Update on the Ionis Development Program for Angelman Syndrome

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Ionis Pharmaceuticals

Disclosure

I am a proud employee of Ionis Pharmaceuticals

- This material contains scientific information about investigational medicines that are not approved by the Food and Drug Administration (FDA) or any regulatory body
- This information is provided exclusively for educational purposes by Ionis and is not intended to provide medical advice
- Questions about medical care should be discussed with your clinical team, who understands your family's unique situation and needs

Thank you to the Angelman Syndrome Community and HALOS and REVEAL participants, their families and caregivers!

Foundation for Angelman Syndrome Therapeutics
FAST

Angelman Syndrome Foundation
ASF

Angelman Biomarkers & Outcomes Measures
A-BOM

Angelman Syndrome Alliance
ASA

Israeli Angelman Syndrome Foundation

Angelman Syndrome Organization
OR.S.A

The Pioneer

in RNA-targeted medicines

Biotechnology Company
Founded 1989

Headquarters
Carlsbad, CA

A Passion to Innovate

Ionis unites groundbreaking science and technology with relentless passion to discover and deliver medicines that enable better futures for people living with serious diseases

Applying our deep neurology antisense oligonucleotide (ASO) expertise to Angelman syndrome

SPINRAZA® (nusinersen) injection 12 mg/5 mL 1#

QALSODY® (tofersen) 100 mg/15 mL injection 2#

WAINUA™ (eplontersen) 45 mg injection for subcutaneous use 3

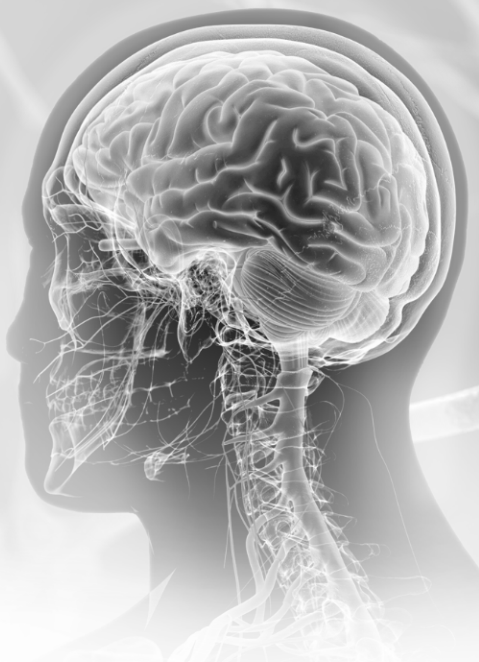
Zilganersen[4]*
Alexander disease
Clinicaltrials.gov NCT04849741

ION440[4]*
MECP2 duplication syndrome
Clinicaltrials.gov NCT06430385

ION464[4]*
Multiple System Atrophy
Clinicaltrials.gov NCT04165486

Salanersen[4]*
Spinal Muscular Atrophy (SMA)
Clinicaltrials.gov NCT05575011

ION717[4]*
Prion disease
Clinicaltrials.gov NCT06153966



Ulefnersen[4]*
FUS amyotrophic lateral sclerosis
Clinicaltrials.gov NCT04768972

Tofersen[4]*
Presymptomatic SOD1 amyotrophic lateral sclerosis
Clinicaltrials.gov NCT04856982

IONIS-MAPT$_{Rx}$/BIIB080[4]*
Alzheimer's disease
Clinicaltrials.gov NCT05399888

Tominersen[4]*
Huntington's disease
Clinicaltrials.gov NCT05686551

ION356[4]*
Pelizaeus-Merzbacher Disease
Clinicaltrials.gov NCT06150716

ION582[4]*
Angelman syndrome
Clinicaltrials.gov NCT06914609
Clinicaltrials.gov NCT05127226

***These investigational medicines are currently in clinical trials and have not been approved by any regulatory authority for marketing purposes in the populations being studied.**

Abbreviations: MECP2, methyl-CpG-binding protein; SOD1, superoxide dismutase; MAPT = microtubule associated protein tau

References: 1. SPINRAZA: www.spinraza.com; 2. QALSODY: www.qalsody.com not approved for use in Australia; 3. WAINUA: www.wainua.com not approved for use in Australia; 4. www.clinicaltrials.gov (Accessed August 4, 2025)

