Clinical Trial Update on GTX-102

Science, Clinical Data and Next Steps

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Presenter Financial Disclosure

- Emil Kakkis, M.D., Ph.D.
  - Employee of Ultragenyx with partnership agreement with GeneTx
  - Stock ownership in Ultragenyx

Disclaimer

- GTX-102 is an investigational drug and is not approved by any regulatory authority
- The data presented here are interim data and do not provide definitive conclusions on efficacy or safety
- Substantially more work is required to prove whether or not GTX-102 is safe and effective

GTX-102 to Knockdown *UBE3A-AS* Transcripts and Increase Expression of Paternal *UBE3A* in Angelman

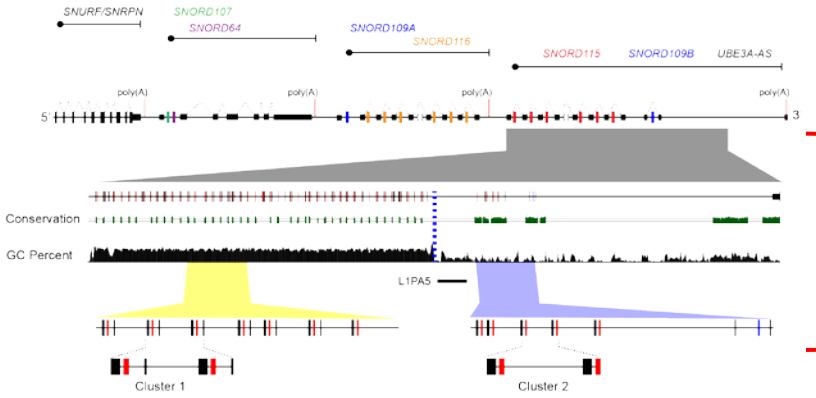
- Science behind GTX-102: targeting region and strategy
- Overview of GTX-102 Clinical Trial
- Additional insights from nonclinical studies
- Evaluation of results and management
- Next Steps in GTX-102 development

GTX-102: Targeting SNORD115 Cluster 2 region
Conserved, unique and retained in multiple AS transcripts

I. RNA-seq and polyA-seq studies showed:

1. SNHG14 is processed into different transcript units (i.e., non-overlapping, 3'-polyadenylated transcripts.
2. *UBE3A-AS* transcript is spliced and polyadenylated and processed as part of the SNORD115/SNORD109B host-gene.
3. Mouse and human antisense transcripts are not conserved, thus ASOs described in Meng paper are not applicable in humans.

SNHG14

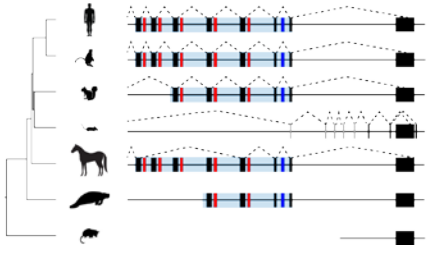


II. Genomic analyses showed:

1. Highly conserved region between SNORD115 genes and beginning of the *UBE3A-AS* transcript.
   a. Host-gene exons in this region are in essence the 5'-exons of the *UBE3A-AS* transcript
2. SNORD115 host-gene exons in the conserved region (cluster 1) are different than the SNORD115 host-gene exons upstream (cluster 2).
3. Region downstream of SNORD109B is poorly conserved and predominantly comprised of repetitive elements.

III. Phylogenetic and comparative genomics studies showed:

1. Host-gene exons in cluster 2 are highly conserved across placental mammals for over 100 million years.
2. Distal host-gene exons in cluster 2 are at beginning of the *UBE3A-AS* transcript in horse, squirrel, macaque, and human: Expression and genetic structure constrained for over 96 million years



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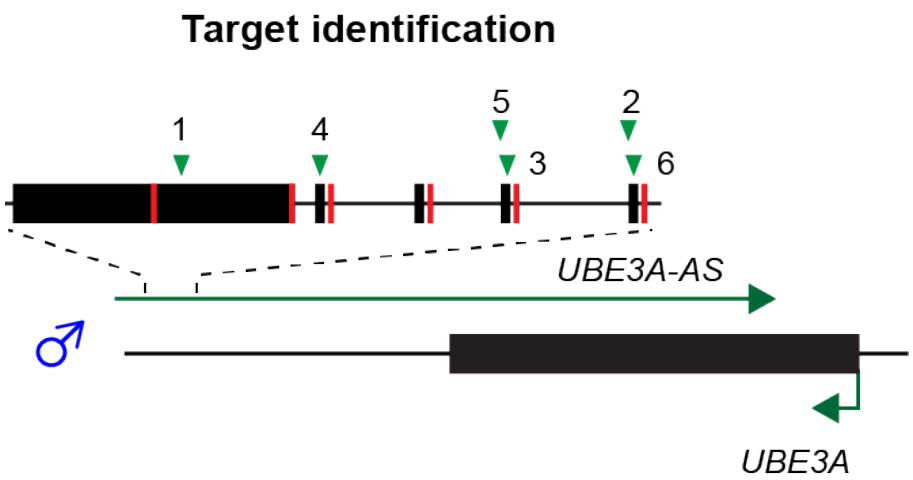
Targeted Cluster 2 Region due to conservation and likely the origin of the AS transcript

