Frequently Asked Questions for Patient Community:
NBI-921352 Phase 2 Clinical Trial for SCN8A-DEE
Sponsored by Neurocrine Biosciences, Inc.

Contents

Background for Families:

On behalf of Neurocrine Biosciences, thank you for your interest in the upcoming clinical trial of NBI-921352 in SCN8A Developmental and Epileptic Encephalopathy Syndrome (SCN8A-DEE). We are working diligently to start the study later this year and will provide as much information as we can prior to the official study launch. However, please understand that many topics can only be addressed by discussion with a physician who can evaluate your child's condition and suitability for participation in the trial.

Our clinical trial consists of two treatment "arms," one in which participants will receive placebo (see question 2 in General Clinical Trial Questions section for description) and another in which participants will receive the study drug, NBI-921352. Participants will be randomly assigned between the placebo vs. study drug arms, and the trial will be double-blinded, meaning neither the participants nor the doctors and nurses administering the trial will know which participants receive placebo vs. NBI-921352. This structure is commonplace in clinical trials as a mechanism to test the safety & efficacy of a potential treatment compared to no treatment while seeking to avoid introducing any biases that could undermine the integrity of the results.

Participants assigned to the placebo arm will receive placebo for up to 18 weeks, while participants in the study drug arm will receive increasing doses of NBI-921352 based on weight for the first six weeks (titration period), followed by ten weeks of treatment at their final dose (maintenance period) and finally two weeks of treatment with decreasing doses (taper period). After this initial 18 weeks, we plan to offer an open label extension to the trial, which will allow participants on **both** placebo and study drug arms to receive NBI-921352 for an extended period.

We look forward to sharing more details of the clinical trial as we move toward trial start. If you have additional questions or concerns, please share them with your patient advocacy group to forward on to Neurocrine Biosciences.

General Clinical Trial Questions

1. **What is a clinical trial?**
    a. A clinical trial is a medical research study involving human participants. It tests the use of a medical procedure, medical device, drug, or potential treatment, and is led by

researchers and study doctors. Clinical trials provide valuable information and may help researchers to understand a condition better and learn how best to treat it or may lead to new or better treatments being made available.

b. A study drug must generally pass multiple phases of clinical testing before it is approved by a country's regulatory authority and made available to the public. Descriptions of the different phases of clinical trials are provided below. This SCN8A-DEE clinical trial is a **Phase 2 trial**.
    i. **Phase 1**: The study drug is given to a small group of healthy volunteers. Researchers assess how much study drug is safe to take and how the human body responds when it receives the drug.
    ii. **Phase 2**: The study drug is given to a small group of people with the target disease or condition it is intended to treat. In this phase, researchers evaluate what dose is appropriate and begin to learn more about how safe the drug is and how well it works in people with the specific disease or condition.
    iii. **Phase 3**: Researchers test the safety and effectiveness of the study drug in a larger group of participants with the target disease or condition it is intended to treat over a longer time period. Sometimes, comparisons are made between the study drug and other medications that are already approved for the same purpose.
    iv. **Phase 4**: A Phase 4 trial is conducted after a study drug has been approved for public use. The approved drug may be compared with other drugs on the market or researchers may monitor the drug's long-term safety and effectiveness, and impact on patients' quality of life.

2. What is a "placebo"?

a. If your child is enrolled in the trial, he/she will be randomly assigned by a computer to receive either NBI-921352 or placebo for the first 18 weeks. The placebo looks like NBI-921352 but does not contain any active drug. Placebos are commonly used in clinical trials to help understand if the drug being researched is effective. In this trial, one of every two participants (50%) will take placebo. Neither you nor the study doctor or nurses will know if your child is receiving NBI-921352 or placebo. Only in the case of an emergency, it is possible for the study doctor to obtain this information.
    i. For information on the possibility of receiving study drug following 18 weeks on placebo, see question 5 in the section entitled *NBI-921352 Phase 2 Clinical Trial: Study Drug and Treatment Questions* below.

3. What about side effects?

a. All medications, both those that are approved and those undergoing clinical trials, may potentially cause side effects – some of these are known, but there could be others that have not previously been observed. Trial procedures may also involve risks. You will be informed about all the known potential side effects of the study drug and study procedures before you decide to take part in this clinical trial. If any further risks are discovered while the trial is ongoing, you will be informed immediately.