Biogen is responsible for commercializing SPINRAZA and QALSODY

IONIS

Collaboration has been critical to advancing our AS research

	Pre-Clinical	Early Clinical Development	Late Clinical Development
Goal	**Understand the illness**	**Inform clinical trial design**	**Collaborate on design and conduct of clinical trial**
Activities	• Research collaborations[1-3] • Natural history data • ASF and FAST conferences and collaboration • Listening and learning from families	• Consortia participation (e.g., A-BOM; LADDER) • ASF and FAST conferences and collaboration • Listening and learning from families	• Community advisor meetings • Global AS Community Advisory Board (CAB) • Clinical trial site recommendations • Listening and learning from families

fast FOUNDATION FOR ANGELMAN SYNDROME THERAPEUTICS

A-BOM ANGELMAN SYNDROME BIOMARKER & OUTCOME MEASURE CONSORTIUM

CAB ANGELMAN SYNDROME COMMUNITY ADVISORY BOARD

angelman SYNDROME FOUNDATION

ASA ANGELMAN SYNDROME ALLIANCE

אנגלמן העמותה הישראלית לתסמונת

OR.S.A. Organizzazione Sindrome di Angelman ONLUS

1. Meng L, et al. *Nature* 2015;518(7539):409-412, 2. Lee D, et al. *eLife* 2023; 12(81892), 3. Spencer E, et al. *Brain Communications* 2022;4(3)

IONIS

Ionis took a rigorous and collaborative process to develop ION582

Increase UBE3A

The mechanism to upregulate *UBE3A* using an ASO was discovered and validated by Ionis and Dr. Beaudet[1]

Collaborate with doctors

Worked with experts in *UBE3A* and AS biology to understand the target

Demonstrate ASOs provide benefit in models of AS

Seminal publication in *Nature* by Ionis and Dr. Beaudet[1]

Identify ION582

Leveraged 30+ years of experience making ASOs

Work with community to understand their disease and develop markers

Important to monitor for changes in disease trajectory

Clinical testing

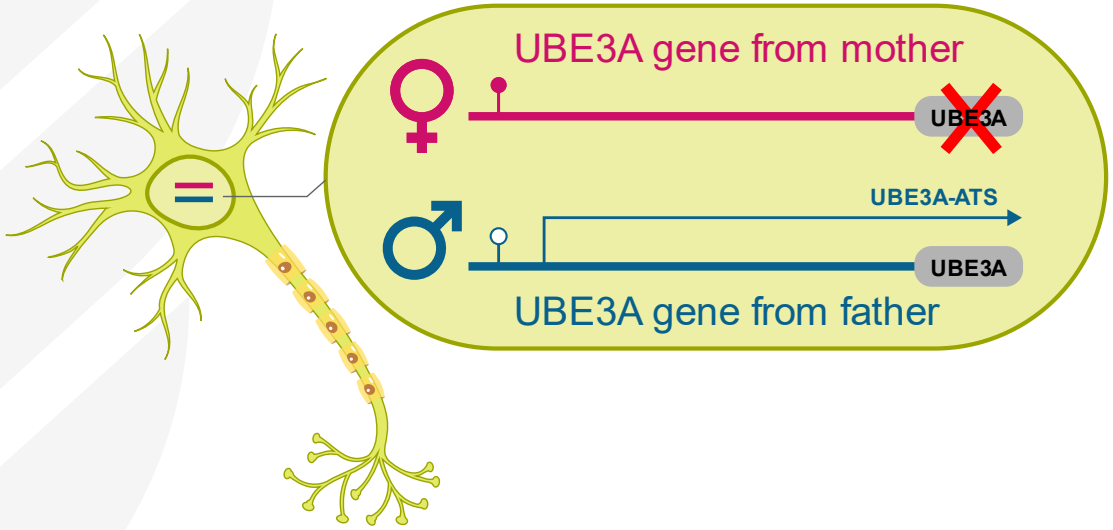
to test safety and efficacy of ASO in individuals

Abbreviations: ASO, antisense oligonucleotide; AS, Angelman syndrome

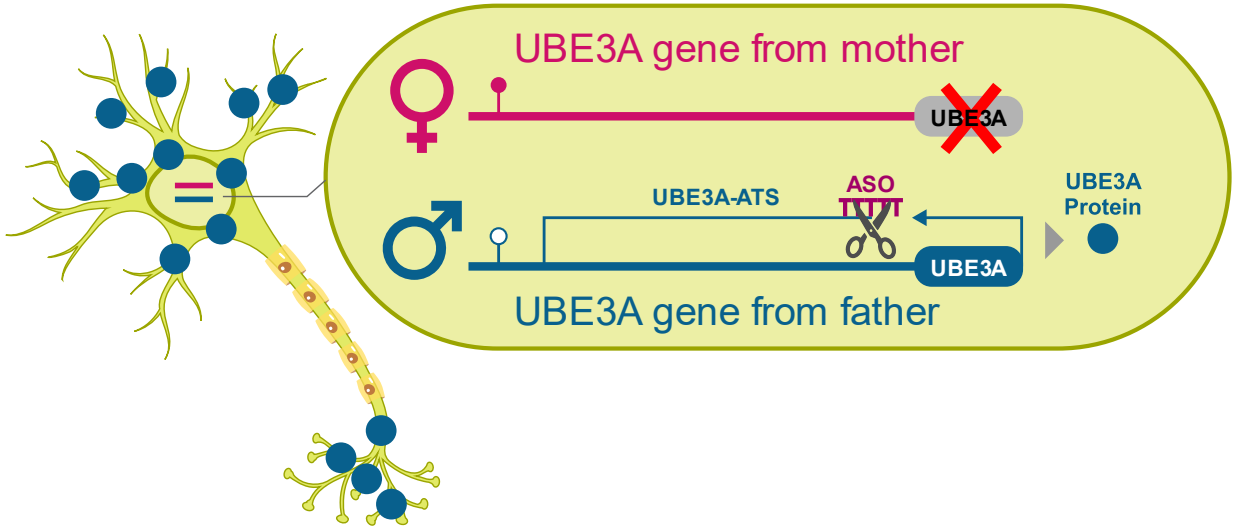
Reference: 1. Meng L, et al. *Nature* 2015;518(7539):409-412

