May 16, 2024

Dear Angelman syndrome Community,

We are writing to share an update on Ionis' Angelman syndrome program, ION582. On May 16, 2024, we announced positive preliminary results from the Phase 1/2a HALOS clinical trial of ION582 in people with Angelman syndrome. The announcement can be found here. We expect to present detailed findings from the trial at the Angelman Syndrome Foundation (ASF) meeting in July.

Ionis is also pleased to share that we will advance ION582 independently moving forward. Ionis has a proven track record in neurology and a leading pipeline of investigational medicines for serious neurological diseases. Biogen elected not to exercise its right to license ION582.

HALOS is an open-label, Phase 1/2a clinical trial intended to assess the safety and tolerability of ION582 in people with Angelman syndrome. Results from this early-phase trial, while encouraging, must be confirmed in a larger, well-controlled clinical trial. To that end, Ionis plans to review the ION582 Phase 1/2a results with regulatory authorities to inform the next steps in development, including the design of a potential phase 3 clinical trial.

As a reminder, Part 1 of the HALOS trial was a three-month, multiple-ascending dose (MAD) study in 51 patients aged 2-50, which evaluated three doses of ION582. All eligible patients transitioned into the Part 2 long-term extension (LTE) portion of the study, which is ongoing. The Part 2 LTE is evaluating the two higher doses of ION582 for an additional 12 months. Part 3 of the study will evaluate eligible patients for an additional three years.

We are grateful to the HALOS clinical trial participants and their families. We recognize the personal sacrifices made by individuals and families involved in clinical trials. Their participation, along with the support of the entire Angelman syndrome community, is critical to advancing the scientific and medical understanding required to make progress toward a treatment for those living with Angelman syndrome. We look forward to working with the community to advance ION582 to the next stage of development.

Sincerely,

The Ionis Angelman Syndrome Team
For additional questions, please contact: patients@ionisph.com

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Key Questions and Answers

1. **What is the current status of the ION582 development program and the HALOS trial?**
   HALOS is an open-label, three-part clinical trial to evaluate safety and tolerability of ION582 in people with Angelman syndrome. Part 1 of the trial, a three-month, multiple-ascending dose study, is complete and all eligible participants transitioned into the Part 2 long-term extension (LTE) portion of the study, which is ongoing. The Part 2 LTE will evaluate ION582 for an additional 12 months. Once eligible participants have completed both Part 1 and Part 2, they can then transition to the Part 3 LTE portion to continue receiving ION582 for an additional three years. Preliminary findings from HALOS were reported at the Foundation for Angelman Syndrome Therapeutics (FAST) meeting in November 2023.

2. **What are next steps for the ION582 development program?**
   Ionis plans to review the ION582 Phase 1/2a results with regulatory authorities to determine the next steps in development, including the design of a potential phase 3 clinical trial. We understand the urgent need for medical advancements in Angelman syndrome and will continue to provide updates to the community when appropriate.

3. **What is ION582?**
   ION582 is an investigational antisense oligonucleotide (ASO) designed to increase the production of the UBE3A protein in the brain.

4. **Can ION582 be accessed outside of the HALOS clinical trial, such as through an expanded access program?**
   Evaluation of the safety and efficacy of ION582 in clinical trials is essential to establishing whether ION582 can help people with Angelman syndrome. For this reason, ION582 is not available outside this clinical trial, including via expanded access. For more information about Ionis' expanded access policy, click here.

5. **Why did Biogen choose not to exercise its option to develop ION582?**
   We defer to Biogen, but they made the decision they felt was best given their internal company considerations.

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