GTX-102 Mid-Year Interim Data and Program Update

July 18, 2022

Legal Warning

Cautionary note regarding forward-looking statements: This presentation contains forward-looking statements, including, but not limited to, statements regarding our expectations and projections regarding our future business plans and objectives for GTX-102, the therapeutic potential and clinical benefits of GTX-102, expectations regarding the safety and tolerability of GTX-102, and future clinical developments GTX-102, the expected timing of release of additional data for GTX-102, expectations regarding the adequacy of clinical data to support marketing applications and approvals of product candidates, our intent to file, and potential timing and success of, marketing applications and other regulatory approvals, expectations regarding timing of receiving potential approval of product candidates, expectations regarding prevalence of patients and future regulatory interactions. 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, our ability to successfully develop GTX-102, the effects of the COVID-19 pandemic on our clinical activities, business and operating results, uncertainty and potential delays related to clinical drug development, the risk that clinical outcomes demonstrated in interim data from our clinical trials may materially change or that there are increased incidents of adverse events as patient enrollment continues and/or more patient data becomes available, our ability to achieve our projected development goals in our expected timeframes, risks and uncertainties related to the regulatory approval process, smaller than anticipated market opportunities for our products and product candidates, manufacturing risks, competition from other therapies or products, our ability to integrate acquired products or businesses, and other matters, and our ability to integrate acquired businesses, which are more fully described in our most recent Form 10-Q or 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.

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This presentation includes a 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.

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Disclaimer: GTX-102 is an investigational product without proven efficacy and safety by FDA or other authority

- The content provided is an interim look of the data from an ongoing open-label study with the limitations of this design
- The presentation is intended to provide a reasonable interim update on an ongoing program due to its importance to stakeholders
- The study is ongoing and not yet complete and further titration of dosing is ongoing
- Ultimate proof of safety and efficacy will depend on the conduct of an adequate randomized controlled study

GTX-102 Study Interim Data and Program Update

Speakers	
Ultragenyx	
Emil Kakkis, M.D., Ph.D.	CEO and President
Camille Bedrosian, M.D.	Chief Medical Officer
Scott Stromatt, M.D.	Chief Medical Officer, Neurology
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GTX-102 Investigators	
Erick Sell, M.D.	Associate Professor, Neurology Children's Hospital of Eastern Ontario
Elizabeth Berry-Kravis, M.D., Ph.D.	Professor, Pediatrics Rush University Medical Center

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Executive Summary

PROMISING CLINICAL DATA UPDATE FOR GTX-102

- No clinically significant safety issues at doses up to 10 mg with new administration strategy
  - No lower extremity weakness, no pattern of increasing inflammation
- Meaningful clinical activity in multiple domains on multiple measures
  - Most subjects with 3 or more improved domains supported by other instruments

REGULATORY APPROVAL TO START NEW COHORTS AT HIGHER DOSES

- Enrollment of Cohorts 6 and 7 has begun: beginning at higher doses already cleared on safety
- Higher dose expansion cohort approved by Canada and UK in May 2022

GENETX ACQUISITION COMPLETED

- GeneTx acquisition triggered and executed based on progress in the program and unique IP

Summary of Amended Canada / UK and US Protocols

	Canada / U.K.		U.S.[1]
	Cohort 4	Cohort 5	Active Group
Age	4 to 7 y/o	8 to 17 y/o	4 to 7 y/o
Number of Patients	6	4	4
Monthly Loading Dose (up to 4 doses)	3.3 mg	5.0 mg	2.0 mg
	Can escalate following 2 doses		
Dose Escalation Criteria	Individually titrated until at least two CGI-C-AS[2] domains of much improved or very much improved		n/a
Maximum Dose	14.0 mg		2.0 mg
Maintenance Dose Frequency	Every 3 months		Every 3 months
Administration Modifications	Trendelenburg and 10 mL artificial CSF flush		n/a

1: The US site will enroll 4, age matched patients into a comparator group and will have limited assessments at Baseline and Day 128. These patients would then be eligible to receive GTX-102 under the same dosing strategy as the active group.
2: CGI-C-AS: Clinical Global Impression of Change-Angelman Syndrome previously known as CGI-I-AS

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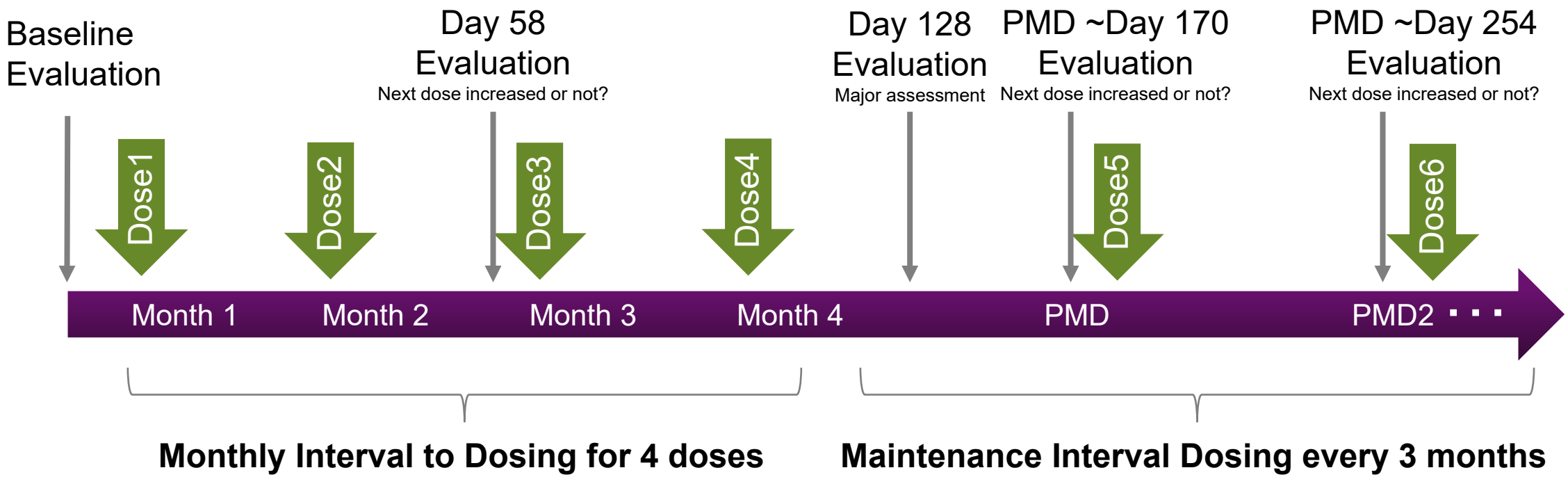
Dosing Schematic for GTX-102 for Cohorts 4 & 5



Day 58 assessment: CGI-C-AS to guide dose escalation for 3rd/4th doses
Baseline and Day 128 assessments: CGI-C-AS; CGI-S-AS; Bayley 4; Vineland 3; ORCA; EEG; Seizure Sleep Diary; Functional Domain Interviews
Day 128 CGI-C-AS and future assessments guide additional dose escalation during maintenance to maximum of 14 mg

CGI-C-AS=clinical global impression of change (improvement), Angelman syndrome; CGI-S-AS=clinical global impression of severity, Angelman syndrome; ORCA=observer-reported communication assessment; PMD=pre-maintenance dose

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14 Patients have been Enrolled with Exposure Duration up to 280 Days

Dosing Status As of July 12th, 2022

Cohort	Patient	Demographics	Cumulative Dose	Number of Doses	Duration of Exposure (Days)	Maximum Exposed Dose (mg)
4 (n=6)	103-001	7 yr	32.4 mg	6	280	10
	103-003	4 yr	24.1 mg	5	259	7.5
	103-004	7 yr	24.1 mg	5	201	7.5
	113-001	6 yr	24.1 mg	5	183	7.5
	110-002	5 yr	14.9 mg	4	153	5
	103-006	6 yr	16.6 mg	4	147	5
5 (n=4)	103-002	10 yr	35 mg	5	267	10
	110-001	13 yr	35 mg	5	237	10
	103-005	8 yr	35 mg	5	180	10
	110-003*	15 yr	10 mg	2	41	5
US – Naïve Treatment Group (n=4)	102-007	4 yr	8 mg	4	182	2
	102-008	5 yr	8 mg	4	175	2
	102-009	5 yr	8 mg	4	175	2
	102-010	7 yr	8 mg	4	166	2

