GTX-102 for Angelman Syndrome Phase 1/2 Interim Data Update

April 15, 2024

Forward Looking Statements

Cautionary note regarding forward-looking statements: This presentation contains forward-looking statements, including, but not limited to, statements regarding the clinical benefit, tolerability and safety of GTX-102 and the corresponding impact on patients, the anticipated dosing of the Phase 2 study for GTX-102, and the timing for initiation of a Phase 3 study for GTX-102 and associated regulatory meetings. Such forward-looking statements involve substantial risks and uncertainties that could cause our clinical development programs, future results, performance or achievements to differ significantly from those expressed or implied by the forward-looking statements. Such risks and uncertainties include, among others, the uncertainty of clinical drug development and unpredictability and lengthy process for obtaining regulatory approvals, the ability of the Company to successfully develop GTX-102, the Company's ability to achieve its projected development goals in its expected timeframes, the risk that results from earlier studies may not be predictive of future study results, risks related to adverse side effects, risks related to reliance on third party partners to conduct certain activities on the Company's behalf, smaller than anticipated market opportunities for the Company's products and product candidates, manufacturing risks, competition from other therapies or products, and other matters that could affect the sufficiency of existing cash, cash equivalents and short-term investments to fund operations, the Company's future operating results and financial performance, the timing of clinical trial activities and reporting results from same, and the availability or commercial potential of the Company's products and drug candidates, which are more fully described in our most recent Form 10-K under the caption "Risk Factors" and elsewhere in such reports. Any forward-looking statements made by us reflect our current views with respect to future events or to our future financial performance and involve known and unknown risks, uncertainties, and other factors that may cause our actual results, performance, or achievements to be materially different from any future results, performance, or achievements expressed or implied by these forward-looking statements. Accordingly, our actual results may materially differ from our current expectations, estimates, and projections. Given these uncertainties, you should not place undue reliance on these forward-looking statements.

Any forward-looking statements made by us in this presentation speak only as of the date of this presentation and represent our estimates and assumptions only as of the date of this presentation. Except as required by law, we assume no obligation, and we disclaim any intent, to update these statements to reflect actual results.

This presentation concerns commercial products as well as discussion of investigational drugs that are under preclinical and/or clinical investigation and which have not yet been approved for marketing by the U.S. Food and Drug Administration (FDA). They are currently limited by Federal law to investigational use, and no representations are made as to their safety or effectiveness for the purposes for which they are being investigated.

Disclaimers

GTX-102 is an investigational drug and is currently not approved by any regulatory authority

The data presented here are open-label interim data and do not provide definitive conclusions on efficacy or safety

Agenda

- Expansion Cohorts A & B data up to Day 170 (n=24)
- Dose-escalation Cohorts 4-7 data up to Day 758
- Phase 3 planning

Efficacy data as of February 27, 2024 and includes data previously shown at October 2023 Analyst Day. Safety data as of April 05, 2024.

GTX-102 for Angelman Syndrome (AS)
Antisense oligonucleotide (ASO) restores UBE3A protein in CNS neurons

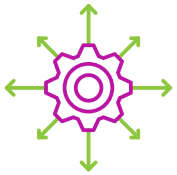
- Devastating neurodevelopmental disorder
- Prevalence*: ~60,000
- No approved treatments
- GTX-102 targets highly conserved region across multiple species
- Phase 1/2 fully enrolled; beginning Phase 3 planning

*Prevalence in commercially accessible geographies

Key Takeaways: GTX-102 Expansion and Dose-escalation Cohorts

-Cohorts A & B showed rapid, clinically meaningful improvement across multiple domains
-Improvements consistent or exceeding Dose-escalation Cohort 4-7 data at Day 170

Cohorts 4-7 showed long-term increasing and sustained clinical benefit far exceeding natural history data at Day 758



Phase 3 planning underway and expect initiation in 2024

Angelman Syndrome Domain Evaluations

Domains	Evaluation[1]	Comparator[2]
Cognition	Bayley-4	Natural History
Behavior	Angelman Severity Assessment (ASA[3]) for Behavior ABC-C Hyperactivity/Noncompliance	CGI-C Anchors Natural History
Sleep	ASA for Sleep	CGI-C Anchors
Receptive Communication	Bayley-4	Natural History
Gross Motor[4]	Bayley-4 ASA for Gross Motor	Natural History --
Overall	MDRI	--

1: New evaluations underlined
2: Not available for all endpoints and shown as representative comparisons
3: Previously CGI-S, Clinician Global Impression – Severity
4: Gross motor assessments as measured by Bayley-4 were not performed at Day 170 in the expansion cohorts and not included in this analysis

Natural History as Comparator for GTX-102 Phase 1/2 Data

Comparable to GTX-102 study population age and genotype; NHS2 recently available

Data from the Angelman Natural History studies[1] are used as a comparator for the treatment effect size observed with GTX-102[2]

	Natural History 1 (NHS1)	Natural History 2 (NHS2)
Collection	2006 to 2014	2018 to Present
Method	Bayley-III GSV converted to Bayley-4 GSV	Bayley-4 GSV
Baseline (N)	84	40
Day 365 (N)	63	11
Genotype	Deletion-type Angelman syndrome	
Age	4-17 years old	

1: Linking Angelman and Dup15q Data for Expanded Research (LADDER)

2: Sadhwani et al., 2021; Keute et al., 2021; Gentile et al., 2010. These data are illustrative only; differences exist between study designs, subject characteristics and geographical regions and caution should be exercised when comparing data across studies.

Angelman Severity Assessment (ASA[1]) Rating Scales
≥ 1 point reductions represent clinically meaningful improvements

ASA rates the severity of the patient's symptoms

The ratings are:

- ❑ 1 – Not at all impaired
- ❑ 2 – Borderline, slightly impaired
- ❑ 3 – Mildly impaired
- ❑ 4 – Moderately impaired
- ❑ 5 – Markedly impaired
- ❑ 6 – Severely impaired
- ❑ 7 – Among the most severely impaired

1: Previously CGI-S, Clinician Global Impression – Severity

Most patients are between mildly and severely (3 and 6) impaired at baseline

Each ASA domain rating scale is anchored to 6-8 questions specific to Angelman disease severity

Clinical meaningfulness of changes based on baseline severity and caregiver/primary investigator interviews

Broad GTX-102 Exposure Across Cohorts 4-7 and Cohorts A to E

74 patients enrolled in Phase 1/2

Dosing ranges from 3.3 -14 mg

Cohorts 4-7 up to 13 doses for ~2.4 yrs
Cohorts A & B up to 7 doses for ~1 yr

	# of Patients Enrolled (N=74*)	Max # of Doses	Max Study Duration (days)
Cohort 4-7	15	13	870
Cohort A	20	7	355
Cohort B	14	7	337
Cohort C	5	4	126
Cohort D	7	4	195
Cohort E**	8	6	232

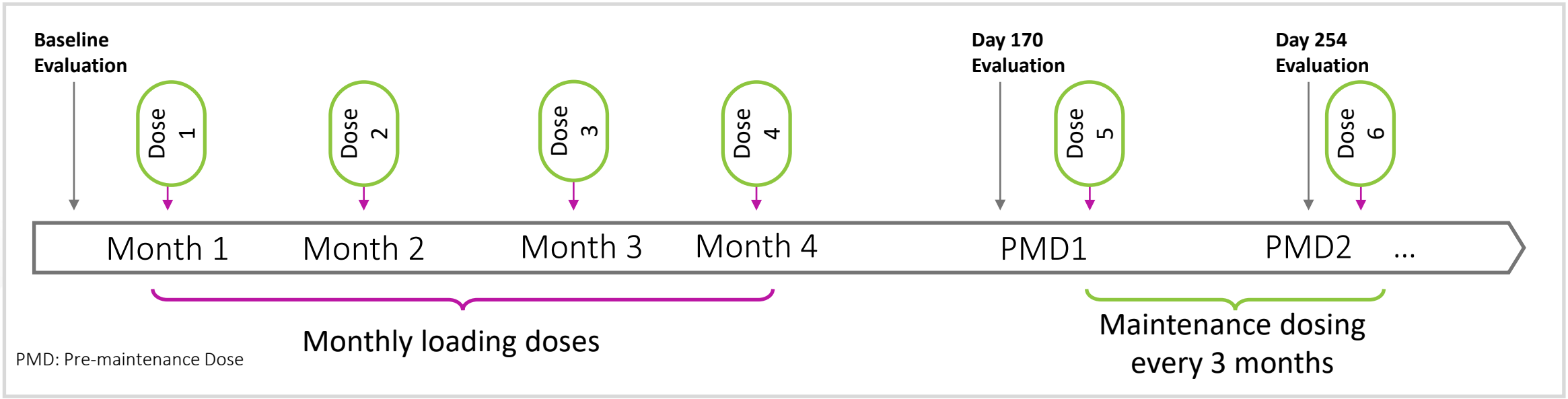
*Includes 5 original Patients in Cohorts 1-3

**Previously the 2mg cohort

GTX-102 Cohorts 4-7 and Cohorts A & B Demographics and Dosing

Enrolled at 19 sites across 7 countries outside of the U.S.

