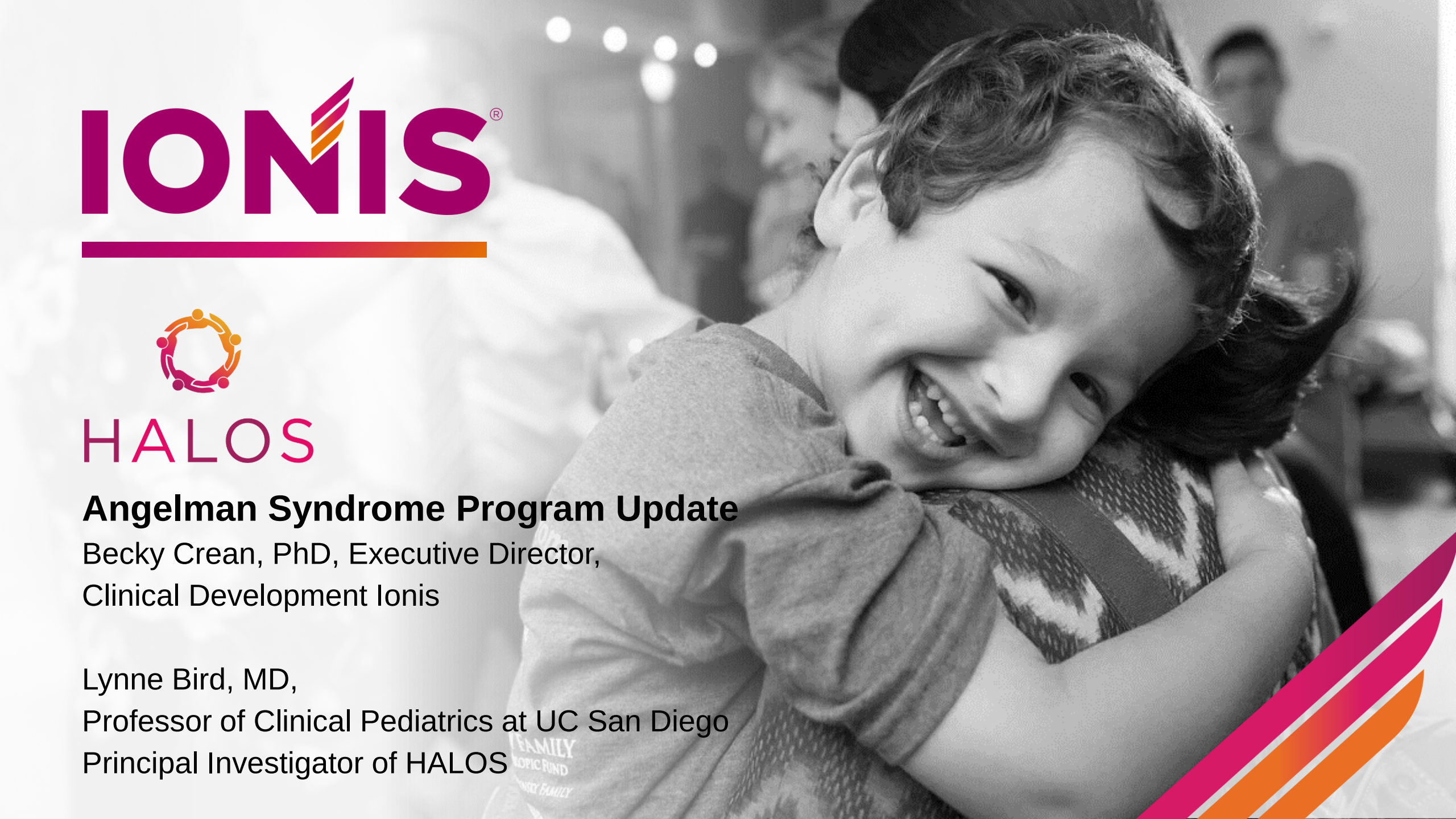


IONIS®

HALOS

Angelman Syndrome Program Update

Becky Crean, PhD, Executive Director,
Clinical Development Ionis

Lynne Bird, MD,
Professor of Clinical Pediatrics at UC San Diego
Principal Investigator of HALOS

Disclosures

Rebecca Crean, PhD is an employee of Ionis Pharmaceuticals

What Will We Talk About Today?

