AS community letter

TANGELO recruitment completed and alogabat study announcement

07 December 2022

Dear global Angelman Syndrome partners,

As part of our ongoing commitment to share important and timely updates about our clinical program in Angelman Syndrome (AS), we are pleased to announce that all participants from the first part or Multiple Ascending Dose (MAD) part of the TANGELO study have successfully transitioned to the second part or Long Term Extension (LTE) part of TANGELO. This part will now evaluate different dose levels with longer intervals between administrations for a prolonged period of time to look at the long-term safety and tolerability of rugonersen.

Additionally, as a testament to our commitment to AS, we are pleased to announce that we are expanding our portfolio to further support the development of treatment options in AS. Building upon the important work carried out together with the AS community, such as the disease concept model, the FREESIAS observational study and many pre-clinical collaborations with academic partners, as well as our ongoing research with rugonersen, we are expanding our drug development portfolio in AS to alogabat, a GABA-modulator which is taken as a once-daily oral tablet. Following on from the information shared at the 2022 FAST Industry Update, we are planning a new clinical study that will explore the potential of alogabat as a treatment for AS individuals with deletion genotype.

This reflects our aim to find potential treatments for rare, neurogenetic disorders like AS. We believe it is important to develop a number of different approaches to tackle complex diseases such as AS. Targeting AS in multiple, and potentially complementary ways, may increase the chances of developing an effective treatment and ultimately improve patient care.

Why are we investigating alogabat?
AS is a complex, heterogeneous disorder caused by a disruption to the *UBE3A* gene, which is vital to how the brain controls speech, movement and learning.

Research shows that individuals with deletion have a more severe presentation than other AS genotypes. This suggests that other genes beyond UBE3A, when deleted, may contribute to more severe symptoms.

Some of these genes, which are located close to the UBE3A gene on the same chromosome 15, are called GABRB3, GABRA5 and GABRG3 and are maternally deleted in individuals with deletion genotype. These three genes contain the information to encode for three proteins that assemble together to form the $GABA_A$ α5 receptors.

A receptor like the $GABA_A$ α5 receptor is a protein that resides on the brain cells and that functions as a keyhole where the key is a neurotransmitter or a substance that the brain uses to communicate within its cells. The key that is recognised by the keyhole $GABA_A$ α5 is a

neurotransmitter called GABA. GABA and the $GABA_A$ α5 receptors play an important role in brain development, sleep, behaviour and seizure control, and because the amount of the $GABA_A$ α5 is reduced in AS individuals with deletion, they may play a role in the more severe presentation or symptoms seen in these individuals.

What is alogabat?

Alogabat is a molecule known as a positive allosteric modulator which means that it enhances the activity of the $GABA_A$ α5 receptors in presence of the neurotransmitter GABA. Alogabat may restore GABA functioning in AS individuals with deletion genotype and may improve some of the symptoms and potentially aid brain development. This has the potential to elicit a benefit in deletion patients independent of and in addition to the benefit expected from treatments aimed purely at restoring UBE3A function.

What will the alogabat study look like?
The alogabat study is a Phase IIa study. The first part of the study will investigate the pharmacokinetics or what the body does to the drug, and the safety and tolerability of alogabat. The second part of the study is a prove of mechanism that will test different doses of alogabat and its effect at the electroencephalogram(EEG).

The details of the study (trial number: NCT05630066) are as follows:
- The study is an open label study, which means all participants will receive alogabat
- Participants will be provided with alogabat as an oral tablet taken once daily for 12 weeks
- The study is planned to be open to children and adolescents (ages 5-17 years) with AS deletion genotype
- The study is planned to be run in up to 6 countries
- Our aim is to start recruiting in the first half of 2023

We will share further details of the study as soon as possible. In the meantime, we have developed a short Q&A document at the end of this letter which covers some of the key points.

What does this mean for the AS community?
Today's announcement is an important milestone. It opens up a new avenue of research and brings us a step closer to our ultimate goal of delivering effective future treatments for AS. As we are all aware, developing a new medicine is a long and complex process. Progress in research is only possible with your continued cooperation and we are extremely grateful for the support of the AS community. Together we can work towards advancing scientific knowledge about AS and improving the lives of those with AS.

Thank you again for your ongoing support and if you have any queries about this announcement, please do not hesitate to contact us.

Sincerely,

Brenda Vincenzi, MD
Senior Medical Director
PD Neuroscience

Shady Sedhom
Global Patient Partnership Director

Questions and answers

Who will the alogabat trial be open to?
The trial will be open to children and adolescents with AS deletion genotype aged 5-17 years.

When will it start?
We are currently holding discussions with health authorities to finalise the details of the study and we aim to start in the first half of 2023.

Where will the trial be run?
The study is planned to be run in up to 6 countries.

Where can I find further information about the trial?
More information can be found in clinicaltrial.gov and forpatients.com.

How can I ensure my child is enrolled in the study?
If you think your child may meet the trial inclusion criteria, once the study details have been announced and the study begins enrolment, you should speak to your child's physician or specialist.

How will the study sites be selected?
Multiple factors will be considered when choosing our study sites for alogabat. These include applicable international, national and local laws and regulations and the level of experience the potential site has with AS studies. We will also review the infrastructure and capacity the potential site has to run the study alongside their usual site activities, how quickly and effectively they can get the study off the ground, the local AS population and geographical and access factors.

Is Roche planning any other clinical trials in alogabat?
This is the first trial we will be conducting with alogabat for AS patients. Depending on the results, we will consider the possibility of setting up further trials.

Will you still be continuing trials with rugonersen in AS?
Yes. We will be continuing our clinical development program with rugonersen. More information can be found via the clinicaltrial.gov website and our ForPatients website.

Do you consider planning for further clinical trials in Rugonersen only in 2026?

In light of the acceptable safety and tolerability profile of rugonersen, as well as additional preliminary promising signals, we will be analysing the dataset including incoming data from the long-term extension phase in the upcoming months in preparation of the next steps with the goal to proceed with the clinical development of rugonersen before 2026.