*Patient 110-003 received his first dose in June will continue to receive doses per the protocol

- Multiple patients tolerated 7.5-10mg
- 7 of 14 patients >20 mg cumulative dose
- 13 patients >147 days exposure
- 8 patients >6 months exposure

- For reference in the original 5 patients[1], lower extremity weakness occurred 28 to 132 days after first dose and 6 to 28 days after last dose of GTX 102

1. Five patients treated under original protocol in the U.S. in 2020.

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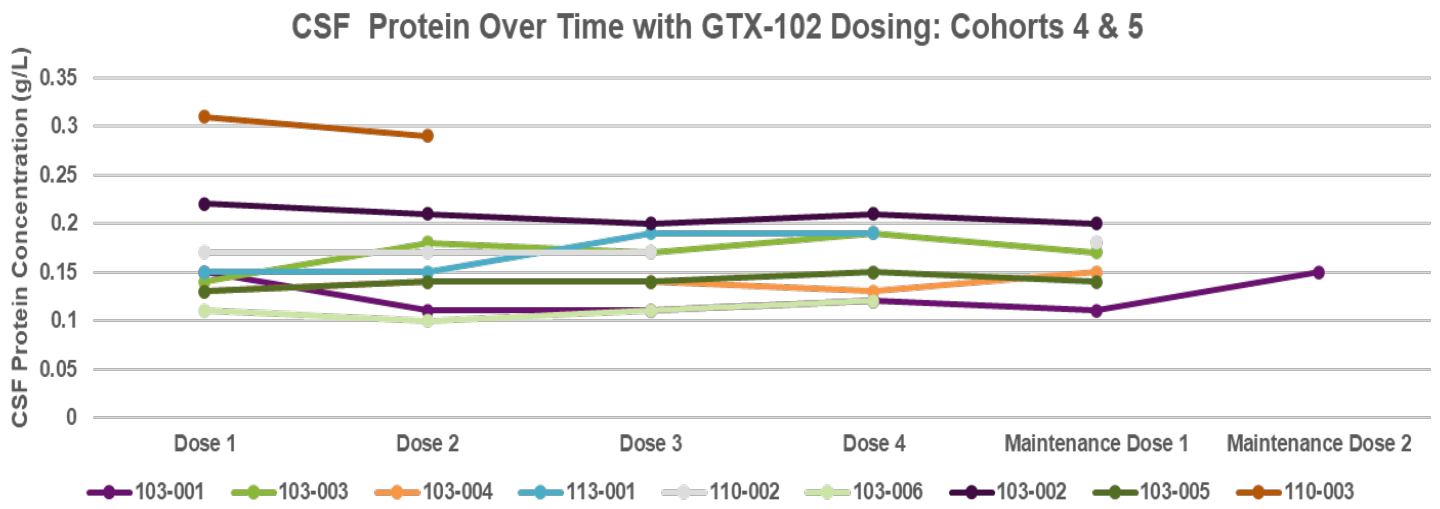
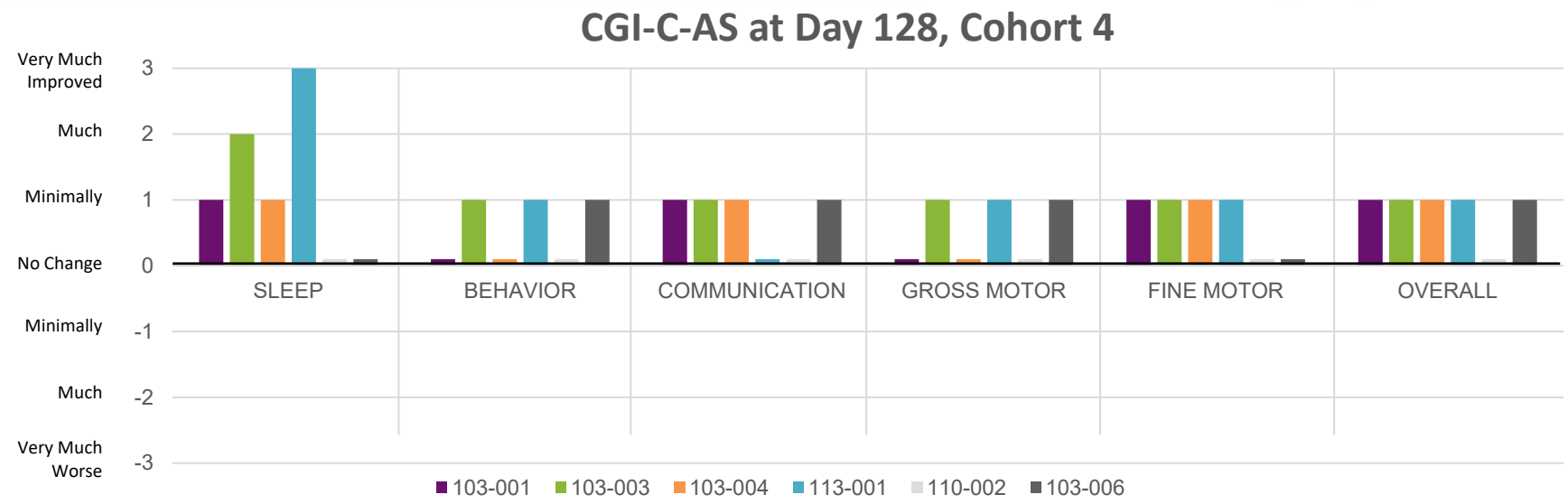
No Drug-Related Serious Adverse Events for Patients (n=10) in Cohorts 4 and 5

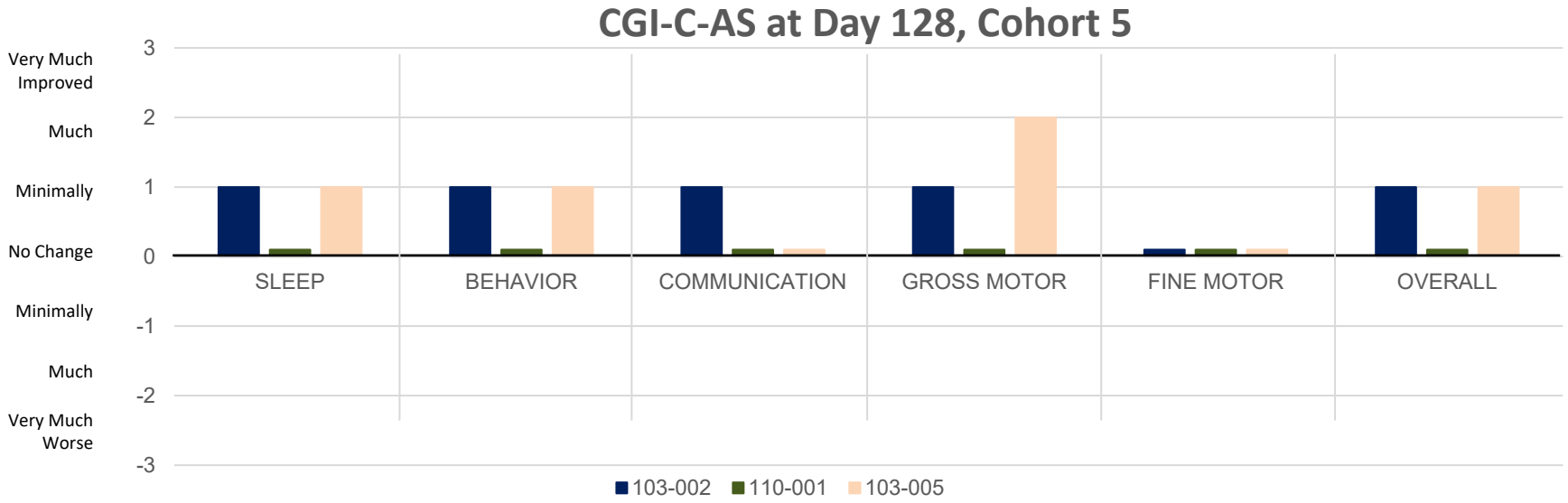
- No drug-related SAE
- No AE or SAE reports of lower extremity weakness
- Unrelated SAE, resolved and did not recur with subsequent doses
  - Asymptomatic varicella zoster virus reactivation in one subject
  - Nausea and vomiting after accidental swallowing of an ECG lead
  - Vomiting related to procedures and anesthesia
- Most common AEs
  - Vomiting (5), COVID (4), upper respiratory infection (3), transient back pain (2)
- No change in CSF total proteins nor trend toward increase, no signs of inflammation