Review the HALOS Phase 1-2a clinical trial testing the safety and tolerability of ION582[1], 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 1 MAD portion (Part 1 Multiple-Ascending Dose: MAD) and then transition to the Part 2/3 Long-Term Extension (LTE) portion of the study

Present Part 1 MAD findings assessing the safety and efficacy of ION582 on clinical measures of symptoms of Angelman syndrome

Summary

Safe and well-tolerated at all dose levels; Preliminary evidence of clinical improvement observed across key functional areas

Discuss next steps for ION582

Summary

Participants will continue in the HALOS LTE to collect long-term safety and clinical data; Gain alignment with regulators on next stage of development for ION582

1. ION582 is an investigational drug and has not been approved by the FDA, EMA, or any other regulatory agency. This study was sponsored by Ionis Pharmaceuticals, Inc.

Ionis is Developing ION582, an ASO Designed to Stop the Silencing Mechanism on the Paternal UBE3A Gene, to Produce UBE3A Protein in the Brain

- **ION582** is a 2'-MOE antisense oligonucleotide which cleaves the UBE3A-ATS by RNase H1 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 with an aim to achieve **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:** > 14,000 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

HALOS Study of ION582[1] for Angelman Syndrome[2]

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

HALOS

DESIGN

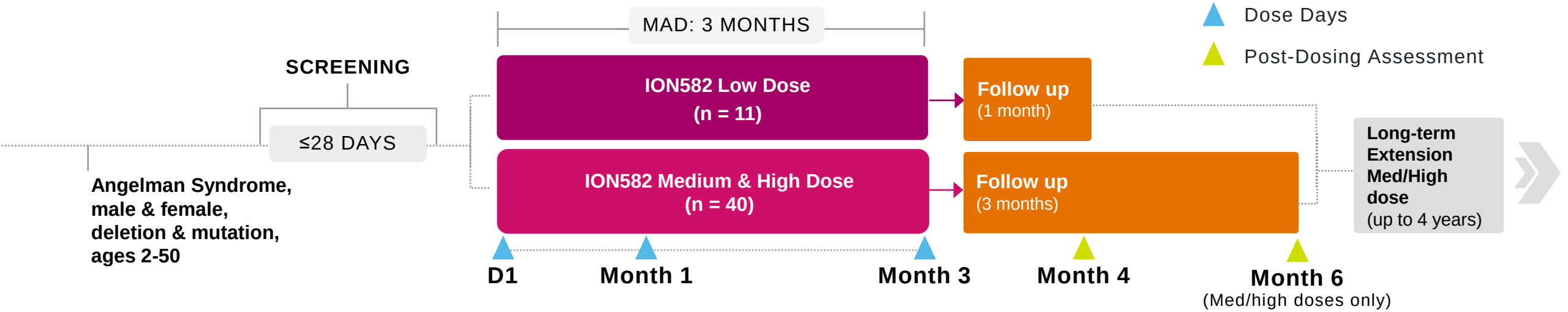
A global, open-label study evaluating 3 dose levels of ION582 in 51 male & female participants, ages 2-50

- Deletion and mutation genotypes
- ION582 given intrathecally into the CSF with lumbar punture; participants are sedated
- Last Post-MAD Assessment[2]:
  - Low dose: assessed month 4
  - Med/high dose: assessed month 6
- Ongoing long-term extension, 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. ION582 is an investigational drug and has not been approved by the FDA, EMA, or any other regulatory agency. This study was sponsored by Ionis Pharmaceuticals, Inc. 2. The HALOS study is an open label study and results should be interpreted with caution until a controlled study is completed (NCT05127226). 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

Assesses the HALOS participant: | Directly | Parent's Perspective | Doctor's Perspective |

	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.

Next Steps for ION582

Continue Advancing HALOS Study

Generate longer-term data in ongoing LTE

All participants who completed MAD continuing in treatment in LTE

Gain Regulatory Alignment[1]

End-of-Phase 2 meeting planned with regulators

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

Initiate Pivotal Study[1]

Expect to initiate Phase 3 study in 1H 2025

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

HALOS

Results from the HALOS Study of ION582

Lynne Bird, M.D.
Professor of Clinical Pediatrics, University of California, San Diego School of Medicine

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

	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 MAD
100% of eligible participants enrolled in the long-term extension

MAD, Multiple Ascending Dose;1. Not deemed related to study drug per Investigator

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 LPs
- No reports of lower limb weakness, ataxia or radiculopathy

