# Angelman Syndrome Webcast

July 22, 2024

Nasdaq: IONS

# Forward-Looking Statements

This presentation includes forward-looking statements regarding our business, financial guidance and the therapeutic and commercial potential of our commercial medicines, ION582, additional medicines in development and technologies. Any statement describing Ionis' goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties including but not limited to those related to our commercial products and the medicines in our pipeline, and particularly those inherent in the process of discovering, developing and commercializing medicines that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such medicines. Ionis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Ionis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Ionis. Except as required by law, we undertake no obligation to update any forward-looking statements for any reason. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Ionis' programs are described in additional detail in Ionis' annual report on our Form 10-K for the year ended December 31, 2023, and our most recent Form 10-Q quarterly filing, which are on file with the SEC. Copies of these and other documents are available at www.ionis.com.

In this presentation, unless the context requires otherwise, "Ionis," "Company," "we," "our," and "us" refers to Ionis Pharmaceuticals and its subsidiaries.

# Agenda

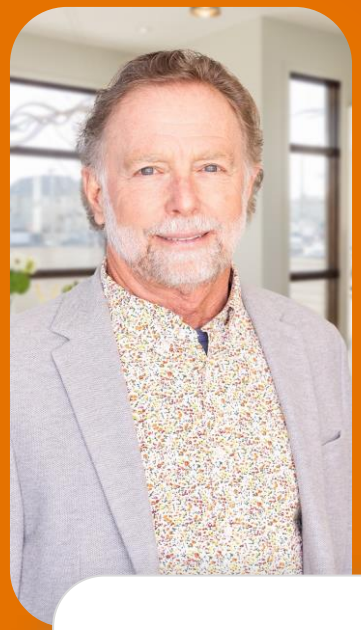
| Topic | Speaker |
| --- | --- |
| **Delivering Next-level Value to Patients & All Stakeholders** | **Brett Monia, Ph.D.** *CEO* |
| **Ionis' Proven Neurology Leadership and Platform** | **Holly Kordasiewicz, Ph.D.** *Senior Vice President, Neurology* |
| **Angelman Syndrome: Perspectives from a Physician and Parent** | **Elizabeth Jalazo, M.D.** *Assistant Professor of Pediatrics, Division of Genetics & Metabolism, University of North Carolina School of Medicine* |
| **ION582: Ionis' Program for the Treatment of Angelman Syndrome** | **Becky Crean, Ph.D.** *Executive Director, Neurology* |
| **Results from the HALOS Study of ION582** | **Lynne Bird, M.D.** *Professor of Clinical Pediatrics, University of California, San Diego, Rady Children's Hospital San Diego* |
| **Concluding Remarks** | **Brett Monia, Ph.D.** *CEO* |
| **Q&A** | |

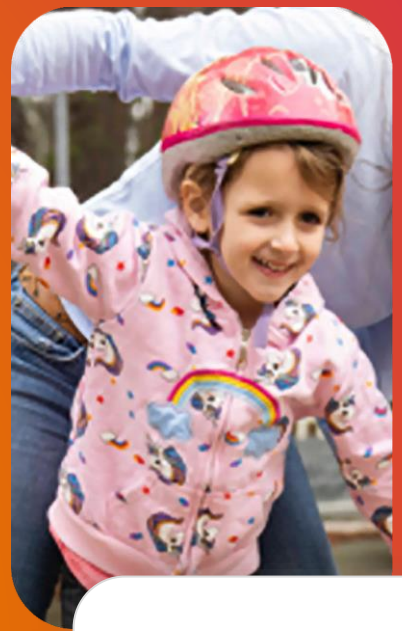
# Delivering Next-level Value to Patients & All Stakeholders

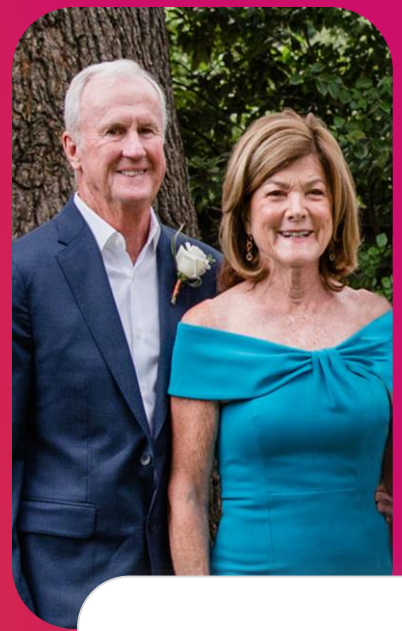
Brett Monia, Ph.D.
Chief Executive Officer

# Next-Level Value for Patients & All Stakeholders

**Turning groundbreaking science and technology into transformational medicines for patients in need**








**Prioritizing and Expanding the Ionis Wholly Owned Pipeline**

**Delivering Ionis Medicines Directly to Patients**

**Leading Technology**

# Realizing the Promise of our Innovative Medicines[1]

## First Ionis-Branded Medicine[2]

WAINUA (eplontersen) 45 mg injection for subcutaneous use

Launched in ATTRv-Polyneuropathy January 2024

Ongoing fully enrolled Phase 3 study for ATTR Cardiomyopathy[3]

Co-developing and commercializing in the U.S. with AstraZeneca

## First Ionis Independent Launches[1,4]

### Olezarsen

Launch in FCS expected by YE:2024[4]

Ongoing fully enrolled Phase 3 program for sHTG

Blockbuster opportunity[5]

### Donidalorsen

Launch in HAE expected in 2025[4]

Efficient commercial organization

Establishing global access

## Next Wave of Wholly Owned Medicines

### Leading Neurology Pipeline

ION582 Angelman syndrome Phase 3 start in H1:2025[1]

7 wholly owned medicines in clinical development by YE:2024[1]

### Emerging Therapeutic Areas

Neuromuscular, cardiac, renal and pulmonary diseases

1. Timing based on current estimates and subject to change. 2. WAINUA: www.wainua.com. 3. Base case data expectation 2026. 4. Assuming approval. 5. In aggregate.

# Ionis-Discovered and Developed Medicines Transforming the Lives of Patients with Devastating Neurological Diseases[1]




**>15,000 Neurology Patients Treated with Transformational Ionis Medicines to Date[2]**

1. Biogen is responsible for commercializing SPINRAZA (www.Spinraza.com) and QALSODY (www.qalsody.com); Ionis is co-commercializing WAINUA (www.wainua.com) with AstraZeneca. 2. Includes patients treated in commercial and clinical settings.

# ION582 for Angelman Syndrome:

Positioned to become the **cornerstone** of Ionis' **wholly owned** neurology **pipeline**


**Jackson**
Living with Angelman Syndrome

## A severe neurodevelopmental disorder of significant unmet need

## Positive early results seen in the HALOS study of ION582[1]:

- Consistent improvements in key areas of clinical function, including communication, cognition and motor function
- Evidence of consistent improvements across age groups and genotypes
- Favorable safety and tolerability profile

## Plan to meet with regulators

## On track to initiate Phase 3 development in H1 2025[2]

1. Based on data generated to date from the Phase 1/2 HALOS study of ION582. 2. Timing based on current estimates and subject to change.

# Ionis' Proven Neurology Leadership and Platform

Holly Kordasiewicz, Ph.D.
Senior Vice President, Neurology

# Leading, Validated and Transformative Neurology Franchise

**3**

**Approved Medicines[1]**

**11**

**Medicines in Clinical Development**

**7**

**Wholly Owned Medicines in Clinical Development by YE:2024[2,3]**

SPINRAZA® (nusinersen) injection 12 mg/5 mL

QALSODY® (tofersen) 100 mg/15 mL injection

WAINUA® (eplontersen) 45 mg injection for subcutaneous use

**Zilganersen**
Alexander disease
(GFAP)

**Ulefnersen**
FUS-ALS
(FUS)

**ION582**
Angelman syndrome
(UBE3A-ATS)

**ION717**
Prion disease
(PRNP)

**ION356**
Pelizaeus-Merzbacher Disease (PLP1)

**ION306**
SMA (SMN2)

**Tofersen**
Presymptomatic SOD1-ALS
(SOD1)

**IONIS-MAPT$_{Rx}$/BIIB080**
Alzheimer's disease
(Tau)

**ION859**
Parkinson's disease
(LRRK2)

**Tominersen**
Huntington's disease
(HTT)

**ION464**
Parkinson's disease and Multiple System Atrophy
(alpha-synuclein)

1. SPINRAZA: www.spinraza.com; QALSODY: www.qalsody.com; Biogen is responsible for commercializing SPINRAZA and QALSODY; WAINUA: www.wainua.com. 2. Wholly owned programs include: zilganersen (Alexander disease), Ulefnersen (FUS-ALS), ION582 (Angelman syndrome), ION717 (Prion disease) and ION356 (PMD). ION440 (MECP2 Duplication syndrome) and an undisclosed genetic dementia target are expected to enter clinical development by YE:2024. 3. Timing based on current estimates and subject to change.

# Advancing and Expanding our Wholly Owned Neurology Franchise[1]

## Pediatric Neurology

**Zilganersen**
Alexander Disease
*Pivotal study underway*

**ION582**
Angelman Syndrome
*Pivotal study to start in H1:2025*

**ION356**
Pelizaeus-Merzbacher Disease (PMD)
*First in patient study underway*

**ION440**
MECP2 Duplication Syndrome
*First in patient study to start in 2024*

## Dementia

**ION717**
Prion Disease
(PRNP)
*First in patient study underway*

**Genetic Dementia Target**
*First in patient study to start in 2024*

## Future Wave

**Neuromuscular and Peripheral Neuropathies**

**Movement Disorders**

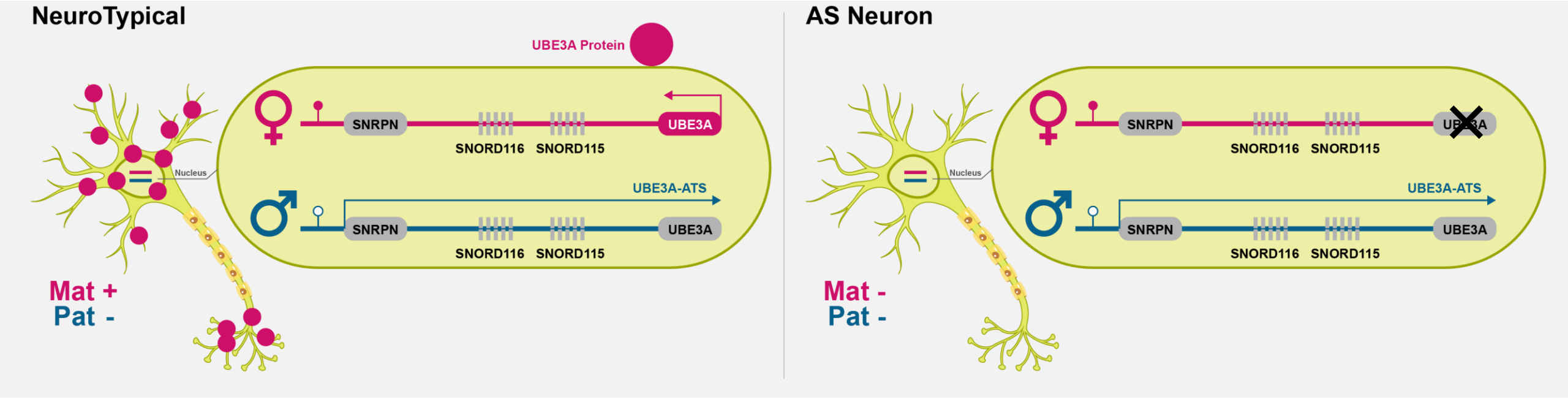
**Expand into Next Key Areas of Neurology**

**Expand into Dementia**

**Rare Pediatric Neurology is the Foundation**

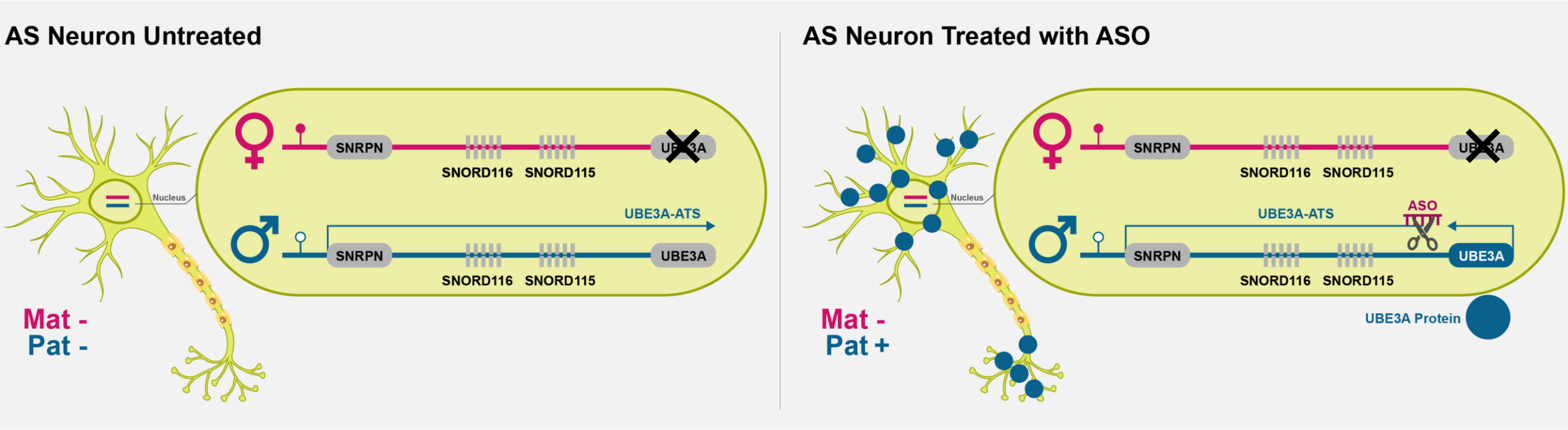
1. Timing based on current estimates, subject to change.