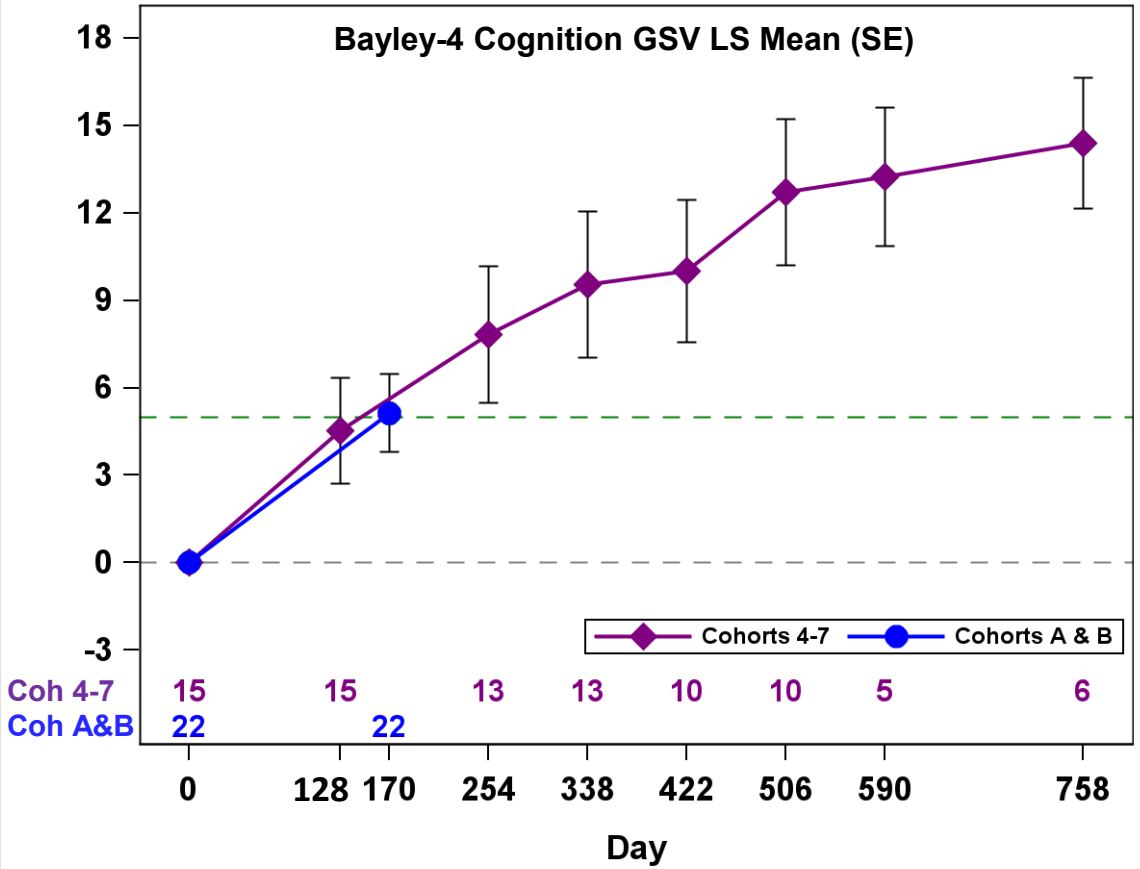
Patients Enrolled	Cohorts 4-7 N=15	Cohorts A & B N=34
Age at Screening mean (SD)	8.4 (3.9)	7.8 (3.8)
Age, n (%) 4 - 11 years 12 - 17 years	 12 (80.0) 3 (20.0)	 27 (79.4) 7 (20.6)
Sex Female, n (%)	8 (53.3)	21 (61.8)



PMD: Pre-maintenance Dose

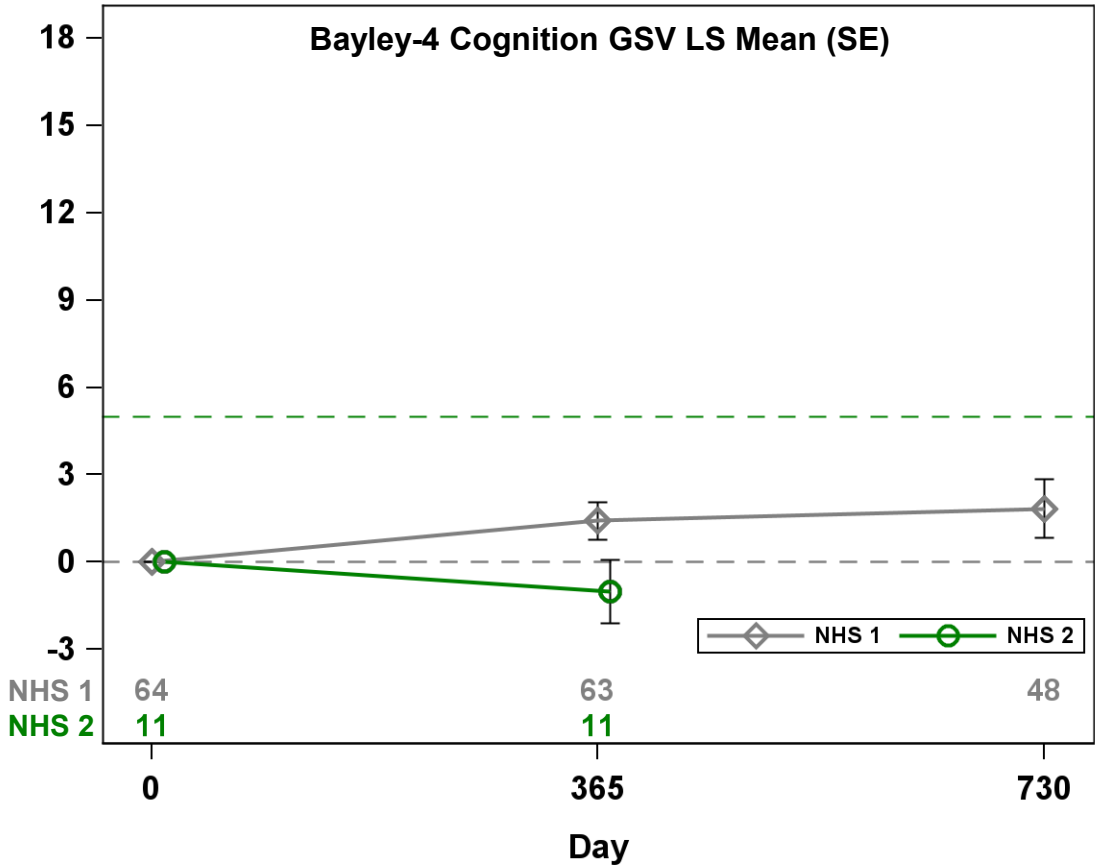
Cognition by Bayley-4: Rapid and Clinically Significant Gains at D170 and Continuing Long-term Improvement Through D758

GTX-102 treated patients showed clinically significant and improving response through Day 758



GEE model adjusted for baseline age was used to estimate changes from baseline. MID ± 5.