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

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

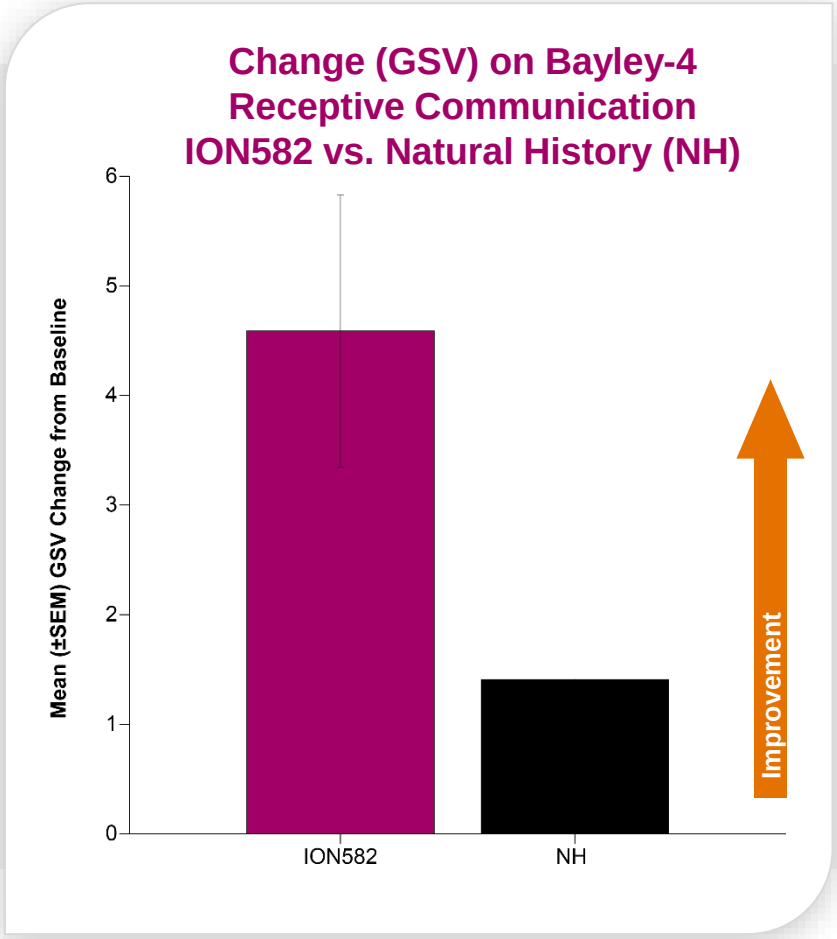
Basis of Functional Data Presentation	**Additional analyses from Bayley-4, Vineland-3, ORCA and SAS-CGI-C in medium and high dose groups, pooled, at 6 months**
Data from 6-month Assessment	• Final post-dose assessment in MAD • 6-month assessment added to provide baseline for LTE • Enables best comparison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

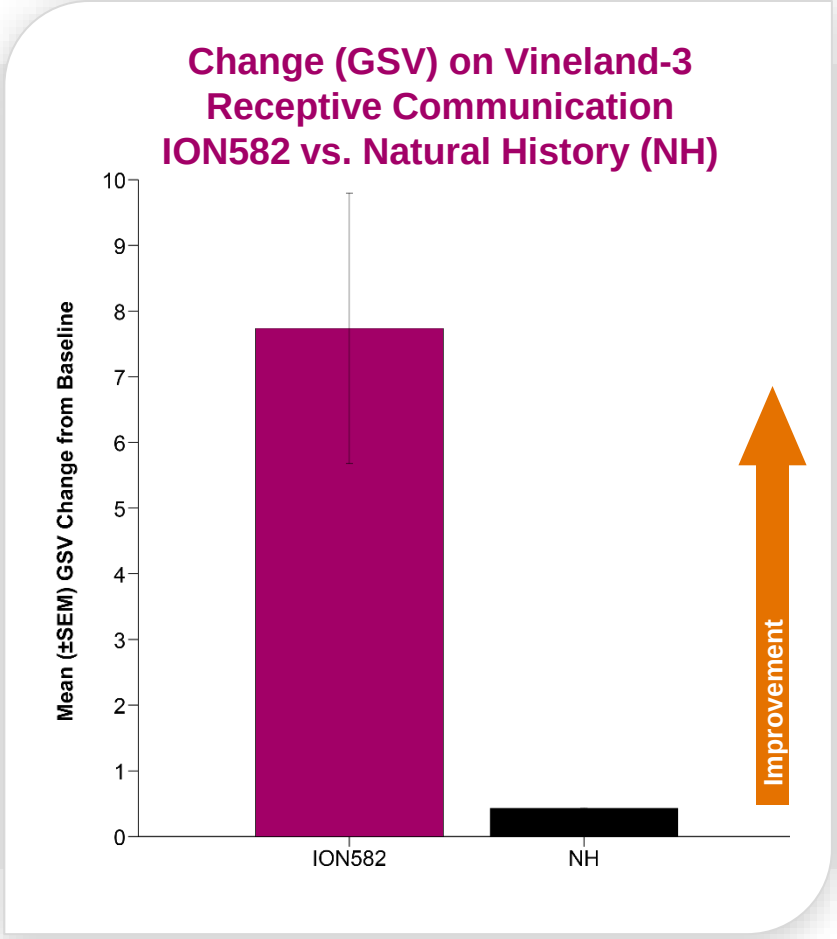
ORCA, Observer-Reported Communication Ability; *SAS-CGI-C,* Symptoms of Angelman Syndrome–Clinician Global Impression-Change