We targeted this region because:

1. Cluster 2 is at beginning of the *UBE3A-AS* transcript.
2. Cluster 2 is genetically and structurally different than Cluster 1, implying differential function.
3. Cluster 2 has evolutionarily constrained exons and splicing motifs, implying regulatory function.
   a. Several exons are identical across humans and NHPs, thus allowing PD studies in a NHP model.
4. Targeting exons would increase ASOs chance of terminating transcription since introns would be spliced out of the nascent transcript during transcription.

SNORD115 Cluster 2 Region



Overview of the GTX-102 Phase 1/2 Study

- First in human study
- 4 monthly doses
- Dose escalation: multiple cohorts (groups) with different starting dose levels
  - Dose levels chosen based on translation of NHP dose levels
- No placebo control group
- ASO given intrathecally by lumbar puncture

Study Objectives and Inclusion/Exclusion

- **Primary**
  - Safety of GTX-102
- **Secondary**
  - Pharmacokinetics (PK) of GTX-102: measure drug in blood and cerebral spinal fluid (CSF)
- **Exploratory**
  - Multiple domains of AS
    - Communication, sleep, behavior, gross motor, fine motor, seizures

Inclusion

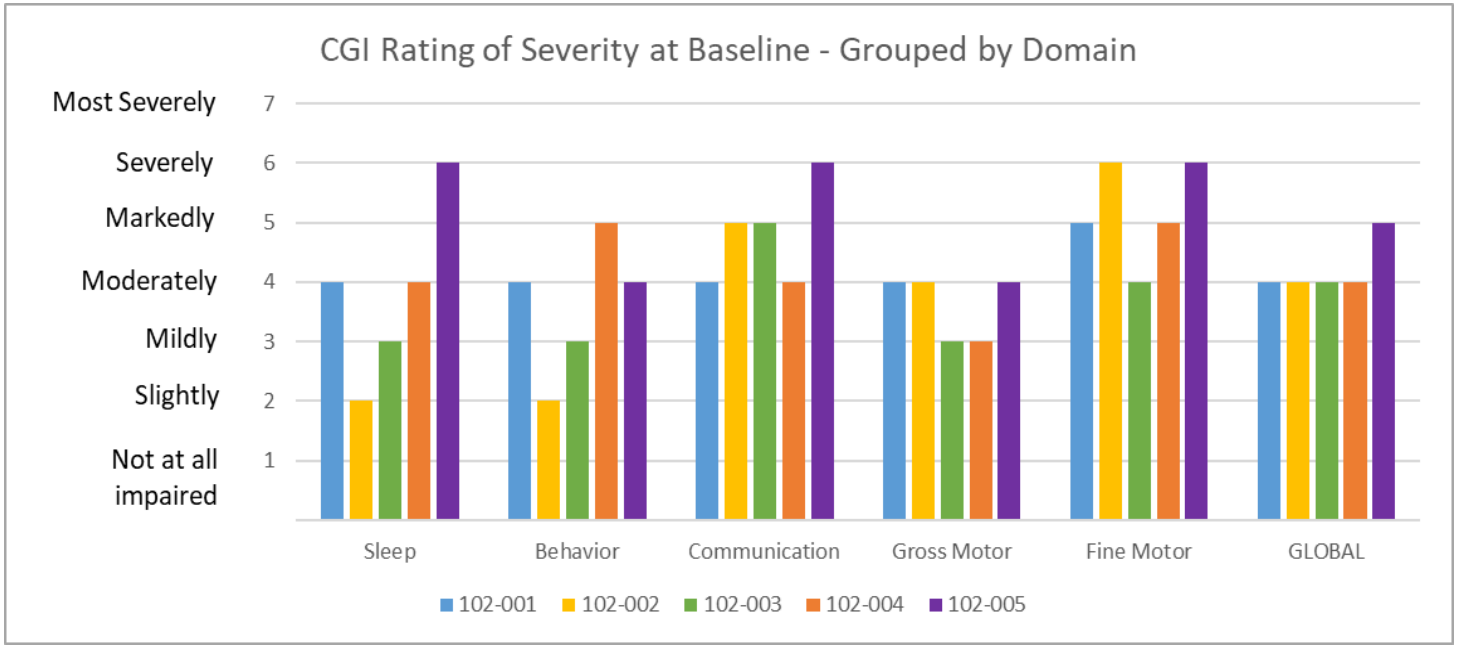
- Documentation of full maternal *UBE3A* gene deletion in region of 15q11.2-q13
- Age ≥ 4 to ≤ 17 yrs at screening
- Stable seizure control
- Normal kidney and liver tests
- Able to tolerate anesthesia