ION582 is an investigational medicine designed to potentially treat Angelman syndrome (AS)[1]

AS Neuron Untreated



AS Neuron Treated with ASO[1]



- AS is caused by loss of the **maternal *UBE3A*** gene (gene deletion, mutation etc.)
- In all people the **paternal *UBE3A*** allele is **silenced** and does not make UBE3A protein **in neurons**
- ION582 is designed to target the UBE3A antisense transcript to unsilence the **paternal allele**

ASO = antisense oligonucleotide

1. Meng L, et al. *Nature* 2015;518(7539):409-412

IONIS

Reminders

- HALOS is small and an open-label clinical trial. It was not designed to establish the safety or efficacy of ION582 as a treatment for Angelman syndrome.
- Results from HALOS were overall encouraging and became the basis for the initiation of a pivotal clinical trial called REVEAL. REVEAL is designed to determine the safety and efficacy of ION582 as a treatment for Angelman Syndrome.
- We are presenting initial results from HALOS only, including newer data from a later data cut from the long-term extension part of the study.

Summary of Ongoing ION582 Clinical Studies

HALOS

Phase 1-2 Global Open-Label Study[1]

- **Designed to evaluate safety and tolerability of ION582 and exploratory measures of clinical function**
  - Deletion and mutation genotypes
  - 55 participants ages 2-50 years old
- **Multiple Ascending Dose (complete)**
  - Evaluated 3 doses of ION582: 20, 40 and 80 mg
- **Long-Term Extension (ongoing)**
  - Participants completing MAD are eligible
  - Participants receive 40 mg or 80 mg ION582 for up to an additional 3 years
- **First under-2-year-old participant was dosed in September 2025**

REVEAL

Phase 3 Global Placebo-Controlled Study[2]

- **Designed to demonstrate safety and efficacy of ION582 in children and adults with AS**
  - Deletion and mutation genotypes
  - Participants ages 2-50 years old
- **Primary objective:** To evaluate if ION582 helps participants improve expressive communication (which is use of sounds, gestures and words to communicate) using the Bayley-4 assessment
- **First participant dosed in June 2025**
- **Study approved in US, Canada, UK, Japan, South Korea and Australia**
- **Ten sites activated**

1. ClinicalTrials.gov. Accessed April 8, 2025. https://www.clinicaltrials.gov/study/NCT05127226; 2. ClinicalTrials.gov. Accessed April 8, 2025. https://clinicaltrials.gov/study/NCT06914609; 3. HALOS data on file

HALOS Ph1/2 Study Update

Participants with
- **UBE3A deletion or mutation**
- **2-50 years old**
- **(enrollment complete)**

Multiple Ascending Dose

Complete → **98%** of participants transitioned to LTE

Long-Term Extension
All Receive ION582 every 12 weeks

~4 years

Average ~2-year treatment duration (up to ~3 years)

Where we are today

Participants with
- **UBE3A deletion or mutation**
- **< 2 years old**
- **(open for enrollment)**

