# HALOS Clinical Trial Update: ION582 in Individuals Living with Angelman Syndrome

FAST 2023


Jackson,
Angelman Syndrome Patient

# What Will We Talk About Today?

HALOS

Review the HALOS Phase 1-2a clinical trial testing the safety and tolerability of ION582, an antisense oligonucleotide (ASO) designed to increase production of the UBE3A protein

**Summary**

**The HALOS trial is on-going and patients move through the Part MAD portion (Part 1 Multiple-Ascending Dose: MAD) and then transition to the Part 2 Long-Term Extension (LTE) portion of the study**

Present high-level findings assessing the safety and tolerability of ION582 from Part 1 MAD

**Summary**

**All doses have been well tolerated and participants will continue dosing in Part 2 Long Term Extension**

Discuss preliminary Part 1 MAD findings assessing the impact of ION582 on clinical measures of symptoms of Angelman syndrome

**Summary**

**Preliminary findings are encouraging; however, a longer period of treatment will be needed to understand and confirm any potential treatment benefit**

# What are the Goals of the HALOS Trial?

HALOS

Every clinical trial, every phase, has a specific question it's trying to answer

The **GOAL** of each trial is to design a study that can answer that question as **quickly and efficiently** as possible

## HALOS
### Part 1 MAD Study

- Designed to tell us if ION582 is **safe and tolerated** in individuals living with Angelman syndrome, over a short period of time in a small number of people

## HALOS
### Part 2 LTE Study

- Designed to tell us if ION582 is safe and shows signs of clinical improvement **over a longer period of time**

# Ionis, in Partnership with Biogen, is Developing ION582/BIIB121: An ASO Designed to Stop the Silencing Mechanism on the Paternal UBE3A Gene, to Produce UBE3A Protein in the Brain

HALOS

- **ION582** is a 2'-MOE antisense oligonucleotide which cleaves the ATS by RNase H mechanism, which results in up-regulation of UBE3A protein

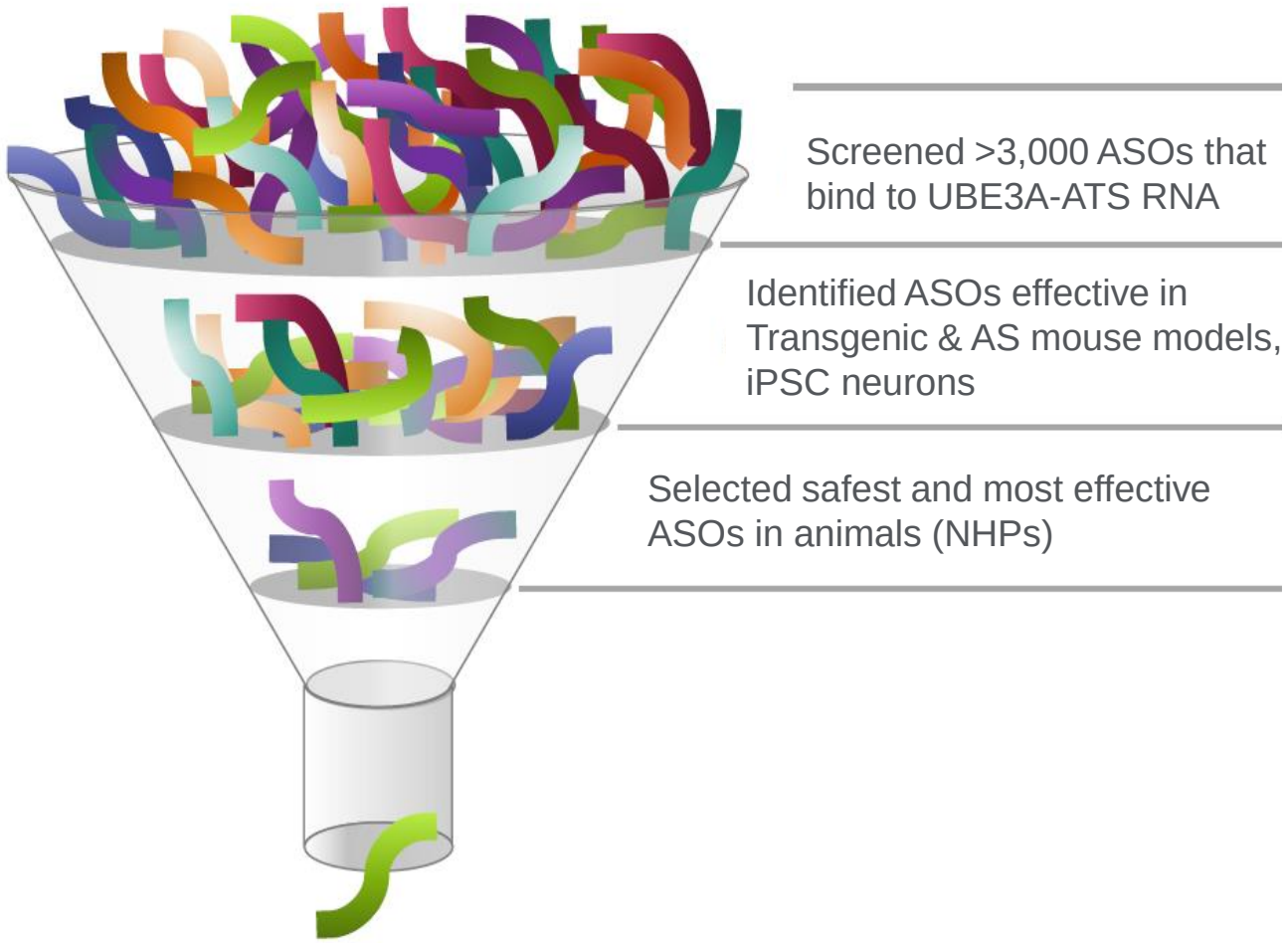
- **Not all ASOs are the same**—different chemistries have different properties
  - 2'-MOE ASOs are designed for **greater potency** for reducing target RNA and **increased tolerability**[1], which is why we choose them for the CNS