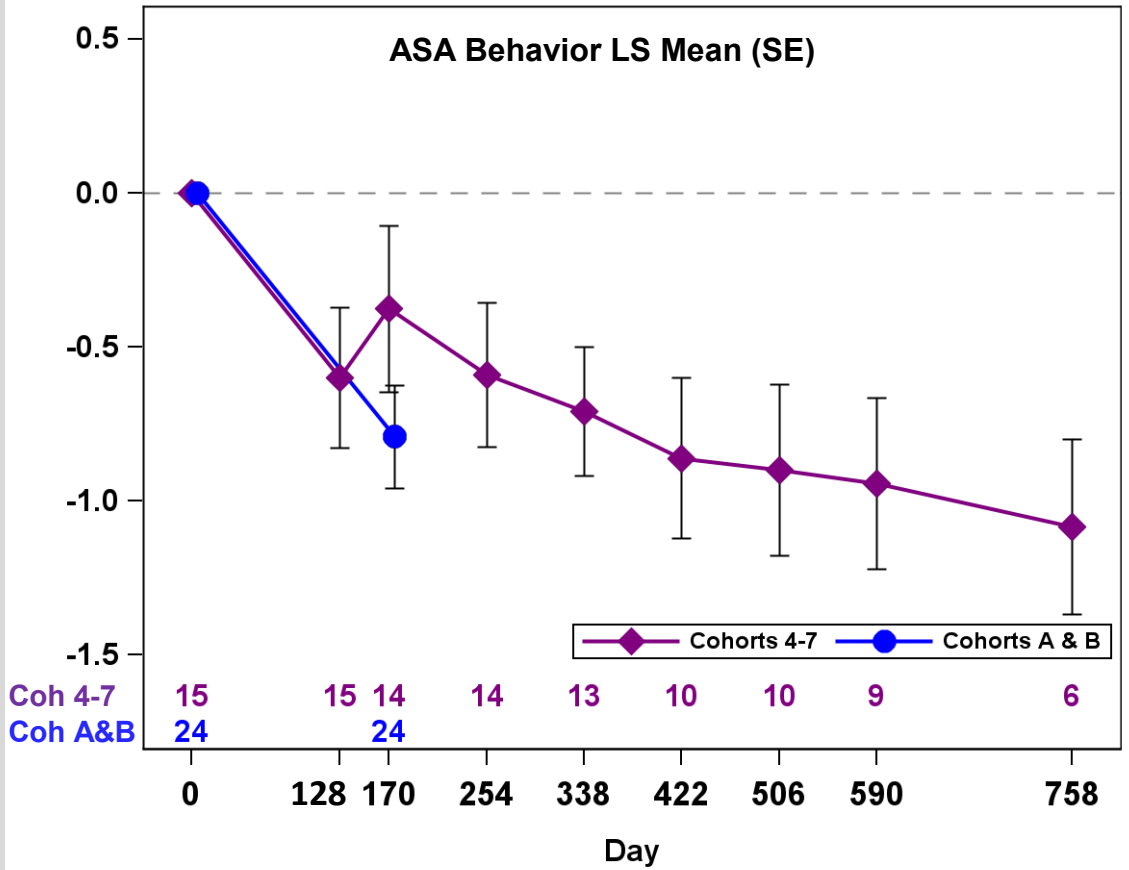
Natural history data changed minimally through Day 730



GEE model adjusted for baseline age was used to estimate changes from baseline. MID ± 5.

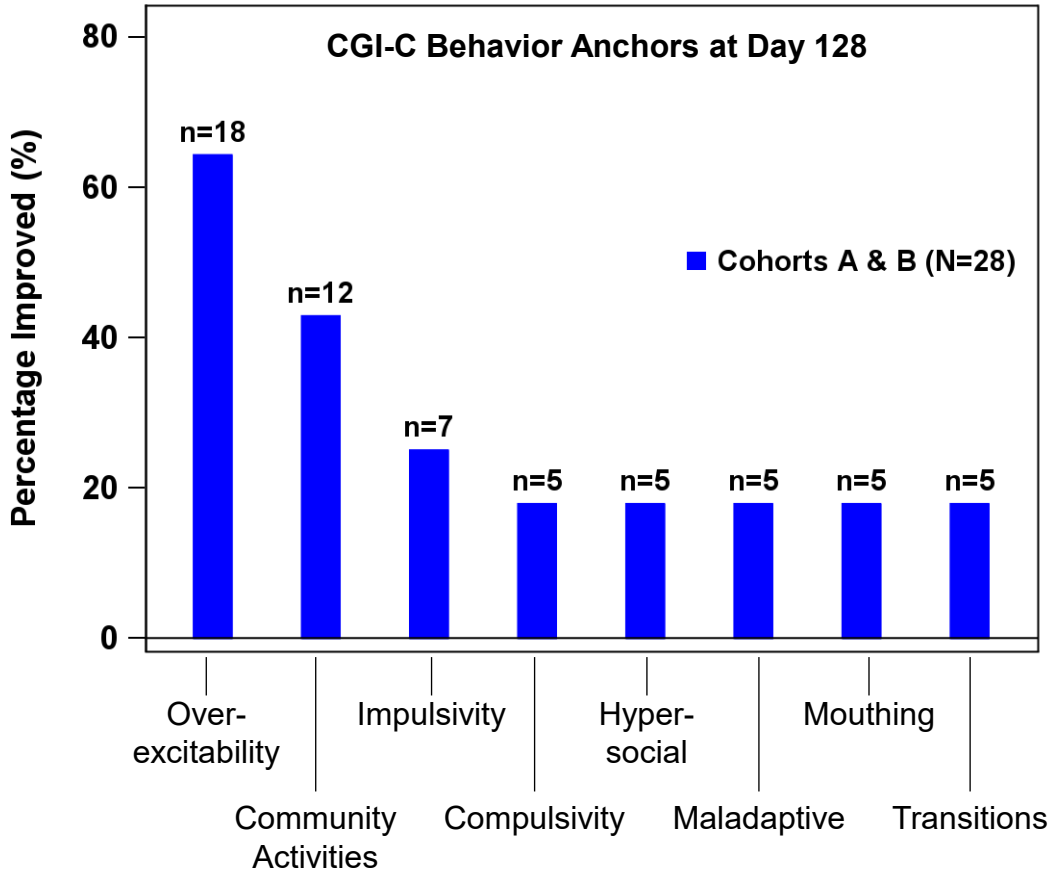
Behavior by ASA in Cohorts A & B Showed Rapid Improvement Compared to Cohorts 4-7 and Supported by CGI-C Anchors

Patients showed rapid and clinically meaningful reductions in behavior severity through Day 758



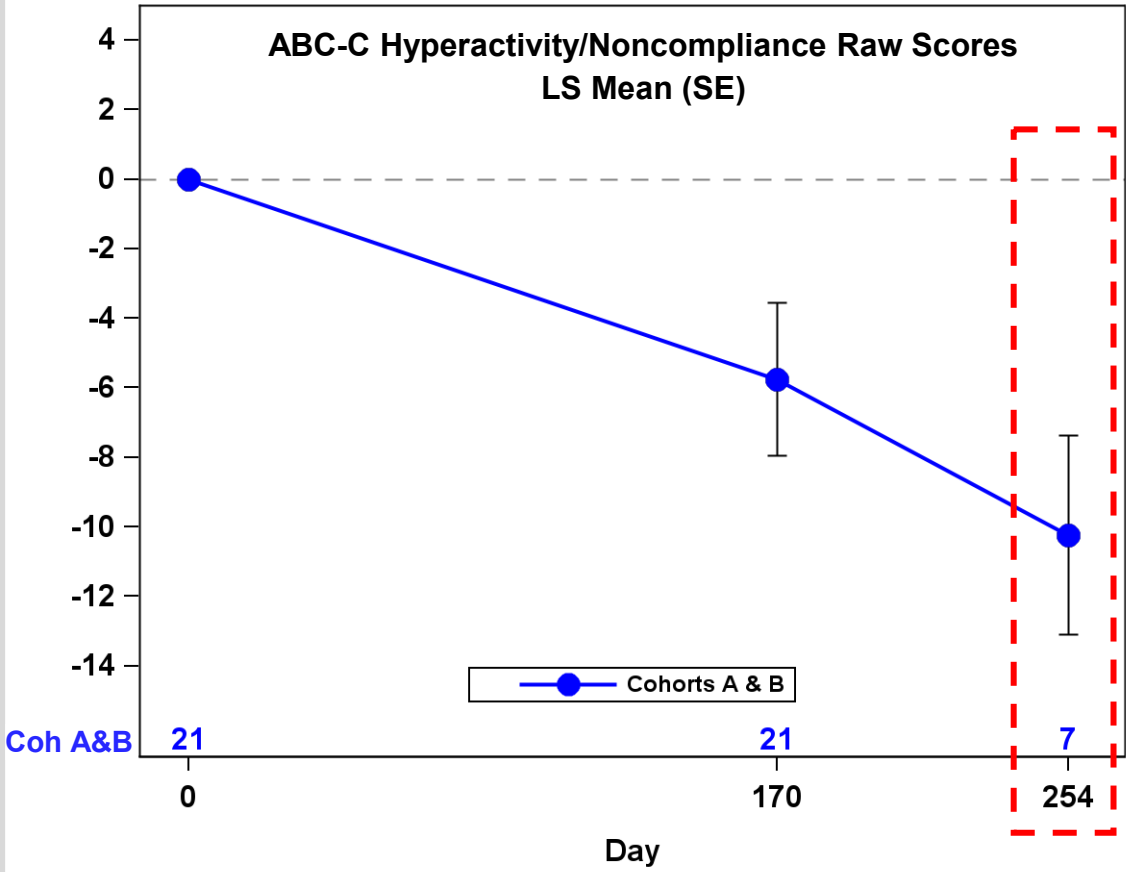
GEE model adjusted for baseline age was used to estimate changes from baseline

