July 11, 2025

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**What is Angelman Syndrome and Why is This Study Important?**

Angelman syndrome (AS) is a rare and severe neurogenetic disorder that affects about 1 in 20,000 people. Children with AS typically have significant developmental delays, little or no speech, motor challenges, sleep problems, epilepsy, and a unique EEG (brain wave) signature. The condition is caused by the lack of a functioning copy of a gene called *UBE3A* in the brain. Although everyone has two copies of this gene—one from each parent—only the maternal copy is active in neurons. If this copy is missing or not working, the child develops Angelman syndrome.

The paternal copy of *UBE3A* is present but naturally turned off or silenced in neurons. Scientists hypothesized that a therapy designed to "wake up" this silent copy in neurons could help restore some of the lost function. Rugonersen is a promising new investigational drug (an "antisense oligonucleotide" or ASO) designed to do just that. It targets the natural brake that silences the paternal gene, with the goal of reactivating *UBE3A* in the brain and treating the root cause of the disorder.

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**What Did the Study Do?**

The clinical study, called TANGELO, was a first-in-human, Phase 1 study to evaluate the safety, tolerability, drug behaviour and effects on brain function and developmental outcomes of rugonersen in children with Angelman syndrome.
Key features of the study were:

- 61 children aged 1 to 12 years participated.
- The study was conducted in multiple countries, and participants had a genetically confirmed diagnosis of AS (deletions of 15q11-13 or UBE3A mutations).
- All children received the medication directly into the spinal fluid (via intrathecal injection).

- The main goals were to assess:
    - Safety (Were there any serious side effects?)
    - Drug behaviour (How does it spread in the body and how long does it last?)
- Exploratory goals were to assess
    - Effects on brain function (Brain waves)
    - Effects on developmental outcomes.

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**How Did Researchers Measure Brain Function and Developmental Changes?**

To understand whether rugonersen had an effect, researchers used several tools, described below. These tests were used at the start of the study to establish each child's baseline and were assessed again over the course of the study. The results on these tests after treatment with rugonersen were compared to the child's baseline as well as to the expected progression for untreated children with AS (natural history).

**EEG (Electroencephalogram):**

EEG measures the brain's electrical activity through sensors placed on the scalp. Children with AS have distinct brain wave patterns, particularly in the delta frequency range (2–4 Hz), which are high compared to children of the same age without AS. These brain wave abnormalities have been linked to symptom severity. A reduction in delta power may indicate a normalization or healthier pattern of brain activity.

**Bayley Scales of Infant and Toddler Development (Bayley-III):**

In this test, a clinician uses a predefined scoring method to assess cognitive, language, and motor development by directly observing a child's abilities. It is widely used in developmental studies and provides

scores based on the child's performance and abilities compared to expected developmental milestones.

**Vineland Adaptive Behavior Scales (Vineland-3):**

In this test, a clinician conducts a structured interview with a child's caregivers to understand how the child is doing in and adapting to everyday life, including communication, motor skills, socialization, and daily living activities. The Vineland may be especially useful in rare disease trials and complements milestone-directed testing, like the Bayley-III (described above).

**SAS-CGI (Symptoms of Angelman Syndrome-Clinician Global Impression)**

In these tests, a clinician provides an overall assessment of the severity (SAS-CGI-Severity) and change in symptoms over a predefined period of time (SAS-CGI-Change).

**What Did the Study Find?**

**Safety:**

- Rugonersen had a safety and tolerability profile that is acceptable for further clinical development.
- The most common side effect was fever (pyrexia), typically starting a few days after injection and resolving within 2–5 days. Pyrexia is known to occur with other ASO drugs, the same broad class of compounds in which rugonersen belongs. Other side effects included vomiting, ataxia, headache, or increased seizures, which are also common in the AS population.
- No participants had to stop the study due to side effects, and most side effects were mild or manageable.
- One serious fever event led to hospitalization but resolved without long-term consequences.

**Brain Activity (EEG):**

- After treatment, EEGs showed a clear reduction in delta power, which is consistent with a normalization of brain activity closer to a more typical pattern.
- The biggest EEG changes occurred about 6 weeks after dosing and then gradually faded over time, suggesting that regular dosing may be needed to maintain benefits.
- The EEG changes increased with the dose, i.e., the higher dose had a stronger effect on the EEG than the low dose.
- The results from the EEG help to select the optimal dose and dosing frequency for the next clinical study.

**Developmental Progress:**

- Children receiving rugonersen showed improvements compared to what is normally expected in AS, across key domains like communication, cognition, and motor skills.
- These gains were observed in both Bayley and Vineland scores and were noticeable as early as approximately 3 months after the first treatment.
- On a third tool, the SAS-CGI (a clinical impression scale), most clinicians reported that the children showed improvement over time.

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**Why Is This Exciting?**

This is the first published report of a clinical trial in Angelman syndrome to show that a treatment targeting the genetic cause can possibly lead to measurable improvements in brain activity and developmental progress.

The EEG findings suggest that rugonersen may be restoring some UBE3A function and, as a consequence, changing brain activity in a

meaningful way. The consistent pattern of improvement across different tools supports the idea that these changes in brain function may lead to a clinical benefit.

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**What's Next?**

While these results are very encouraging, the study was open-label, meaning everyone knew they were receiving treatment and there was no control arm. As a result, outcomes for the study participants can only be compared to those from natural history studies, which makes comparisons less reliable. To gather sufficient information about effectiveness and safety to evaluate the overall benefit-risk profile of rugonersen, a larger placebo-controlled Phase 3 trial is needed—and is being planned.

The journey toward a disease-modifying therapy for Angelman syndrome is still ongoing, but this study is a major milestone—and a hopeful step forward for families and the AS community worldwide.