Protheragen

Protheragen Inc.

Oral KCNQ2/3 Potassium Channel Opener for Epilepsy Treatment

With Favorable Pharmacokinetics and High Safety Profile

Overview

Drug Name	ZM-003
Description	Epilepsy is one of the most common neurologic diseases affecting approximately 70 million people worldwide. In the pathophysiology of epilepsy, KCNQ2/3 potassium channels play key role for cellular excitability in the brain. Modified from Retigabine (the first approved KCNQ2/3 potassium channel activator drug but withdrawn from market in 2017), ZM-003 is a more potent KCNQ2/3 as shown in cell-based assay and is highly efficacious in a broad range of epilepsy and pain animal models. Many research data support ZM-003 to have a much more favorable pharmacokinetics and safety profile for a once daily dosing in human. ZM-003 is currently under IND-enabling studies.
Target	KCNQ2; KCNQ3
Drug Modality	Small molecule
Indication	Epilepsy
Product Category	Voltage-Gated K(V) 7.2/7.3 (KCNQ2/3) Channel Activators
Mechanism of Action	ZM003 reduces nerve excitability by activating KCNQ2/3 potassium channel.
Status	IND
Patent	Granted

Collaboration Opportunity

Protheragen Inc. is actively seeking partnership for ZM-003. Potential collaboration can be strategic alliance, licensing, or marketing agreement.
We look forward to hearing from you.

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Target

The M channel is a slowly activating and deactivating potassium channel that plays a critical role in determining the subthreshold electrical excitability of neurons as well as the responsiveness to synaptic inputs. The M channel is formed by the association of the protein encoded by KCN2 and a related protein encoded by the KCNQ3 gene, both are integral membrane proteins. KCNQ2 and KCNQ3 are expressed in an overlapping distribution in brain, with high levels in critical areas for seizures, including the hippocampus, neocortex and thalamus, but are not expressed in most other tissues.

KCNQ2 potassium channel (Kv7.2)

Approved Name	Potassium voltage-gated channel subfamily Q member 2
Official Symbol	KCNQ2
Gene Type	Protein coding
Synonyms	EBN; BFNC; EBN1; ENB1; HNSPC; KV7.2; KCNA11
Ensembl	ENSG00000075043
Gene ID	3785
mRNA Refseq	NM_172109
Protein Refseq	NP_742107
OMIM	602235
UniProt ID	O43526
Chromosome Location	20q13.33

KCNQ3 potassium channel (Kv7.3)

Approved Name	Potassium voltage-gated channel subfamily Q member 3
Official Symbol	KCNQ3
Gene Type	Protein coding
Synonyms	EBN2; BFNC2; KV7.3
Ensembl	ENSG00000184156
Gene ID	3786
mRNA Refseq	NM_004519
Protein Refseq	NP_004510
OMIM	602232

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UniProt ID	O43525
Chromosome Location	8q24.22

Clinical Resources

Gene Function	Defects in KCNQ2 or KCNQ3 are the cause of benign familial neonatal convulsions. At least five transcript variants encoding five different isoforms have been found for KCNQ2. Alternative splicing of KCNQ3 results in multiple transcript variants.
Pathway	KCNQ3 associates with KCNQ2 to form a potassium channel to regulate neuronal excitability.
Major Conditions	Pain; Neurological Disorders; Musculoskeletal and Connective Tissue Disorders

Drug Modality

Small Molecule

ZM-003 is a small-molecule KCNQ2/3 modulator modified from Retigabine (INN). Comparing with Retigabine, ZM-003 has better chemical and metabolic stability, antiepileptic activity, pharmacokinetic properties, and safety/tolerability profile. It does not form colored dimers like Retigabine, eliminating the side effect of forming skin and retinal pigmentation.