Improvements in behavior supported by CGI-C Anchors at Day 128



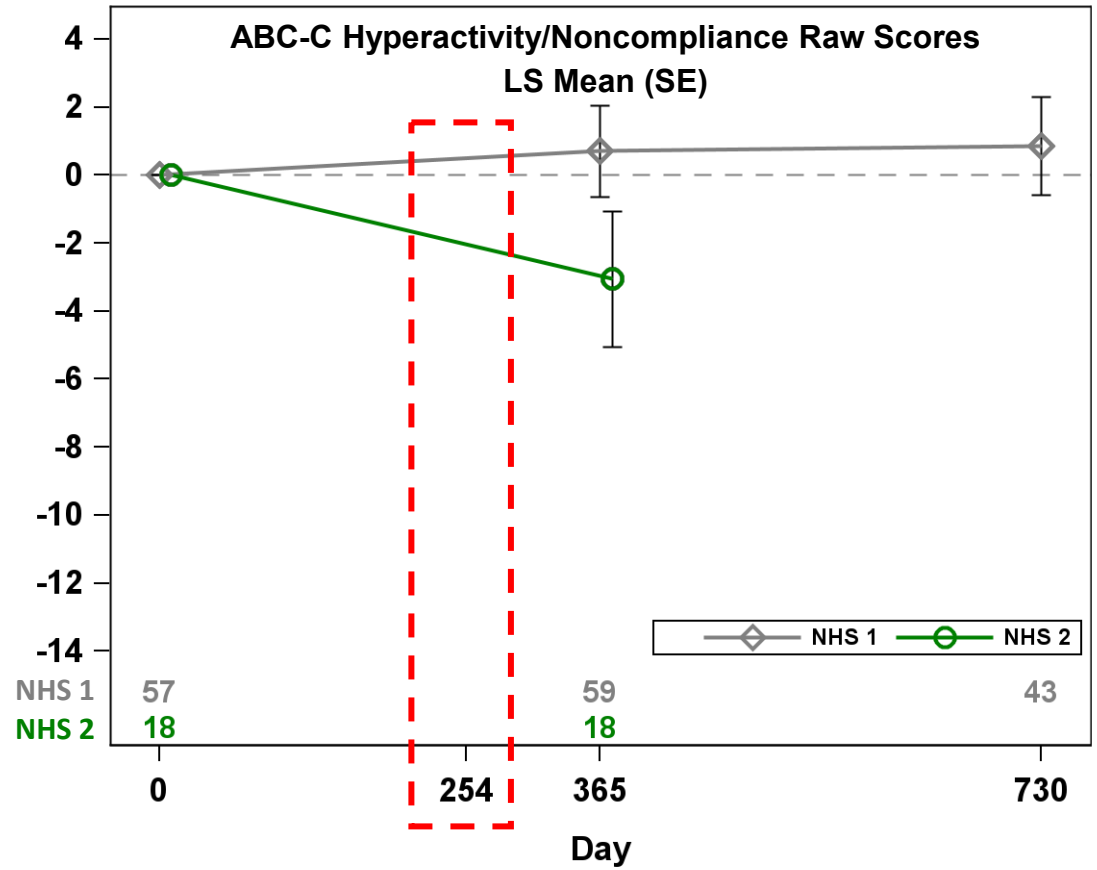
Behavior by ABC-C for Cohorts A & B Showed Clinically Significant Improvements Over Time Compared to Natural History

Rapid and clinically significant improvements in behavior at Day 170



GEE model adjusted for baseline age was used to estimate changes from baseline.

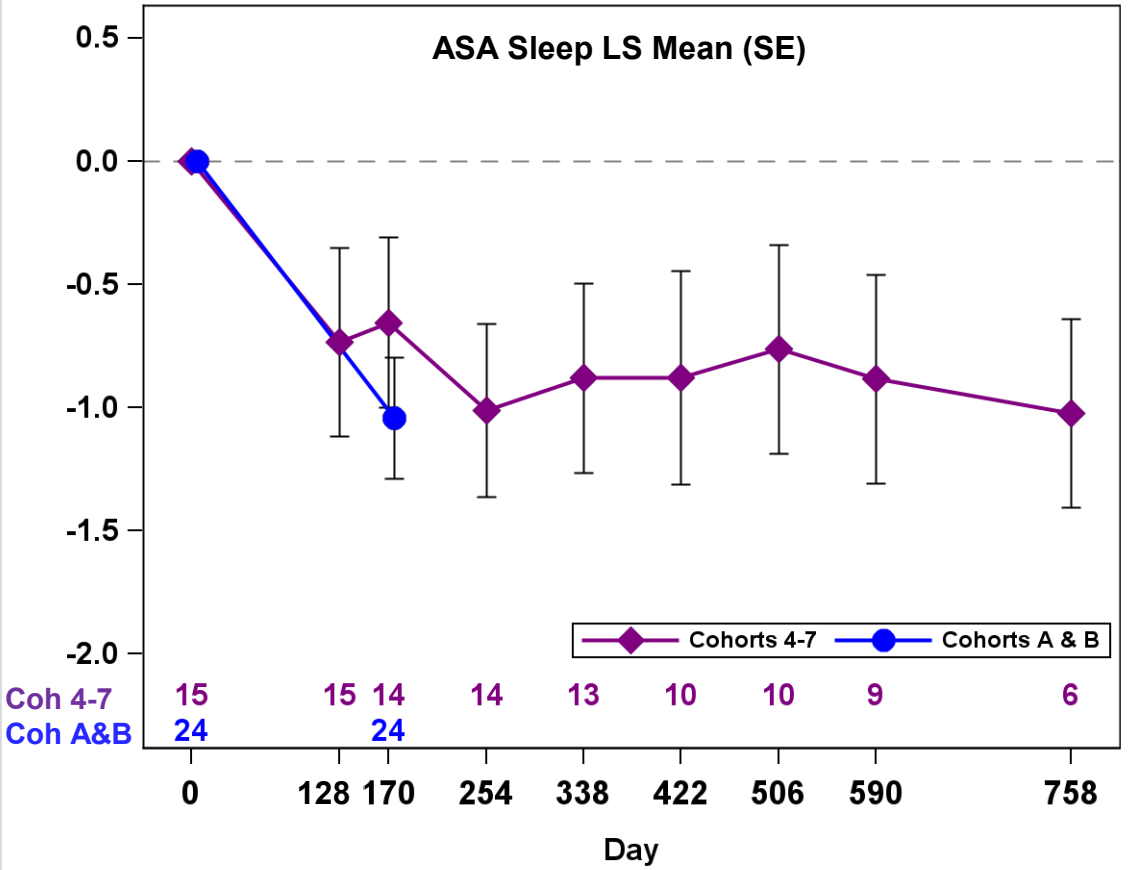
Natural history data changed minimally through Day 730



