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Update on Rugonersen Development and Planned Phase 3 Study (BEACON)

Dear Members of the Angelman syndrome community,

We would like to share an important update on the next steps of the development of rugonersen, our investigational therapy designed to restore UBE3A expression in individuals living with Angelman syndrome (AS).

We recognize how much hope, emotion, and anticipation accompanies every milestone in Angelman syndrome research, and we are deeply grateful to the families, caregivers, clinicians, and advocates who continue to make this work possible.

Following constructive discussions with the U.S. Food and Drug Administration (FDA), Oak Hill Bio has finalized the design of the global Phase 3 pivotal (meaning intended to support regulatory approval) clinical trial called BEACON. This trial is intended to evaluate the efficacy and safety of rugonersen in individuals with Angelman syndrome.

This represents a significant milestone in our development program and an important step toward bringing a potentially disease-modifying therapy to the individuals and families of the AS community.

About the Phase 3 Study (BEACON)

BEACON is designed as a randomized, multi-center, double-blind, sham-controlled, Phase 3 clinical study to evaluate the efficacy and safety of intrathecally administered rugonersen in pediatric and adult participants with Angelman syndrome.

The study is expected to:

- Enroll approximately 165 individuals aged 1–50 years with genetically and clinically confirmed diagnosis of Angelman syndrome (mutation or deletion)
- Randomize participants 1:1 to either rugonersen or sham control arm

- Evaluate the impact of rugonersen on clinically relevant outcomes, including cognition, expressive communication, and other key domains
- Evaluate the safety profile of rugonersen

The BEACON study consists of two parts. Part 1 includes screening, a 48-week double-blind treatment period, and follow-up through Week 60. During this phase, participants will be randomly assigned to receive either rugonersen or sham treatment, and neither families nor study staff will know which treatment the participant is receiving.

Participants who complete Part 1 may then enter Part 2, an approximately 2 year open-label extension (OLE). In the OLE, all participants will receive rugonersen every 12 weeks, regardless of the treatment assignment they received during the double-blind portion of the study. Total participation in the study may therefore extend to approximately 3 years.

Building on the Results from TANGELO

The Phase 3 program is informed by results from the phase 1 TANGELO study of rugonersen (Link) published in Nature Medicine, which showed:

- Reductions in abnormal brain activity (epileptiform discharges), measured by EEG, compared with natural history
- Observed improvements in certain developmental and communication measures in some participants, compared with natural history
- A safety profile that supports continued clinical investigation of rugonersen

While these results are encouraging and suggest that rugonersen's therapeutic approach may help address the underlying cause of Angelman syndrome, they are still preliminary. The upcoming Phase 3 BEACON study is designed to help us demonstrate these findings in a larger, well-controlled trial and better understand the potential benefits of rugonersen for the treatment of Angelman syndrome. We have designed this study with the feedback and advice of the regulatory agencies, clinicians, and patient organizations to support our goals of obtaining regulatory approval for rugonersen and bringing a potentially disease-modifying therapy to the individuals and families of the AS community.

Our commitment to the Angelman syndrome community

We recognize the urgency felt by families and caregivers and the need for effective therapies. There are currently no approved disease-modifying treatments for Angelman syndrome, underscoring the importance of continued research in this field.

We are deeply grateful to all individuals living with Angelman syndrome, their families and caregivers, patient advocacy organizations, and study teams.

Your partnership is essential to advancing research and making progress toward new treatment options.

Next Steps

We are actively preparing to initiate the Phase 3 study in the middle of 2026 and will share additional details, including study locations and eligibility criteria, as they become available, on clinicaltrials.gov (NCT07605429).

OHB is actively collaborating with local agencies in additional regions to expand the BEACON study and will continue to provide updates to the community as progress is made.

We especially want to recognize and thank the individuals and families who participated in the TANGELO study. Their participation and trust helped make this important milestone possible.

We remain committed to transparency and will continue to provide updates as the program progresses.

Sincerely,

Brenda Vincenzi, MD

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Head of Clinical Development
Oak Hill Bio

Q&A

What is rugonersen and how does it work?

Rugonersen is an investigational antisense oligonucleotide (ASO) designed to target the UBE3A-antisense transcript (UBE3A-ATS). In Angelman syndrome (AS), the maternal UBE3A gene is not functioning properly, while the paternal copy is intact but naturally silenced in neurons. Rugonersen is designed to reduce UBE3A-ATS, which may allow the paternal UBE3A gene to become active and produce UBE3A protein in the brain. The goal is to address the underlying molecular cause of AS rather than only treating symptoms.

How is rugonersen administered and why?

Rugonersen is given by intrathecal (IT) administration, meaning it is injected into the cerebrospinal fluid (CSF) through a lumbar puncture (LP) in the lower back. This route is used because ASOs do not effectively cross the blood-brain barrier when given by mouth or standard intravenous injection. IT administration allows the rugonersen to reach the central nervous system directly.

What age groups are in included in the BEACON ph3 study?

The BEACON Phase 3 trial plans to enroll participants aged 1 to 50 years. Approximately 135 pediatric participants aged 1–17 years and approximately 30 adult participants aged 18–50 years are expected to participate. Participants will be randomised 1:1 to the sham arm or to the rugonersen arm.

Is there a placebo included in the BEACON ph3 study? And what does the sham procedure look like?

The BEACON study uses a sham-controlled design (and not a placebo) to maintain blinding and ensure unbiased assessment of outcomes.

The sham procedure is designed to closely mimic the active treatment experience, including participant preparation, positioning, procedural timing, and use of sedation or anesthesia when appropriate. During the sham procedure, a superficial needle prick at the lumbar region will be performed to simulate the active procedure and create a comparable local experience, without administration of rugonersen into the cerebrospinal fluid.

How long is the BEACON study?

The BEACON study has two parts. Part 1 includes screening, a 48-week double-blind treatment period, and a follow-up period through Week 60. Participants who complete Part 1 may enter Part 2, an approximately 116-week open-label extension (OLE), where all participants receive rugonersen every 12 weeks. Total participation could therefore extend to approximately 3 years.

My family is interested in participating in BEACON. How do we enroll in the study?

Families interested in participating in the study may contact the study site team or participating study site to learn more about the trial and determine whether their child may be eligible. After initial contact, the study site team will explain the study procedures, review the eligibility criteria, and answer any questions.

Where will the BEACON study sites be located?

The BEACON study is planned as a global, multicenter trial. Information regarding participating sites and study contacts will be shared as sites become activated and enrollment begins. Updated information will be shared through the study website (soon to be made available), ClinicalTrials.gov, patient advocacy organizations, and study communications.