# Angelman Syndrome (AS): Severe Rare Disorder Caused by a Loss-of-function of UBE3A Protein




- AS is caused by loss of the **maternal *UBE3A*** gene (gene deletion, mutation etc.)
- Due to genomic imprinting, in all people the **paternal *UBE3A*** allele is **silenced in neurons**

# Pioneering Solutions: Ionis' Innovative Path to Treating Angelman Syndrome




- The mechanism of **paternal *UBE3A* unsilencing** was first pursued, validated and patented by Ionis in collaboration with Professor Arthur Beaudet (Baylor College of Medicine)[1]
- ASOs target the UBE3A antisense transcript in the **nucleus** to unsilence the **paternal allele**[2]
- **Strategic placement** of ASOs can avoid off-target effects[2]

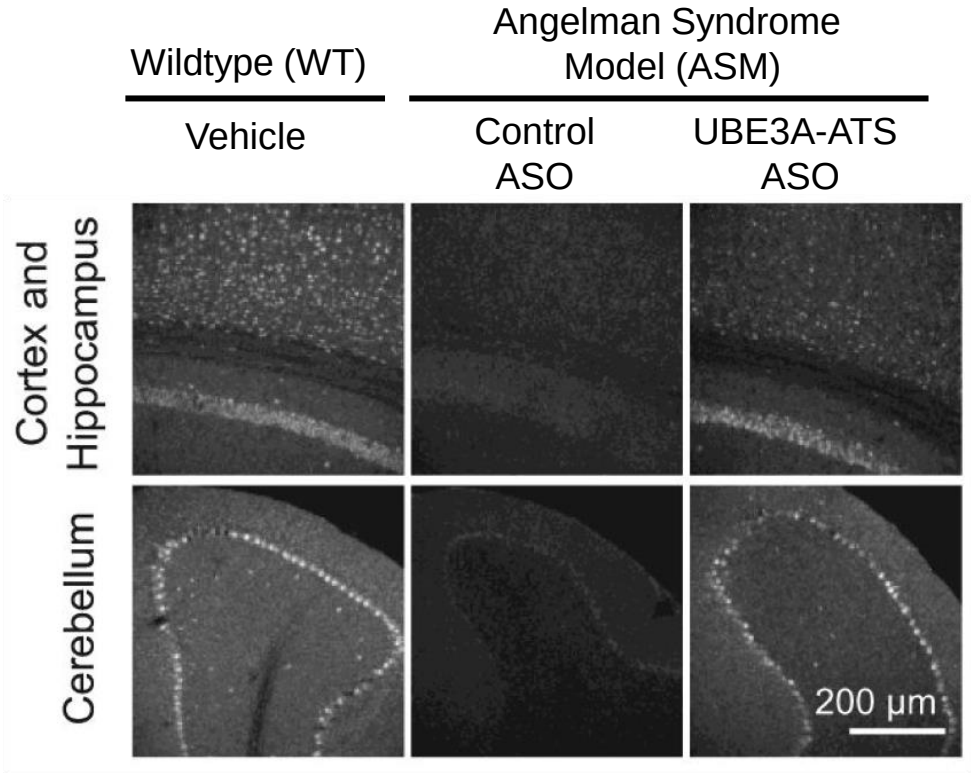
1. Modulation of UBE3A-ATS expression, e.g. US Patent US9617539B2, Ionis Pharmaceuticals Inc and Baylor College of Medicine. 2. Meng et al. *Nature (*2015).

# Robust, Reproducible Reversal of Key Symptoms with Ionis' ASO Treatment in Preclinical Models of Angelman Syndrome[1]

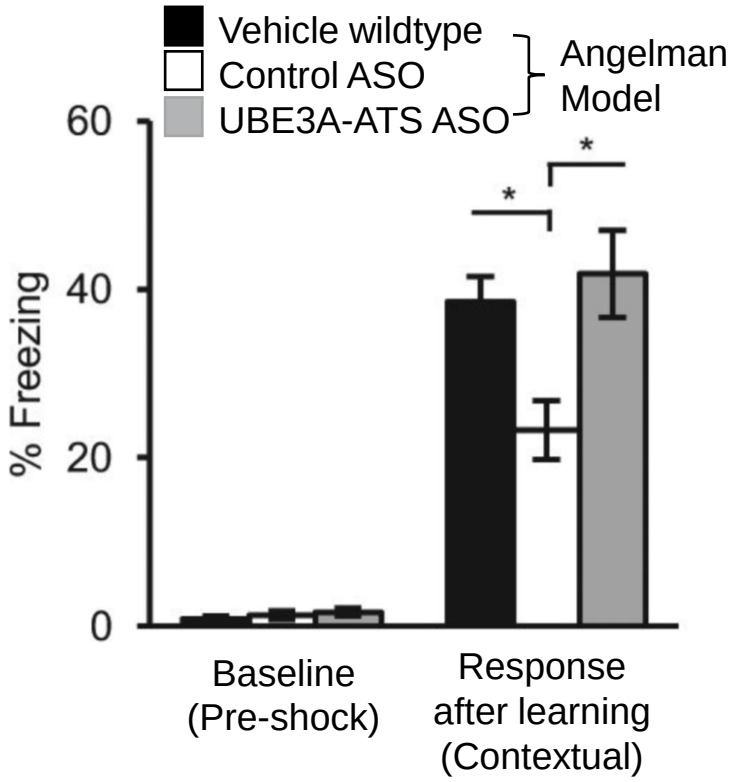
ASO treatment in preclinical models resulted in:

- UBE3A protein levels restored[2,3]
- Learning and memory improved
- REM sleep increased[2]
- Brain activity normalized[2,3]

## UBE3A Protein Restored[1]



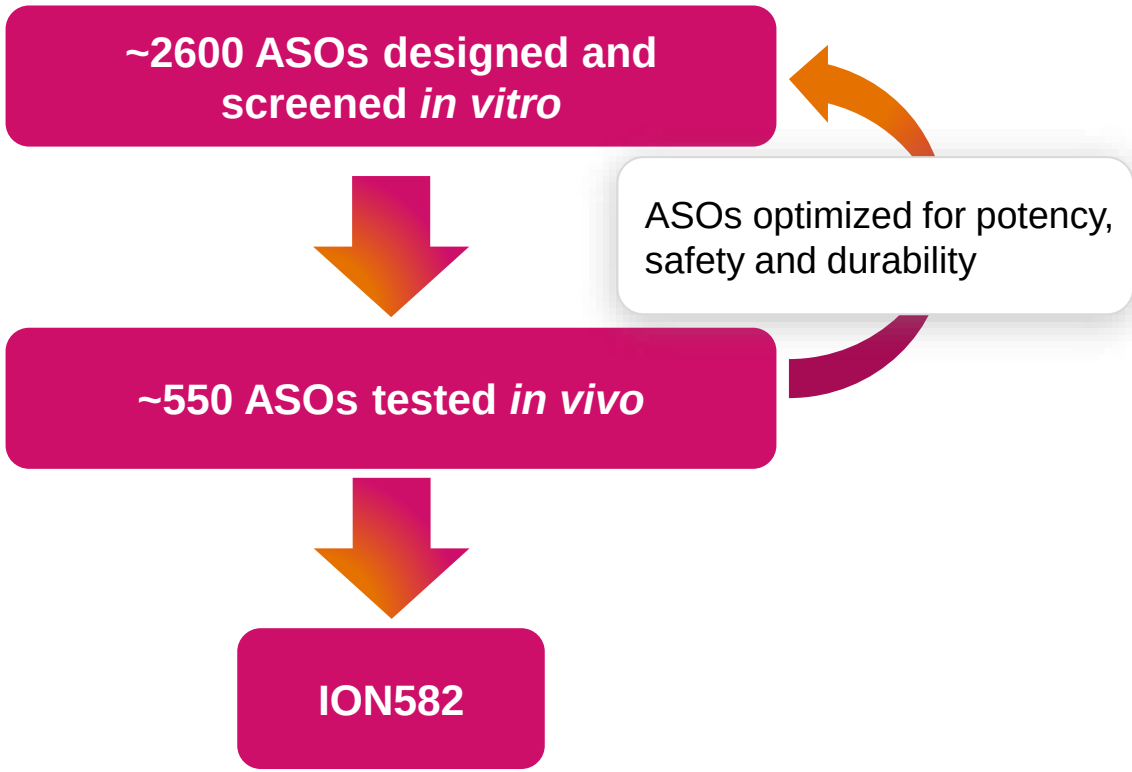

## Learning and Memory Improved[1]




1. Meng et al. *Nature* (2015); 2. Lee et al. *eLife* (2023); 3. Spencer et al. *Brain Communications*, (2022).

# ION582: Designed Using Our Deep Experience and Validated CNS Chemistry

- Pioneered RNA-therapeutics in the CNS
- Designed using proven CNS platform
- Best-in-class chemistry for CNS delivery
- Defined methods for identification of best-in-class CNS molecules with extensive experience and rigorous optimization



# Uniquely Positioned to Bring a Steady Flow of Innovative Neurology Medicines to Patients

**Ionis is leading the field** in advancing transformative RNA-targeted medicines for neurological diseases

Proven innovation with **3 approved transformational medicines** and **11 medicines in clinical development**

**ION582 for Angelman syndrome** is positioned to become the **cornerstone** of Ionis' **wholly owned** neurology pipeline

**ION582** is the next opportunity for Ionis' **innovation** and ability to deliver **transformative disease-modifying medicines** to patients with severe neurological diseases

Plan to **grow** our **wholly owned neurology pipeline** into additional disease areas and larger more common diseases

# Angelman Syndrome: Perspectives from a Physician and Parent

Elizabeth Jalazo, M.D.
Assistant Professor of Pediatrics, Division of Genetics & Metabolism
University of North Carolina School of Medicine

# Disclosures

**Dr. Elizabeth Jalazo** is a consultant to Ionis Pharmaceuticals on their Angelman syndrome program.

# Angelman Syndrome: Severe Neurodevelopmental Disorder with a Clear Unmet Medical Need

## Severe, Rare Neurodevelopmental Disorder[1-4]

- Estimated 1 in 21,000 people with Angelman syndrome worldwide
  - >100,000 people in major geographies
- Caused by loss of function of the *UBE3A* gene
- Symptom onset and diagnosis ~2 years old
- Not progressive, associated with normal life expectancy

## Significant Burden on People with Angelman Syndrome and their Caregivers[5]

- Profound developmental and cognitive delay
- Results in need for lifelong, fulltime supervision

## Clear Unmet Medical Need[5,6]

- No approved disease-modifying treatments
- Current standard-of-care treatments only for symptom management

1. Yakoreva et al. *A Eur. J. Hum*. Genet. (2019). 2. Luk. *Eur. J. Méd. Genet*. (2016). 3. Mertz et al. *Am. J. Méd. Genet. Part A* (2013). 4. Wheeler et al. *J Neurodev Disord*. (2023). 5. Clayton-Smith. *J Med Genet* (2003). 6. Besten, et al. *Am. J. Méd. Genet. Part A* (2021).