GEE model adjusted for baseline age was used to estimate changes from baseline

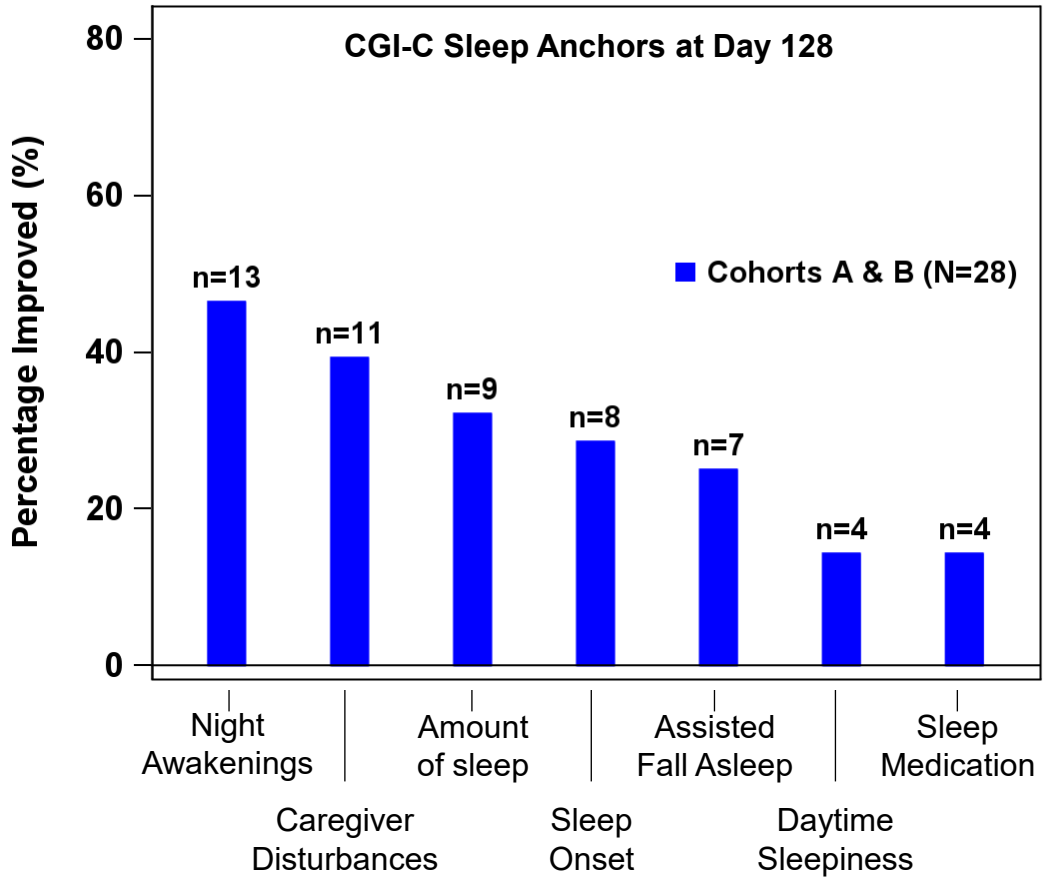
Sleep by ASA in Coh A & B Showed Rapid Clinically Meaningful Improvements Compared to Coh 4-7 & Supported by CGI-C Anchors

Patients showed rapid and clinically meaningful reductions in sleep severity through Day 758



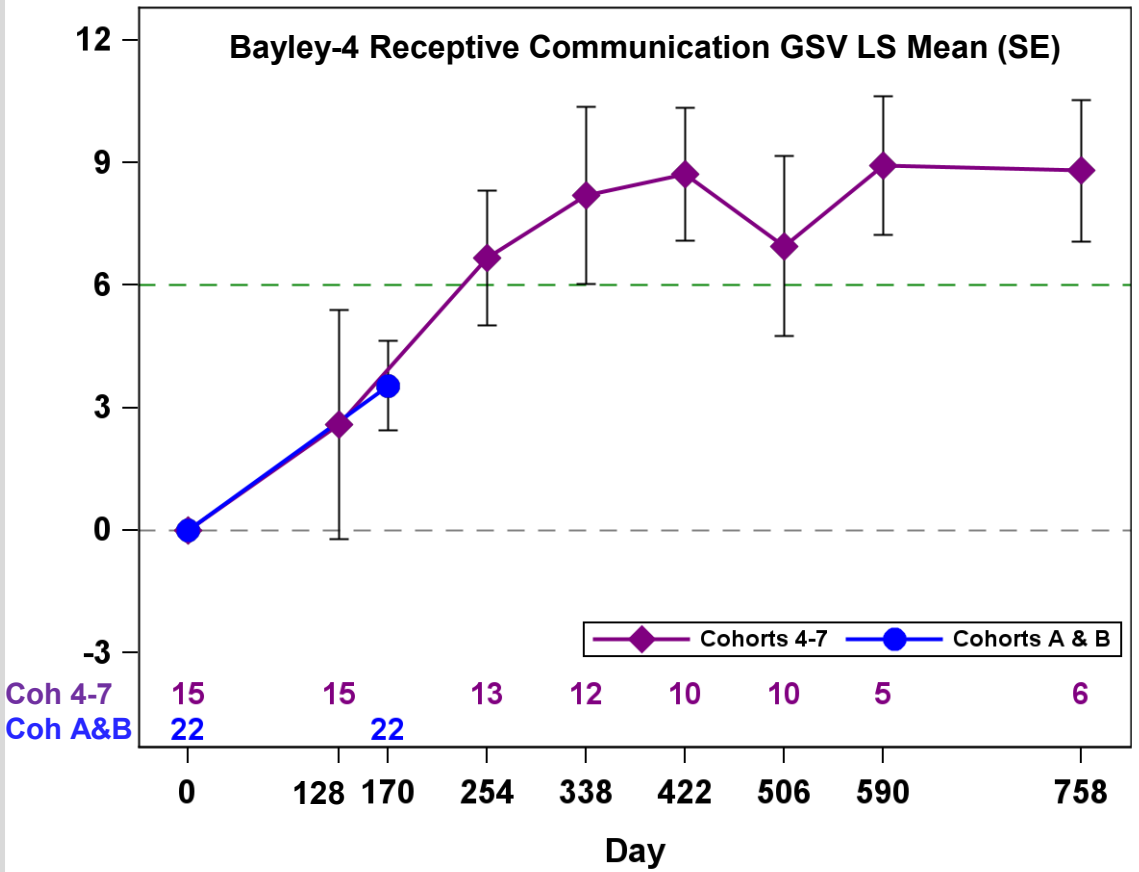
GEE model adjusted for baseline age was used to estimate changes from baseline

Improvements in sleep supported by CGI-C Anchors at Day 128



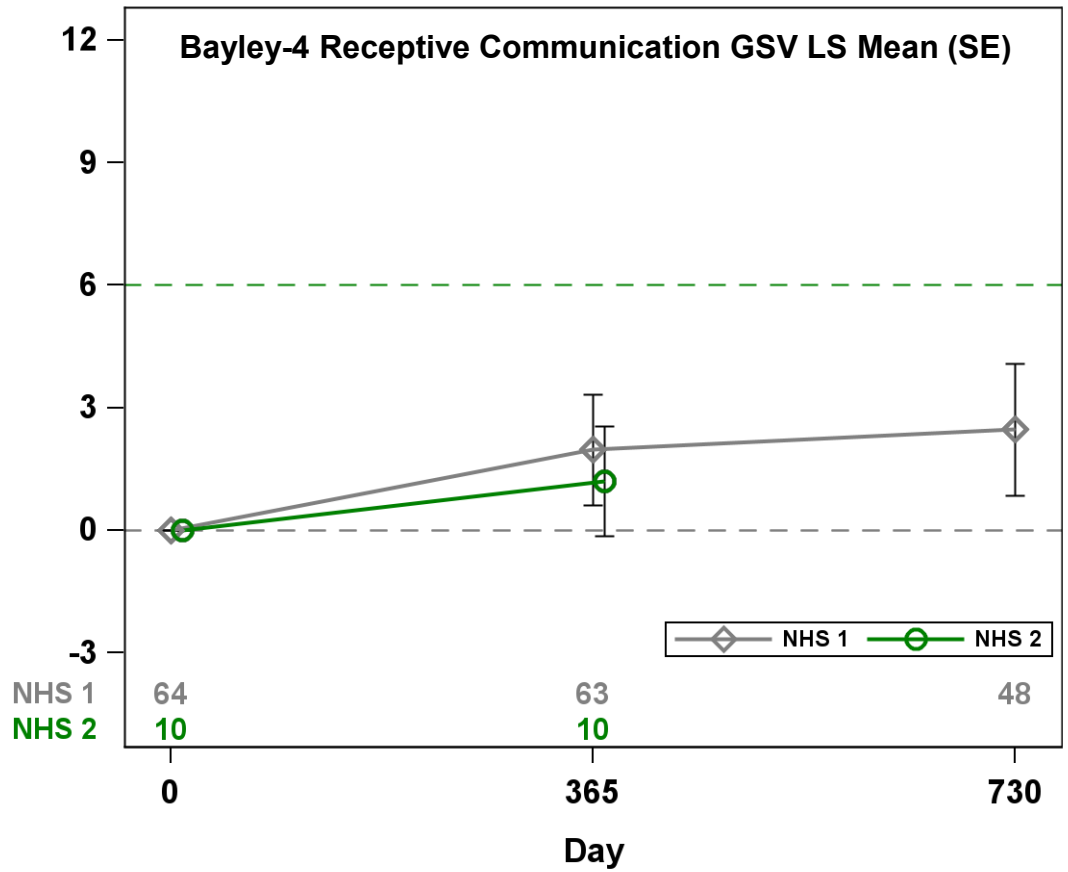
Receptive Comm. by Bayley-4: Rapid and More Consistent Gains at D170 and Sustained Clinically Significant Improvement Through D758

