

Angelman Syndrome Community Statement – Patient Q&A

Joint Collaboration Community Statement for Angelman Syndrome – Q&A

COLLABORATION

Why are there 3 companies (Roche, Biogen and Ionis) but only 2 research programs?

All 3 companies are working towards finding potential treatments for Angelman Syndrome (AS). Biogen and Ionis have partnered and are working together on one program, and Roche is working separately on their own program.

How does the collaboration between the 3 companies work?

All 3 companies have come together and designed 2 different studies to better understand AS. We all worked closely on designing the studies and funding them. Roche will be managing the *AS Endpoint Study*, so all the activities for running that will be done by Roche. The *AS CSF and Biomarker Study* will be managed by Biogen, so they will have responsibilities for the day to day activities of that study. All 3 companies will meet and collaborate regularly to guide the studies and eventually share the data so that all the data collected can help inform our potential treatment trials.

What is the relationship between Ionis and Biogen?

Ionis and Biogen have a research and development partnership that spans across several neurological disorders, including Angelman Syndrome, therefore we are working collaboratively to develop a single medicine for the potential treatment of Angelman Syndrome.

NATURAL HISTORY STUDIES

How are these 2 studies different from the on-going NIH Natural History (NH) study?

The NIH NH study, being managed by Boston Children's Hospital, is a prospective, longitudinal study in both children and adults with AS. The study will gather information about many different aspects of AS, and how it changes over time by having participants come back every year for an assessment. The 2 new studies are separate and different from the NH study, but they are complementary, and will add new information about AS that we don't already know and that the NH study may not be measuring.

Can we only enroll in 1 of the studies, or all of them?

Participating in the NH study does not make you ineligible to participate in the 2 new studies, and vis-a-versa. In fact, if you are deemed eligible, you could potentially participate in all 3 studies, even at the same time, as none of the studies involve an experimental drug, and they are all observational.

If we're participating in an investigational drug clinical trial and can potentially be on drug, can I participate in the other studies?

The requirements for participating in an investigational drug study (clinical trial) may not allow you to participate in an observational study, you would need to check with the Investigator for the study you are enrolled in to better understand what's allowed.

The same goes for the 2 new observational studies, each of those will have their own requirements and restrictions regarding current participation in an investigational drug clinical trial. When the study details are made available, we will share that information and we encourage you to speak with the Investigator to determine your eligibility once that information is available.

How can we get more information and also participate?

Each company is working vigorously with potential sites to get the studies up and running. Some sites will be participating in just one of the 2 new studies, while other sites may be participating in both, and maybe even the on-going Natural History study. As soon as we have 1 site 'open' and ready to enroll participants, we will let the AS community members know and provide further details on the studies. At that time, we will also list the studies on ClinicalTrials.gov.

FUTURE STUDIES

What happens after these 2 new studies are completed? Will the companies start their clinical trials?

Ionis/Biogen and Roche are actively working to develop potential therapies to treat AS. The information gathered from these 2 new studies will be used to help design future drug trials. We will announce plans for additional studies as this information is available.

ABOUT IONIS

Who is Ionis?

As the leader in RNA-targeted drug discovery and development, Ionis has created an efficient, broadly applicable, drug discovery platform called antisense technology that can treat diseases where no other therapeutic approaches have proven effective. Our drug discovery platform has served as a springboard for actionable promise and realized hope for patients with unmet needs. We created the first and only approved treatment for children and adults with spinal muscular atrophy as well as the world's first RNA-targeted therapeutic approved for the treatment of polyneuropathy in adults with hereditary transthyretin amyloidosis. Our sights are set on all the patients we have yet to reach with a pipeline of more than 40 novel medicines designed to treat a broad range of diseases including cardiovascular diseases, neurological diseases, infectious diseases, pulmonary diseases and cancer.

To learn more about Ionis follow us on twitter @ionispharma or visit <http://ir.ionispharma.com/>.

What is antisense and how does it work?

Antisense therapies, also known as antisense oligonucleotides, or ASOs, are designed to bind precisely with RNA, halting the process of creating a disease-causing protein. To appreciate how Ionis is using antisense technology to revolutionize drug discovery, we must first look at how traditional medicines work in the body.

Traditional approaches vs. antisense. The human body is made up of billions of cells, each containing the unique genetic information, or DNA, that defines a person. Contained within DNA are instructions for making all the proteins in the human body.

Proteins are crucial building blocks for the structure and function of all organs and systems within the human body. But over or under production of a protein, or production of a mutated protein, are common causes of many human diseases. For more than 100 years, most traditional medicines like small molecule inhibitors or, more recently, antibody-based therapies have worked to target these proteins once they are produced and doing damage in the body.

Antisense therapies change the process of producing a protein before it even begins. To build a protein, a cell must make a copy of the DNA, which contains specific instructions for how to make that particular

protein. This copy, called messenger RNA (mRNA), carries the instructions to the part of the cell where proteins are made.

Antisense therapies are designed to seek out, bind to and destroy a mRNA in a highly specific manner, so that the amount of disease-causing protein is dramatically decreased. Antisense therapies can also treat diseases caused by too little protein by increasing the production of the protein, thereby restoring the protein to normal levels.