# Angelman Syndrome: Wide Range of Symptoms Impacting Key Areas of Function[1]

## Communication[2,3,4]

- Severe impairment in **receptive** and **expressive communication**
- Minimal to no **verbal ability**

## Cognition[3,5,6]

- Severe to profound **intellectual disability**
- **Cognitive abilities** plateau at developmental age of **~2-4 years**
- Impaired **social cognition** including **aggressive** and **challenging behaviors**

## Physical Function[1,7]

- Severe **motor function delay** and impairment
- Slow **unsteady gait**, **poor muscle coordination**, **tremors**
- **Walking**, **grasping**, **feeding**, other **daily living activities** impacted

1. Clayton-Smith. *J Med Genet* (2003). 2. Mertz et al. *Am. J. Méd. Genet. Part A* (2013). 3. Gentile*et al. J. Dev. Behav. Pediatr.* (2010). 4. Besten et al. Am. *J. Méd. Genet. Part A* (2021). 5. Sadhwani et al. *J. Autism Dev. Disord*. (2023). 6. Pereira et al. *Am. J. Méd. Genet. Part A*. (2020). 7. Xia et al. *Pediatr. Neurol.* (2023).

# Significant Impact on Parents and Caregivers of People Living with Angelman Syndrome[1]

- Profound, lifelong disability associated with Angelman syndrome significantly impacts parents, caregivers and families

## Caregiver-Reported Symptoms Most Relevant for Angelman Syndrome Treatment[2-5]

- Impaired communication
- Maladaptive, disruptive behavior
- Cognitive impairment
- Motor function disabilities
- Sleep disturbances and limited self-care

1. Wheeler. *Orphanet J. Rare Dis.* (2017). 2. Willgoss et al, *Child Psychiatry & Human Development*, (2020). 3. Sadhwani et al. *Am. J. Méd. Genet. Part A* (2019). 4. Hagenaar. et al. *J. Intellect. Disabil. Res*. (2024).
5. Parents and caregivers also report uncontrolled seizures as an important symptom to treat.

# Assessment Tools Used to Measure a Broad Range of Symptoms

Assessments as administered to study participants (Bayley-4) or reported by caregivers (Vineland-3, ORCA) and clinicians (SAS-CGI-C)

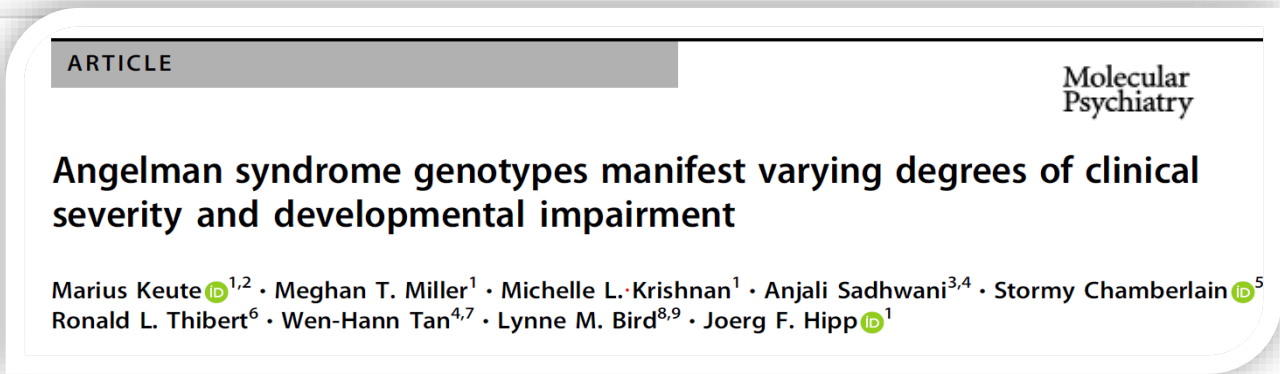
| | Bayley-4[1] | Vineland-3[2] | ORCA[3,4] | SAS-CGI-Change[6,7] |
|---|---|---|---|---|
| Functional Areas | • Communication<br>• Cognition<br>• Motor functions<br>• Adaptive behavior<br>• Socialization<br>• Daily living skills | • Communication<br>• Motor functions<br>• Maladaptive behavior<br>• Socialization<br>• Daily living skills | • Communication:<br>– Receptive<br>– Expressive<br>– Pragmatic | • Overall AS symptoms<br>• Expressive communication<br>• Cognitive/Intellectual impairment<br>• Motor functions<br>• Maladaptive behavior<br>• Daily living skills<br>• Sleep disturbance<br>• Seizures |
| Assessment & Administration | Objective (Clinician administered, direct participant assessment) | Subjective (Clinician administered, caregiver reported) | Subjective (Caregiver reported) | Subjective (Clinician reported) |
| Score | GSV | GSV | Total T-score[5] | 7-point Likert scale[8] |

*ORCA*, Observer-Reported Communication Ability; *SAS-CGI-C,* Symptoms of Angelman Syndrome–Clinician Global Impression-Change; *GSV,* growth scale values, derived from raw domain scores to track within-subject performance change

1. Bayley N. Aylward GP. *Bayley Scales of Infant and Toddler Development-Fourth Edition*. NCS Pearson. (2019). 2. Sparrow S, et. Al. *Vineland Adaptive Behavior Scales-Third Edition (Vineland-3).* NCS Pearson. (2016). 3. Zigler CK, et al. *Am J Intellect Dev Disabil*. (2023). 4. Duke University. *Observer-Reported Communication Ability (ORCA) measure scoring manual.* Pattern Health. (2023). 5. ORCA T-score range: 25.8–83.8, (standardized, mean=50, SD=10). 6. Connor-Ahmad, S. et al. *Orphanet J. Rare Dis.* (2023). 7. Adapted from Standard CGI-C. 8. SAS-CGI-C response range: Very Much Worse-Very Much Improved.

# People with Angelman Syndrome Demonstrate Minimal Functional Improvement After 4 Years of Age[1,2]

**Per natural history, people with Angelman syndrome show profound developmental delay from birth through adulthood**


ARTICLE

Molecular Psychiatry

Angelman syndrome genotypes manifest varying degrees of clinical severity and developmental impairment

Marius Keute[1,2] · Meghan T. Miller[1] · Michelle L. Krishnan[1] · Anjali Sadhwani[3,4] · Stormy Chamberlain[5] · Ronald L. Thibert[6] · Wen-Hann Tan[4,7] · Lynne M. Bird[8,9] · Joerg F. Hipp[1]

- People with UBE3A deletions generally plateau in overall function at the level of a neurotypical 2-year-old
- People with UBE3A mutations have a higher level of function, generally plateauing in overall function at the level of a neurotypical 4-year-old
- Function remains stable with minimal to no improvement after ~4-6 years of age

1. Keute. *Mol Psychiatry.* (2021). 2. Bayley-III vs. Bayley-4: What's changed? Pearson. (2019).

# What is Clinically Meaningful?

| | Bayley-4[1] | Vineland-3[2] | ORCA[4,5,6] | SAS-CGI-Change[7,8,9] |
|---|---|---|---|---|
| Clinically meaningful change | Not established | | ≥ 2 points | ≥ 1 point (out of maximum 3-point change) |
| Comparator | Compared to age and genotype-matched natural history data[3] | | • Compared to established clinically meaningful change<br>• Compared to age and genotype-matched natural history[3] | • Clinically meaningful change anchored to Standard CGI overall score<br>• Not compared to natural history |

**There are ongoing efforts in the Angelman syndrome community to establish clinical meaningfulness for all four measures**

*ORCA*, Observer-Reported Communication Ability; *SAS-CGI-C,* Symptoms of Angelman Syndrome–Clinician Global Impression-Change

1 . Bayley N. Aylward GP. *Bayley Scales of Infant and Toddler Development-Fourth Edition*. NCS Pearson. (2019). 2. Sparrow S, et. Al. *Vineland Adaptive Behavior Scales-Third Edition (Vineland-3).* NCS Pearson. (2016). 3. Angelman Syndrome Natural History Study www.clinicaltrials.gov/NCT04507997. 4. Zigler CK, et al. *Am J Intellect Dev Disabil*. (2023). 5. Duke University. *Observer-Reported Communication Ability (ORCA) measure scoring manual.* Pattern Health. (2023). 6. ORCA T-score range: 25.8–83.8, (standardized, mean=50, SD=10). 7. Connor-Ahmad, S. et al. *Orphanet J. Rare Dis.* (2023). 8. Adapted from Standard CGI-C. 9. SAS-CGI-C response range: Very Much Worse-Very Much Improved.

# Angelman Syndrome: Key Takeaways

**Angelman syndrome (AS)** is a **severe neurodevelopmental disorder** of high unmet medical need

Angelman syndrome results in **profound disabilities** resulting in the need for **life-long, round the clock care**

Cognitive abilities **plateau ~2-4 years old**, with **minimal** improvement in skills through adulthood

Angelman syndrome **assessments** can accurately **measure symptom improvement,** particularly when conducted and viewed **in aggregate**

Significant need for **disease-modifying** treatments

# ION582: Ionis' Program for the Treatment of Angelman Syndrome

Becky Crean, Ph.D.
Executive Director, Neurology

# HALOS Study of ION582 for Angelman Syndrome[1]

Phase 1/2 Open-label Study, Multiple-Ascending Dose (MAD) Part 1

HALOS

**DESIGN**

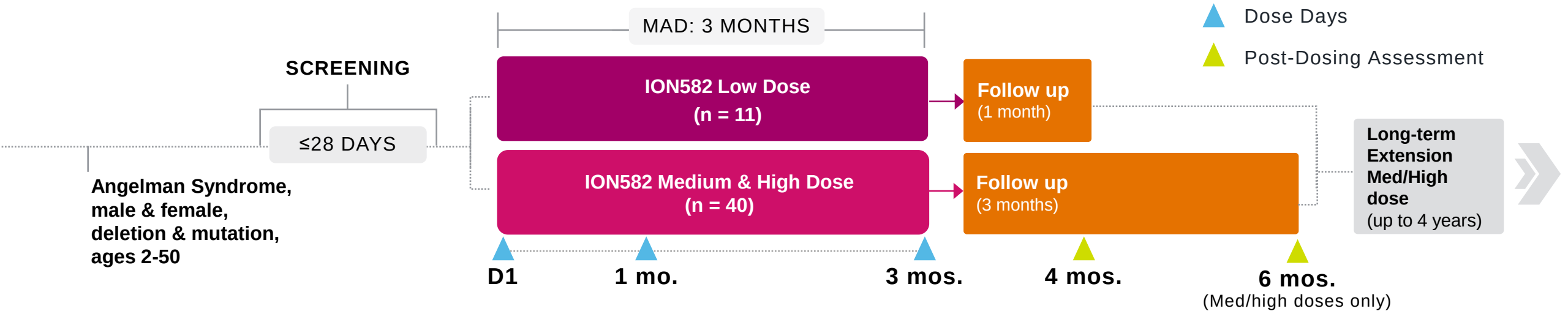
**A global, open-label study** evaluating 3 dose levels of ION582 in male & female participants, ages 2-50

- Deletion and mutation genotypes
- Last Post-MAD Assessment[2]:
  - Low dose: assessed month 4
  - Med/high dose: assessed month 6
- Ongoing long-term extension (LTE), additional ≥ 4 yrs

**OBJECTIVES**

**Primary outcome measure:** Safety and tolerability of multiple doses of ION582 administered by intrathecal administration

**Key exploratory measures:** change in measures of clinical function: communication, cognition, motor function, sleep, seizures and daily living skills




1. The HALOS study is an open label study and results should be interpreted with caution until a placebo-controlled study is completed. 2. Assessment at month 6 added to study design after initiation in low-dose cohort to enable baseline assessment in LTE. Month 6 assessment does not include evaluation of low dose.

# The HALOS Study: Key Functional Domains Using Robust Set of Assessment Tools

Assessments as administered to participants (Bayley-4) or reported by caregivers (Vineland-3, ORCA), clinicians (SAS-CGI-C)

| | Bayley-4[1] | Vineland-3[2] | ORCA[3,4,5] | SAS-CGI-Change[6,7,8] |
|---|---|---|---|---|
| Cognition | | -- | -- | |
| Receptive Communication | | | | -- |
| Expressive Communication | | | | |
| Gross Motor | | | -- | |
| Fine Motor | | | -- | |
| Daily Living Skills | * | | -- | |
| Socialization | * | | -- | -- |
| Sleep | -- | -- | -- | |
| Behavior | * | * | -- | |

* Analyzed with alternate assessment tool(s)

-- Not in assessment

*ORCA*, Observer-Reported Communication Ability; *SAS-CGI-C*, Symptoms of Angelman Syndrome–Clinician Global Impression-Change

1. Bayley N. Aylward GP. *Bayley Scales of Infant and Toddler Development-Fourth Edition*. NCS Pearson. (2019). 2. Sparrow S, et. Al. *Vineland Adaptive Behavior Scales-Third Edition (Vineland-3).* NCS Pearson. (2016). 3. Zigler CK, et al. *Am J Intellect Dev Disabil*. (2023). 4. Duke University. *Observer-Reported Communication Ability (ORCA) measure scoring manual*. Pattern Health. (2023). 5. ORCA T-score range: 25.8–83.8, (standardized, mean=50, SD=10). 6. Connor-Ahmad, S. et al. *Orphanet J. Rare Dis.* (2023). 7. Adapted from Standard CGI-C. 8. SAS-CGI-C response range: Very Much Worse-Very Much Improved.