Exclusion

- Any change in meds or diet to treat AS symptoms in prior 3 months (i.e. sleeping aids, supplements, ketogenic diet, etc)
- Inability to ambulate independently, or with an assistive device, or caregiver hand-hold
- Any bleeding or platelet disorder
- Would require intubation

AS Patients enrolled in the Phase 1/2 Study

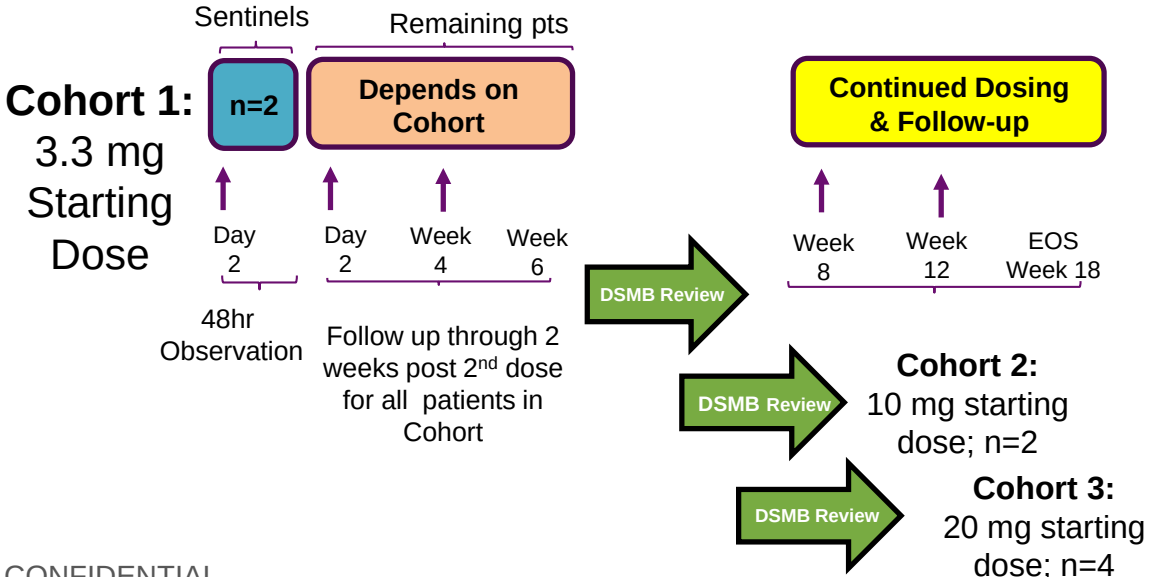
- Communication, fine motor, and global scales moderate to severely affected in all patients
- Variable but broad set of affected domains in all patients



Study Design/Conduct: Within-Patient Dose Escalation

Increased starting dose level in each cohort

- 3 Cohorts started monthly dosing in sequence before pause in dosing
- Dose was increased one step *at each dose administered*
  - Cohort 1 dose sequence is 3.3, 10, 20 and 36 mg