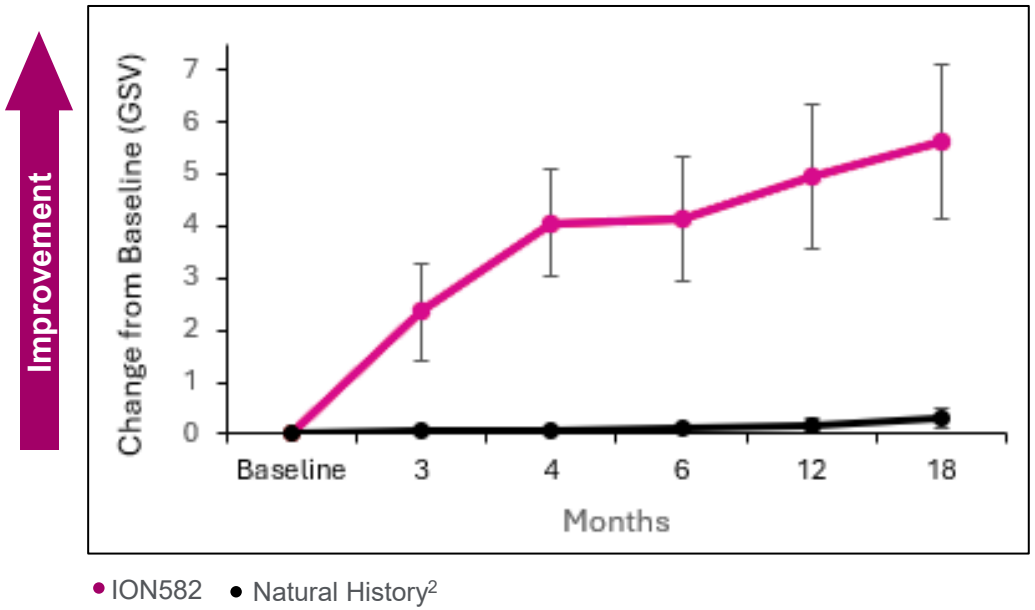
Open-label
All Receive ION582 every 12 weeks

~4 years (up to 15 participants)

Dosed first participant in September 2025
Enrolling in US, EU, and Israel

Expressive Communication: Continued Improvement Observed on Bayley-4 at 18 Months, All Ages and Genotypes[1]

Change on Bayley-4 Expressive Communication ION582 vs. Natural History



Improvements on Bayley-4 measure of expressive communication at 40 mg and 80 mg ION582 exceed natural history[2]

GSV, Growth scale values 1. ≥2 years of age, UBE3A deletion and mutation genotypes, n=35-40 for ION582 treatment. Excludes patients who dose escalated or had a gap in dosing between MAD and LTE. Natural history data compiled from two studies and includes Bayley-3 to Bayley-4 conversion by Pearson. Natural history studies www.clinicaltrials.gov/study/NCT04507997 and www.clinicaltrials.gov/study/NCT00296764.

EEG as a Biomarker in Angelman Syndrome

Non-invasive procedure

20 electrodes (small metal discs) are secured to the scalp while the individual is awake. There are no medical risks with this procedure.

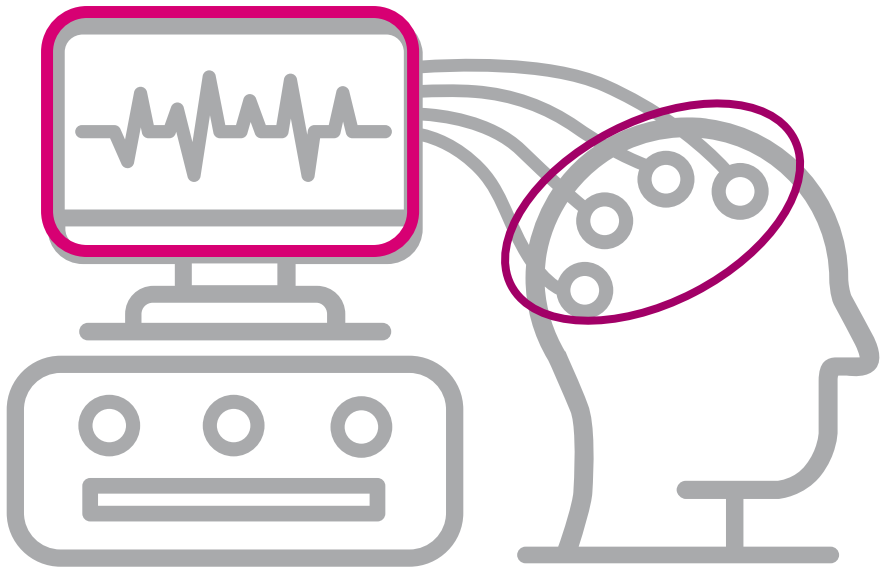
Detects electrical activity from the brain

Brain cells produce small electrical charges which produce waves of electrical activity measurable at the scalp.