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.

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

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





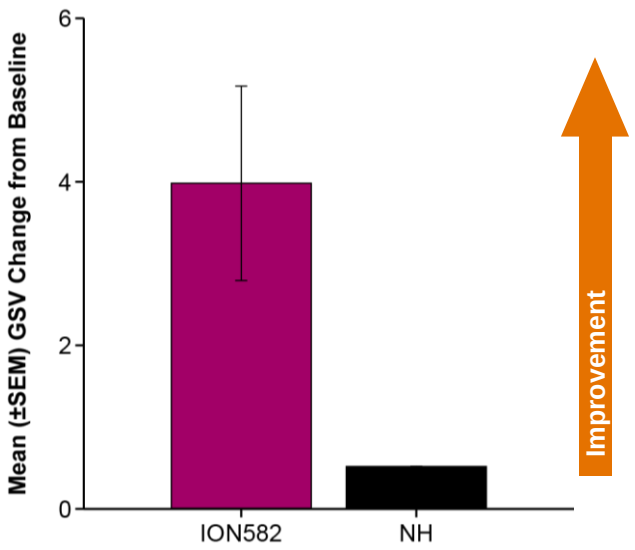
GSV, Growth scale values; *SEM*, Standard error mean

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

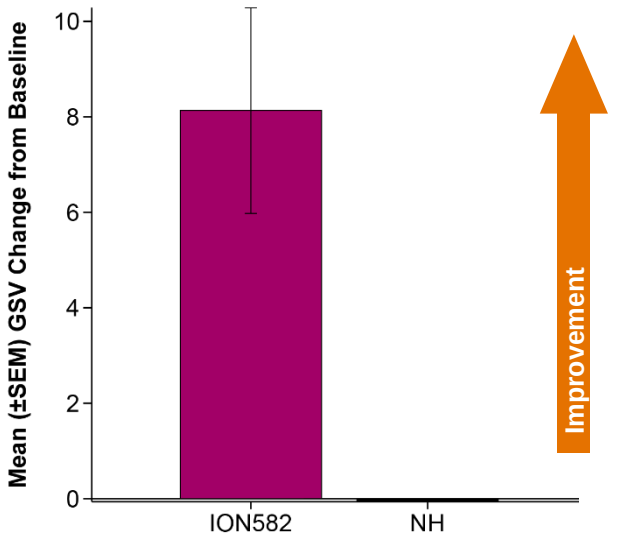
Expressive Communication: Improvement Observed on Bayley-4, Vineland-3 and SAS-CGI-C[1]