One patient, Pt 110-001 had asymptomatic varicella zoster virus reactivation with transient elevation in CSF protein on dose 2, resolved (not shown here)

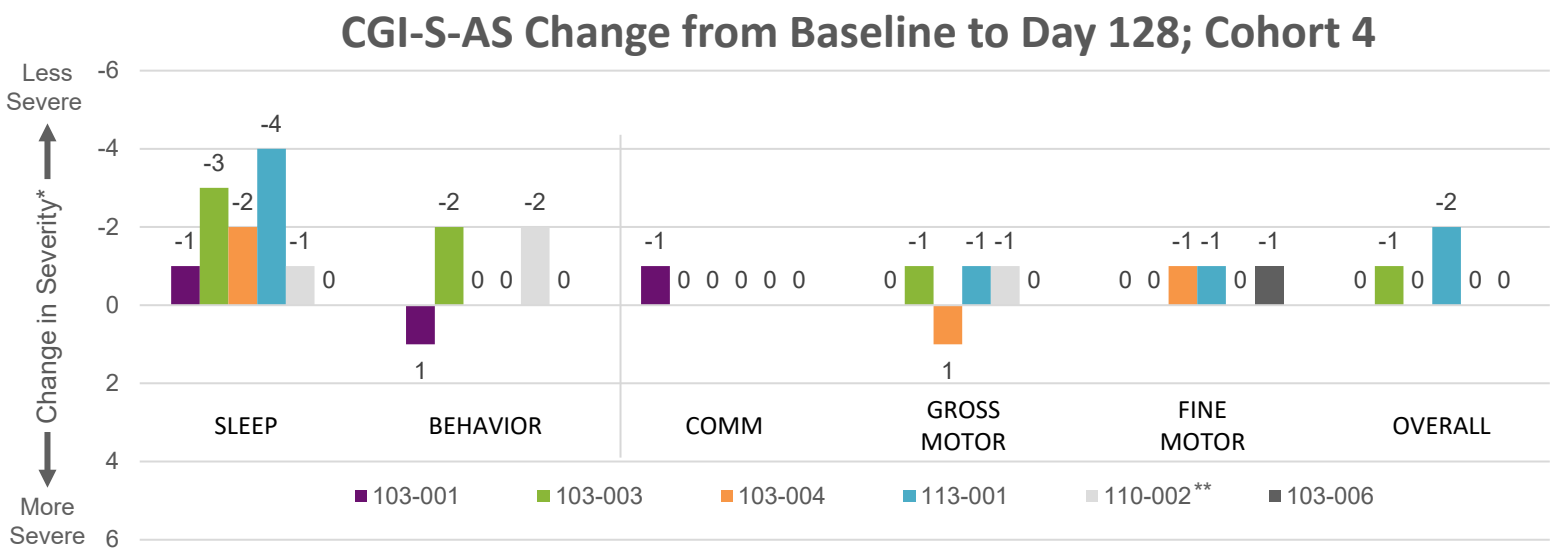
CGI-C-AS: 7 of 9 Patients Show Improvement from Baseline in at Least Three Domains



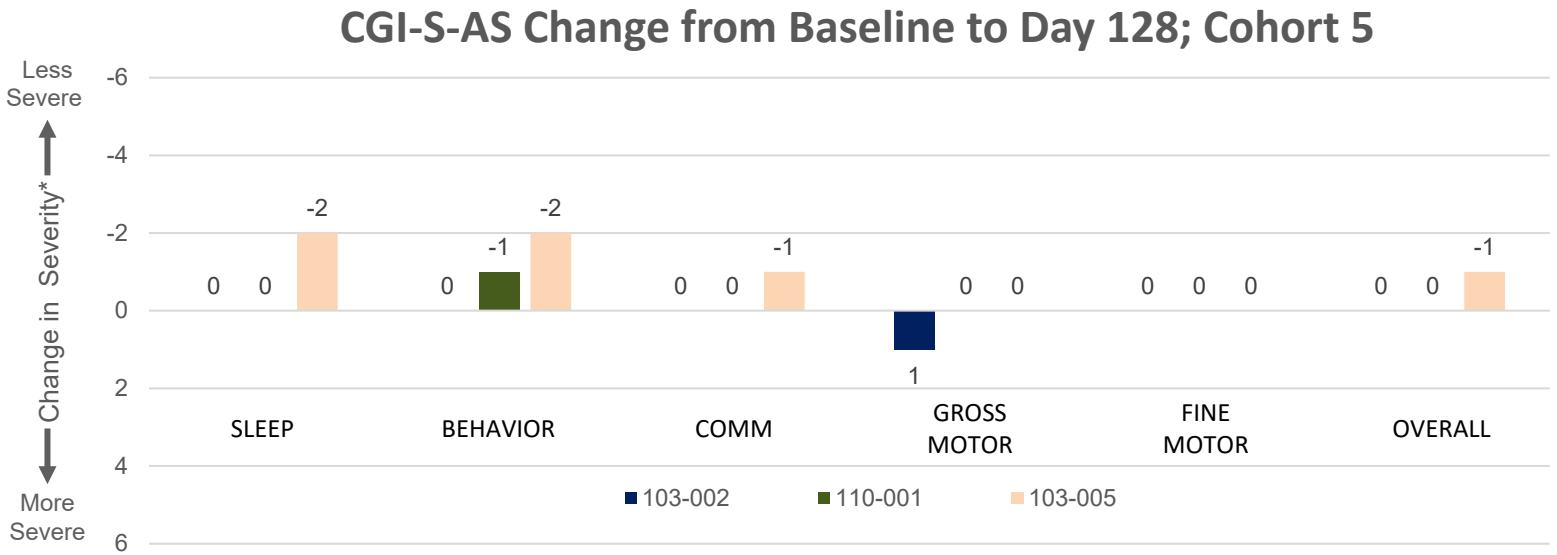


CGI-C-AS=clinical global impression of change (improvement), Angelman syndrome

CGI-S-AS: Cohorts 4 & 5 AS Severity Score Change from Baseline to Day 128
Improvement in multiple domains on objective criteria



The Angelman Severity Score (CGI-S-AS) is an objective and specific graded scale of changes and is a complement to the CGI-C-AS which is the relative change scale



*Maximum change is 6 points positive or 6 points negative. 0 means no change occurred. A negative change in points is considered an improvement as it means the subject was rated at a less severe level of function at Day 128, and this change is displayed in the upward direction. A positive change in points would indicate the subject is presenting in a more severe manner at Day 128, and this change is displayed in the downward direction. The starting point for each subject is variable based on the CGI-S-AS rating at Baseline.
**For subject 110-002, the follow-up visit occurred on Day 100 instead of Day 128 due to subject meeting the protocol definition of clinical improvement at Day 58.