- **Ionis has extensive experience with MOE ASOs:** > 11,000 patients treated
  - Spinal muscular atrophy (SMA)
  - ALS / Lou Gehrig's disease
  - Huntington's disease
  - Alzheimer's disease
  - Parkinson's disease

[1] Swayze et al. (2007). Nucleic Acids Res. 35(2): 687-700

# ION582/BIIB121 Chosen For Its Superior Safety and Tolerability

HALOS

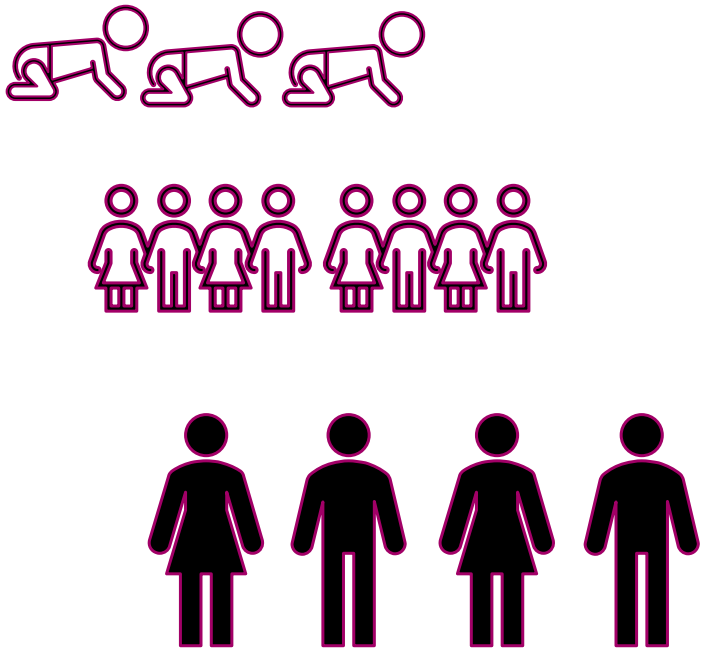


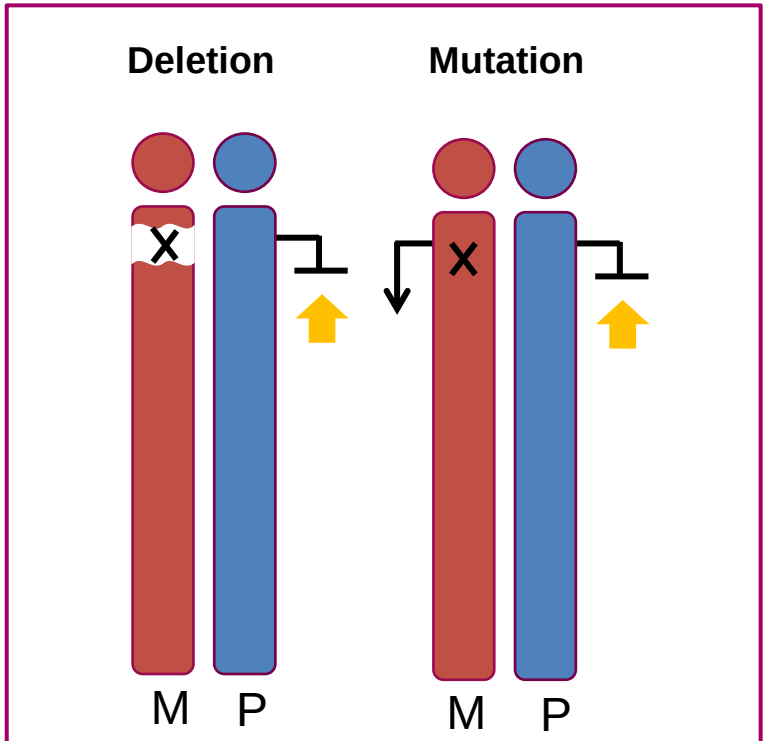

Safe in multiple animal studies at much higher doses and frequency than the regimen in the **HALOS** trial

# All individuals with Angelman may benefit from ION582

HALOS

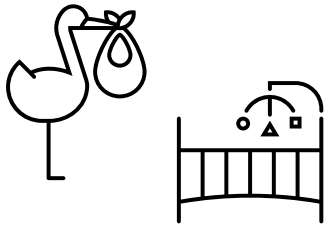
HALOS study includes toddlers (2 years and up) through Adults (up to 50 years) and Deletions (all sizes) and Mutations

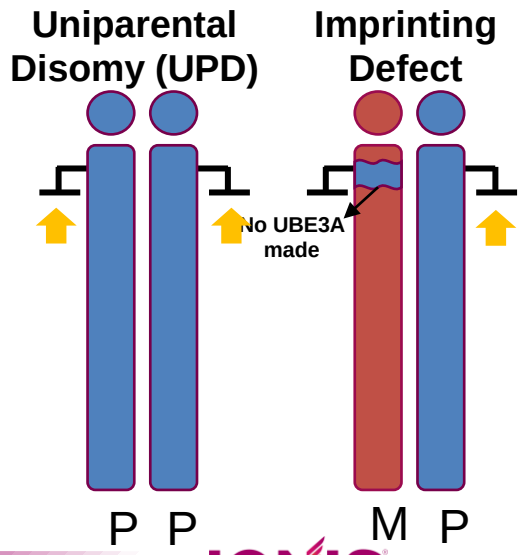





**Additional studies needed**

- *We will include these in future studies*





# HALOS is a Global Clinical Trial Across **11 Sites** in **6 Countries**

HALOS

**All sites have contributed to enrollment**

# HALOS Study Design

HALOS


## GOALS

Assess **Safety and Tolerability** of **ION582**

The ASO is administered intrathecally into the cerebral spinal fluid with a lumbar puncture

All participants are given sedation prior to each drug administration

## Safety and Tolerability

### Participants:

- A minimum of 44 Males and Females
- 2-50 years old
- Deletions and mutation genotypes

### Study Design:

Phase 1-2, First-in-Human

**Part 1 MAD**

Three doses of **ION582 over 3 months**

**Part 2 LTE**

Dosing with **ION582** for an **additional 12 months**

- All receive active drug; **No Placebo**

### Outcomes:

- Measure clinical changes in areas like communication, cognition, motor, sleep, seizures and everyday functioning
- **Generate data to select optimal doses and regimens for next phase**