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NBI-921352 Phase 2 Clinical Trial: Enrollment Questions

1. **When will the locations where the clinical trial will be offered, commonly called trial sites, be made public?**
    a. We will post new trial sites on clinicaltrials.gov as each site is ready to enroll patients into the trial. Neurocrine will also share any relevant trial updates with the SCN8A patient advocacy groups.

2. **Will my child need to stop taking any drugs in order to participate in the trial?**
    a. Your doctor should review and discuss your child's medications with you because each clinical trial is very specific regarding concurrent (at the same time) & past medications and trial eligibility. Please do not change or stop any medications unless directed by your doctor.

3. **Should I change something now so that my child can be enrolled in the trial?**
    a. No, stable medication use is an important requirement for trial participation, so please do not make any changes to your child's current treatment plan unless instructed by your doctor.

4. **Will accommodations be made to facilitate participation for families that do not live near the trial sites (participating trial locations)?**
    a. Yes, we understand it may be difficult logistically and financially to participate in a clinical trial, and the study team will work with you and your family regarding travel, accommodations, and other logistical challenges to study participation.

5. **Will there be possibilities for some participation directly from families' homes through home visits or telemedicine (i.e. using online platforms like telephone, Zoom, etc.)?**
    a. Yes, we have worked to allow telehealth or home visits when feasible and permissible by your trial site, but certain visits will require assessments that can only be conducted in a healthcare setting.

6. **Will there be trial sites outside of the United States? When?**
    a. We intend to conduct this trial internationally, including trial locations in Europe and other regions. We are currently selecting trial sites and will share more when international (ex-US) trial sites are confirmed.

7. **How do I get my doctor/healthcare practice/hospital to enroll to be a trial site (participating trial location)?**
    a. Trial sites are being selected based upon a rigorous review and qualification process, with input from the SCN8A patient advocacy groups.
    b. If you think your doctor would be interested in participating, please refer her/him to the study contact listed on the clinicaltrials.gov website found here (ClinicalTrials.gov Identifier: NCT04873869).

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8. **When should I talk with my doctor about the trial?**
    a. Feel free to inquire at any time. More information will be available as trial sites launch, which we anticipate will begin later this year.
    b. If your doctor is interested in learning more about the trial, please refer her/him to trial listing on the clinicaltrials.gov website found here (ClinicalTrials.gov Identifier: NCT04873869).

9. **Can we get on a waiting list for trial participation?**
    a. A study website will soon launch that will allow you to register your interest. We will share this study website with the SCN8A patient advocacy groups when available.

10. **When will the younger kids (age 2 - 11) be able to enroll in the trial?**
    a. A specific date for enrollment of participants aged 2-11 is unknown at this time. We are working diligently to obtain the additional information required to support opening the trial to children in this age group, and then the U.S. Food and Drug Administration (FDA), as well as international regulatory agencies for any ex-U.S. trial sites, must review and approve expansion of the trial to younger children.

11. **Can I enroll my child if his/her age is right on the cusp (about to turn 12 or 22 this year)?**
    a. Eligibility is determined by age upon the date of trial enrollment. If your child is between 12 and 21 on the date of enrollment, he/she will be of an eligible age to participate.

12. **If my child is not enrolled in the original clinical trial (i.e. initial 18 weeks of either placebo or study drug), can he/she still participate in the open label extension part of the trial?**
    a. No. Currently the planned open label extension will only be available to patients that participate in the double-blind, placebo-controlled trial (see *Background for Families* section above for trial design description). The open label extension is designed this way to allow us to collect the specific data needed by the regulatory agencies (e.g., FDA) to thoroughly assess both the short-term and long-term effects of the study drug.

13. **Are there any reasons that parents of SCN8A-DEE patients should consider one clinical trial over another?**
    a. We encourage you to discuss potential clinical trial participation with your doctor, as each clinical trial varies across multiple aspects (e.g. trial design, scientific rationale for the treatment, etc.). NBI-921352 is being studied as a study drug for SCN8A-DEE because it targets the sodium channel in the brain associated with the SCN8A gain of function mutation known to contribute to seizures.