# ION582:

# Important wholly owned program for the treatment of Angelman Syndrome

## Encouraging Emerging Clinical Profile

- HALOS study designed to demonstrate benefit in key functional areas most impactful for study participants, clinicians and caregivers
- Open-label study evaluating ION582 in a broad range of ages and genotypes, representative of the Angelman syndrome population
- Favorable safety and tolerability in the HALOS study

## Advancing Towards Phase 3 Development

- Plan to meet with regulators
- Totality of data generated to date support advancing to Phase 3

## Priority Wholly Owned Opportunity

- Potential to address a severe unmet medical need
- Significant transformational potential
- Strengthens Ionis' wholly owned neurology pipeline

HALOS

# Results from the HALOS Study of ION582

Lynne Bird, M.D.
Professor of Clinical Pediatrics, University of California, San Diego
Rady Children's Hospital San Diego

# Disclosures

**Lynne Bird, M.D.** is Principal Investigator on the following studies for Angelman syndrome:

- Ionis Pharmaceuticals – phase I/II HALOS trial of ION582 (antisense oligonucleotide)
- Roche/Genentech – phase I/II TANGELO trial of rugonersen (antisense oligonucleotide)
- Ultragenyx – phase I/II trial of GTX-102 (antisense oligonucleotide)
- Roche/Genentech – phase IIa trial of alogabat (small molecule)

Dr. Bird is a consultant to Ionis Pharmaceuticals on their Angelman syndrome program.

# Patient Disposition

HALOS

| | Low Dose (n=11) | Medium Dose (n=13) | High Dose (n=27) |
|---|---|---|---|
| Mean age at screening, years (min, max) | 5.7 (2.1, 11) | 7.6 (4.4,17.5) | 12.1 (2.7, 34.3) |
| Genotype, n (%) | | | |
| • Mutation | 1 (9) | 3 (23) | 4 (15) |
| • Deletion | 10 (91) | 10 (77) | 23 (85) |
| Completed treatment, n (%) | 11 (100) | 12 (92) | 27 (100) |
| Discontinued treatment, n | 0 | 1[1] | 0 |

**98% of enrolled participants completed Part 1 MAD**
**100% of eligible participants enrolled in the long-term extension**

1. Not deemed related to study drug.

# Favorable Safety and Tolerability Profile in the HALOS Study

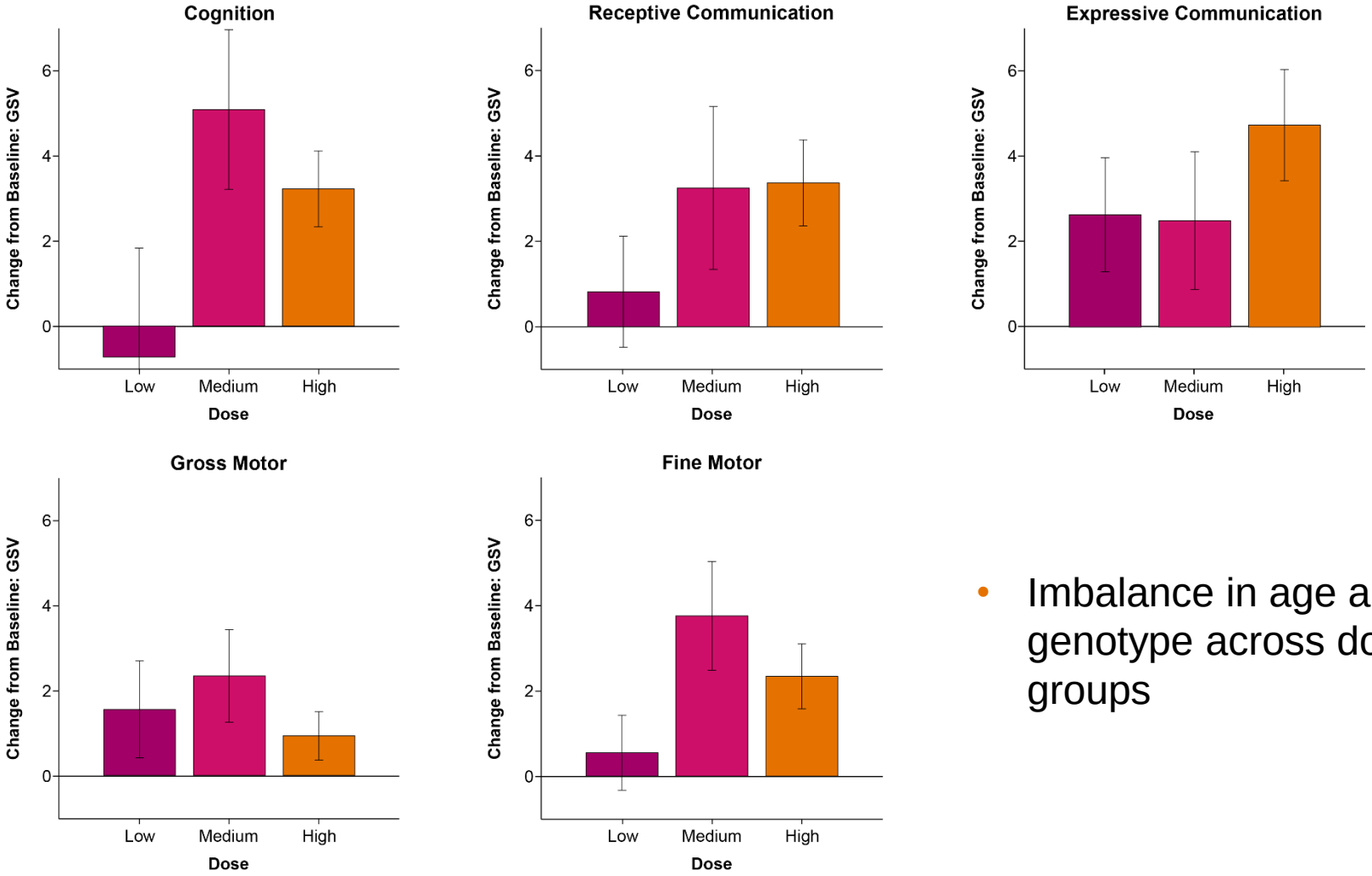
HALOS

- No discontinuations or adverse events deemed related to study drug
- Majority of adverse events were consistent with the participant medical histories and/or AS diagnosis, and/or findings related to lumbar puncture
- No reports of lower limb weakness, ataxia or radiculopathy

| | Events in >10% of Participants | | |
|---|---|---|---|
| | Events (n) | Participants (n) | Participants (%, N = 51) |
| Pyrexia | 13 | 10 | 19.6% |
| Vomiting | 11 | 10 | 19.6% |
| Upper Respiratory Tract Infection | 10 | 9 | 17.6% |

# Greater Improvements Observed in Medium, High Dose vs. Low Dose on Bayley-4 Assessments at 4 Months

Measures of cognition, communication and motor function in low, medium and high dose groups assessed at 4 months[1]




- Imbalance in age and genotype across dose groups

1. Low, medium and high dose groups at 4 months. Standard error mean (SEM).

# Key Considerations for Analysis and Interpretation of HALOS Data[1-9]

| | |
|---|---|
| **Basis of Functional Data Presentation** | **Additional analyses from Bayley-4, Vineland-3, ORCA and SAS-CGI-C in medium and high dose groups, pooled, at 6 months** |
| **Data from 6-month Assessment** | • Final post-dose assessment in MAD<br>• 6-month assessment added to provide baseline for LTE<br>• Enables best comparison to natural history data, which shows minimal changes over 12 months |
| **Low Dose Group** | • Not assessed at 6 months<br>• Establishes minimal safety and efficacy<br>• Receiving medium dose in LTE |
| **Pooled Medium and High Dose** | • Increases sample size<br>• Enables more robust comparison to age- and genotype-matched natural history |

*ORCA*, Observer-Reported Communication Ability; *SAS-CGI-C,* Symptoms of Angelman Syndrome–Clinician Global Impression-Change

1 . Bayley N. Aylward GP. *Bayley Scales of Infant and Toddler Development-Fourth Edition*. NCS Pearson. (2019). 2. Sparrow S, et. Al. *Vineland Adaptive Behavior Scales-Third Edition (Vineland-3).* NCS Pearson. (2016). 3. Angelman Syndrome Natural History Study www.clinicaltrials.gov/NCT04507997. 4. Zigler CK, et al. *Am J Intellect Dev Disabil*. (2023). 5. Duke University. *Observer-Reported Communication Ability (ORCA) measure scoring manual.* Pattern Health. (2023). 6. ORCA T-score range: 25.8–83.8, (standardized, mean=50, SD=10). 7. Connor-Ahmad, S. et al. *Orphanet J. Rare Dis.* (2023). 8. Adapted from Standard CGI-C. 9. SAS-CGI-C response range: Very Much Worse-Very Much Improved.

# Natural History Data Represents the Best Comparator to Demonstrate ION582 Treatment Effect in Key Functional Domains

| | HALOS[1-7] | NHS[1,8] | NHS[2,8] | NHS[3-5,8] |
|---|---|---|---|---|
| Assessment tool | Bayley-4, Vineland-3 ORCA | Bayley-3, Bayley-4[9] | Vineland-3 | ORCA |
| Analysis set, month 6, n | 39 | 150 | 30 | 15 |
| Mean age, years | 10.7 | 6.4 | 10.2 | 14.7 |
| Genotype, n | | | | |
| Mutation | 8 | 22 | 7 | 2 |
| Deletion | 31 | 128 | 23 | 13 |

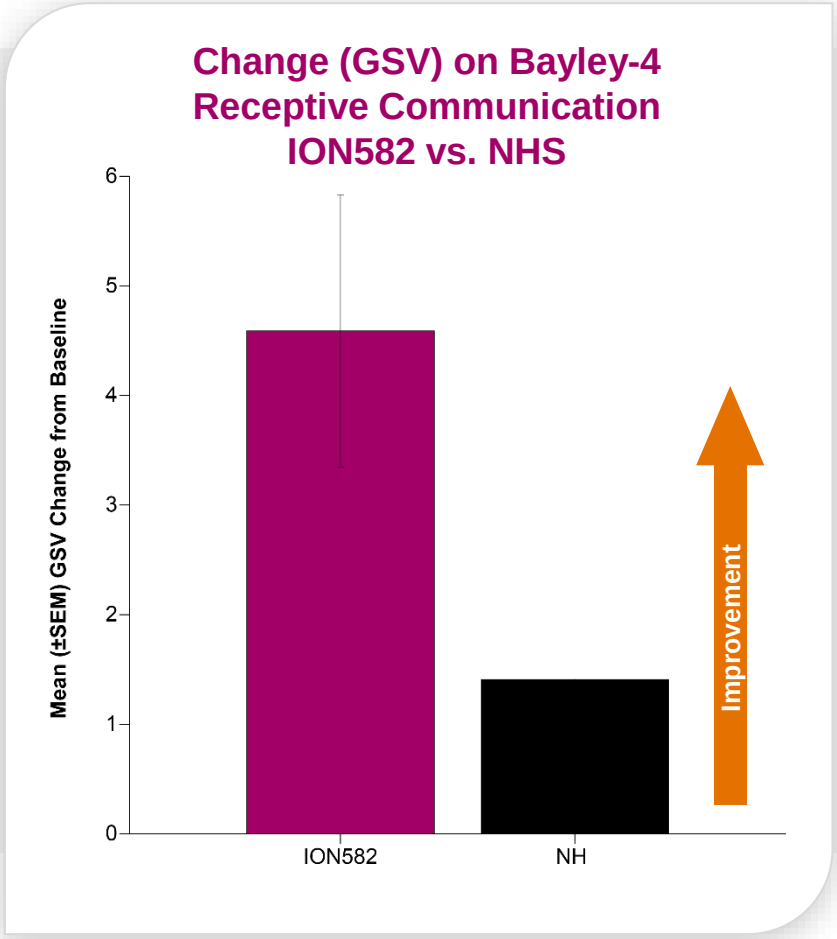
- Bayley-4, and Vineland-3: Clinical meaningful change not yet established
- Bayley-4, Vineland-3 and ORCA: compared to age, genotype matched natural history data to demonstrate treatment effect
- ORCA: ≥ 2 points considered clinically meaningful; also compared to natural history
- SAS-CGI-C: anchored to Standard CGI overall score; ≥ 1 point change considered clinically meaningful[10-12]
- SAS-CGI-C: natural history comparator not available