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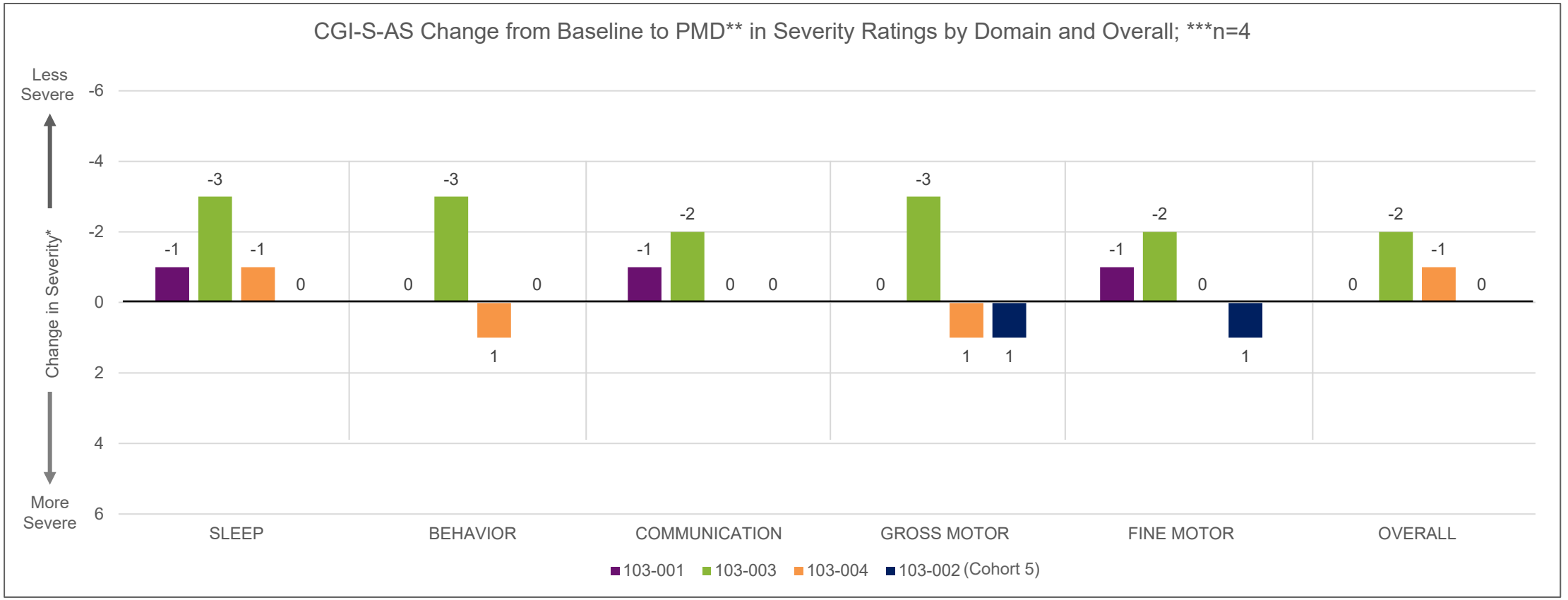
CGI-S-AS: AS Severity score change over longer term from Baseline to PMD

Further improvement during 6 weeks of additional follow-up without dosing (n=4)

Patient 103-003: A 4 year old with 2 point or greater reduction in severity in all five domains



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**PMD: Pre- Maintenance Dose. ***n = 4, These 4 subjects had their PMD visit occur prior to 23Jun2022. 103-001, 103-003, and 103-004 are in Cohort 4 and 103-002 is in Cohort 6.

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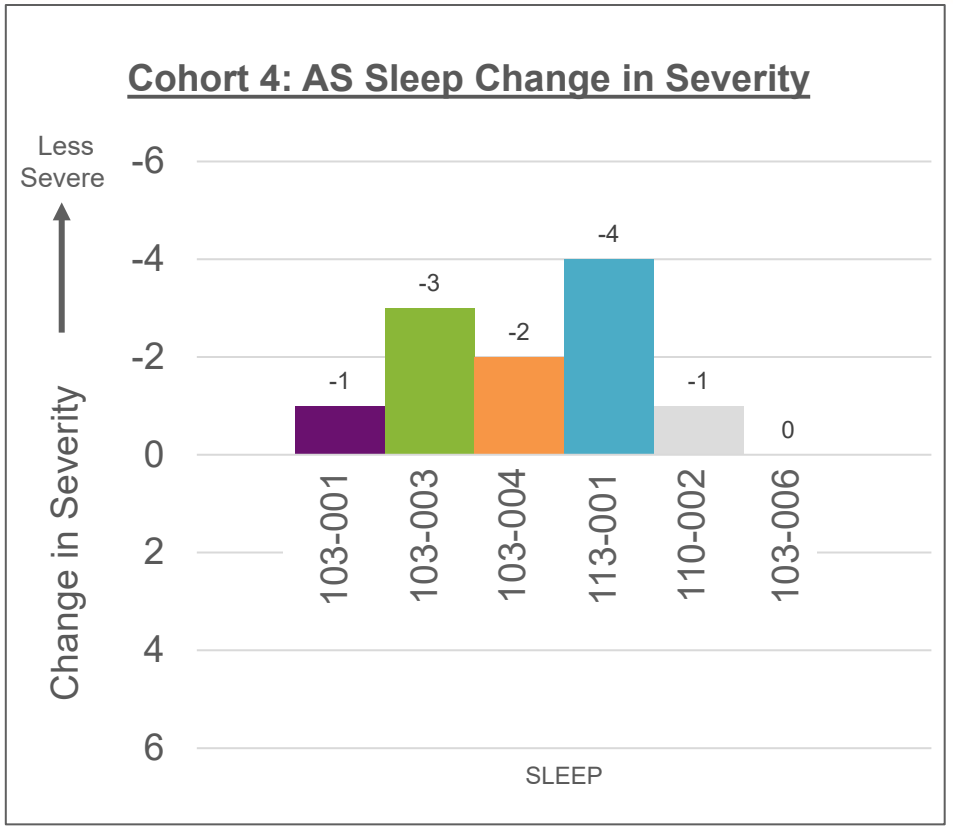
Sleep Domain: Substantial, clinically meaningful changes



Comments from Caregivers on Sleep

- **103-003:** "Her sleep has improved which is humongous…. She's more rested, we're all more rested. So everyone's able to function better and she's able to do more."
- **103-004:** "…I use "sleep talk" [app] with my cell phone, so this way I can really see all the time that he woke up during the night. So at the beginning of the study, we had 2.5 to 3.0 hours of awakening at night. Now, I would say, 15, 30 minutes…."
- **113-001:** "Before [the trial], she would wake up like three, four times in the night. Now, she doesn't wake up at all, and she'll sleep for a good 12 hours. And before, she'll sleep for two, three hours max."
- **(Cohort 5, not shown) 103-005: (-2 improvement in AS Sleep score)** "…before the trial, I would hear her more often in the middle of the night… I could hear her wrestling and reading a book or shaking her water bottle and I can say that since mid-trial, I think she's sleeping much more soundly…. So I think – her sleep has improved."

SLEEP DOMAIN : SAMPLING OF DOMAIN TWO SCORING ITEMS

	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
Duration of sleep	☐ Age appropriate	☐ at LEAST 8 HOURS/night		☐ 6-8 HOURS/night		☐ 4-6 HOURS/night	☐ LESS THAN 4 HOURS/night
Time to sleep onset	☐ NOT >30 min	☐ RARELY >30 min	☐ OCCASIONALLY >30 min (not every week)	☐ SOME nights >60 min (1-2/week)	☐ SEVERAL nights >60 min (3-4/week)	☐ MOST nights >60 min (5-6/week)	☐ EVERY night >60 min

