepsy in the United States
Administration	Oral
Expected Timing	Phase 2 initiated in Q4 2021

FDA, US Food and Drug Administration; MOA, mechanism of action

1. Neurocrine Biosciences and Xenon Pharmaceuticals announce agreement to develop first-in-class treatments for epilepsy [press release]. December 2, 2019. https://neurocrine.gcs-web.com/news-releases/news-release-details/neurocrine-biosciences-and-xenon-pharmaceuticals-announce. Accessed September 21, 2021. **2.** ClinicalTrials.gov. https://www.clinicaltrials.gov/ct2/show/record/NCT04873869?term=NBI-921352&draw=2&rank=1. Accessed November 16, 2021. **3.** Larsen J et al. *Neurology*. 2015;84(5):480-489.

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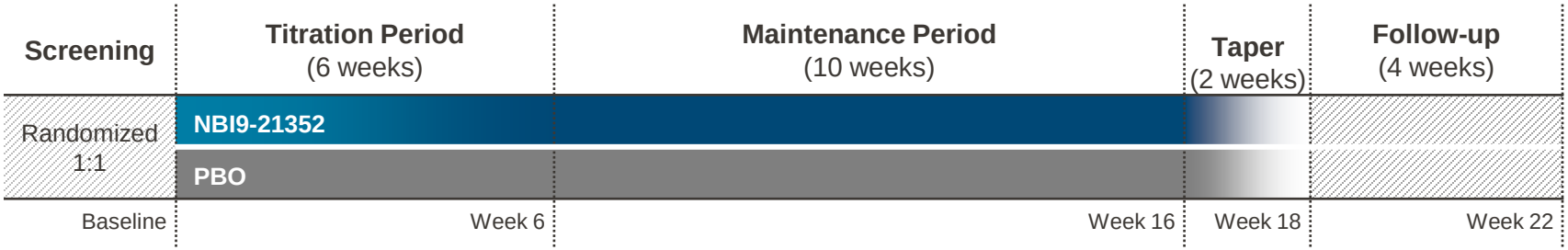
NBI-921352-DEE2012: Study Design[1,2]

Phase 2 randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, tolerability, and pharmacokinetics of NBI-921352 as adjunctive therapy in participants with SCN8A developmental and epileptic encephalopathy syndrome (SCN8A-DEE)

Study Timeline



Study Details

- 52 male and female patients ages 12 to 21 will be enrolled, randomized 1:1 study drug:placebo
  - It is anticipated that age range will be expanded to 2 to 21 in a future amendment, pending additional nonclinical data supporting dosing in ages 2 to 11
- In the first 6 weeks participants will receive increasing doses of NBI-921352 based on weight, followed by 10 weeks of treatment at their final tolerated dose and 2 weeks of treatment with decreasing doses
  - Patients will receive matching placebo for up to 18 weeks

1. Clinicaltrials.gov. Accessed November 15, 2021. https://clinicaltrials.gov/ct2/show/record/NCT04873869?term=neurocrine&draw=2&rank=1&view=record | 2. Data on file. Neurocrine Biosciences.

The use of NBI-921352 for the treatment of SCN8A-DEE is investigational and not approved by the FDA

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NBI-921352-DEE2012: Key Inclusion and Exclusion Criteria

Key Inclusion Criteria

- Male or female 12 to 21 years of age
- Have a diagnosis of SCN8A-DEE supported by both clinical and genetic findings
- Have ≥1 countable motor seizure per week and not be seizure-free for >20 consecutive days
- Being treated with between 1 to 4 other antiseizure medication (ASM)
  - Epidiolex®/Epidyolex® will be considered an ASM
- Must be using a nocturnal alerting system or practice consistent with standards of care
- Have a body weight of ≥10 kg
- The patient's parent/caregiver able to accurately identify seizure types and complete seizure diary

Key Exclusion Criteria

- Have symptoms that would be more consistent with another seizure disorder
- Are currently receiving cannabinoids or medical marijuana
- Are currently taking systemic steroids (excluding inhaled medications for asthma treatments)
- Have a history of moderate or severe head trauma
- Have, at the screening visit, an ECG finding of a QTcF >450 msec or presence of any significant cardiac abnormality

DEE, developmental and epileptic encephalopathy; ECG, electrocardiogram; kg, kilogram; QTcF, corrected QT interval using Fridericia's formula

1. Clinicaltrials.gov. Accessed November 15, 2021. https://clinicaltrials.gov/ct2/show/record/NCT04873869?term=neurocrine&draw=2&rank=1&view=record | 2. Data on file. Neurocrine Biosciences.