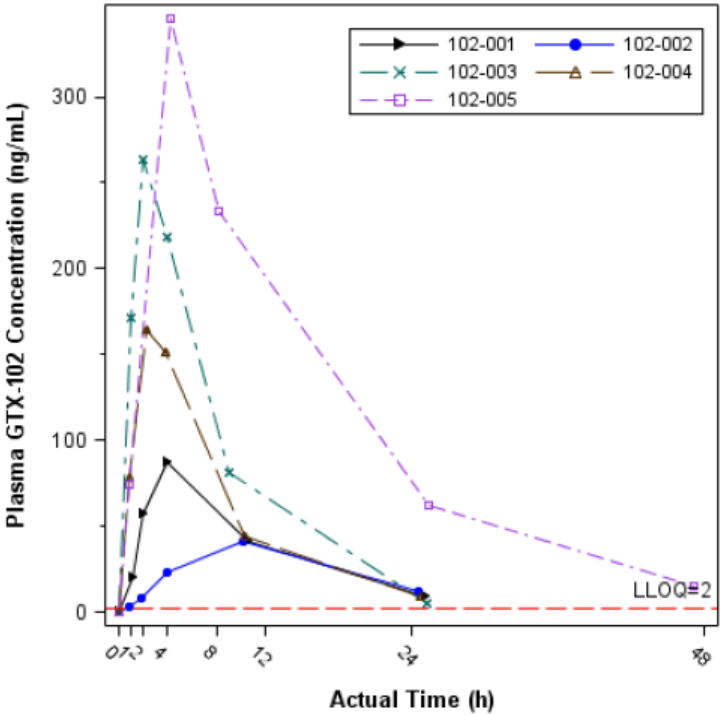
Cohort	Actual # Enrolled
1	2
2	2
3	1

Dosing administered to each enrolled patient

- 5 patients total treated to date
- All patients treated at Rush as it was open prior to the COVID pandemic
- 11 fold difference from lowest to highest doses tested

Study Day	Cohort 1 n=2		Cohort 2 n=2		Cohort 3 n=1
Age	*10 yr*	*5 yr*	*12 yr*	*15 yr*	*5 yr*
Dose 1	3.3 mg	3.3 mg	10 mg	10 mg	20 mg
Dose 2	10 mg	10 mg	20 mg	20 mg	--
Dose 3	20 mg	20 mg	36 mg	36 mg	--
Dose 4	36 mg	36 mg	--	--	--
Dose 5	36 mg	--	--	--	--
Cumulative Dose	**105.3 mg**	**69.3 mg**	**66 mg**	**66 mg**	**20 mg**

Plasma Pharmacokinetics for First Dose
Linear Scale



- GTX-102 blood levels were dose proportional
- As expected GTX-102 was not detectable 28 days later prior to next dose in the blood or CSF
- Doses given for PK shown
  - Patient 1 and 2 = 3.3 mg
  - Patient 3 and 4 = 10 mg
  - Patient 5 = 20 mg

Lower limit of quantification (LLOQ) = 2 ng/mL

Safety – Adverse Events

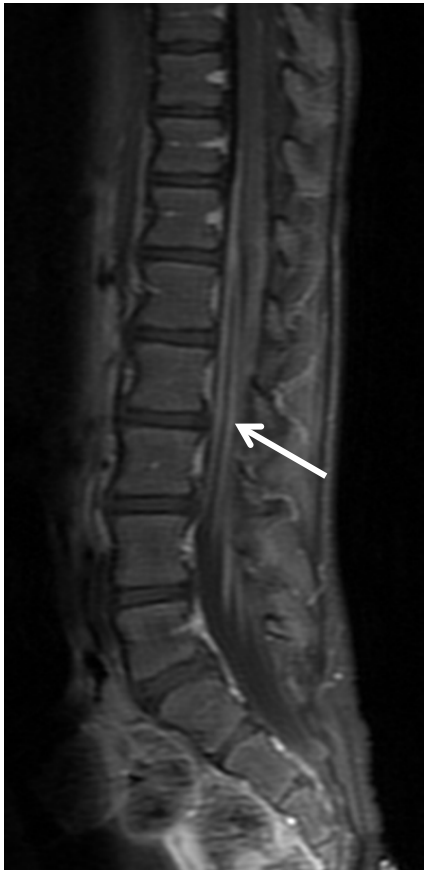
- Transient ataxia and fatigue
  - Dose related; primarily observed at 20 mg and higher
  - Variable severity between patients
  - Started 2 to 6 hours after injection
  - Lasted 1-3 days
  - Patients back to normal when resolved
  - Able to eat and interact normally during symptoms
- Other mild events like headache, UTI and typical childhood infections
- Patients tolerated LPs and anesthesia well