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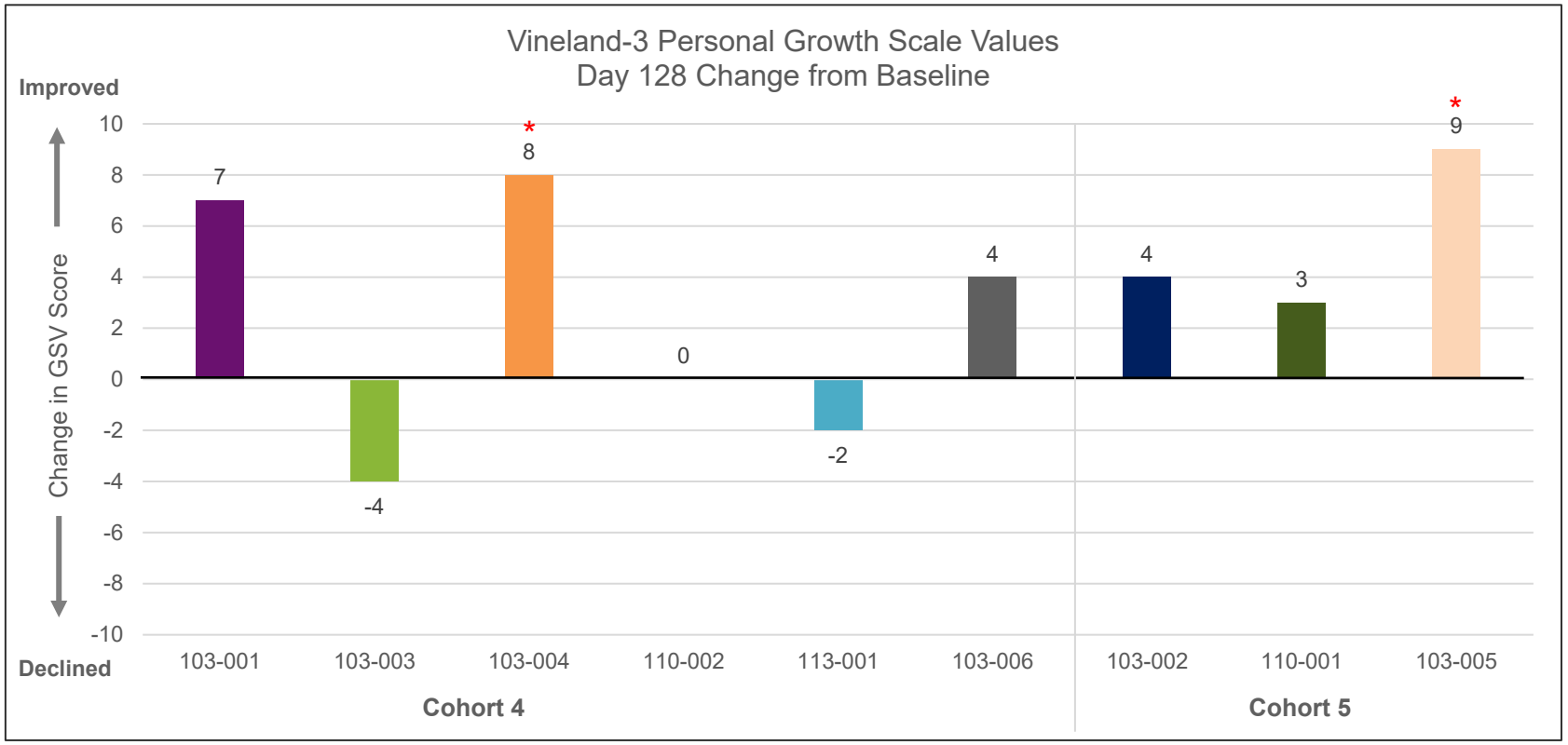
Behavior: Vineland-3 Change from Baseline to Day 128

Growth Scale Values (GSV); Personal (self-care) Subdomain



- **Using eating utensils**
  - **103-004:** "It was progressively better [using a fork]. He [will] take it with the tip of his fork. And there's a movement of the wrist. You see when he just bends his wrist to bring it up, and then he reach(es) to his mouth."
- **Toileting**
  - **103-005**: "I still need to lead her to the toilet and put her on the toilet, but she is quicker…to relieve and much fewer accidents. There's a handful of times where I'll put her on and she pees almost immediately, which is amazing."
- **Opening containers and doors**
  - **103-005:** "we've noticed she's become much more effective at opening containers, latches, doorknobs. So in that particular area, there's been gains for sure."

*Threshold for statistically significant difference. GSVs are scores with equal intervals that allows tracking of performance of the individual patient with repeat testing. A positive change in GSV scores represents improvement. Changes in GSV from one testing session to another reflect both substantive change and the measurement error inherent in the two test scores.

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General Behavior Beginning to Show Improvements in Some Patients

COHORT 4

103-003: Regarding adaptability challenges: “We’d never stayed in a hotel with her until we got involved with the study. And now we’ve realized that she can actually sleep well in a hotel, which was something we always feared.”

103-003: Regarding anxiety about new situations: “I do feel like she’s definitely gotten much better with visiting our family and friends…sometimes even I have been surprised thinking that normally she would have been more standoffish, and she wasn’t.”

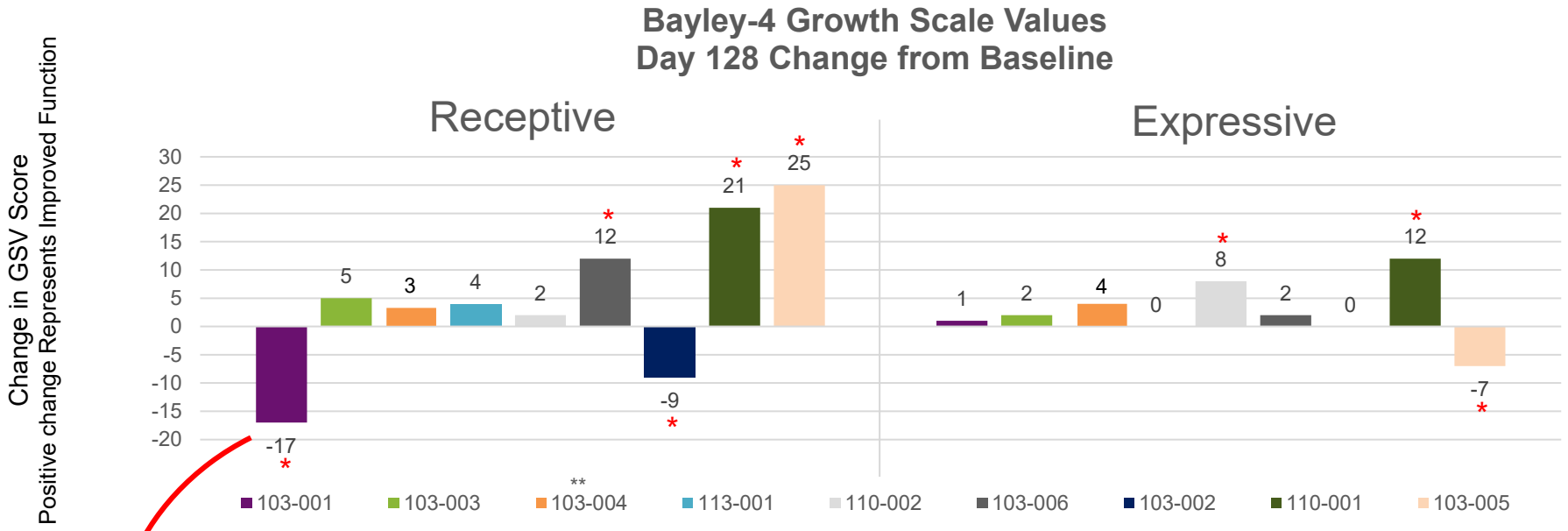
110-002: Regarding General Behavior: “There was a sense after the first dose and then again after the second dose that a sense of calm was there, that less hyperactivity, less excitability about being touched, just less sensory overload in some ways.”

COHORT 5

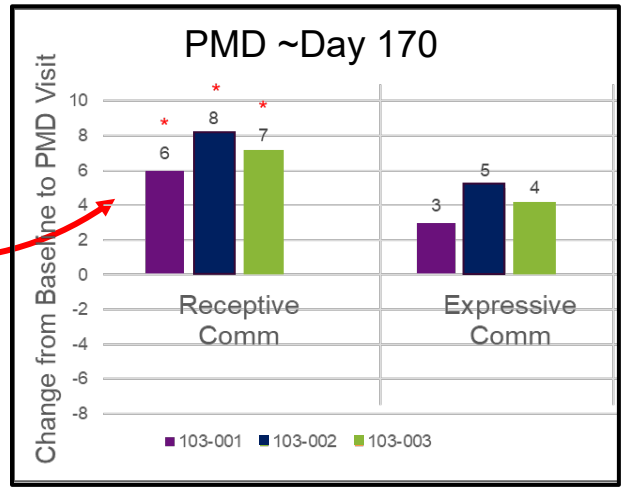
103-005: Regarding General Behavior/Improved Quality of Life “I think just with the changes that we’ve seen with the trial, she’s just in a better position – with less maladaptive behaviors- for other kids to be responsive and be comfortable and feeling safe around her. So she’s not pulling hair, she’s not banging her head on the ground.”

Communication by Bayley-4: Improved Expressive/Receptive Communication

Supported by PI/CG Interviews



*Threshold for statistically significant difference (p < .05): RC and EC =6. **103-004 Day 128 compared versus D30. BL not captured due to COVID.



