September 2021

SCN2A Community Questions

At Praxis, we're on a mission to develop novel therapies for SCN2A. We believe collaboration with the SCN2A community is critical in this work. We have compiled some questions we have received from you, along with our responses, to keep you informed on our journey.

Q1. How does ASO (Antisense Oligonucleotides) therapy affect the SCN2A gene?

A1. Praxis is currently advancing a novel ASO for patients with an SCN2A gain-of-function variant (also sometimes called a genetic mutation). As you may already know, SCN2A is the gene that encodes the voltage-gated sodium channel NaV1.2 that is primarily found in excitatory neurons (brain cells) and plays a critical role in communication between neurons.

The SCN2A gene itself sits in the nucleus of the neuron, the place where our genetic code lives for each cell. To make the NaV1.2 protein from the SCN2A gene, the cell has to go through two steps.

1) Transcription: This is a process that occurs in the nucleus. A single stranded exact copy of the SCN2A gene is created, called mRNA, which is able to leave the nucleus and go to the cytoplasm of the neuron.
2) Translation: Ribosomes, which work like a small little assembly machine, take the mRNA and turn it into the protein, and with SCN2A, the NaV1.2 channel. This then gets transported by other proteins to where it needs to go. In this case, the cell membrane.

In the case of SCN2A GoF[1] mutations, there is an increase in the flow of NaV1.2, leading to an abnormal increase of neuronal activity in the brain (hyperexcitability). The ASO[2] is small enough to travel into the cell and into the nucleus where it can bind to the mRNA strand. This binding event activates enzymes that lead to the breakdown of the mRNA, and therefore translation to the protein channel is prevented. PRAX-222 is being developed to reduce the number of NaV1.2 channels, thereby counteracting excessive activity of the channel.

[1]Gain of function is an increase in NaV1.2 activity that leads to an increase in neuronal activity.
[2]ASO stands for antisense oligonucleotides; they are short, synthetic, single-stranded oligodeoxynucleotides that can alter RNA and reduce, restore, or modify protein expression through several distinct mechanisms.

Q2. What is the difference between PRAX-562 and PRAX-222?

A2. PRAX-562 is a small molecule and the first selective, persistent sodium current blocker in development for the treatment of a wide range of rare central nervous system disorders, including epilepsies and pain disorders. PRAX-222, an ASO, is designed to directly target the cause of disease by down-regulating NaV1.2 expression.

Q3. Are other pharmacological approaches also being studied?

A3. Praxis announced in March 2021 that we have entered into a partnership with The Florey Institute of Neuroscience and Mental Health to develop an ASO for the treatment of SCN2A loss-of-function mutations, the leading cause of genetically associated autism. Before the partnership, Praxis had two compounds in its pipeline related to SCN2A gene mutations (PRAX-222 and PRAX-562), and both are for gain-of-function mutations. Now, Praxis has programs in development for both SCN2A gain-of-function and loss-of-function mutations, further demonstrating our commitment to the SCN2A community.

Q4. Currently, at what stage are PRAX-562 and PRAX-222?

A4. PRAX-562 is in Phase 1 of clinical development, in which we are administering the study drug to healthy adult volunteers. The focus of this study is to understand the safety of PRAX-562 and how it acts in the body (e.g., how is it absorbed?; does taking it with food make a difference?). In the future, if we continue to see a favorable safety profile, we plan to study the treatment in patients who have developmental and epileptic encephalopathies, including SCN2A-DEE and SCN8A-DEE.

PRAX-222 is in the late pre-clinical phase, meaning that the studies are being conducted in animals only. In the studies completed so far, PRAX-222 has completed preclinical efficacy testing and we are continuing to evaluate safety and tolerability. If the results are favorable, we intend to use our preclinical results to support our Investigational New Drug (IND) submission to the U.S. Food and Drug Administration. An IND is a request for authorization to begin clinical trials in humans.

Q5. Are these two therapies ok for both SCN2A Gain of Function and Loss of Function mutations?

A5. Currently, PRAX-222 would only be studied in patients with a SCN2A gain of function mutation. We are working to better understand the best populations to target for PRAX-562.

Q6. Will PRAX-562 be available soon as a therapy to treat people in the US?

A6. Praxis is still early in the clinical process of PRAX-562. We have received both Rare Pediatric Disease Designation and Orphan Drug Designation from the FDA for both PRAX-562 and PRAX-222. This is exciting news for us at Praxis as receiving these designations means that the FDA recognizes that SCN2A is a rare pediatric disease and that the scientific data emerging to date show promise for the continued advancement of the clinical programs. These early interactions with the FDA are critical for understanding if our rationale for investigating a disease is sound.

Q7. Once the therapies are available, do you already know if there will be some kind of parameters to keep with or if everybody could have access to them?

A7. We are still in the research phase of drug development, so it is not yet possible to know if or when PRAX-562 or PRAX-222 will be available. We will continue to connect with the community to share what progress Praxis is making.

Q8. My child is enrolled in a SCN2A Natural History Study. Is there anything else we can do further?

A8. As a community, every piece of data collected about SCN2A can help us better understand how complex it is. Praxis will continue to let the community know about any additional research or opportunities to share data.

Do you have a question?
We invite you to contact us at patientadvocacy@praxismedicines.com