Used to evaluate brain function

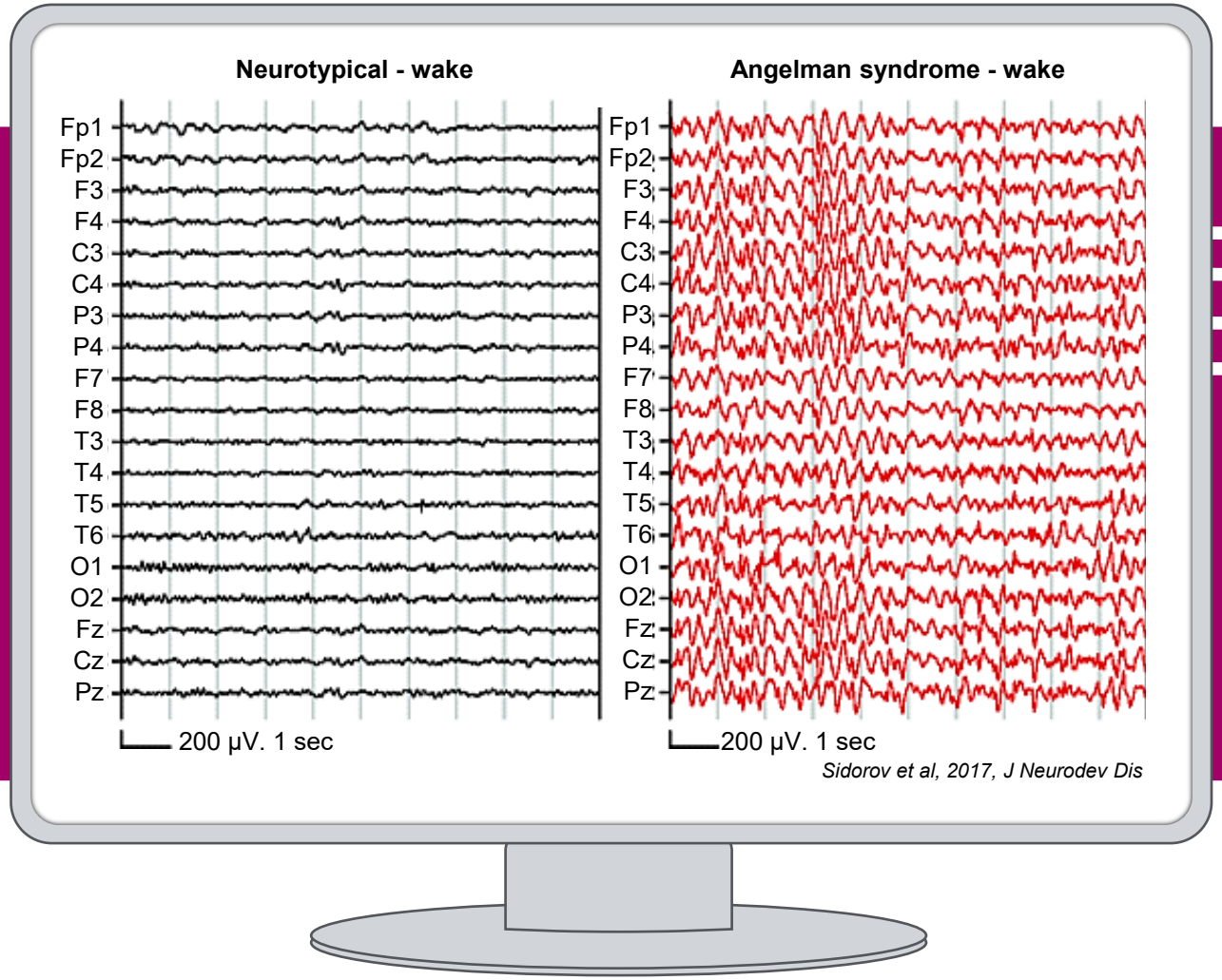
EEG data collected in the HALOS Ph1/2 Study provides more information about brain wave patterns.

What is an EEG?