NBI-921352 Phase 2 Clinical Trial: Study Drug and Treatment Questions

1. **What is the mechanism of action? Is this drug targeted to the SCN8A genetic mutation?**
    a. NBI-921352 selectively inhibits the sodium channel in the brain associated with the SCN8A gain of function mutation (Nav 1.6) known to contribute to seizures. It is not a gene therapy and therefore does not directly target the SCN8A genetic mutation itself.

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2. **What form will the medication be in?**
    a. This study uses a granule (small particles similar in size to table salt or pepper) form of NBI-921352, which can be mixed with soft foods or liquid prior to dosing.
    b. Using this form allows us to move forward with the trial as quickly as possible, but we are evaluating other forms for future development beyond this trial.

3. **The study says administered orally. What about feeding tubes?**
    a. Feeding tubes are permitted. NBI-921352 can be administered via a gastrostomy tube, often called a G-tube.

4. **Is there information on whether NBI-921352 may be effective in children for whom sodium channel blockers have <u>not</u> been effective in the past?**
    a. NBI-921352 is an investigational drug and has not previously been evaluated directly in epilepsy patients, and therefore we do not have data to answer this question at this time.

5. **If my child participates in the trial and receives placebo for 18 weeks, can he/she eventually receive the study drug, NBI-921352?**
    a. Yes, participants who complete the double-blind, placebo-controlled trial consisting of 18 weeks will be eligible to enroll in an open-label extension trial beyond this period. **All participants** in the open label extension trial will receive the study drug, including those who were on placebo in the initial 18-week trial.

6. **If my child participates in the trial and receives the study drug for the 18 weeks, can he/she continue taking it after the 18-week trial is over?**
    a. Yes, participants who complete the double-blind, placebo-controlled trial will be eligible to enroll in an open-label extension trial. **All participants** in the open label extension trial will receive the study drug.

NBI-921352 Phase 2 Clinical Trial: Efficacy and Results Measurement Questions

1. **How do you determine what levels of efficacy are enough to advance the development further beyond this trial?**
    a. We will evaluate outcomes including seizure frequency in study participants who received the study drug, NBI-921352, compared to those who received placebo and look for differences between the two groups.
    b. Scientists have formed hypotheses, or scientific theories, about the study drug's effect based on what is known about NBI-921352 and will test these hypotheses in the clinical trial.

2. **Will parents of trial participants be trained to appropriately count and document seizures in the seizure journal?**
    a. Yes, parents and caregivers will receive training on seizure definitions and how to count seizures for this trial.

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3. **The start date on clinicaltrials.gov is listed as August 2021. When will my trial site be open?**
    a. It's best to check with the trial site closest to you to see when they expect to be able to screen patients for this study. Not all sites will open at the same time.
    b. Right now, we expect our first site to open around August 2021 with additional sites to open over the following months.
    c. Trial sites each have local requirements for conducting clinical trials and will likely open at different times. These requirements may include review by their institutions (e.g., hospitals, universities), laboratory and pharmacy set up, and regulatory document review.

4. **The trial completion date on clinicaltrials.gov is listed as December 2023, but when will you know the results of the trial?**
    a. December 2023 is when we estimate the last patient will complete their last trial visit. After all the data are collected, it will take several months to verify and interpret the data to know the final trial results.

5. **When will we know whether the investigational drug is approved for SCN8A-DEE?**
    a. Once we know the results of this study, we will assess whether any further data or clinical trials are needed to understand whether the study drug NBI-921352 is safe and shows an effect in children with SCN8A-DEE.
    b. When we have collected enough data to support a thorough FDA review, we generally spend several months compiling, summarizing, and organizing all the information into the application for regulatory approval.
    c. Then, FDA review of drug approval applications generally takes approximately eight to 12 months. Other countries may have different timelines for review and approval.

Future-Looking Questions

1. **If my child participates in the clinical trial and the FDA approves NBI-921352, will my health insurance cover it?**
    a. There is no cost to you for the study drug while your child is participating in the clinical trial.
    b. Upon potential FDA approval, we cannot guarantee that NBI-921352 would be covered by all insurance plans, but our team would seek coverage by all U.S. insurance plans, supported by the best data package we can provide.
    c. For countries outside of the U.S., there are other local & national government bodies and/or private insurers that review new drugs and make pricing & reimbursement determinations.