# HALOS Study Design

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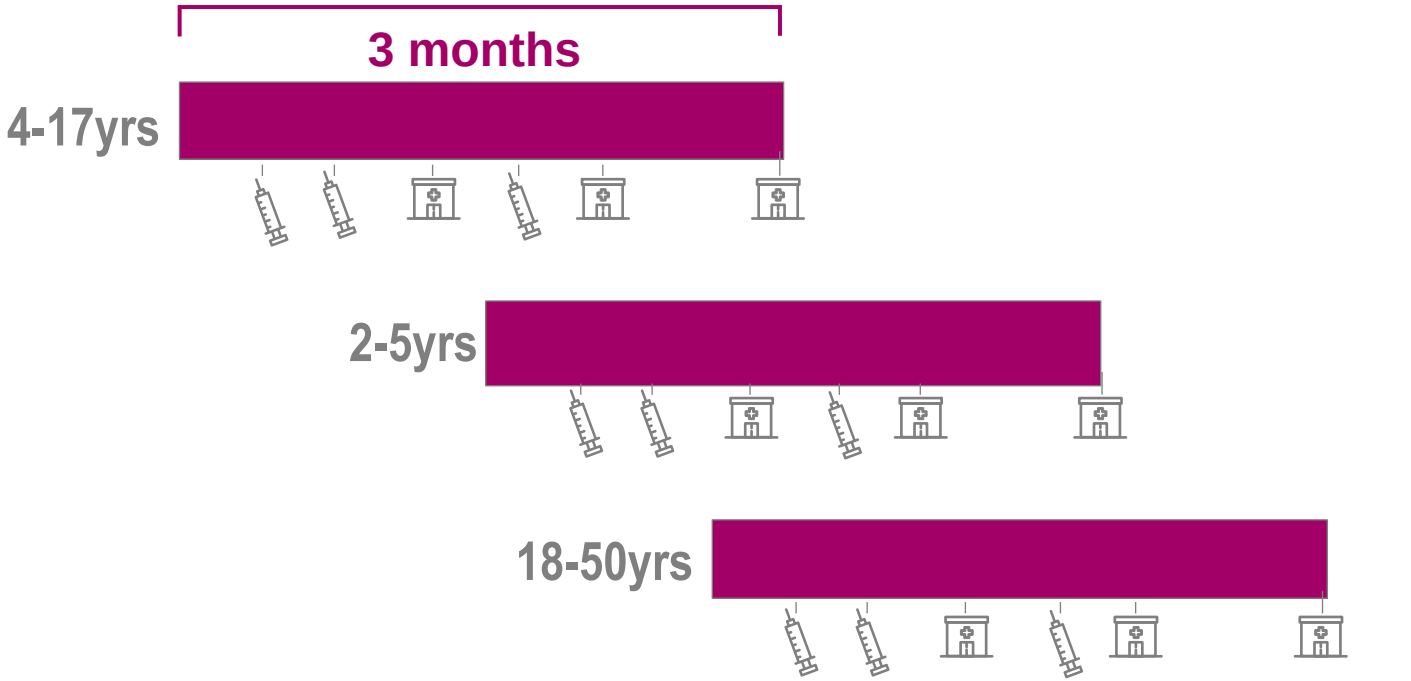
## Part 1 MAD

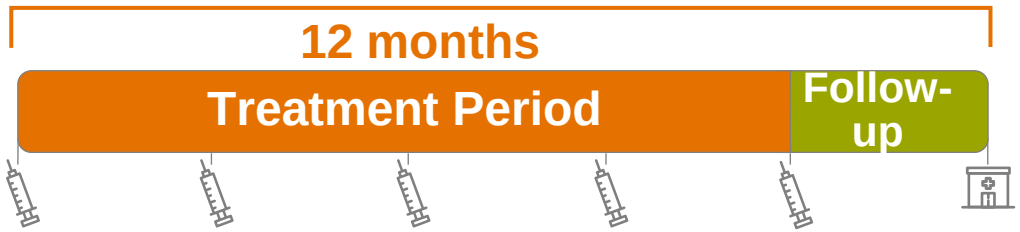



Dosing with ION582 and clinical assessment

In-clinic safety & clinical assessments

ALL Participants

## Part 2 LTE



# Part 1 MAD has Completed Enrollment!

## All 11 Sites Enrolled Participants and Families into the HALOS Trial

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This is an important milestone that **the community helped us accomplish**

We'd like to share some preliminary findings from this **Part 1 MAD**

- These data are from an early data cut, as of October 2023, and are not the final data from the entire study
- Data are pooled for all dose groups