GTX-102 treated patients showed sustained and clinically significant response through Day 758



GEE model adjusted for baseline age was used to estimate changes from baseline. MID ± 6.

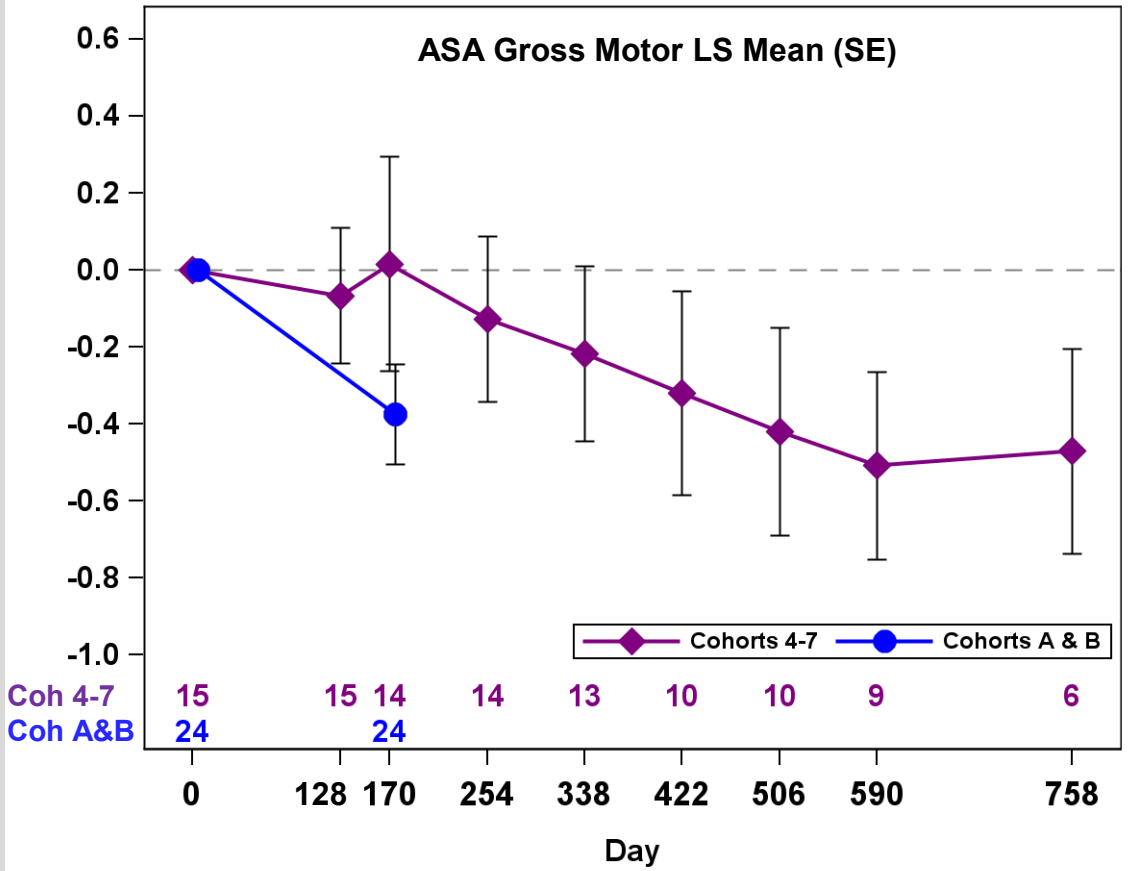
Natural history data changed minimally through Day 730



GEE model adjusted for baseline age was used to estimate changes from baseline. MID ± 6.

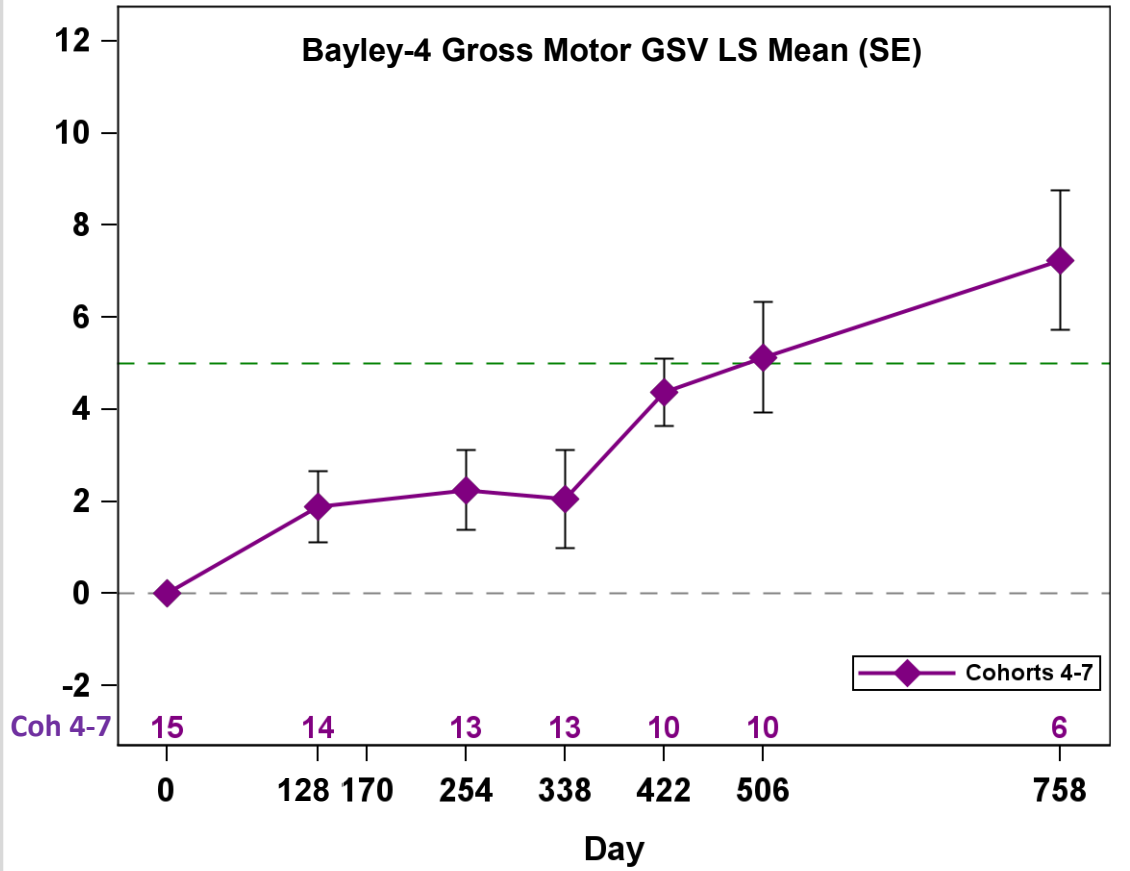
Gross Motor by ASA Showed More Rapid Improvement by Day 170 Compared to Cohorts 4-7