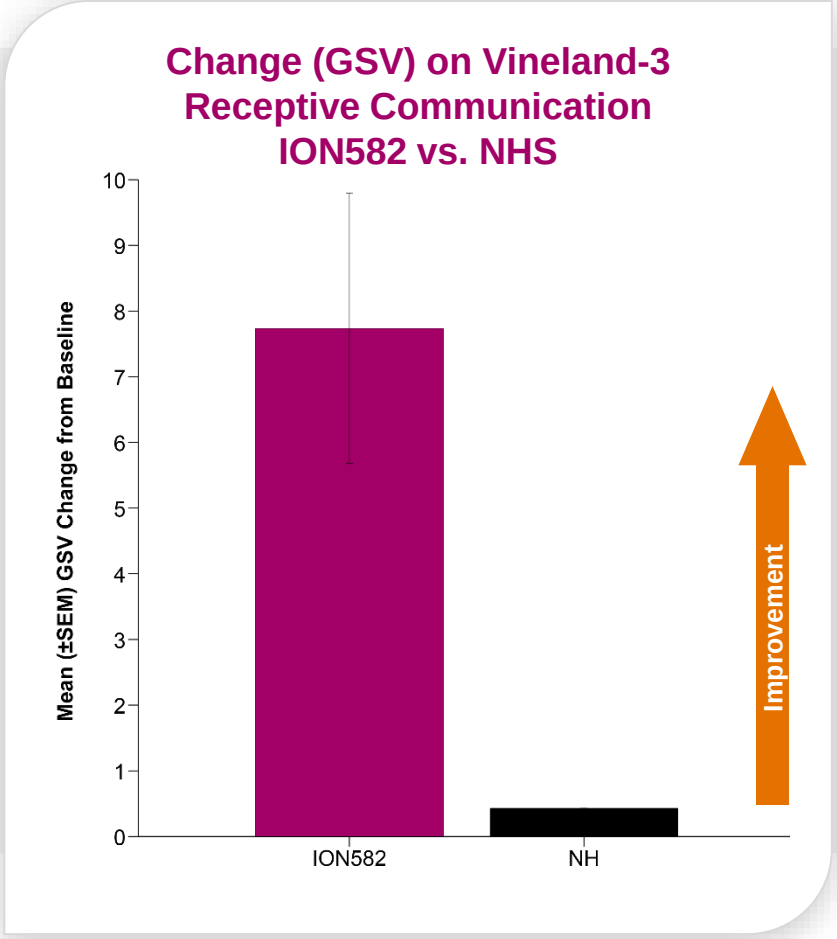
*ORCA*, Observer-Reported Communication Ability; *SAS-CGI-C,* Symptoms of Angelman Syndrome–Clinician Global Impression-Change

1 . Bayley N. Aylward GP. *Bayley Scales of Infant and Toddler Development-Fourth Edition*. NCS Pearson. (2019). 2. Sparrow S, et. Al. *Vineland Adaptive Behavior Scales-Third Edition (Vineland-3).* NCS Pearson. (2016). 3. Zigler CK, et al. *Am J Intellect Dev Disabil*. (2023). 4. Duke University. *Observer-Reported Communication Ability (ORCA) measure scoring manual.* Pattern Health. (2023). 5. ORCA T-score range: 25.8–83.8, (standardized, mean=50, SD=10). 6. Medium and high dose groups at 6 months. 7. 39 of 39 participants evaluated by Bayley-4 as compared to NH, 38 of 39 participants evaluated by Vineland-3 as compared to NH, and 37 of 39 participants evaluated by ORCA as compared to NH. 8. Angelman Syndrome Natural History Study www.clinicaltrials.gov/NCT04507997. 9. Bayley-3 vs. Bayley-4 – What's Changed? Pearson (2019). 10. Connor-Ahmad, S. et al. *Orphanet J. Rare Dis.* (2023). 11. Adapted from Standard CGI-C. 12. SAS-CGI-C response range: Very Much Worse-Very Much Improved.

# Receptive Communication: Improvement Observed on Bayley-4 and Vineland-3 Compared to Natural History[1,2]

Improvements on Bayley-4 and Vineland-3 measures of receptive communication exceed natural history



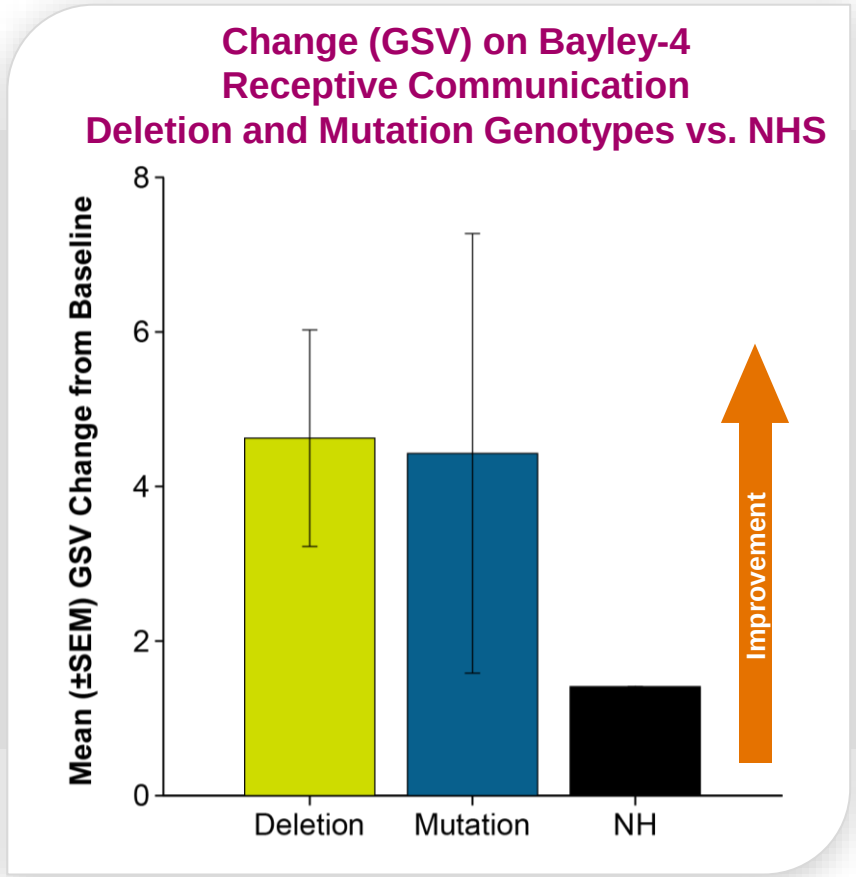

*GSV*, Growth scale values; *SEM*, Standard error mean

1. Medium and high dose groups at 6 months. 2. Angelman Syndrome Natural History Study www.clinicaltrials.gov/NCT04507997.

# Receptive Communication: Similar Improvements Observed on Bayley-4 in Participants with Deletion and Mutation Genotypes Compared to Natural History[1,2]

Similar improvements on Bayley-4 receptive communication with varying levels of baseline impairment

| Bayley-4: Receptive Communication | |
|---|---|
| **Genotype** | **Baseline Mean (±SEM) GSV** |
| UBE3A Deletion (n=32) | 493 (±2.3) |
| UBE3A Mutation (n=7) | 516 (±3.3) |



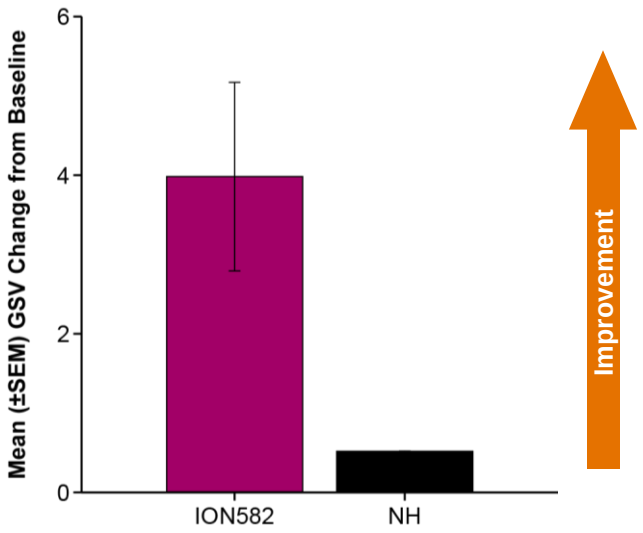

*GSV*, Growth scale values; *SEM*, Standard error mean

1. Medium and high dose groups at 6 months. 2. Angelman Syndrome Natural History Study www.clinicaltrials.gov/NCT04507997.

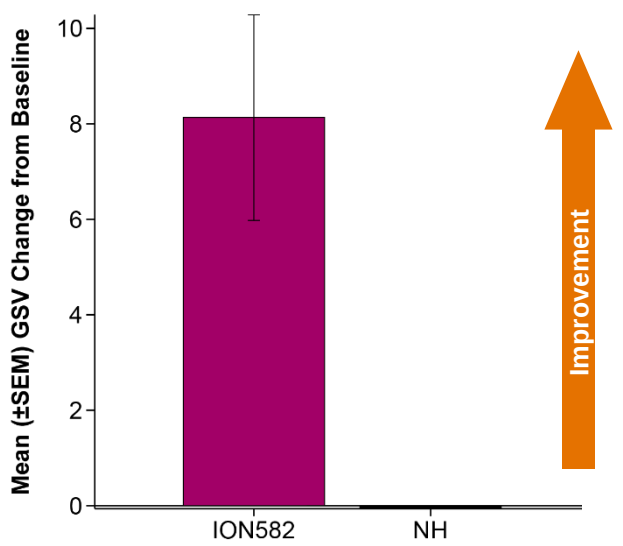
# Expressive Communication: Improvement Observed on Bayley-4, Vineland-3 and SAS-CGI-C[1]

Improvements on Bayley-4 and Vineland-3 measures of expressive communication exceed natural history[2]; SAS-CGI-C shows clinically meaningful change[3-8]

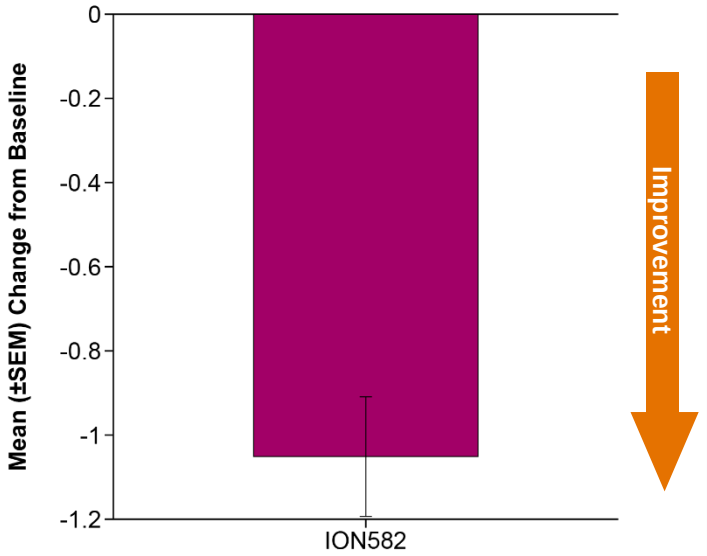
## Change (GSV) on Bayley-4 Expressive Communication ION582 vs. NHS




## Change (GSV) on Vineland-3 Expressive Communication ION582 vs. NHS




## Change on SAS-CGI-C Expressive Communication Anchored, CGI-C




*GSV*, Growth scale values; *SEM*, Standard error mean; *SAS-CGI-C*, Symptoms of Angelman Syndrome–Clinician Global Impression-Change

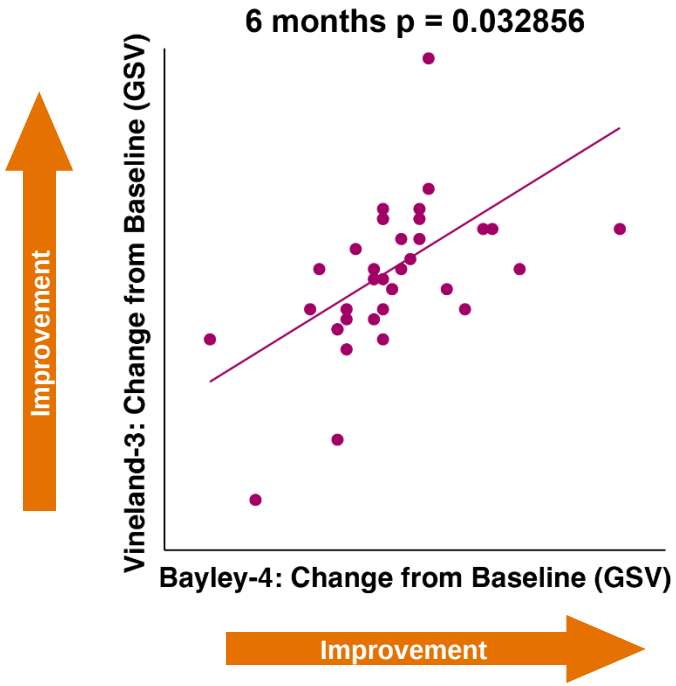
1. Medium and high dose groups at 6 months. 2. Angelman Syndrome Natural History Study www.clinicaltrials.gov/NCT04507997. 3. SAS-CGI-C anchored to Standard CGI-C overall score; ≥1 point change considered clinically meaningful. 4. Out of a maximum improvement of 3 points. 5. Not compared to natural history. 6. Connor-Ahmad, S. et al. *Orphanet J. Rare Dis.* (2023). 7. Adapted from Standard CGI-C. 8. SAS-CGI-C response range: Very Much Worse-Very Much Improved.