# ION582 Has Been Well-Tolerated at All Dose Levels

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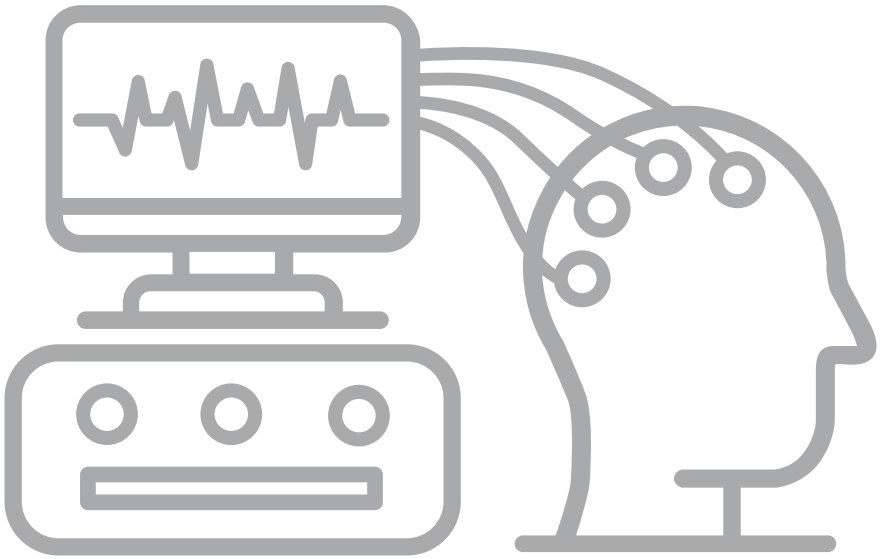
- **Independent Safety Monitoring Committee** reviews all data on an on-going basis, and to date, no concerning safety trends have been observed
- **Adverse events (AEs) have been reported during the trial**, and the majority of AEs are consistent with the patients' medical histories, diagnosis of AS, and/or findings related to the LPs
- **No trends** in safety labs (CSF, blood, or urine)

| Age Group | N | Mean Age (Range) | Sex | Molecular Diagnosis |
|---|---|---|---|---|
| 4-17 years old | 28 | 8.0 (4 - 17) | 17M, 11F | 22 Del 6 Mut |
| 18-50 years old | 9 | 23.9 (20 - 34) | 5M, 4F | 9 Del |
| 2-5 years old | 14 | 3.0 (2 - 5) | 7M, 7F | 12 Del 2 Mut |
| **Total** | **51** | **9.9 (2 - 34)** | **29M, 22F** | **43 Del 8 Mut** |

# EEG as a Biomarker in Angelman Syndrome

## What is an EEG?



**Non-invasive and painless**

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. The intensity of these waves can be measured

**Used to evaluate brain function**

Commonly used in neurology to detect brain activity associated with seizures or to look for evidence of damage to the brain cause by tumors or stroke