Indication

Epilepsy

Epilepsy is a chronic neurological symptom complex that confers susceptibility to recurrent, unprovoked seizures caused by abnormal neuronal firing in the brain, affecting up to 70 million people worldwide. The psychological and social consequences of epilepsy are significant and may seriously affect the quality of life. As a hidden disability, patients are vulnerable to stigmatization and subsequent discrimination and, in many cases, violation of common rights. This is especially common in underdeveloped societies, where the disorder is more

prevalent and at the same time, there is a poorer understanding of the disease.
According to the world health organization's global burden of disease (GBD) 2015 study, epilepsy was the cause of death of 124,900 (range 119,300 to 131,000) people worldwide in 2015, yielding an age-standardized death rate of 1.7 (range 1.6 to 1.8) per 100,000.
Every human being has a brain seizure threshold, which makes them more or less resistant to seizures. Epileptic patients have an abnormally low seizure threshold that can be normalized through treatment. Most antiepileptic drugs increase the threshold of electrical energy in the epileptic focus required for a seizure to occur. Therapeutic strategies include potentiating the inhibitory pathways within the central nervous system, inhibiting excitatory glutamatergic pathways or inhibiting excessive neuronal firing.

Mechanism of Action

Reducing Nerve Excitability by Activating KCNQ2/3 Potassium Channel

The existence of a low-threshold, non-inactivating voltage-dependent potassium current in neurons, referred to as the M-current, plays a dominant role in regulating excitability because of its unique activity in the voltage range of action-potential initiation. The M-current slowly activates when an excitatory stimulus depolarizes the neuron toward spike threshold, repolarizing the membrane towards resting potential and suppressing firing. In this way, the M-current limits repetitive spike firing in response to a persistent depolarizing stimulus and is therefore, a key mechanism for "spike-frequency adaptation." Suppression of the M-current results in membrane depolarization and an increase in neuronal input resistance, making the cell more likely to fire action potentials.
Because KCNQ2 and KCNQ3 constitute an M-current in native neurons, ZM-003 acts as an opener (activator) of the KCNQ2/KCNQ3 potassium channel by dramatically shifting the activation voltage to more negative potentials, and also speeding the rate of activation and slowing deactivation, which means that the M-current is enhanced to reduce excitability and counteract convulsions.

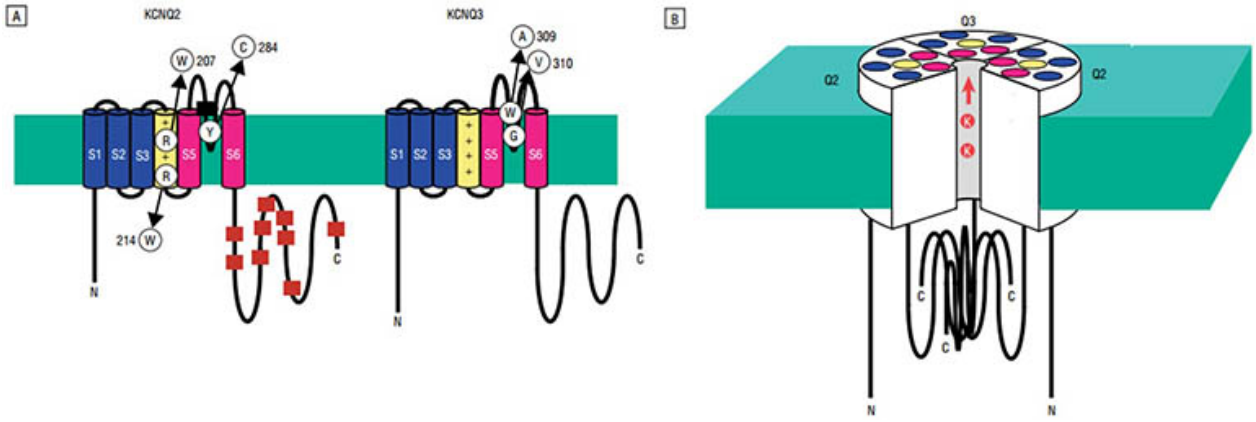

Figure. The structure of M-channels. (JAMA Neurology 60(4):496-500, May 2003)

Status

The Status of ZM-003

ZM-003 is currently in IND-enabling studies. Part of the efficacy, therapeutic index, and safety studies in vivo have been completed.

	Discovery/Optimization	Pre-clinical	Phase I	PhaseII	PhaseIII
ZM-003					

Data

Please feel free to contact us for more research data.

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