# Communication: Consistent Improvements Observed with Bayley-4 and Vineland-3 Measures of Communication[1]

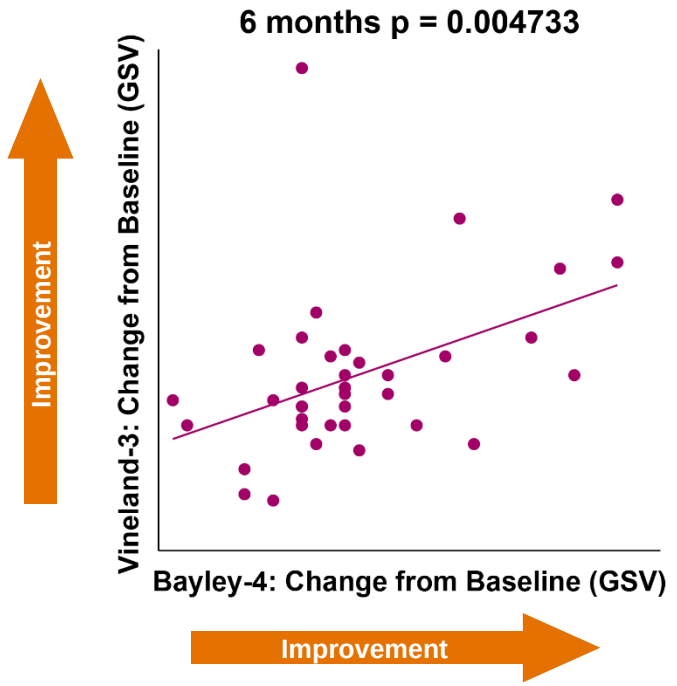
HALOS

Consistent improvements in Bayley-4 and Vineland-3 measures of receptive and expressive communications

## Change in Receptive Communication: Bayley-4 and Vineland-3

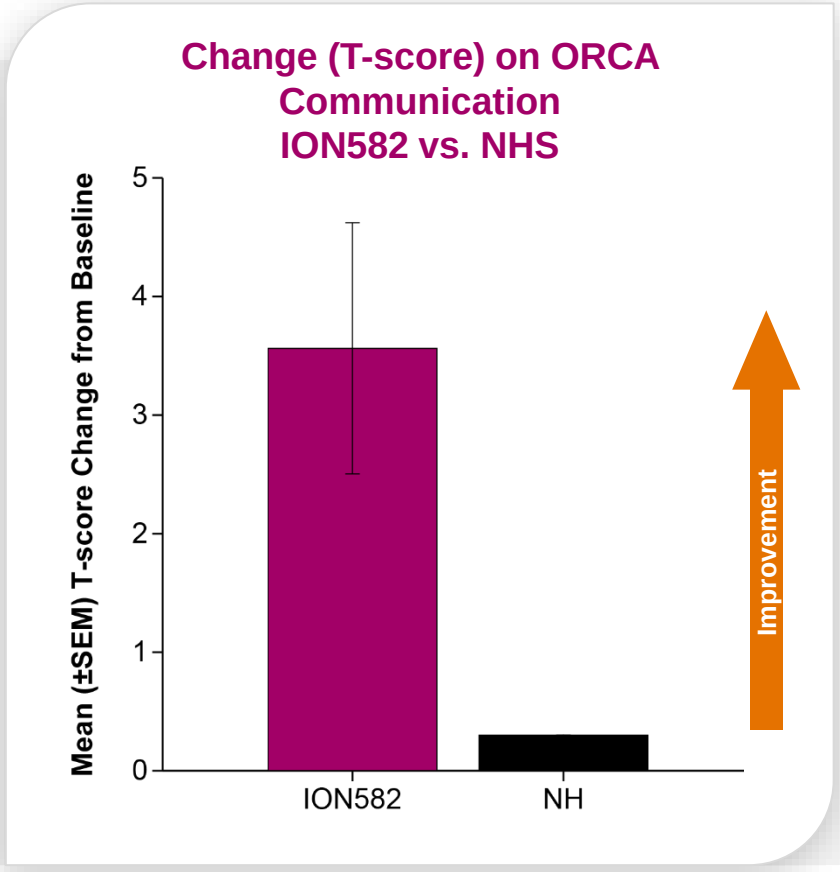



## Change in Expressive Communication: Bayley-4 and Vineland-3




*GSV*, Growth scale values
1. Medium and high dose groups at 6 months.

# Communication: Clinically Meaningful Improvement Observed on ORCA Measure of Communication[1]



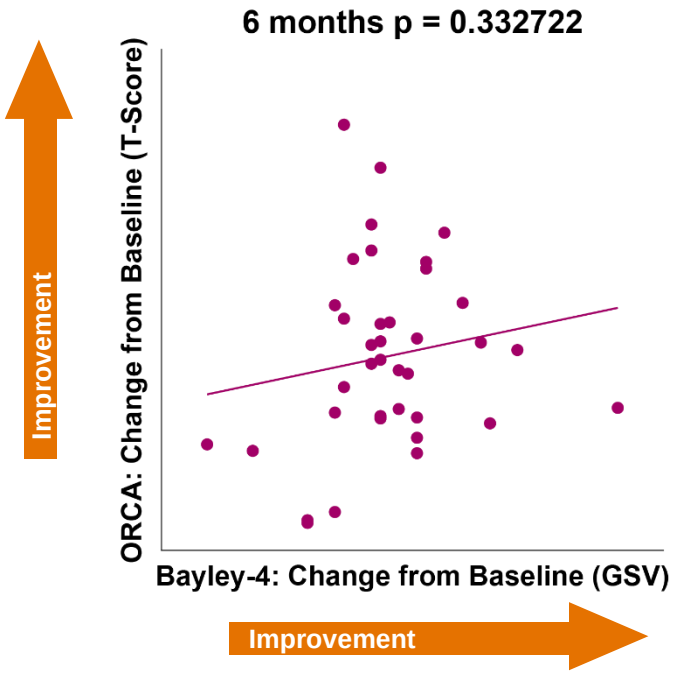

- 3.6-point improvement achieved with ION582 at 6 months of treatment
- ≥ 2-point improvement considered clinically meaningful[2-4]
- Improvement at 6 months also exceeds natural history[5]

*ORCA*, Observer-Reported Communication Ability; *SEM*, Standard error mean

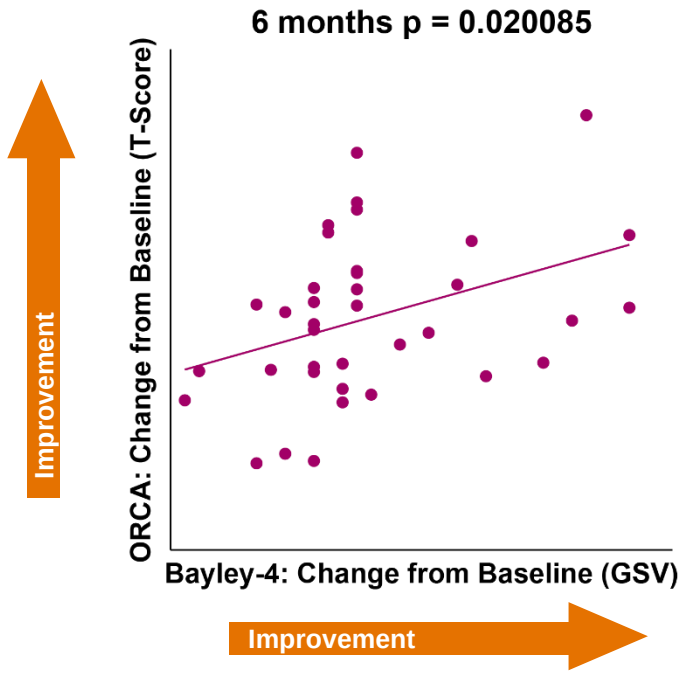
1. Medium and high dose groups at 6 months. 2. Zigler CK, et al. *Am J Intellect Dev Disabil*. (2023). 3. Duke University. *Observer-Reported Communication Ability (ORCA) measure scoring manual*. Pattern Health. (2023). 4. ORCA T-score range: 25.8–83.8, (standardized, mean=50, SD=10). 5. Angelman Syndrome Natural History Study www.clinicaltrials.gov/NCT04507997.

# Communication: ORCA Measure of Communication Correlates Well with Improvements Seen with Bayley-4[1]

## Change in Receptive Communication: ORCA and Bayley-4



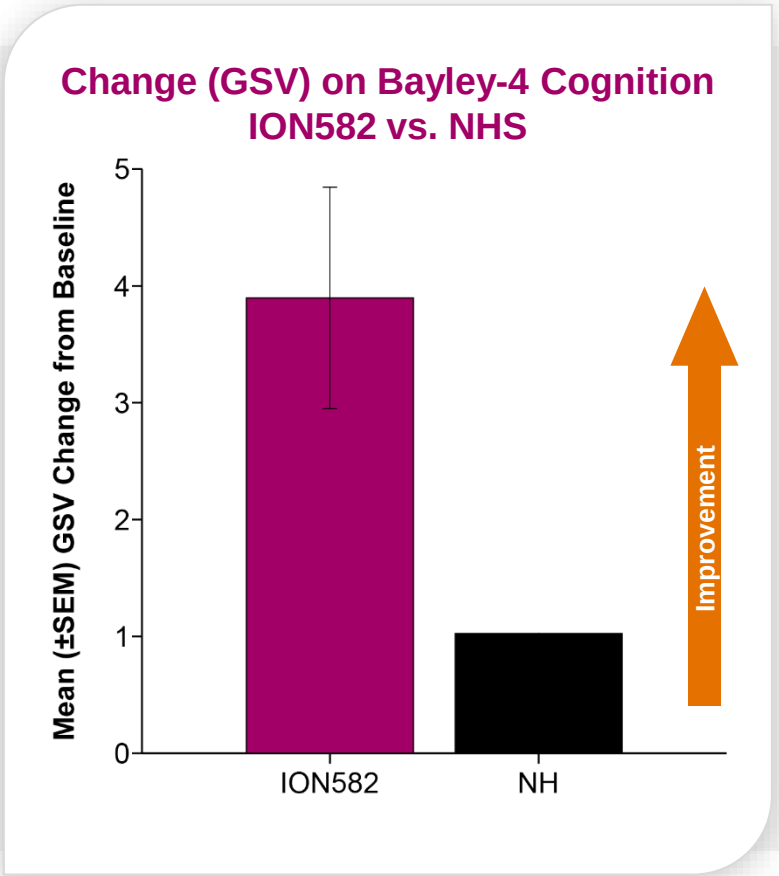

## Change in Expressive Communication: ORCA and Bayley-4

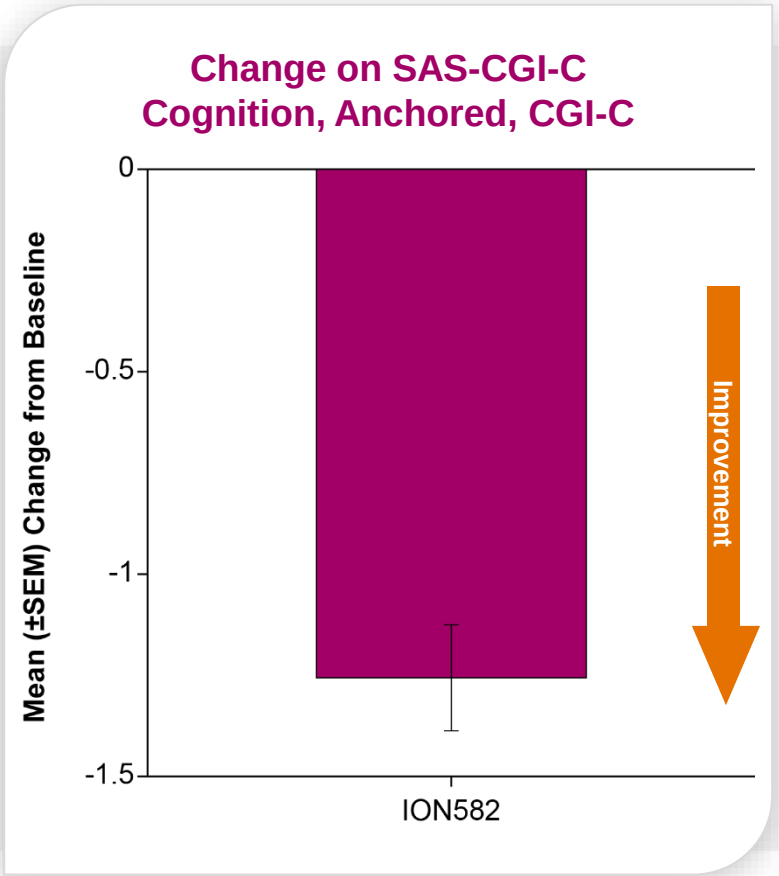



*GSV*, Growth scale values *ORCA*, Observer-Reported Communication Ability; *SEM*, Standard error mean.
1. Medium and high dose groups at 6 months.