# What Do We Know About EEGs in Angelman Syndrome?

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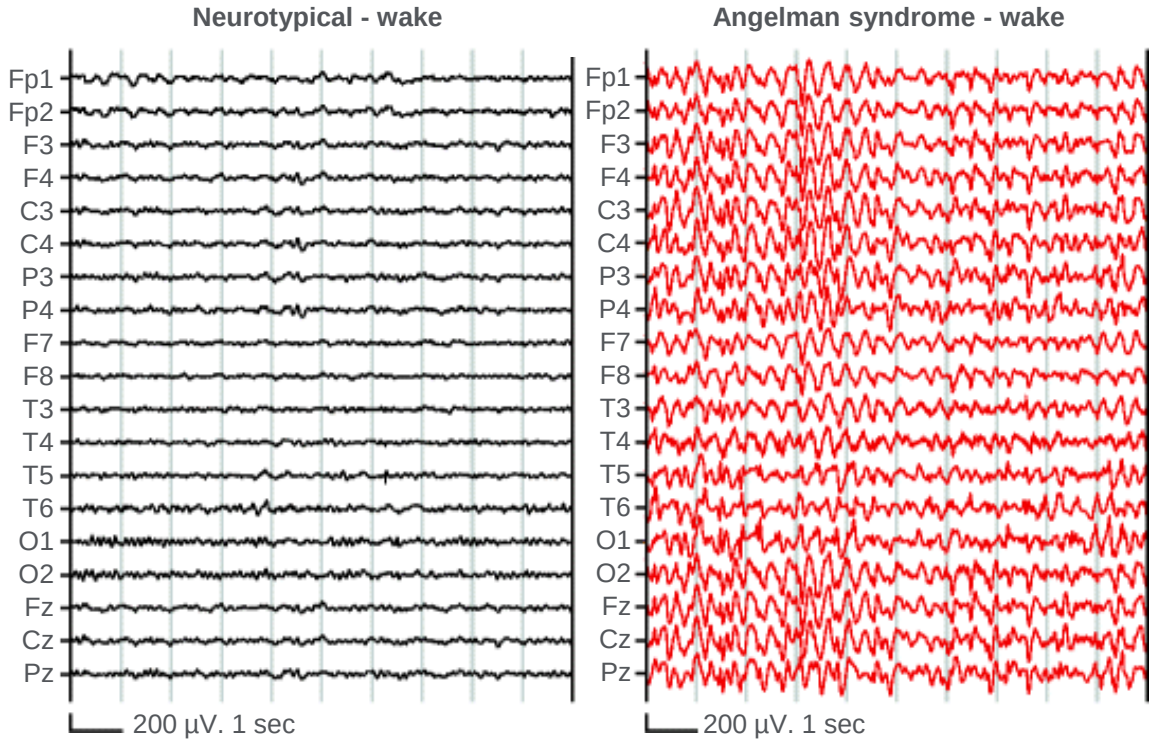
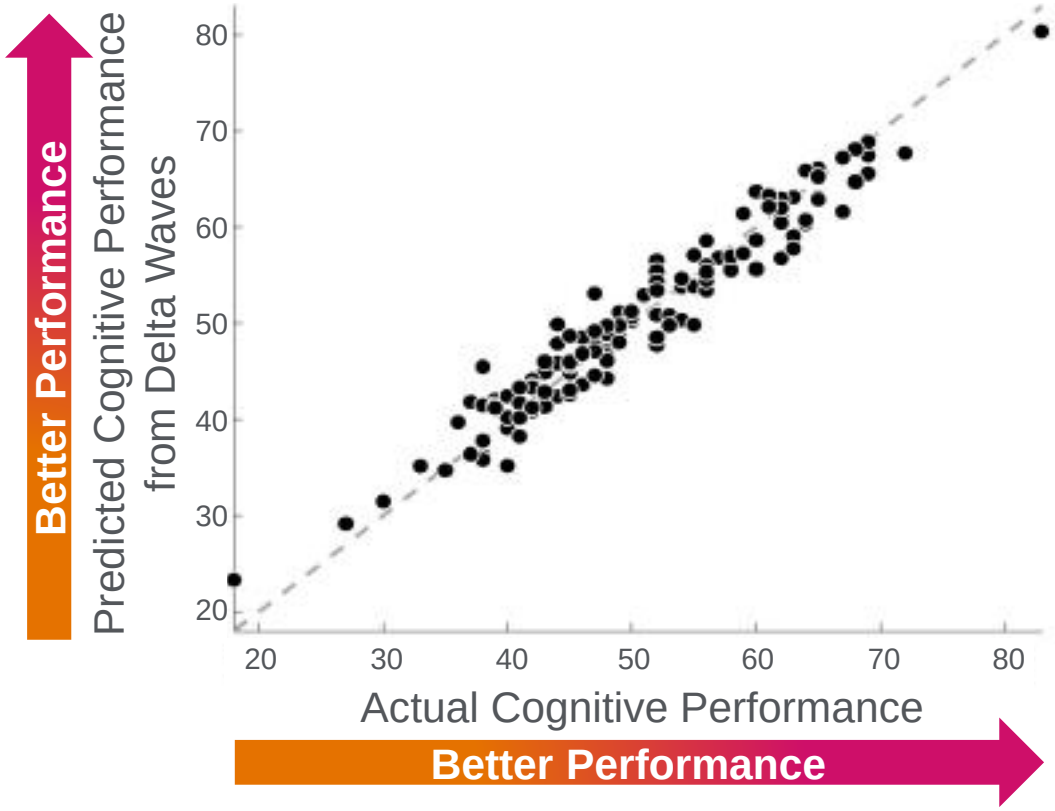
## EEGs are Abnormal in Angelman Syndrome