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

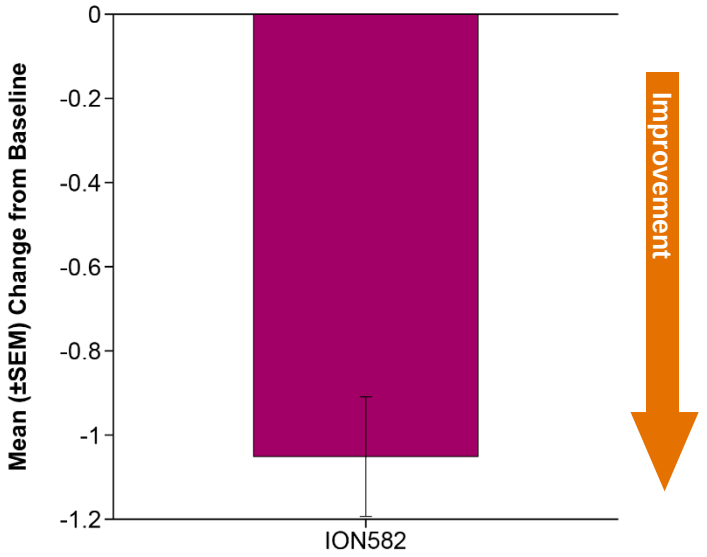
Change (GSV) on Bayley-4 Expressive Communication ION582 vs. Natural History (NH)



Change (GSV) on Vineland-3 Expressive Communication ION582 vs. Natural History (NH)



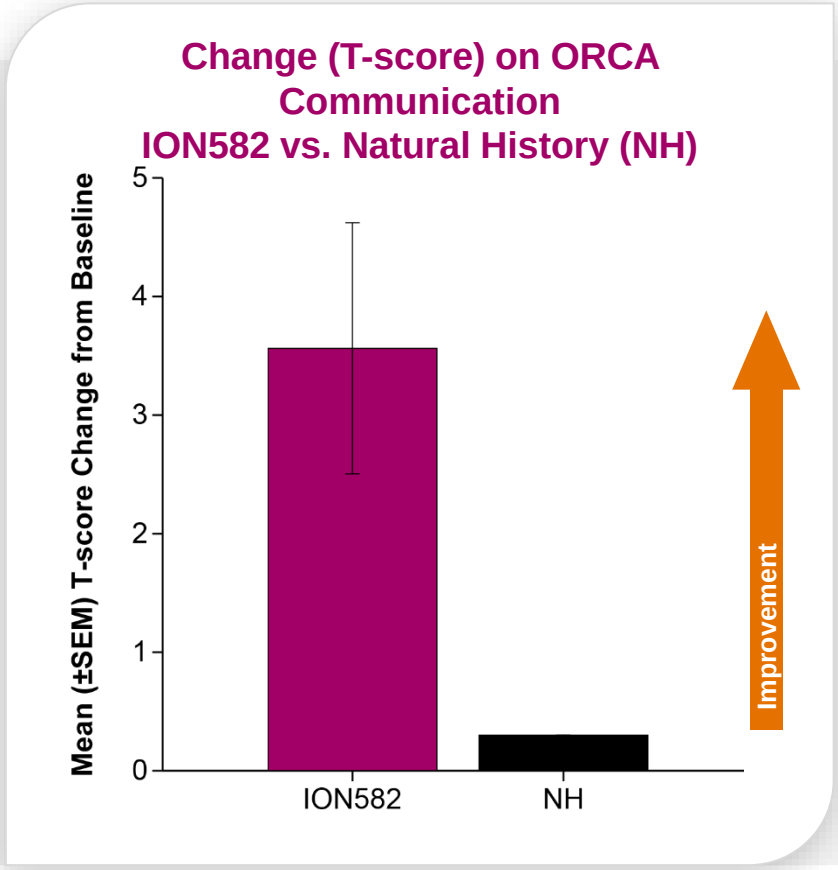
Change on SAS-CGI-C Expressive Communication Anchored, CGI-C