One unexplained low score due to "bad day"; ORCA positive at day 128. At next PMD visit, 103-001 was improved like other subjects at the first maintenance dose visit

At next PMD visit (~day 170), significant improvement in Bayley Communication in all three subjects reaching this point

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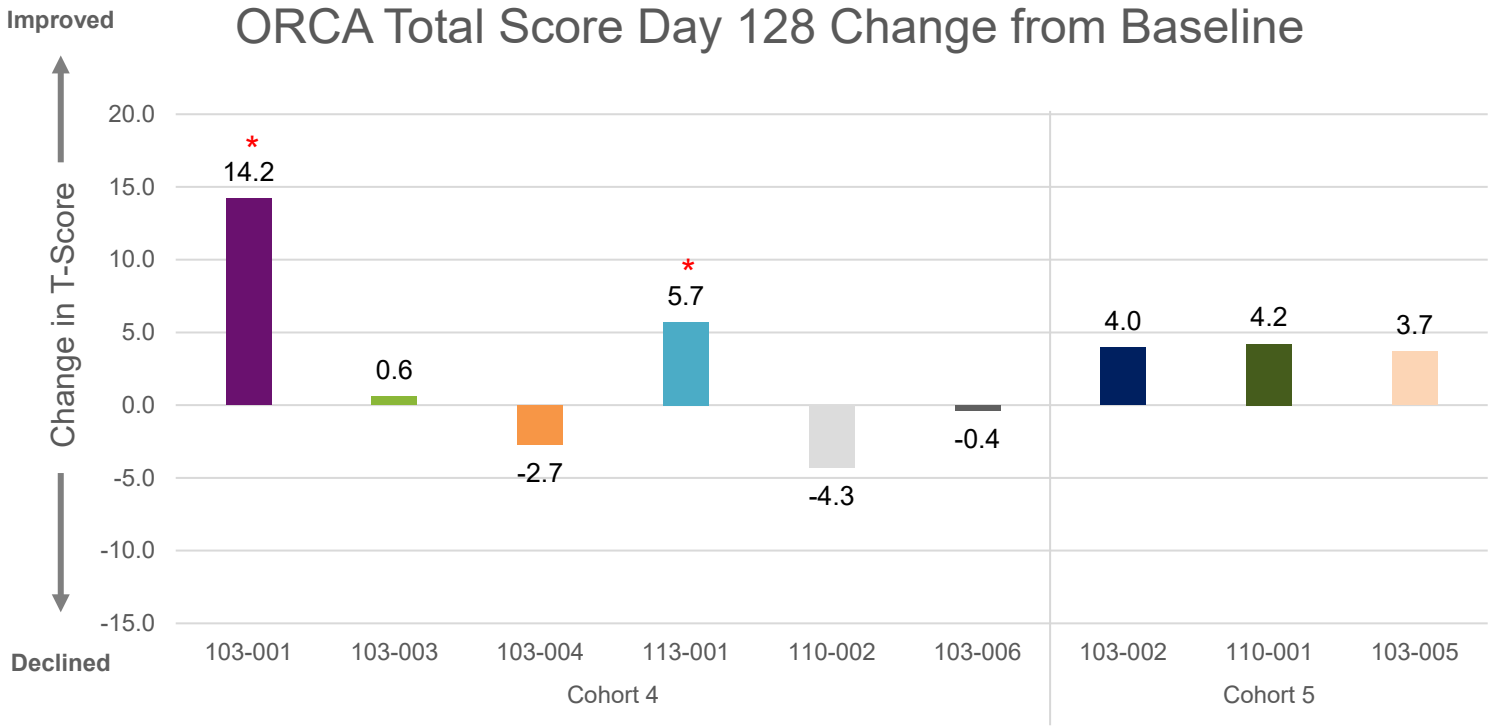
Communication Improved from Caregiver Evaluation: ORCA Change from Baseline to Day 128



*Two subjects with statistically significant improvement including 103-001. Threshold for statistical significance is a 5-point change.

Comments from Caregivers

Receptive

103-001: "…it's been really nice again to hear and to see that he's understanding and communicating more... This is ... where we've noticed the most change…he uses a high-tech AAC device…and he's putting it together in a string of words to make a sentence…."

103-006: "… we think she is a little bit more focused, so when we ask her something, we have the feeling that she understands more what we say. And she is more also imitating what other kids are doing at the kindergarten. And the times she's participating in an activity, it's a longer period also."

103-005: "Overall a greater sense of understanding and attention and focus as well."

Expressive

103-001: "… he has more word approximations and sounds, so he now says like bye and bye bye..."

110-002: "I suppose the only change that we would have noticed is he is vocalizing more different sounds, and I suppose babbling in a way –so making different sounds and stringing those sounds together….He also can use his hand or his arm in front of his mouth to then create different types of sounds, which is new. We haven't derived meaning to them."

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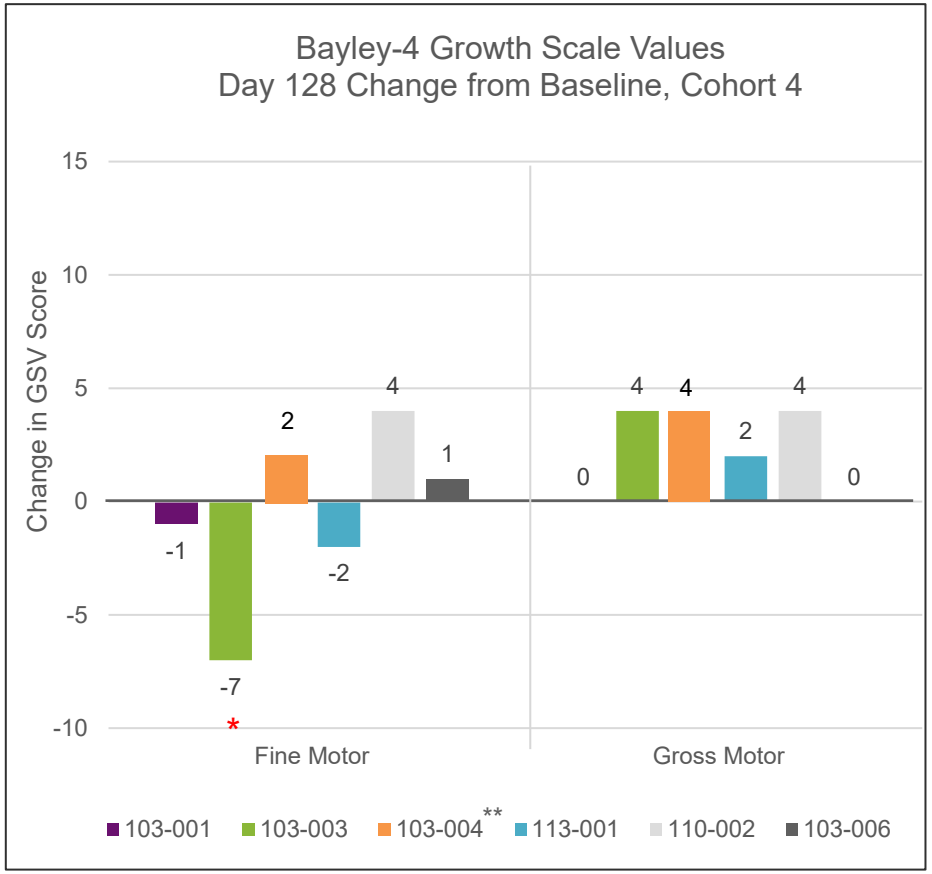
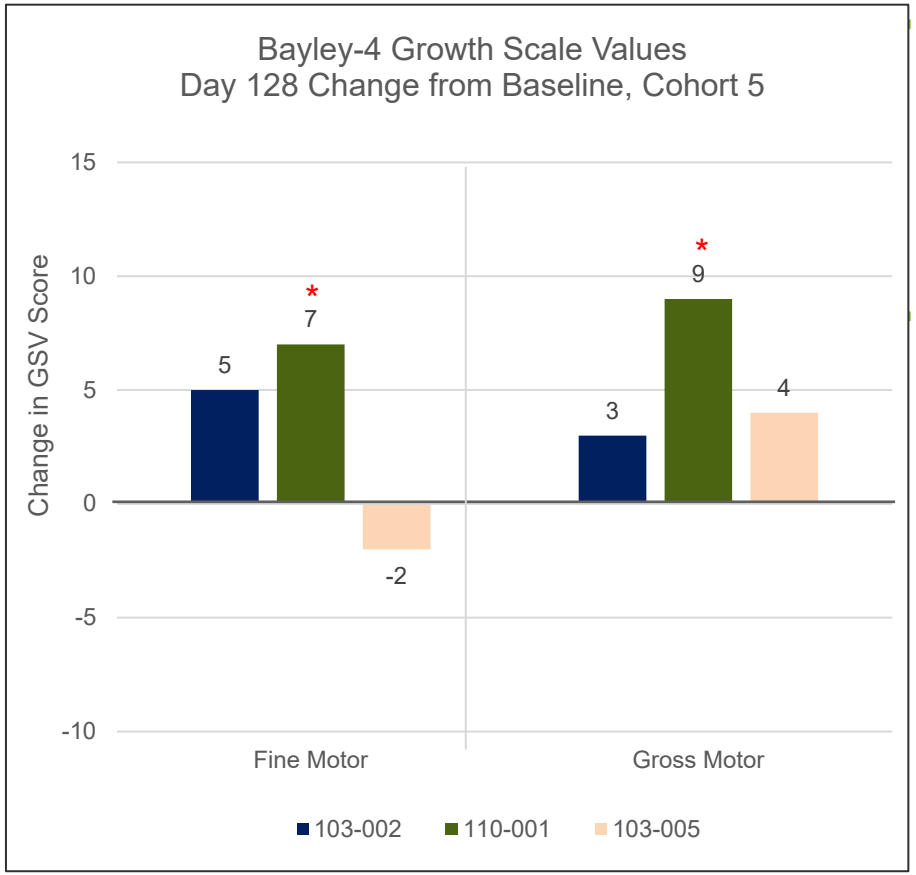
Some Improvement in Fine and Gross Motor Function
Bayley-4 score: changes in absolute GSV score