EEGs are Abnormal in Angelman Syndrome

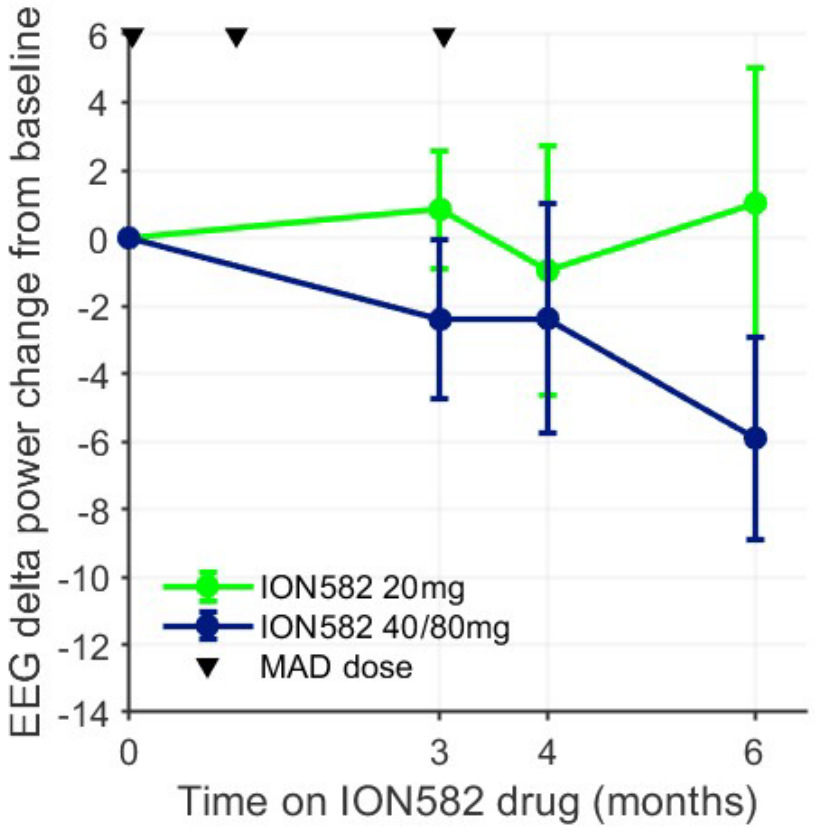
Slow brain waves (Delta waves) are increased in AS



Sidorov et al, 2017, J Neurodev Dis

- **Delta power** has been shown to correlate with cognitive function in AS
- May serve as a **biomarker for treatment** response in clinical trials

ION582 Demonstrates Delta Suppression at 40mg and 80mg Dose Levels



Data are shown as mean / 90%CI; excludes adults

Key takeaways

- Robust delta power suppression at Month 6
- Similar reduction for the 40mg and 80mg cohorts – no observed effect for the 20mg cohort

Number of participants for each ION582 dose group: 20 mg (N=4), 40 mg and 80 mg (N=25-28)

HALOS Conclusions

Participants have **received ION582 for ~2 years on average and up to ~3 years**

Similar reduction in EEG delta power at 40 mg and 80 mg ION582

Expressive communication data indicate improvement through 18 months in both children and adults receiving 40 mg or 80 mg of ION582

Plan to publish HALOS 18-month data in 2026

REVEAL is a global phase 3 trial for children and adults with Angelman syndrome[1]

UBE3A
Mutation & Deletion

Children & Adults
Ages 2-50

Double-blind Placebo
Controlled

Dosing
Every 3 Months

REVEAL

Trial Objectives*

Primary: Evaluate the effect of ION582 on expressive communication (Bayley-4)

Other objectives:

- Cognition (learning and memory)
- Receptive communication (ability to understand others)
- Overall disease severity
- Sleep problems
- Motor function (ability to move)
- Daily living skills

Safety:
Monitored by a board of independent physicians

Trial is currently enrolling

Global study:

- 9 sites actively recruiting in US
- Clinical sites around the world will open later this year
- Sites will be posted on clinicaltrials.gov when they are ready to screen potential participants

Trial will last ~3.5 years

Two parts of the trial:

- ~1-year double-blind, placebo-controlled period; patients receive ION582 or placebo
- ~2-year long-term extension; everyone receives ION582

*As measured by Bayley-4, Symptoms of Angelman Syndrome-Clinical Global Impression-Change (SAS-CGI-C), Vineland Adaptive Behavior Scales-3, Observer-Reported Communication Ability (ORCA) Measure

1. ClinicalTrials.gov. Accessed April 8, 2025. https://clinicaltrials.gov/study/NCT06914609

IONIS

Bayley-4 Expressive Communication

EXPRESSIVE COMMUNICATION

Preverbal (babbling, gesturing)

Verbal (naming objects/pictures)

RECEPTIVE COMMUNICATION

Comprehension of verbal and non-verbal communication, identify object/pictures

COGNITIVE

Learning, memory, concept formation

FINE MOTOR

Reaching, object manipulation, and grasping

GROSS MOTOR

Locomotion and coordination, balance

What does it evaluate?

- How your child communicates with others through sounds, gestures, words, and other ways of expressing themselves