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



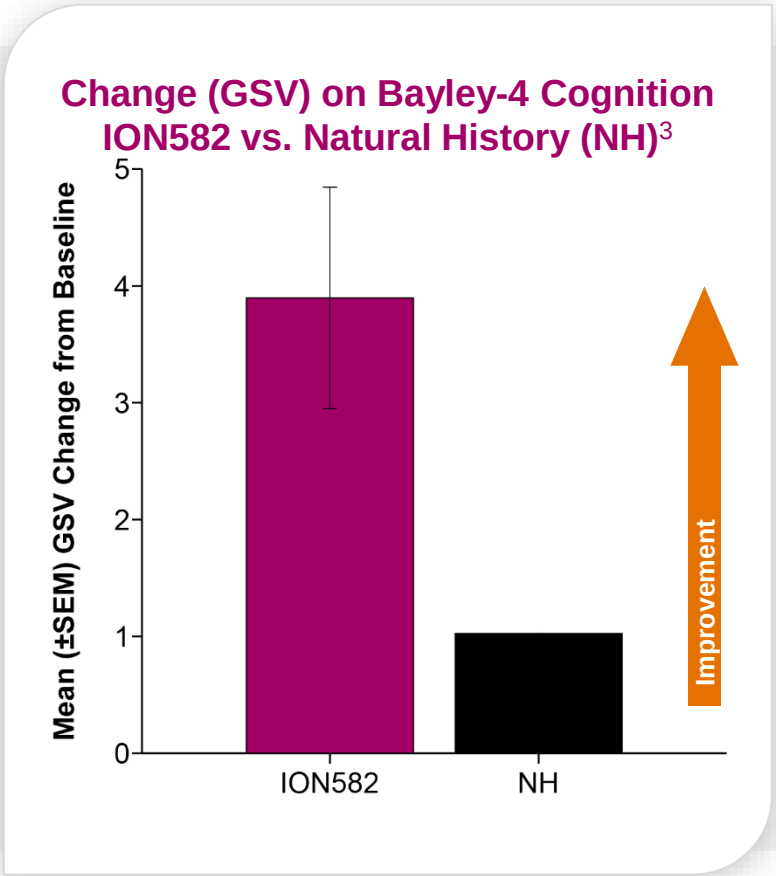
- Mean 3.6-point improvement achieved with ION582 at 6 months of treatment
- ≥ 2-point improvement considered clinically meaningful[2-5]
- Improvement at 6 months also exceeds natural history

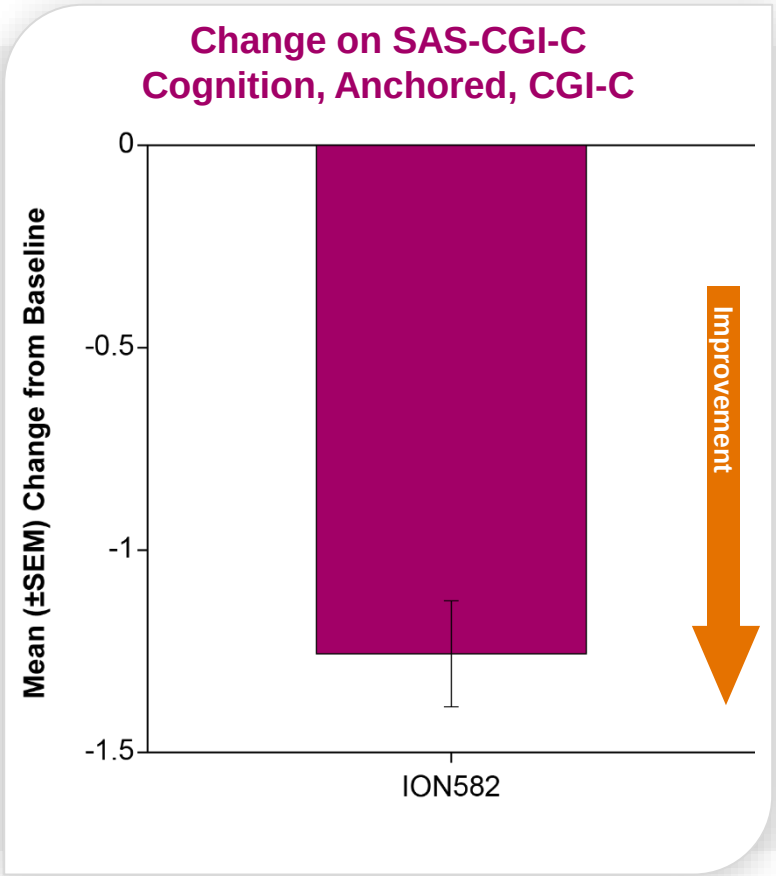
ORCA, Observer-Reported Communication Ability; *SEM*, Standard error mean

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.

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

Improvement in cognition on Bayley-4 exceeds natural history; SAS-CGI-C shows clinically meaningful change[3-8]





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 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). 7. Adapted from Standard CGI-C. 8. SAS-CGI-C response range: Very Much Worse-Very Much Improved.

SAS-CGI-C All Domains: Clinically Meaningful Improvement Observed in Majority of HALOS Study Participants[1-9]

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=39 for SAS-CGI-C assessments. 9. Patients ≥4 years old were required to be on stable anti-seizure medication prior to enrollment.