Fine Motor

- **113-001**: "She can feed herself better, because before, she wouldn't really use any spoon or fork, but now, she will use a spoon to feed herself."

Gross Motor

- **103-005**: "…walking along the street and she would just collapse and not be interested if she wasn't in the stroller. And now – she's very comfortable to leave the house walking."

- **113-001**: "It's (balance) improved quite a lot. So she got a certificate at school, because she walked four steps by herself. Since then, it's been more consistent. Like she'll be walking more steps by herself."

* Threshold for statistically significant difference ($p < .05$): FM = 6 and GM = 5.
** 103-004 Day 128 compared versus D30. BL not captured due to COVID.

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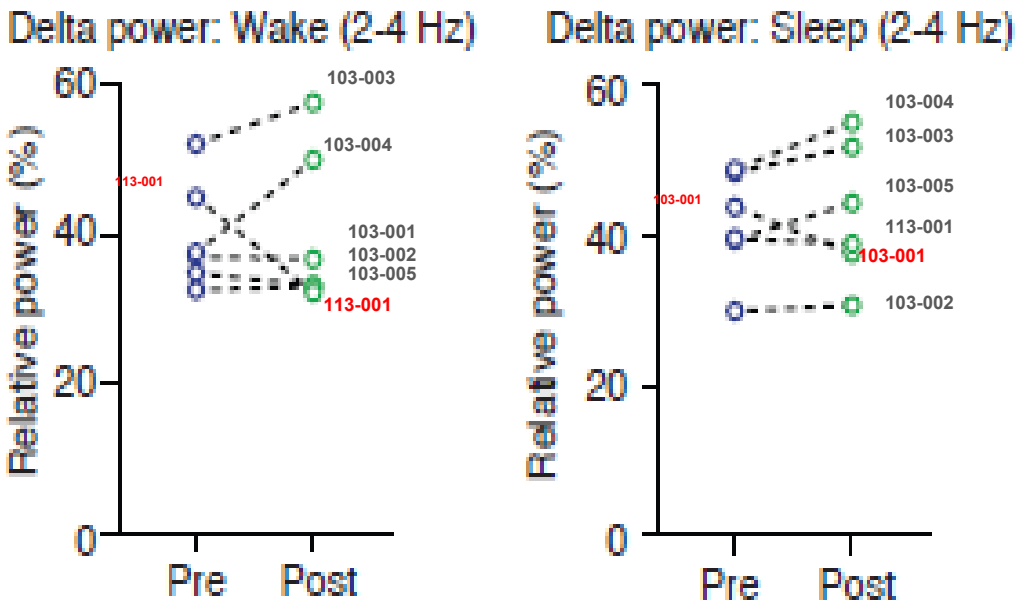
EEG Data: Not significant improvement so far compared with first 5 patients: Expect higher dose needed

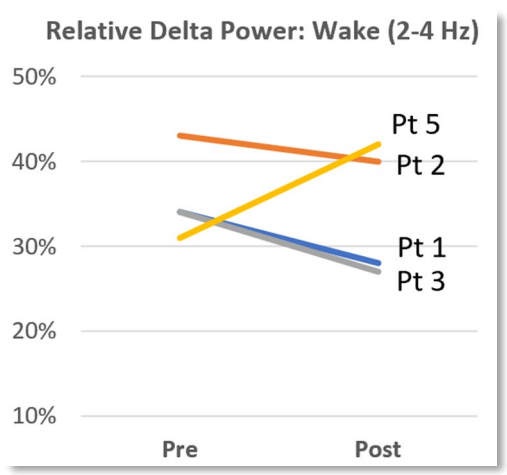
Cohorts 4 and 5

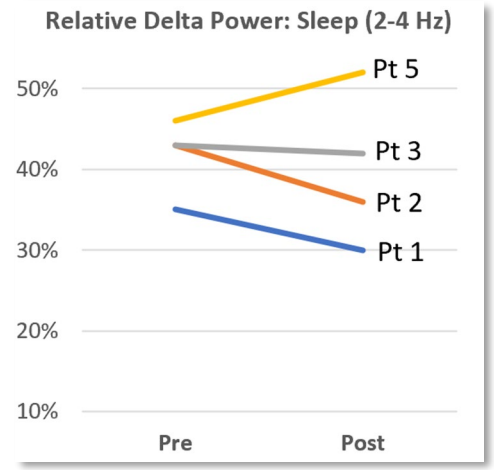


Post=Day 128

Post=Day 128

Original EEG Data on First 5 patients





Cohorts 4 and 5
Entering Therapeutic Range with Acceptable Safety

- GTX-102 has acceptable safety results at current dose and administration
  - No drug-related SAE, no LE weakness, stable normal CSF proteins
- Encouraging clinical activity comparable to original 5 patients at similar dose levels
  - Multiple domains positive in most patients
  - Further progress over extended duration when looking at first PMD evaluation
  - Comparable patterns of response
- Doses up to 7.5-10 mg tolerated and new cohort should test higher loading
  - Higher dose during loading phase should enhance efficacy further

Clinician’s Perspective

Dr. Erick Sell, M.D.

GTX-102 Investigator

Associate Professor, Neurology, Children's Hospital of Eastern Ontario (CHEO)