ASA Gross Motor for Cohorts A&B showed more rapid improvement by Day 170



GEE model adjusted for baseline age was used to estimate changes from baseline

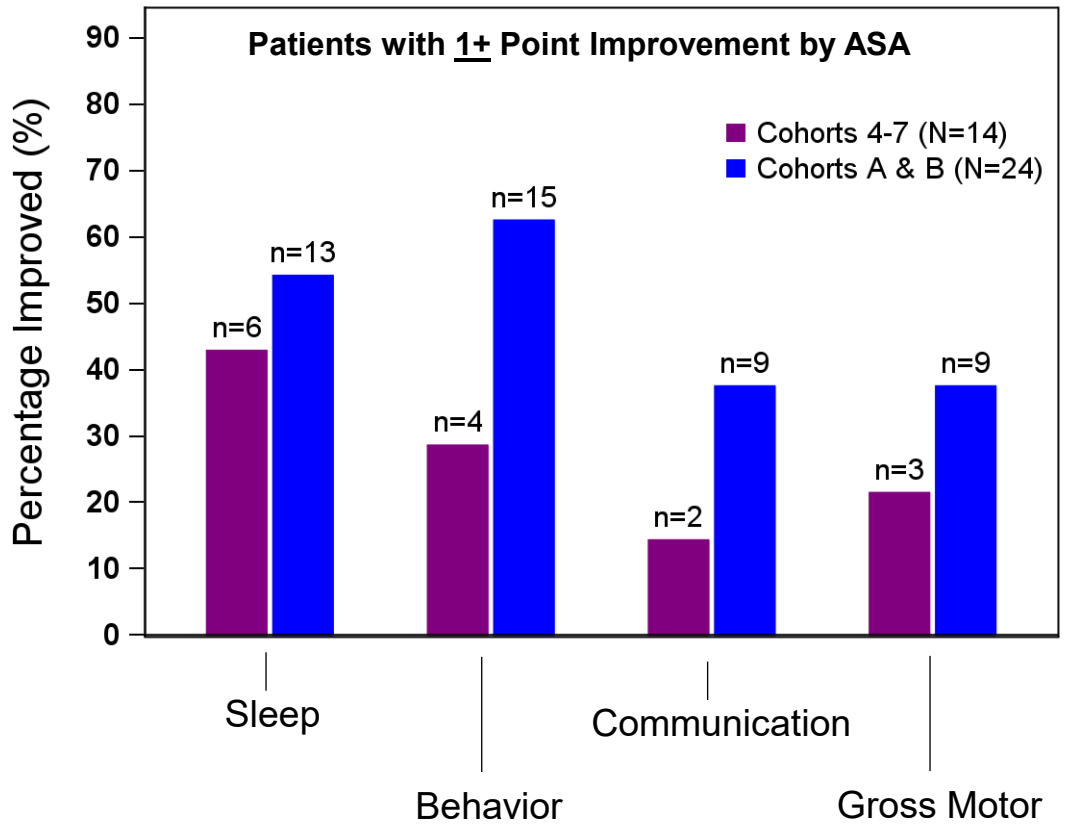
Bayley-4 Gross Motor Continued Improvement, Reaching Clinically Significant Improvement



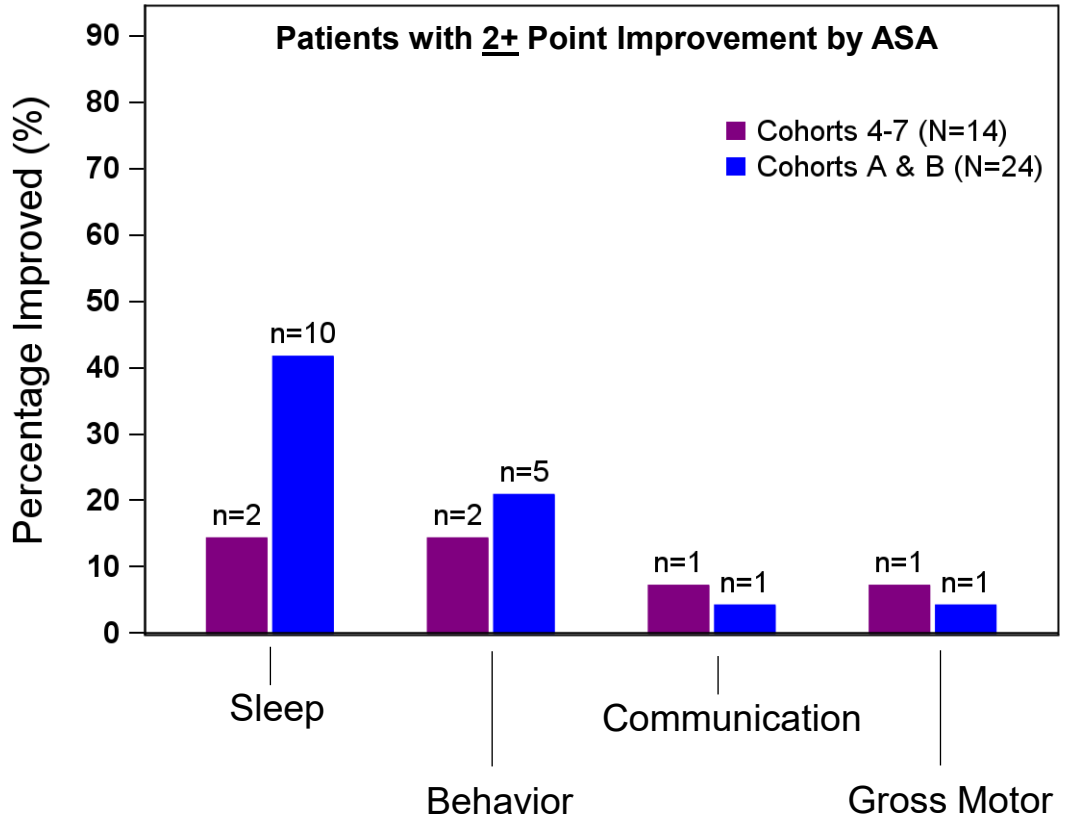
GEE model adjusted for baseline age was used to estimate changes from baseline. MID ± 5.
Bayley-4 Gross Motor not assessed for Cohorts A & B at Day 170

ASA Scores in Cohorts A & B Showed More Clinically Meaningful Improvements at Day 170 Compared to Patients in Cohorts 4-7

Cohorts A & B had a greater percent of patients with at least **1+ point improvement** at Day 170



Sleep and Behavior showed greater percent of patients with **2+ point improvement** at Day 170



Multi-domain Responder Index

Net response in Cohort A & B at Day 170 similar to Cohort 4-7 at Day 338

Day 170 Cohorts A & B Net Response: +2; p-value <0.0001

Pt	ASA Sleep	ASA Behavior	Bayley-4 Rec Comm	Bayley-4 Cognition	Total Net Response
1	0	0	0	+2	0
2	0	-1	+10	+2	+2
3	0	0	0	0	0
4	0	-1	+2	+6	+2
5	-1	-2	+1	+2	+2
6	-2	-2	+4	+19	+3
7	0	-1	+2	+4	+1
8	-4	-2	-2	+8	+3
9	-2	0	+8	+1	+2
10	-2	+1	+6	+2	+1
11	-2	0	-1	+1	+1
12	0	0	-2	-2	0
13	0	0	+3	+2	0
14	-1	-1	+2	0	+2
15	0	-1	-9	+5	+1
16	-3	-2	+6	+10	+4
17	-2	0	+6	+1	+2
18	-2	-1	+2	+23	+3
19	0	-1	+11	+15	+3
20	-1	0	+2	-1	+1
21	0	-1	+10	+4	+2
22	+1	-1	+15	+1	+1
23	-2	-1	+3	+6	+3
24	-2	-2	+5	+3	+2

Day 338 Cohorts 4–7 Net Response: +2; p-value 0.0007

Pt	ASA Sleep	ASA Behavior	Bayley-4 Rec Comm	Bayley-4 Cognition	Total Net Response
1	-1	0	+1	-3	+1
2	-3	-2	+7	+17	+4
3	-1	-1	+16	+20	+4
4	0	0	+14	+23	+2
5	-1	-2	+6	+4	+3
6	-4	0	+7	-1	+2
7	-2	-1	+10	+16	+4
8	-1	-1	+15	+25	+4
9	+2	0	+23	+11	+1
10	+1	0	-2	+3	-1
11	0	0	+3	+16	+1
12	-1	-1	+4	+1	+2
13	-1	-2	-11	-2	+1
14	-1	0	+16	+6	+3
15	0	0	-1	-3	0