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NBI-921352-DEE2021 Assessments[1]

Primary Efficacy Endpoint

- Percentage change from baseline in 28-day seizure frequency for countable motor seizures* during the treatment period

Secondary Objectives

- Percentage of participants with a ≥ 50% treatment response for countable motor seizures* during the treatment period
- Percentage change from baseline in 28-day seizure frequency for countable motor seizures* during the maintenance period
- Percentage of participants with a ≥ 25%, ≥ 75%, or 100% treatment response during the treatment period
- Percentage of participants with a ≥ 25%, ≥ 50%, ≥ 75%, or 100% treatment response during the maintenance period
- Clinical global impression of change (CGIC)
- Parent/caregiver global impression of change (GIC)
- Change from baseline in clinical global impression of severity (CGIS)
- Change from baseline in parent/caregiver global impression of severity (GIS)

Scales explained

Safety Endpoints

- AEs, clinical laboratory tests, vital signs, physical examinations 12-lead ECG, Columbia-Suicide Severity Rating Scale (Children's Version)

*Countable motor seizures defined as defined as generalized tonic-clonic, tonic, atonic or focal onset seizures with noticeable motor component
AEs, adverse events; ECG electrocardiogram

1. Clinicaltrials.gov. Accessed November 15, 2021. https://clinicaltrials.gov/ct2/show/record/NCT04873869?term=neurocrine&draw=2&rank=1&view=record

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Backup

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Voltage-Gated Calcium Ion Channel Family[1]

Voltage-Gated Calcium Ion Channel Family[1]

Type	Gene Symbol	Current	Primary Tissue[a]
$Ca_v1.1$	*CACNA1S*	L-type	Skeletal, cardiac, and smooth muscles, endocrine cells, and neurons
$Ca_v1.2$	*CACNA1C*		
$Ca_v1.3$	*CACNA1D*		
$Ca_v1.4$	*CACNA1F*		
$Ca_v2.1$	*CACNA1A*	P/Q-type	Purkinje neurons
$Ca_v2.2$	*CACNA1B*	N-type	CNS and PNS
$Ca_v2.3$	*CACNA1E*	R-type	Cerebellar granule cells, other neurons
$Ca_v3.1$	***CACNA1G***	**T-type**	**Neurons, pacemaker cells, bone (osteocytes)**
$Ca_v3.2$	***CACNA1H***		
$Ca_v3.3$	***CACNA1I***		

[a]*Primary tissue indicates where there is a high level of expression but does not mean the channel is exclusively expressed at that site.*

Ca_v, voltage-gated calcium ion channel, CNS, central nervous system; PNS, peripheral nervous system

1. Heyes S, Pratt WS, Rees E, et al. Genetic disruption of voltage-gated calcium channels in psychiatric and neurological disorders. Progress in Neurobiology. 2015;134:36-54.

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Voltage-Gated Sodium Ion Channel Family[1]

Voltage-Gated Sodium Ion Channel Family[1]

Type	Gene Symbol	Old Nomenclature	Primary Tissue[a]
$Na_v1.1$	*SCN1a*	Type I	CNS, heart
$Na_v1.2$	*SCN2a*	Type II	CNS
$Na_v1.3$	*SCN3a*	Type III	
$Na_v1.4$	*SCN4a*	SkM1 (μ1)	Skeletal muscle
$Na_v1.5$	*SCN5a*	SkM2 (H1)	Heart
$Na_v1.6$	***SCN8a***	**NaCh6**	**CNS, PNS, glia**
$Na_v1.7$	*SCN9a*	PN1	SNS, CNS
$Na_v1.8$	*SCN10a*	SNS, PN3	DRG
$Na_v1.9$	*SCN11a*	NaN (SNS2)	
Na_vx	*SCN7a*	NaG	Sciatic nerve, lung

[a]*Primary tissue indicates where there is a high level of expression but does not mean the channel is exclusively expressed at that site.*
CNS, central nervous system; PNS, peripheral nervous system; SNS, sympathetic nervous system; DRG, dorsal root ganglia

1. Wood JN, Iseppon F. Sodium Channels. *Brain and Neuroscience Advances*. 2018. Available from https://doi.org/10.1177/2398212818810684. Accessed November 16, 2021.

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Secondary Endpoint Rating Scales: NBI-921352-DEE2021

Clinical Global Impression of Change (CGIC)

Rates overall global improvement since the initiation of study drug dosing as assessed by the investigator

Clinical Global Impression of Severity (CGIS)

Rates overall symptom severity as assessed by the investigator

Parent/Caregiver Global Impression of Change (GIC)

Rates the overall global improvement since the initiation of study drug dosing as assessed by the caregiver

Parent/Caregiver Global Impression of Severity (GIS)

Rates overall symptom severity as assessed by the caregiver

1. Clinicaltrials.gov. Accessed November 16, 2021. https://clinicaltrials.gov/ct2/show/record/NCT04873869?term=neurocrine&draw=2&rank=1&view=record.
2. Data on File. Neurocrine Biosciences.

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