Slow brain waves (Delta waves) are increased in AS




*Sidorov et al, 2017, J Neurodev Dis*

## Size of Delta Waves Predicts Clinical Severity in AS




*Modified from Ostrowski et al., 2021, Annals of Clinical Translational Neurology*

**Prediction**: An effective drug for treating Angelman syndrome should improve brain function and reduce Delta Waves

# EEG Delta Activity Shows Early Signs of Improvement in Part 1 MAD

HALOS

**~70%**
of subjects showed

**a reduction**
in slow-wave delta activity compared with baseline, 1 month after last dose in Part 1 MAD

- These findings are consistent with AS animal models treated with ASOs
- **Decrease in delta activity suggests EEG activity is improved**
- Early analyses suggest that the **magnitude of delta reduction over 4 months exceeds the decrease in delta activity observed in EEGs in Angelman natural history studies**

**Over 80%**
of subjects showed

**an increase**
of faster frequency rhythms (theta) compared with baseline, 1 month after last dose in Part 1 MAD

- Increase in higher frequency rhythms also suggests EEG activity is improved

# How are We Measuring Improvement in Symptoms of Angelman Syndrome in HALOS?

HALOS

## Symptoms of Angelman Syndrome-Clinical Global Improvement-Change (SAS-CGI-C)

- **Subjective** assessment of clinical functioning on a 7-point scale

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very much improved | Much improved | Minimally improved | No change | Minimally worse | Much worse | Very much worse |

- Clinician impression of the subject anchored to 9 key areas of functioning in Angelman syndrome

1) Cognitive Impairment
2) Expressive Communication
3) Fine Motor
4) Gross Motor
5) Maladaptive behaviors
6) Activities of daily living
7) Seizures
8) Sleep
9) Overall AS

## Bayley Scales of Infant and Toddler Development- 4 (Bayley-4)

- **Direct** assessment of clinical functioning
- Measures general cognitive functioning, gross and fine motor skills, expressive and receptive language
- Performance on previous version of Bayley in Natural History & Freesias NH data shows stable performance with some improvement over time (⬆ = a few points per year)

# Early Signals of Clinical Changes Observed 1 Month After Final Part 1 MAD Dose

HALOS

Majority of the participants demonstrated some level of improvement in overall functioning, as rated by the clinician on the CGI-Change

- Clinicians reported that improvement in overall AS symptoms was considered meaningful

Majority of participants showed some level of improvement in total Bayley score

- This change is beyond changes in Natural History studies over the same time period

# What Happens Next?

HALOS

## 1. Complete data accrual and analysis from Part 1

- Preliminary findings in Part 1 demonstrate ION582 is well-tolerated and showing encouraging signals of clinical improvement compared to Natural History
- Early findings are promising but the safety of ION582 and trends for improvement need to be assessed with the full data set
- Final data read-out from Part 1 MAD expected mid-2024

## 2. Participants will continue in Part 2 LTE of HALOS

- Longer-term dosing will provide the necessary safety and clinical data to determine next stage of development for ION582

## 3. Complete analyses and publish results from pre-competitive natural history studies

- UBE3A CSF biomarker assay
- FREESIAS natural history study

# Thank You to the HALOS Participants, their Families and Caregivers!

HALOS

## Study Sites

-Boston Children's Hospital
-Children's Hospital Colorado
-Rady Children's Hospital
-Rush University Medical Center
-Texas Children's Hospital
-University North Carolina
-Sheba Medical Center, Israel
-Necker Infant's Hospital, France
-University Pisa, Italy
-Sydney Children's Hospital, Australia
-Oxford University Hospital, UK

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fast cureangelman.org

**Foundation for Angelman Syndrome Therapeutics**
FAST

angelman SYNDROME FOUNDATION

**Angelman Syndrome Foundation**
ASF

ASA ANGELMAN SYNDROME ALLIANCE

**Angelman Syndrome Alliance**
ASA

A-BOM ANGELMAN SYNDROME BIOMARKER & OUTCOME MEASURE CONSORTIUM

**Angelman Biomarkers & Outcomes Measures**
A-BOM