Frequently Asked Questions about the **FX-LEARN** study:

Why is this study being done?

There are two purposes of this study. First, to find out if the drug AFQ056, which is made by the pharmaceutical company named Novartis, is safe and has beneficial effects on language learning in children who have fragile X syndrome (FXS). Second, to find out if a structured language intervention can help children with fragile X syndrome communicate better.

What is AFQ056?

AFQ056 is an investigational drug that is not approved for use for the treatment of people with FXS by the U.S. Food and Drug Administration (FDA) except in studies such as this one and is not currently "on the market" (available for you to buy) in any country.

It is being developed for patients with fragile X syndrome because it blocks a specific type of glutamate (a form of brain chemical or "neurotransmitter") receptor called the mGluR5 receptor in the brain. A receptor can be thought of as a 'lock' and AFQ056 as a 'key' which fits into the lock to stop it from being active. The mGluR5 receptor is thought to be overactive in patients with fragile X syndrome due to lack of FMRP. AFQ056 can block the mGluR5 receptor and decrease activity in the mGluR5 pathway. By blocking the mGluR5 receptor and pathway in the brain, it is thought that AFQ056 may be able to compensate for some of the function of the missing FMRP and symptoms of fragile X Syndrome may be reduced. Because mGluR5 blockers reverse many of the problems seen in the mice studied who have fragile X it is thought these drugs could be helpful in humans with fragile X syndrome.

How is AFQ056 given?

It is given as an oral medication (given by mouth). You will learn how to dissolve the powder in the bottles while you are at the Screening visit. The medication is good for approximately a week after you dissolve it.

You will be given an Instruction Sheet for Preparation of the AFQ056/Placebo Study Medication to take home with you to reinforce the instructions for reconstitution. Video conferencing calls

will be done each week with you to watch you combine the bottle(s) of powder and water to make sure this is being done correctly at home.

What do I need to tell my doctor before taking the study drug?

Please inform the Study Doctor about all drugs that your child is currently taking, intends to take, or will receive while in the study, even those available without prescription. This includes prescription drugs, over-the-counter drugs, vitamins and herbal extracts. This is very important.

What are the risks and possible discomforts from being in the research study?

Expected side effects would be those observed in prior studies using the drug in adults and children. Your child may experience dizziness, insomnia (difficulty falling asleep and/or staying asleep), headache, decreased appetite, nausea, vomiting, diarrhea, and behavioral "activation" with irritability, aggression, hyperactivity, anxiety, and impulsive behavior. These side effects are expected to be relatively infrequent and mild-moderate in degree. Insomnia and behavioral side effects will in most cases be manageable by dose adjustments in the flexible dosing period. Insomnia may be managed by moving the dose earlier in the day.

Other possible side effects could include hypoesthesia (reduced sense of touch or sensation), somnolence (drowsiness), syncope (fainting), dry mouth and euphoric mood (a feeling of great happiness or well-being). In addition, visual perceptual disturbances described as visual hallucinations and illusions (incorrect perception of reality) have been reported.

There are other risks related to blood draws, ECG, ERP and other aspects of the study protocol. Please ask your doctor or the study coordinator for details.

How long will my child take part in this research study?

It will take your child approximately 21 months to complete this study. During this time, we will ask you and your child to make 15 in-person study visits. We may ask you to make additional visits if the Study Doctor thinks it is necessary. There will also be many visits via teleconference, for which equipment will be provided. For more details, please speak to the Study Coordinator.

What will happen in this research study?

If you choose to let your child take part in this study, we will ask you to sign a consent form before we do any study procedures. Your child will be given either AFQ056 or a placebo that contains no medicine (like a sugar pill) throughout the course of the trial. At some time during the course of the study, your child will receive placebo per study procedures, but you will not be told when this will be taking place. For the rest of the first 12 months of the study, your child will be randomly assigned (like rolling a dice), and either take AFQ056 or placebo. Your child has a 50% chance of getting the drug and a 50% chance of getting placebo. The Study Doctor will not know what your child has been given. Your child's doctor can, however, find out what your child was taking if there is an emergency.

After 12 months, all participants will take AFQ056 for 8 months during the open-label extension portion of the trial.

Subjects will take between 12.5 mg and 100 mg AFQ056 or placebo. Doses are increased or decreased depending on how your child tolerates the medicine and if your child has side effects.

The dose adjustment will be done at specific times during the study during weekly video conferencing calls with the study team. The dose can go as low as 12.5 mg if your child is having trouble tolerating the medicine. If your child cannot tolerate the minimum dose of 12.5 mg, we will have to withdraw your child from the study.

As part of this study, we will provide you with a language intervention designed to improve your child's communication skills. A speech/language pathologist will be teaching you some different ways to interact and communicate with your child to support their language development. The speech/language clinician will work with you throughout the study to provide you with information as well as to coach you as you interact with your child. The SLP will train you on how to administer the intervention via teleconference. These teleconference calls will begin 6 months into the study. They will be weekly for the first 4 months, and then monthly after that. All equipment will be provided by the Study Team.

What types of tests will I have during study visits?

There will be numerous surveys, tests, and questionnaires related to early learning, language, and behavior. They will take between an hour to a few hours depending on the visit. Some of

them will be done while your child is alone with a member of the study staff. You will be asked to complete some of the assessments or questionnaires as the parent/caregiver.

At several visits, we will take a sample of your child's blood. Blood will be taken at 5 of the 15 study visits and no more than 77 ml (approximately 6 tablespoons) of blood are planned to be collected during this study.

At some of the visits, the Study Doctor will perform an eye exam at Screening to monitor and screen for any eye abnormalities.

An ECG will be done at a few of the visits as well to assess the electrical activity in your child's heart.

Will I or my child be paid to take part in this research study?

We will pay $34/day in compensation for parking and your child's participation in this research study at all 15 in-person Study Visits. If your child participates in all study visits, you will be paid a total of $510.

Who do I call if I have questions about this research study?

Please contact Anna De Sonia at (312) 942-7250 or Anna_M_DeSonia@rush.edu or Katie Friedmann at (312) 942-9841 or Katherine_J_Friedmann@rush.edu to talk about this research study. You can also visit the NeuroNEXT website at www.NeuroNEXT.org to learn more. This study is also listed at www.clinicaltrials.gov under NCT # 02920892.