Ottawa, Ontario

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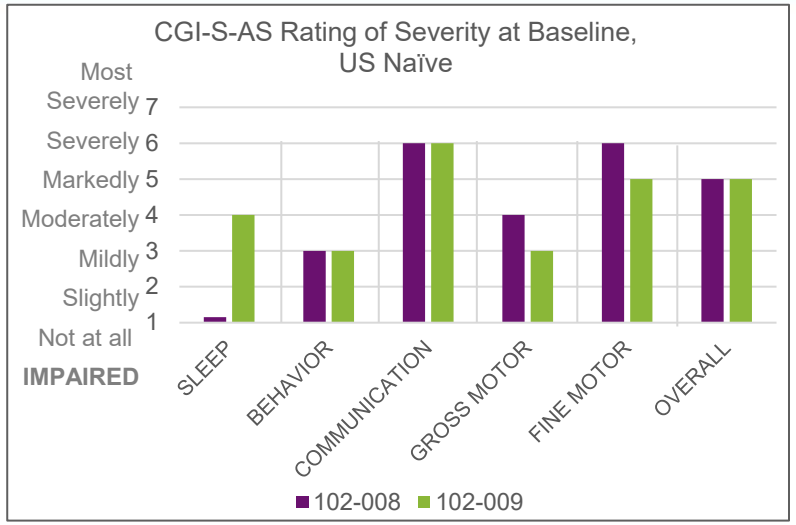
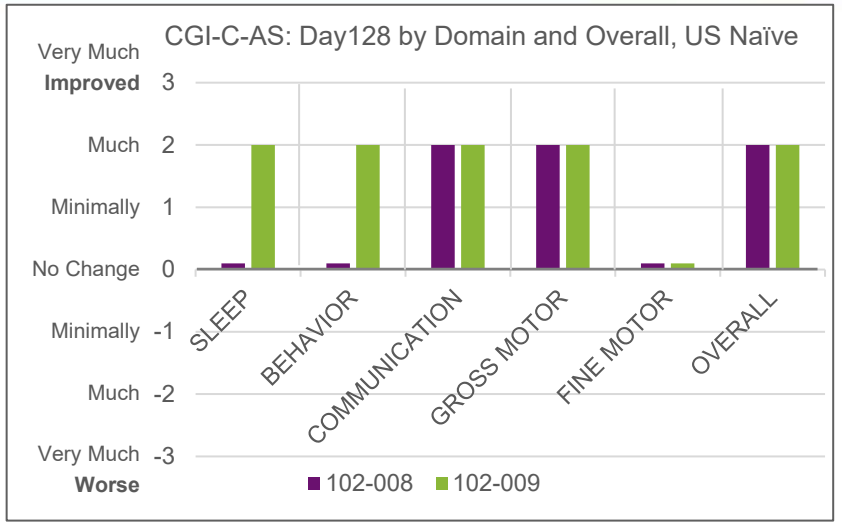
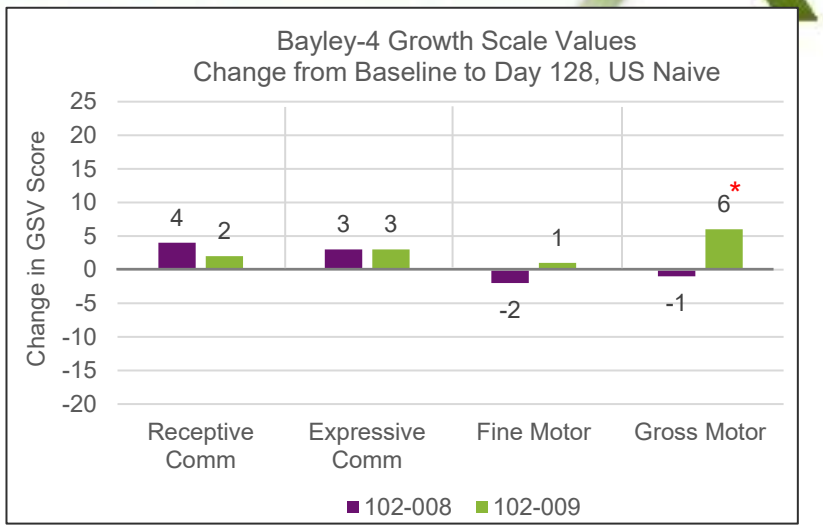
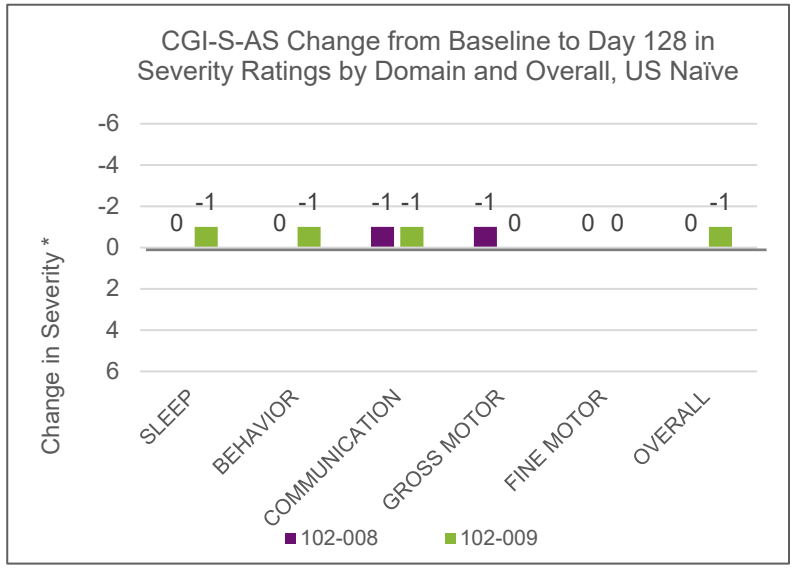
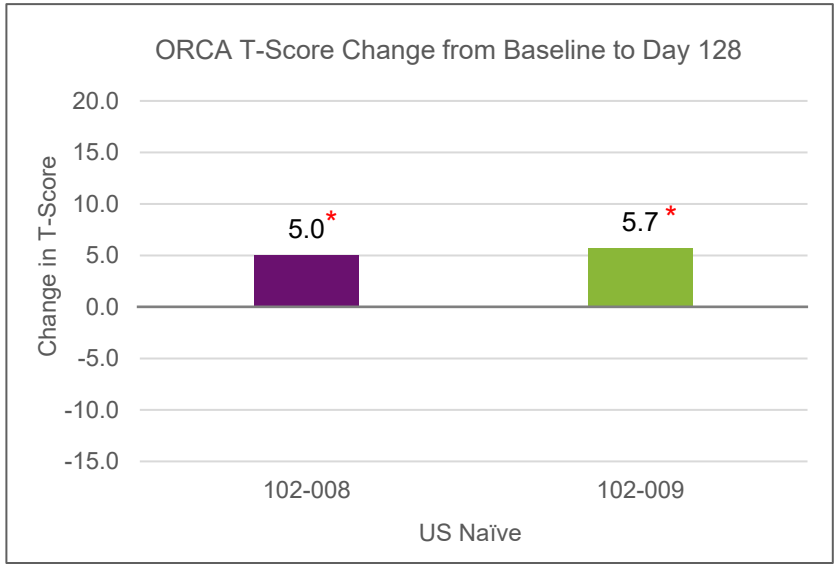
US Clinical Study at 2 mg dosing, Day 128 in two patients











Safety

- At 2 mg, monthly repeat doses, GTX-102 has been safe and well tolerated
- No drug-related SAE
- No AE or SAE reports of leg weakness events
- AEs – 2 patients had no AEs
- 3rd Patient: Transient difficulty sleeping, resolved
- 4th Patient: Vomiting, URI, asymptomatic EBV hepatitis (resolved and dosing resumed)
- No change in CSF total proteins nor trend toward increase, no signs of inflammation
  - One patient had a transient elevation at one dose that resolved by next measurement

*ORCA threshold for statistically significant improvement is 5 points. *Bayley-4 threshold for statistically significant difference ($p < .05$): RC, EC, and FM = 6, GM = 5.

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Clinician’s Perspective

Dr. Elizabeth Berry-Kravis, M.D. Ph.D.

GTX-102 Investigator

Professor, Pediatrics

Rush University Medical Center

Chicago, IL

Next Steps: Protocol Amendment Already Approved to Initiate Cohort 6 and 7 Expansion

- Canada and UK Regulatory filed and approved in May 2022
- Design: 2 patients in each cohort, if safe then escalate to next age matched cohort
  - <8 y/o: 7.5 mg x 2 doses, if not 2+ score in 2 domains, then 10 mg x 2 doses
  - ≥8 y/o: 10 mg x 2 doses, if not 2+ in 2 domains, then 12 mg x 2 doses
- Screening began and first patient in Cohort 7 dosed (10 mg)
- Redosing of original five US patients to begin in Canada
- Opening of US to depend on a submission and review of an interim CSR from UK/Canada and US patients

Expect next program update in late 2022 or early 2023

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Rationale for Executing Acquisition of GeneTx
We are confident in the value of the program for AS

Rationale

- Convincing safety and efficacy
- Unique IP and AS biology
- Greater efficiencies and control of Ph3 planning and regulatory interactions

Summary of deal terms

- $75M upfront + $30M milestone for Ph3 FPI
- Regulatory and commercial milestones; tiered mid-single up to low double-digit royalties on net sales of GTX-102
- Exclusive global rights to data and IP in support of GTX-102 and additional alternate ASOs

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We are “All In” for Angelman Syndrome

- GTX-102 is showing acceptable safety and encouraging efficacy
- Objective is to optimize therapeutic benefit without safety issues
- Unique IP value established by scientific basis
- Knowledge that AS clinical symptoms can respond quickly
- We have executed the early option acquisition
- A great story of families fighting for the children, driving research funding and changing the medical future for all families.

We intend to develop the first approved therapy for AS based on the GeneTx science and the original work by Scott Dindot supported by FAST

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Questions

GTX-102 Mid-Year Interim Data and Program Update

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