# Cognition: Improvement Across Measures of Cognition on Bayley-4 and SAS-CGI-C[1,2]

Improvement in cognition on Bayley-4 exceeds natural history[3]; SAS-CGI-C shows clinically meaningful change[4-9]



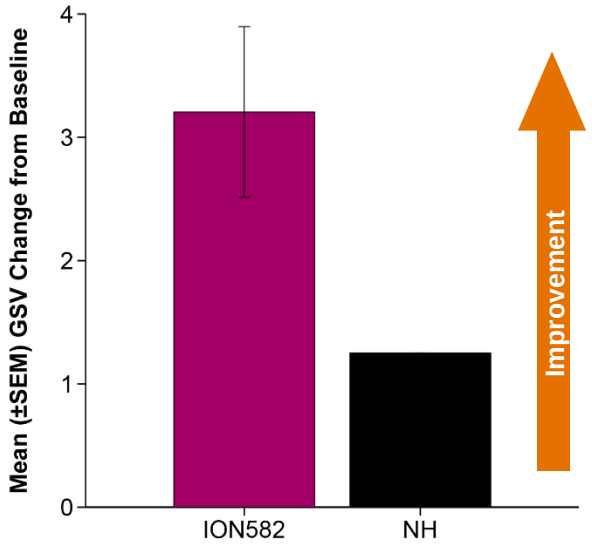

*GSV*, Growth scale values; *SEM*, Standard error mean; *SAS-CGI-C,* Symptoms of Angelman Syndrome–Clinician Global Impression-Change

1. Medium and high dose groups at 6 months. 2. Cognition domain not assessed with Vineland-3 or ORCA. 3. Angelman Syndrome Natural History Study www.clinicaltrials.gov/NCT04507997. 4. SAS-CGI-C anchored to Standard CGI-C overall score; ≥1 point change considered clinically meaningful. 5. Out of a maximum improvement of 3 points. 6. Not compared to natural history. 7. Connor-Ahmad, S. et al. *Orphanet J. Rare Dis*. (2023). 8. Adapted from Standard CGI-C. 9. SAS-CGI-C response range: Very Much Worse-Very Much Improved.

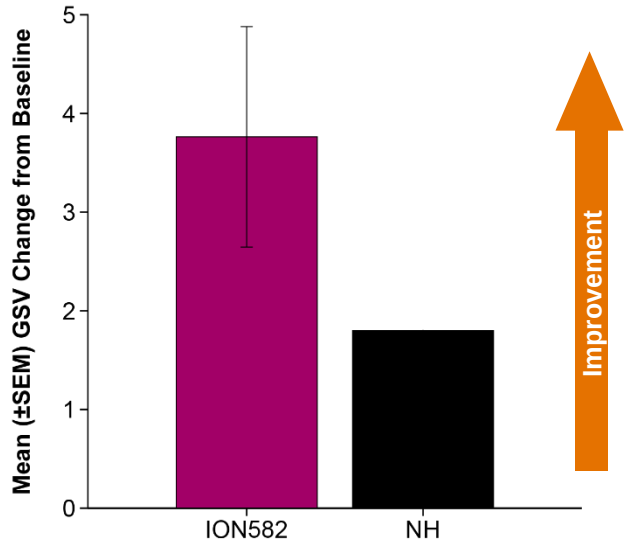
# Fine Motor Function: Improvement Observed on Bayley-4, Vineland-3 and SAS-CGI-C[1,2]

Improvements on Bayley-4 and Vineland-3 measures of fine motor function exceed natural history[3]; Directional improvement seen with SAS-CGI-C[4-9]

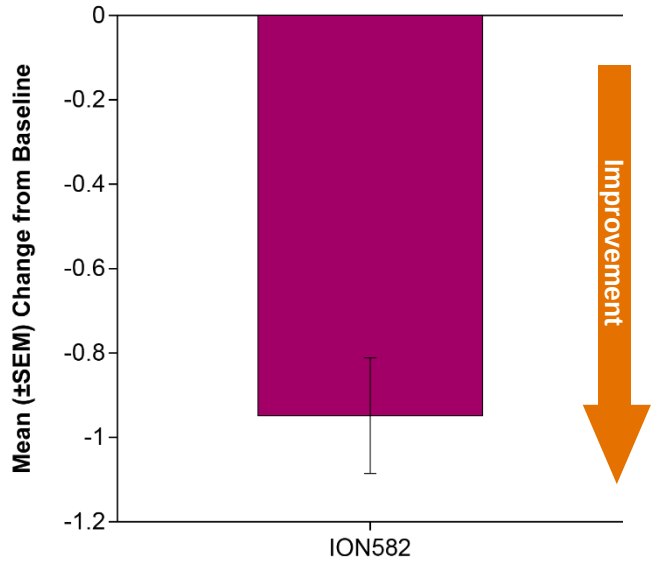
### Change (GSV) on Bayley-4 Fine Motor ION582 vs. NHS




### Change (GSV) on Vineland-3 Fine Motor ION582 vs. NHS




### Change on SAS-CGI-C Fine Motor, Anchored, CGI-C



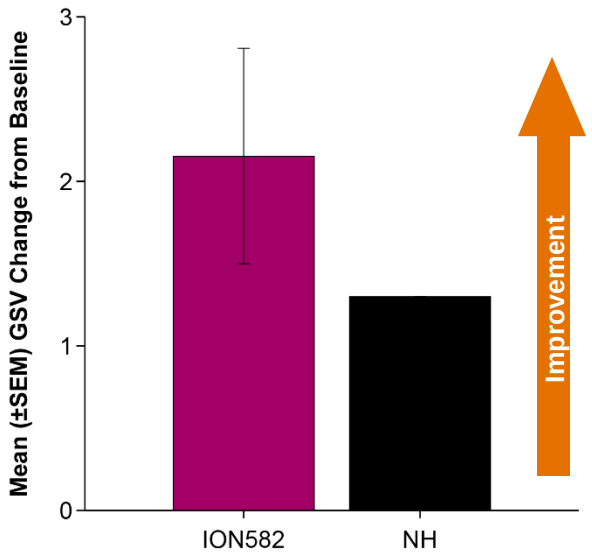

*GSV*, Growth scale values; *SEM*, Standard error mean; *SAS-CGI-C,* Symptoms of Angelman Syndrome–Clinician Global Impression-Change

1. Medium and high dose groups at 6 months. 2. Fine motor function not assessed by ORCA. 3. Angelman Syndrome Natural History Study www.clinicaltrials.gov/NCT04507997. 4. SAS-CGI-C anchored to Standard CGI-C overall score; ≥1 point change considered clinically meaningful. 5. Out of a maximum improvement of 3 points. 6. Not compared to natural history. 7. Connor-Ahmad, S. et al. *Orphanet J. Rare Dis*. (2023). 8. Adapted from Standard CGI-C. 9. SAS-CGI-C response range: Very Much Worse-Very Much Improved.

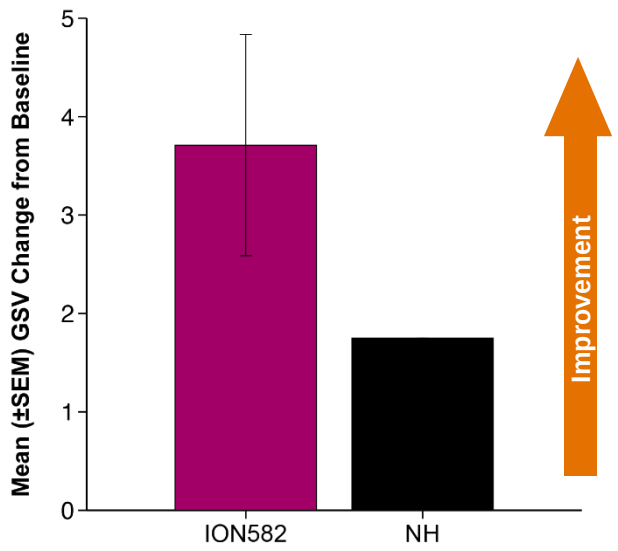
# Gross Motor Function: Improvement Observed on Bayley-4, Vineland-3 and SAS-CGI-C[1,2]

Improvements on Bayley-4 and Vineland-3 measures of gross motor function exceed natural history[3]; SAS-CGI-C shows clinically meaningful change[4-9]

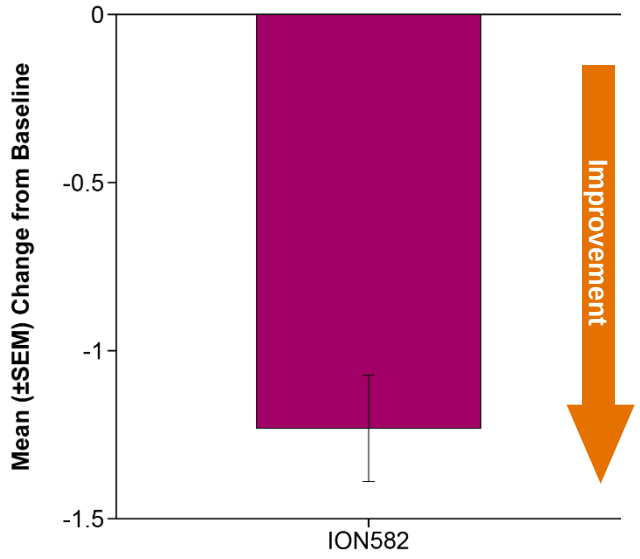
## Change (GSV) on Bayley-4 Gross Motor ION582 vs. NHS




## Change (GSV) on Vineland-3 Gross Motor ION582 vs. NHS



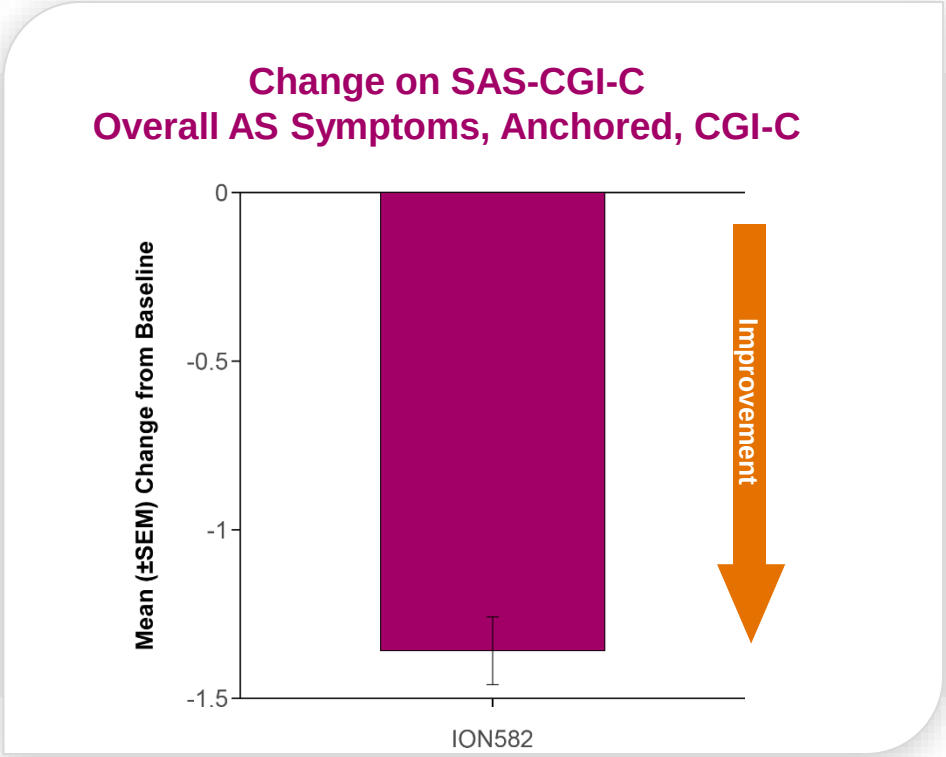

## Change on SAS-CGI-C Gross Motor, Anchored, CGI-C




*GSV*, Growth scale values; *SEM*, Standard error mean; *SAS-CGI-C,* Symptoms of Angelman Syndrome–Clinician Global Impression-Change.