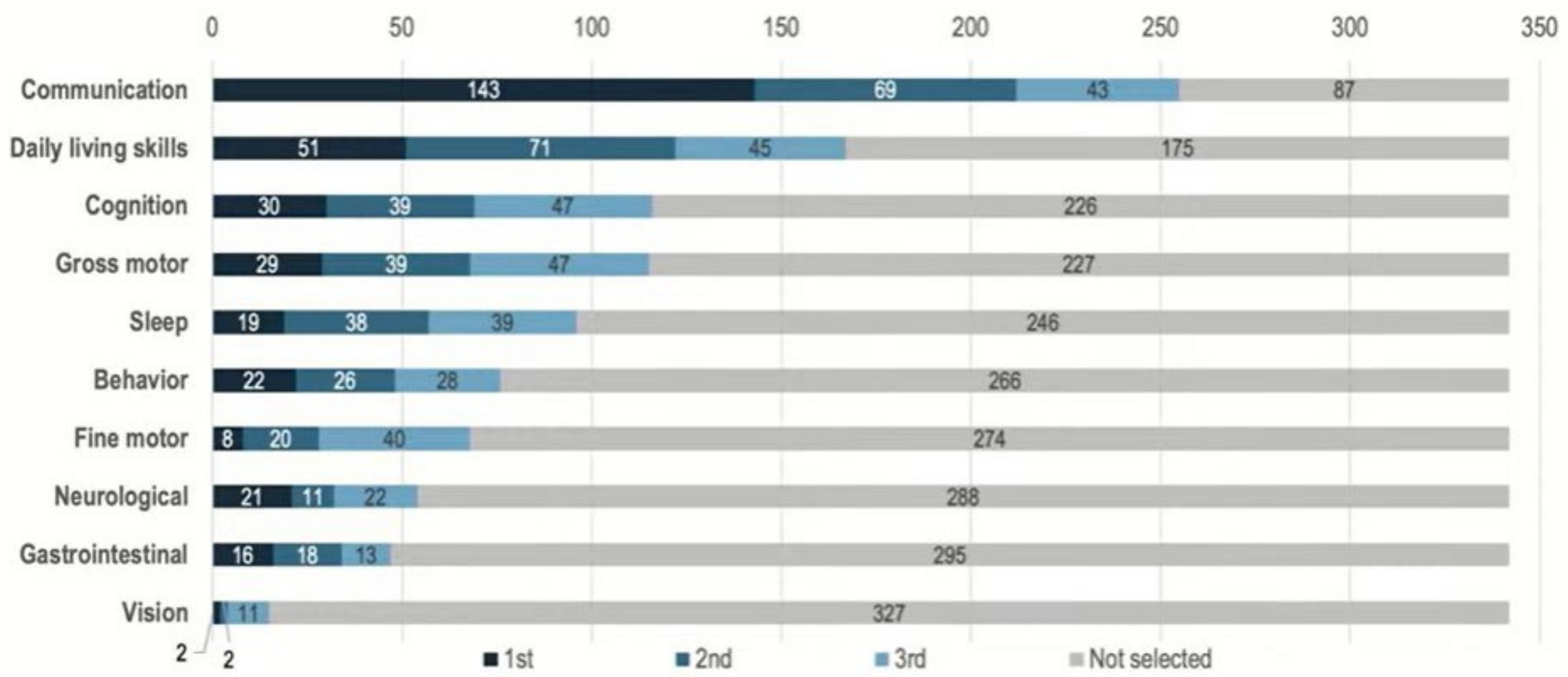
How is it administered in the clinic?

- Clinician will talk or play with your child to see how they respond
- Observe how your child uses gestures or vocalizations to get attention or show interest
- Look for signs that your child understands how communication works — even if spoken words aren't used yet

Most Impactful Symptom for Families of People Living with Angelman Syndrome: Communication

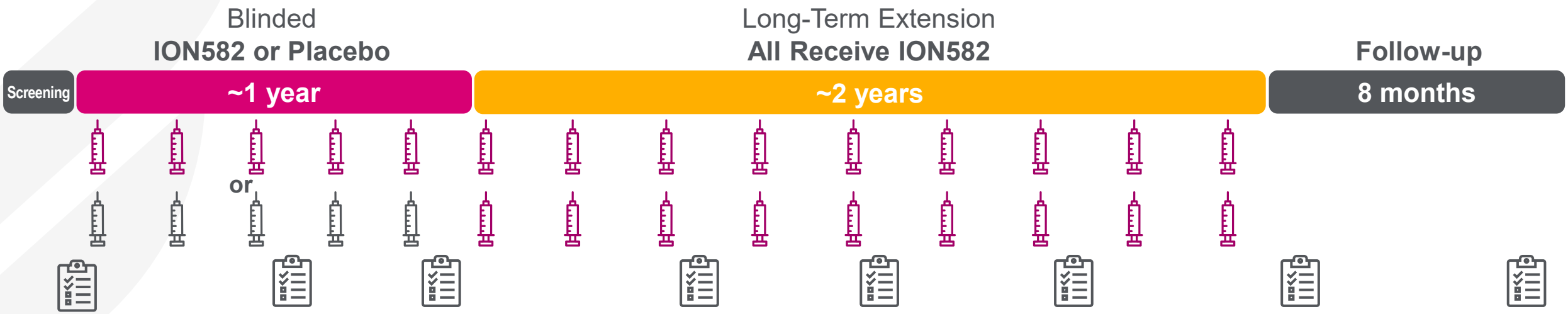
ASF/FAST survey from Angelman syndrome EL-PFDD meeting in April 2025[1]

Top 3 'symptom domains' having most impact on individuals with Angelman syndrome



1. ASF and FAST Hope in Action Survey results from the April 7, 2025, Externally-led PFDD meeting. Survey included n=342 caregiver respondents, reporting on people living with Angelman Syndrome who were 53% male, 64% deletion, 16% mutation and 13% UPD/ID, with a mean age 11.3 years (1-51). Meeting recording available: https://angelmanadvocates.org/el-pfdd-meeting. Voice of the Patient report pending.