Minimal important difference (MID):

ASA: Sleep = ± 1; Behavior = ± 1

Bayley-4: Receptive Communication = ± 6; Cognition = ± 5

Green color code indicates an improvement: ≥ +1 MID

Pink color code indicates a decline: ≤ -1 MID

ASA: Negative change from baseline indicates improvement

Bayley-4: Positive change from baseline indicates improvement

Changes in Dose Administration Provided Acceptable Safety Data and Support Phase 3 Planning

- No unexpected serious adverse events
- Three patients had serious adverse events (mild to moderate) of lower extremity weakness assessed as related to study treatment
  - One in Cohort 7, two in Cohorts A and B; none reported in Cohorts C–E to date
  - All resolved rapidly without sequelae and remain in the study without ongoing safety concerns
- Patients redosed with multiple doses following resolution of lower extremity weakness
  - Five original patients from Cohorts 1–3 safely re-dosed multiple times and are receiving maintenance treatment without recurrence
  - The Cohort 7 patient has also re-dosed safely multiple times and is receiving maintenance treatment without recurrence
  - Two patients in Cohorts A & B remain in the study and are expected to continue dosing

FDA and other regulators notified of safety events;
no issues raised and no additional actions requested

Data as of April 5, 2024

Physician and Caregiver Feedback

Physician Feedback from Cohorts A & B

Cognition
Now follows directions
Learning new routines
Improved memory
Now demonstrates understanding of serial processes

Behavior
Milder excitability
Improved focus at school
Improved attention
Improved situational awareness
Less impulsive
Can now go out in public

Sleep
Now sleeping 7-10 hours consistently
Less time to fall asleep
Waking up less frequently
Better sleep quality
Reduced need for melatonin

Language
Gaining first words
More attentive to speech
New sounds and word approximations
Pointing, more precise use of device

Motor Skills
More independence
Self-feeding, using utensils
Now running, dancing, jumping, swimming
More stable, walking on uneven ground
Less tremor and ataxia

Caregiver Feedback from Cohorts A & B

Cognition
"Follows directions and steps into her pants" (when dressing)
"She remembers the way and walks independently anticipating the wheelchair ramps and turns around the corners" (when walking to the gym or library at school)
"Now – for the first time in her life – I can imagine my daughter living assisted in a shared apartment and contributing something of value in a workshop for people with disabilities."

Behavior
"He understands "let go, stop" when he grabs someone's hair"
"They can go to a restaurant with him now"
"They sit calmly in a public area, they used to run around the room touching and mouthing everything"

Language
"She is able to point now"
"More attentive to speech"
"Lot of new sounds and word approximations"
"Babbling with intentionality"
"She overhears conversation and reacts to what we are saying"

Sleep
"Bad sleep is now what we would have called good sleep pretrial"
"There are more days when it takes less time to fall asleep. Rare for him to wake up at night."

Motor Skills
"Can navigate different surfaces and walk for much longer periods of time"
"Could not use a spoon pre-trial…now she eats a good chunk of her food with supervision, but with less assistance"
"He is getting on more swings independently, and that makes him enjoy the park much more"

Patient Videos

Do not copy or redistribute without express consent

Summary of FDA Interactions in 1Q24

Proposed Study Design

Key parameters discussed:

- Single randomized, placebo-controlled pivotal study
- Sample size: 100-120 patients
- FDA aligned with these elements

Endpoints

FDA expressed:

- Phase 1/2 included relevant domains and endpoints needed for Phase 3
- Flexibility with instruments utilized and supportive of proposed endpoint strategies
- Flexibility with MDRI as secondary endpoint

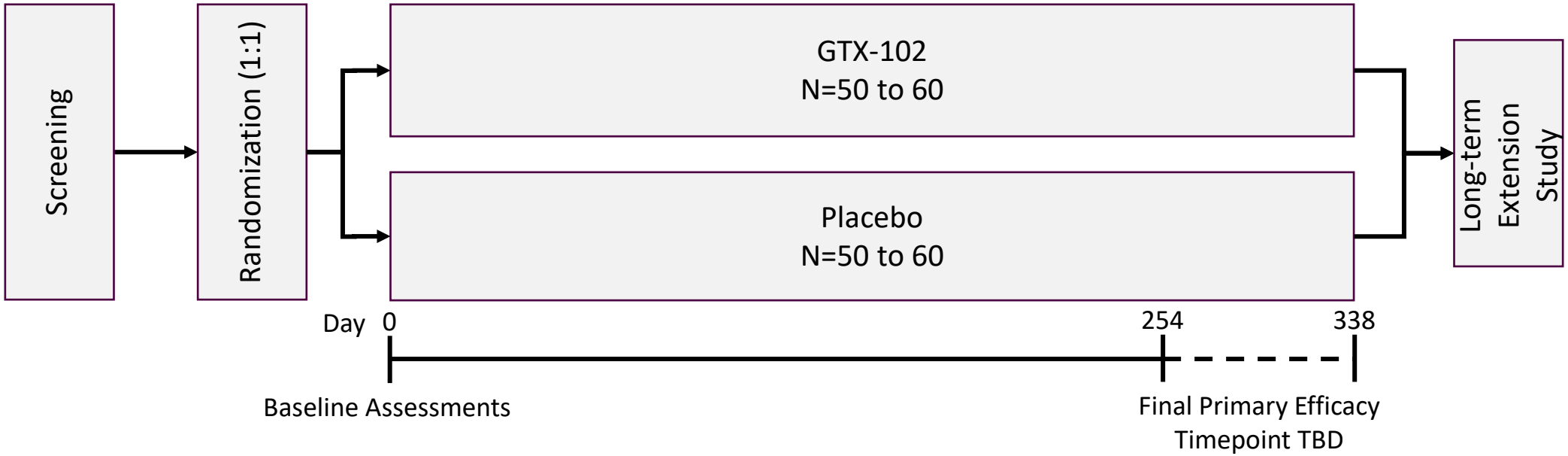
Safety

- Recent lower extremity weakness discussed, no issues raised and no additional actions requested
- Study continues with current drug administration strategies
- We believe totality of safety data continues to support positive benefit/risk assessment and progression to Phase 3

Data presented today will be included at an
End of Phase 2 meeting planned for mid-2024

Potential Phase 3 Study Design and Upcoming Agency Interactions

Potential Phase 3 Study Design



Phase 3 Design Considerations

- Randomized, placebo-controlled study
- Deletion patients, 4-17 years of age
- Duration: Day 254 to Day 338
- Global Sites: US, EU, LATAM, Japan

Upcoming Agency Interactions

- FDA EOP2 planned mid-2024
- EU Scientific Advice 2H-2024
- PMDA consultation 2H-2024

The Magnitude of Benefit Could Readily Support a Phase 3 Study

Example power calculation for Bayley-4 Cognition (NHS1 & NHS2 Pooled Data)

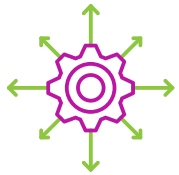
Data Source	GTX102 Arm Mean (SD)	NHS1 & NHS2 Pooled Data (D365) Mean (SD)	Hypothesized Difference $\mu_T - \mu_c$	SD*	Power** ($\alpha = 0.05$)
Cohorts 4-7 D338	10.4 (9.8)	1.3 (4.8)	9.1	9.8	99.8%
Cohorts 4-7 D254	8.9 (9.0)	1.3 (4.8)	7.6	9.0	99.2%
Cohorts A & B D170	5.1 (6.4)	1.3 (4.8)	3.8	6.4	86.4%
Cohorts 4-7 D338	10.4 (9.8)	3.9^ (4.8)	6.5	9.8	92.7%

Key Assumptions: N=120 randomized (1:1) with 10% drop out rate; *Most conservative SD assumption; ** Based on two-sided t-test

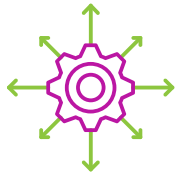
^ 3X observed NHS1&2 Pooled data at D365

Strong Consistent Results Set up GTX-102 for Phase 3 Transition

-New positive data showed rapid and sustained clinically meaningful improvements
-Trajectory of improvements at Day 170 are equal or better than prior data



Phase 3 planning underway and expect initiation in 2024



GTX-102 is one of five approvals expected in the next 2-3 years

Thank you

ir@ultragenyx.com