1. Medium and high dose groups at 6 months. 2. Fine motor function not assessed by ORCA. 3. Angelman Syndrome Natural History Study www.clinicaltrials.gov/NCT04507997. 4. SAS-CGI-C anchored to Standard CGI-C overall score; ≥1 point change considered clinically meaningful. 5. Out of a maximum improvement of 3 points. 6. Not compared to natural history. 7. Connor-Ahmad, S. et al. *Orphanet J. Rare Dis*. (2023). 8. Adapted from Standard CGI-C. 9. SAS-CGI-C response range: Very Much Worse-Very Much Improved.

# Clinically Meaningful Improvement in Majority of Participants in Overall AS Symptom Change[1-7]




**97%**

**of Patients Improved**

SAS-CGI-C Overall
Angelman Syndrome Symptom Change

**Nearly all patients showed ≥1 point change in overall symptom severity at 6 months**

*SEM*, Standard error mean; *SAS-CGI-C*, Symptoms of Angelman Syndrome–Clinician Global Impression-Change.
1. Medium and high dose groups at 6 months. 2. SAS-CGI-C anchored to Standard CGI-C overall score; ≥1 point change considered clinically meaningful. 3. Out of a maximum improvement of 3 points. 4. Not compared to natural history. 5. Connor-Ahmad, S. et al. *Orphanet J. Rare Dis*. (2023). 6. Adapted from Standard CGI-C. 7. SAS-CGI-C response range: Very Much Worse-Very Much Improved.

# SAS-CGI-C: Clinically Meaningful Improvement Observed in Majority of HALOS Study Participants[1-8]

HALOS

| Participants with ≥ 1 Point Improvement on SAS-CGI-Change between Baseline and 6 months | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Overall Angelman Syndrome Symptoms | Cognitive Impairment | Gross Motor Skills | Expressive Communication | Fine Motor Skills | Impairment of Activities of Daily Living | Sleep problems | Maladaptive Behaviors | Seizures[9] |
| 97% | 85% | 74% | 69% | 64% | 62% | 61% | 56% | 18% |

**Clinically meaningful improvement across all domains assessed on Angelman syndrome specific SAS-CGI-C**

1. Medium and high dose groups at 6 months. 2. SAS-CGI-C anchored to Standard CGI-C overall score; ≥1 point change considered clinically meaningful. 3. Out of a maximum improvement of 3 points. 4. Not compared to natural history. 5. Connor-Ahmad, S. et al. *Orphanet J. Rare Dis*. (2023). 6. Adapted from Standard CGI-C. 7. SAS-CGI-C response range: Very Much Worse-Very Much Improved. 8. n=37 for SAS-CGI-C assessments. 9. Patients ≥4 years old were required to be on stable anti-seizure medication prior to enrollment.

# Vineland-3: Improvements Observed in Majority of Participants Compared to Natural History[1-3]

HALOS

| Participants Improvement Beyond NH on Vineland-3 between Baseline and 6 months | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Communication | | Motor Skills | | Daily Living Skills | | | Socialization | | |
| Receptive Communication | Expressive Communication | Gross Motor | Fine Motor | Personal | Community | Domestic | Interpersonal Relationships | Play and Leisure | Coping Skills |
| 89% | 84% | 53% | 63% | 74% | 79% | 82% | 79% | 87% | 63% |

**Improvements exceeding natural history across all domains assessed on Vineland-3**

1. Medium and high dose groups at 6 months. 2. Angelman Syndrome Natural History Study www.clinicaltrials.gov/NCT04507997. 3. n = 38.

# Majority of Participants Demonstrated Benefit in Nearly all Domains Assessed in the HALOS Study[1]

HALOS

| | Bayley-4[2,3] | Vineland-3[2,4] | ORCA[2,5-8] | SAS-CGI-Change[9-12] |
|---|---|---|---|---|
| Cognition | 67% | -- | -- | 85% |
| Receptive Communication | 67% | 89% | 60% | -- |
| Expressive Communication | 69% | 84% | | 69% |
| Gross Motor | 46% | 53% | -- | 74% |
| Fine Motor | 72% | 63% | -- | 64% |
| Daily Living Skills | * | 74-82%[13] | -- | 62% |
| Socialization | * | 63-87%[14] | -- | -- |
| Sleep | -- | -- | -- | 61% |
| Behavior | * | * | -- | 56% |

Improvement in ≥50% participants[1]

Improvement in <50% participants[1]

* Analyzed with alternate assessment tool(s)

-- Not in assessment

*ORCA*, Observer-Reported Communication Ability; *SAS-CGI-C,* Symptoms of Angelman Syndrome–Clinician Global Impression-Change

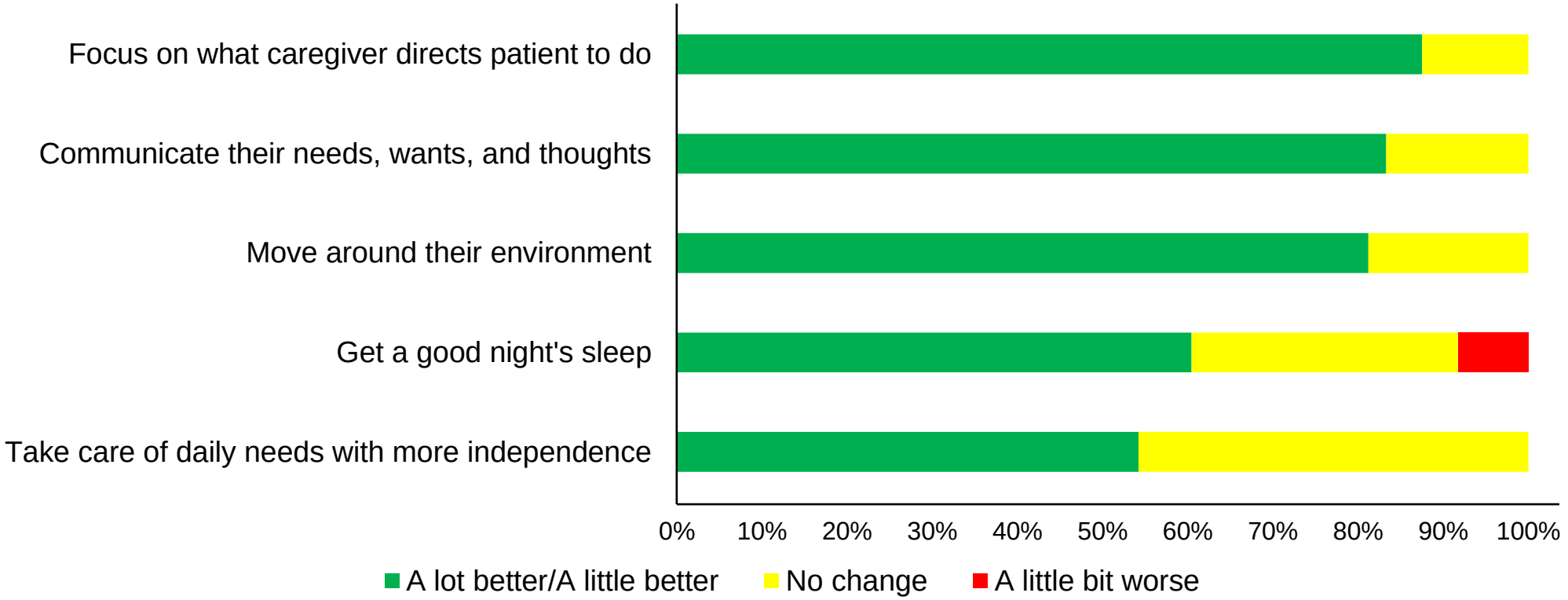
1. Medium and high dose groups at 6 months. 2. Improvement exceeds Natural History. 3. Bayley N. Aylward GP. *Bayley Scales of Infant and Toddler Development-Fourth Edition*. NCS Pearson. (2019). 4. Sparrow S, et. Al. *Vineland Adaptive Behavior Scales-Third Edition (Vineland-3).* NCS Pearson. (2016). 5. Improvement on ORCA exceeding proposed minimal clinically meaningful difference of ≥2. 6. Zigler CK, et al. *Am J Intellect Dev Disabil*. (2023). 7. Duke University. *Observer-Reported Communication Ability (ORCA) measure scoring manual.* Pattern Health. (2023). 8. ORCA T-score range: 25.8–83.8, (standardized, mean=50, SD=10). 9. Improvement on SAS-CGI-C exceeding proposed minimal clinically meaningful difference of ≥1 point. 10. Connor-Ahmad, S. et al. *Orphanet J. Rare Dis.* (2023). 11. Adapted from Standard CGI-C. 12. SAS-CGI-C response range: Very Much Worse-Very Much Improved. 13. Range across 3 subdomains (personal, community and domestic). 14. Range across 3 subdomains (Coping skills, interpersonal relationships and play and leisure)

IONIS

# Caregivers Reported Improvements in Abilities Across All Functional Domains[1]

HALOS

**Formal survey of caregiver report of child's change in abilities after 4 months on treatment**




1. Survey completed at 4-month timepoint, included low, medium and high-dose participants.

# Select Clinician and Caregiver Impressions from the HALOS Study of ION582

HALOS

> …big improvement in focus…

> …faster more stable gait…

> …sleeping through the night.

> …said ‘mama’ for the first time.

Clinician and caregiver-identified improvements in ***functional areas most impactful*** for people living with Angelman syndrome

# HALOS Study: Consistent Benefit Observed with ION582 Treatment in People with Angelman Syndrome

- Favorable safety and tolerability observed at all dose levels
- Reductions in EEG delta power observed at 6 months
- Evidence of clinical improvement observed across key functional areas[1]
  - 97% of participants showed clinically meaningful improvement in overall Angelman syndrome symptoms on SAS-CGI-C[2-7]
  - Improvements in communication, cognition and motor function exceeding natural history on Bayley-4, Vineland-3 and ORCA[8-13]
  - Consistent benefit seen across all ages and genotypes

**Conclusion: The totality of HALOS study results are encouraging, supporting evaluation in a controlled Phase 3 study**

1. Medium and high dose groups at 6 months. 2. SAS-CGI-C anchored to Standard CGI-C overall score; ≥1 point change considered clinically meaningful. 3. Out of a maximum improvement of 3 points. 4. Not compared to natural history. 5. Connor-Ahmad, S. et al. *Orphanet J. Rare Dis*. (2023). 6. Adapted from Standard CGI-C. 7. SAS-CGI-C response range: Very Much Worse-Very Much Improved. 8. Bayley N. Aylward GP. *Bayley Scales of Infant and Toddler Development-Fourth Edition*. NCS Pearson. (2019). 9. Sparrow S, et. Al. *Vineland Adaptive Behavior Scales-Third Edition (Vineland-3).* NCS Pearson. (2016). 10. Improvement on ORCA exceeding proposed minimal clinically meaningful difference of ≥2. 11. Zigler CK, et al. *Am J Intellect Dev Disabil*. (2023). 12. Duke University. *Observer-Reported Communication Ability (ORCA) measure scoring manual.* Pattern Health. (2023). 13. ORCA T-score range: 25.8–83.8, (standardized, mean=50, SD=10).

# Conclusion

Brett Monia, Ph.D.
Chief Executive Officer

# Next Steps in Advancing ION582 for People Living with Angelman Syndrome


## Continue Advancing HALOS Study

Generate longer-term data in ongoing LTE

All participants who completed MAD low, medium and high doses continuing in treatment in LTE

## Gain Regulatory Alignment[1]

**End-of-Phase 2 meeting planned with FDA**

Align on proposed study design including population, primary and secondary endpoints

Meet with regulators from outside the U.S.

## Initiate Pivotal Study[1]

Expect to initiate Phase 3 study in H1 2025

1. Timing based on current estimates, subject to change.

# Q&A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# Appendix

# Angelman Syndrome Glossary

| Term | Definition |
|---|---|
| CGI-C | Clinician Global Impression-Change |
| EEG | Electroencephalogram |
| GSV | Growth scale value |
| NHS | Natural history study |
| ORCA | Observer-Reported Communication Ability |
| SAS-CGI-C | Symptoms of Angelman Syndrome-Clinician Global Impression-Change |