What would participation in REVEAL look like?



- **9 in-person clinic visits** during Screening and Double-Blind Period
- 5 doses of ION582 or Placebo

- **14 in-person clinic visits** during Long-Term Extension and Follow-up Periods
- 9 doses of ION582

In Clinic and Home Assessments*

- Cognition
- Communication
- Overall disease severity
- Sleep problems
- Motor function
- Daily living skills

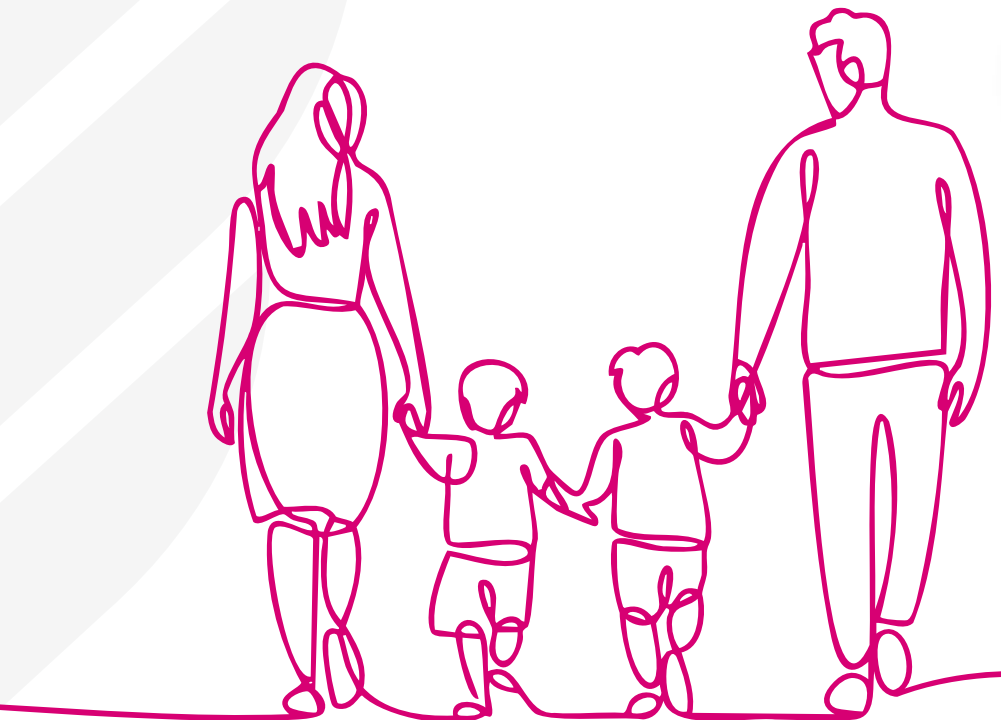
ION582 Intrathecal Injection

Placebo Intrathecal Injection

*As measured by Bayley-4, Symptoms of Angelman Syndrome-Clinical Global Impression-Change (SAS-CGI-C), Vineland Adaptive Behavior Scales-3, Observer-Reported Communication Ability (ORCA) Measure

NOTE: Trial design elements represent our current thinking and may be modified.

CHAMPION will be a Phase 3 study in individuals with AS and a genetic diagnosis of Uniparental Disomy (UPD) or Imprinting Defect (ID)



Plan to include **children** and **adults** with **UPD or ID**

Study initiation planned for **2026**

Summary

REVEAL Pivotal Study is ongoing

On track to complete enrollment in REVEAL Phase 3 study in 2026[1]

Open label HALOS Ph1/2 Study is ongoing

Continue generating longer-term data in ongoing LTE[2]

Currently enrolling 0-2-year-old infants in US, EU, and Israel

Initiating UPD/ID study next year

Advancing study with input from FAST/ASF Hope in Action survey and UPD/ID Caregiver Advisory Board

1. ClinicalTrials.gov. Accessed April 8, 2025. https://clinicaltrials.gov/study/NCT06914609
2. ClinicalTrials.gov. Accessed April 8, 2025. https://www.clinicaltrials.gov/study/NCT05127226
*Timing based on current estimates and subject to change.