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A Message to the Angelman Syndrome Community

Dear Angelman syndrome families and community,

We are writing to you directly because we understand that the recent announcement regarding the negative outcome of the Phase 3 ASPIRE trial of apazunersen (GTX-102) is difficult news, and we have heard requests from the community for an update on our plans and thoughts.

We know how much hope the AS community brings to every clinical trial, and how much families give their time, trust, and commitment to research. Ultragenyx's news is disappointing, and we share that disappointment with you. To every family who participated in ASPIRE, and to the investigators, study teams, and advocates who made it possible: thank you. Your contributions matter and will help move the field forward.

We also know that news like this naturally raises questions about other investigational antisense oligonucleotides (ASOs), including rugonersen and our ongoing Phase 3 BEACON trial, and we want to address those questions as openly as we can.

Rugonersen is different from apazunersen.

We do not believe the outcome for apazunersen predicts the outcome of rugonersen, nor does it change our commitment to rigorously evaluate rugonersen in the ongoing Phase 3 BEACON trial.

Although rugonersen and apazunersen belong to the same broad class of investigational medicines, called ASOs, **they are distinct molecules**, with different sequences, chemistry, and targets within UBE3A-ATS (the antisense transcript that normally prevents the paternal gene from producing UBE3A protein).

We remain confident in the potential for rugonersen and the BEACON Phase 3 trial.

We remain confident that ASOs targeting UBE3A biology are a promising target for AS therapeutic development. Investigational products or medicines belonging to the same therapeutic class can differ substantially in their potency, molecular properties, biological activity, dose, exposure and distribution in the brain.

Rugonersen was selected after evaluation of more than 2,500 ASOs through extensive *in vitro* (in cells) and *in vivo* (in animals) testing. The combination of promising potency (ability to show effects at low doses) and selectivity (only binding to its target) led to rugonersen being tested in the Phase 1 TANGELO trial.

The TANGELO Phase 1 trial showed that rugonersen has promising potential for improvement in multiple meaningful domains (including cognition and communication), improved the important EEG delta-band, and has an acceptable safety and tolerability profile. All of these data together generate confidence to study rugonersen in the ongoing BEACON Phase 3 trial, where rugonersen is being studied at a dose of 120 mg every 12 weeks.

To be clear, all of this doesn't mean that rugonersen will work. We cannot know how any trial will turn out in advance, and we are not suggesting otherwise to a community that deserves honesty and transparency. The purpose of the Phase 3 BEACON trial is to determine whether rugonersen can provide meaningful benefit to individuals with Angelman syndrome.

Our commitment

What we can promise is to follow the science, put participant safety first, conduct BEACON with the greatest rigor, and communicate openly and promptly with this community about what we learn.

We remain hopeful about the potential of rugonersen and, above all, deeply committed to the individuals and families living with Angelman syndrome. Thank you for your continued trust.

Sincerely,

Brenda Vincenzi

Brenda Vincenzi, MD

Chief Medical Officer, Oak Hill Bio

Frequently Asked Questions

Does the ASPIRE result mean that ASOs do not work in Angelman syndrome?

We don't believe so. One clinical trial cannot determine whether every ASO will or will not work in Angelman syndrome. Investigational products or medicines belonging to the same therapeutic class can differ substantially in their potency, molecular properties, biological activity, dose, exposure, and distribution in the brain. Clinical trials can also differ in the participants studied, treatment duration, and how benefit is measured. As previously stated, laboratory and animal studies showed that rugonersen had greater potency than apazunersen when restoring UBE3A protein production.

We will carefully evaluate the ASPIRE results when they become available, but ultimately rugonersen will be evaluated on its own data.

What makes rugonersen different?

Rugonersen is a distinct ASO that was selected through an extensive discovery program evaluating more than 2,500 candidate ASOs. Rugonersen was selected for further development based on demonstrating exceptional potency in restoring UBE3A protein and specificity. We believe it is also supported by the most extensive peer-reviewed data showing its preclinical and clinical activity.

Could the ASPIRE results affect BEACON?

We take results from every Angelman syndrome study seriously and will carefully review the complete ASPIRE data when they become available.

We remain committed to the Angelman syndrome community.

What if BEACON does not show benefit?

No clinical trial outcome can be guaranteed. BEACON is being conducted to determine whether rugonersen provides meaningful clinical benefit and to further characterize its safety profile.

Whom should families contact with questions?

We know you may have questions that are specific to your own situation, and we want you to have somewhere to bring them. If you are part of a clinical study, your study investigator or study team is the best first call; they know your circumstances and can talk it through with you. Also consider reaching out to your

treating physician, your Angelman syndrome clinic, or your patient advocacy organization.