Vineland-3 All Domains: Improvement Observed in Majority of Participants Compared to Natural History[1-3]

Participants Improvement Beyond NH[4] 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 for vineland-3. 4. Natural History were age and genotyped matched to HALOS participants. Any score above NH was considered 'improved' beyond NH.8

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

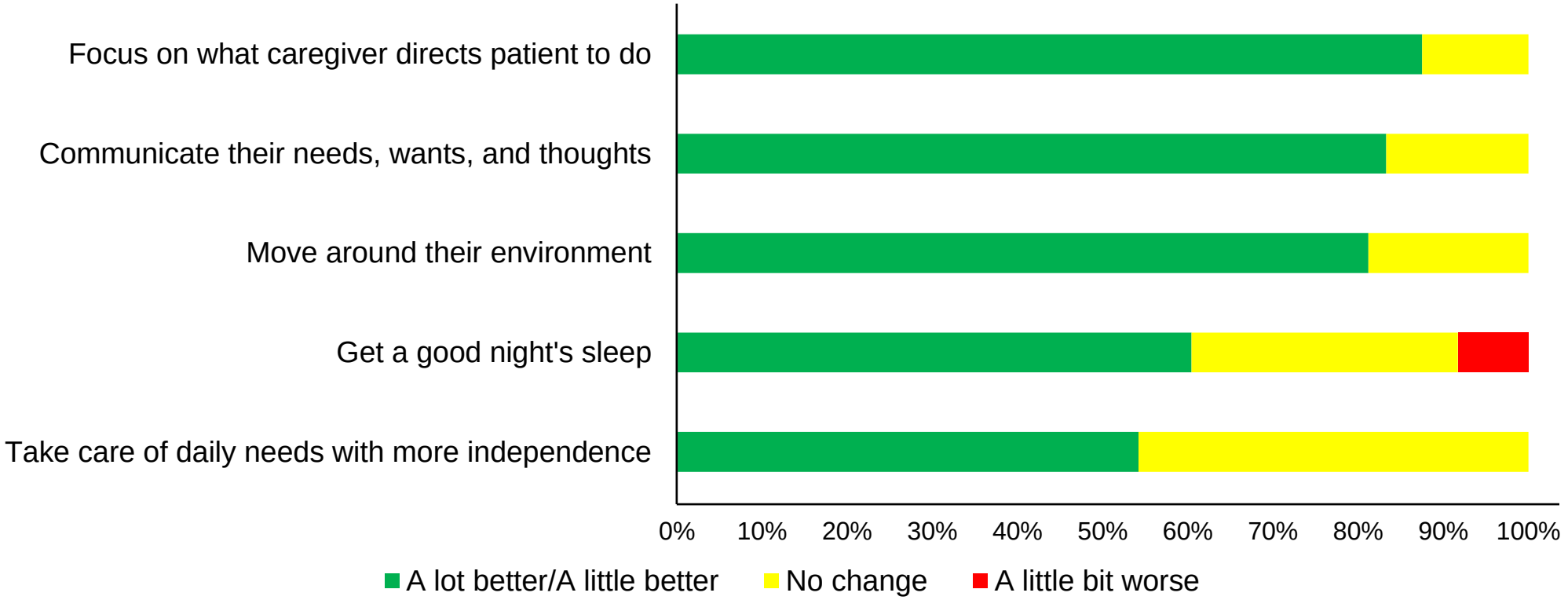
1. Medium and high dose groups at 6 months. 2. Improvement exceeds Natural History. 3. Bayley N. Aylward GP. *Bayley Scales of Infant and Toddler Development-Fourth Edition*. NCS Pearson. (2019). 4. Sparrow S, et. Al. *Vineland Adaptive Behavior Scales-Third Edition (Vineland-3).* NCS Pearson. (2016). 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 Parent 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.

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).

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

Ionis

Frank Bennett
Valerie Colletta
Becky Crean
Rob Komorowski
Mei Li
Eugene Schneider
Jeff Smith
Angelman HALOS Team

Academic Collaborators

Arthur Beaudet, Baylor
Catherine Chu, MGH
Mark Kramer, Boston University

Angelman Syndrome Foundation
ASF

Foundation for Angelman Syndrome Therapeutics
FAST

Angelman Biomarkers & Outcomes Measures
A-BOM

Angelman Syndrome Alliance
ASA

Israeli Angelman Syndrome Foundation


IONIS®
Thank you!