Serious Adverse Event (SAE) Lower Extremity Weakness

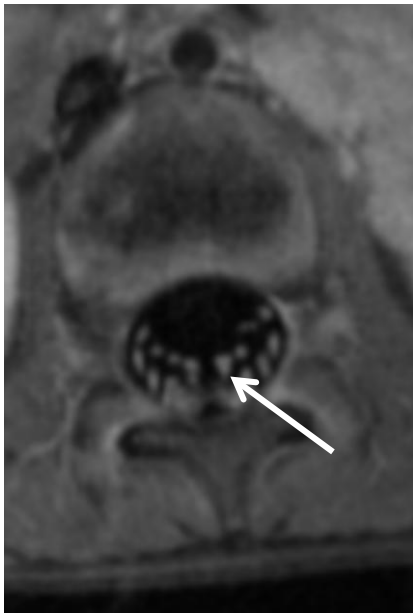
- Mild to Moderate SAE of lower extremity weakness seen in all 5 patients
  - Occurred 6 to 30 days after last infusion
  - Significant weakness in 3, and unable to walk in 2 youngest patients
  - 4 patients after the highest dose (36 mg)
  - 1 patient after the second highest dose (20 mg), smallest patient
- Dosing paused for all patients after first case observed
- Most severe aspects lasted 1 to 3 weeks
  - Full resolution generally took 19 to 86 days
- Clinical improvements were sustained longer than the SAE and are continuing

Safety – SAE evaluations
MRI shows local impact on meninges and nerve roots

- Lower extremity weakness consistent with inflammation of the nerve roots due to GTX-102 intrathecal delivery
  - MRI consistent with inflammation in nerve roots and lumbosacral meninges
  - Did not appear to be clinically similar to post-dose ataxia
  - Severity of post-dose ataxia was not predictive of the severity of delayed nerve root related weakness
  - CSF protein increases during SAE
- No other SAEs



L1-L2



T1 weighted MRI images

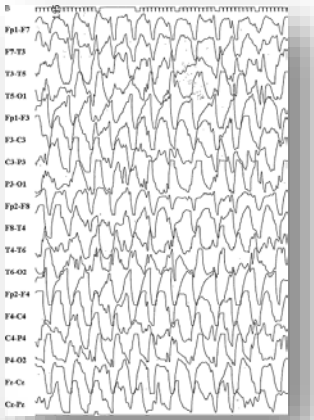
Clinical Evaluations

Exploratory Endpoints Measure Multiple Domains

Clinical Global Impression Scale of Change also used

SLEEP

- ActiGraph
- Diary
- EEG

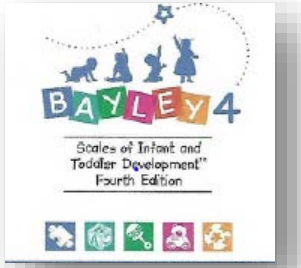


SEIZURES

- EEG
- Diary

COMMUNICATION

- ORCA
- Bayley
- Vineland



COGNITION

- Bayley-4
- Vineland

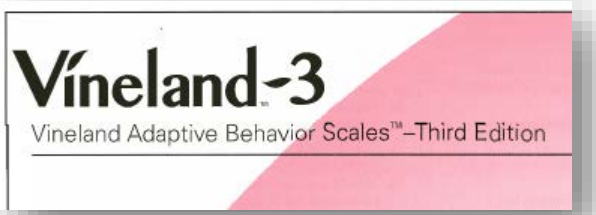
MOTOR

- ActiMyo
- Bayley-4
- Vineland

Aberrant Behavior Checklist

BEHAVIOR

- ABC
- Vineland



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Interim Clinical Evaluation Summary Results

- All 5 patients improved in multiple domains as assessed by CGI-I-AS
  - Mean global CGI-I-AS score of +2.4 across patients (scale of -3 to +3)
  - All patients with at least 2 domains much or very much improved
  - All patients had 3 domains minimally improved or better
- Positive CGI-I-AS results supported by other measures
  - Increases in Bayley-4 expressive or receptive communication scales
  - Increases in 3 patients in Observer-Reported Communication Ability (ORCA)
  - EEG improves in 3 of 4 subjects in qualitative reading, and 2 of 2 in quantitative
  - Trending improvements in Actimyo supporting motor gains and documented deficits during SAE
- Responses began after lowest doses in some patients

What is the Clinical Global Impression (CGI) of change?

-3	-2	-1	0	1	2	3
Very much Worse	Much Worse	Minimally Worse	No Change	Minimally improved	Much improved	Very Much Improved

Improvement Scale (CGI-I-AS) Definitions

- **Minimally improved** is a meaningful improvement or worsening (not just normal week to week variation, or a good period) in one area
- **“Much” improved** is a meaningful improvement or worsening in at least two areas, or sometimes a really large improvement in one area
- **“Very much” improved** is a large and meaningful improvement in multiple areas
- Measure both global score separately from individual domain ratings
- Domain rating may not change if no problems exist at baseline and so might score as 0

Clinical Global Impression-Improvement-AS

Change by Patient at Day 128*

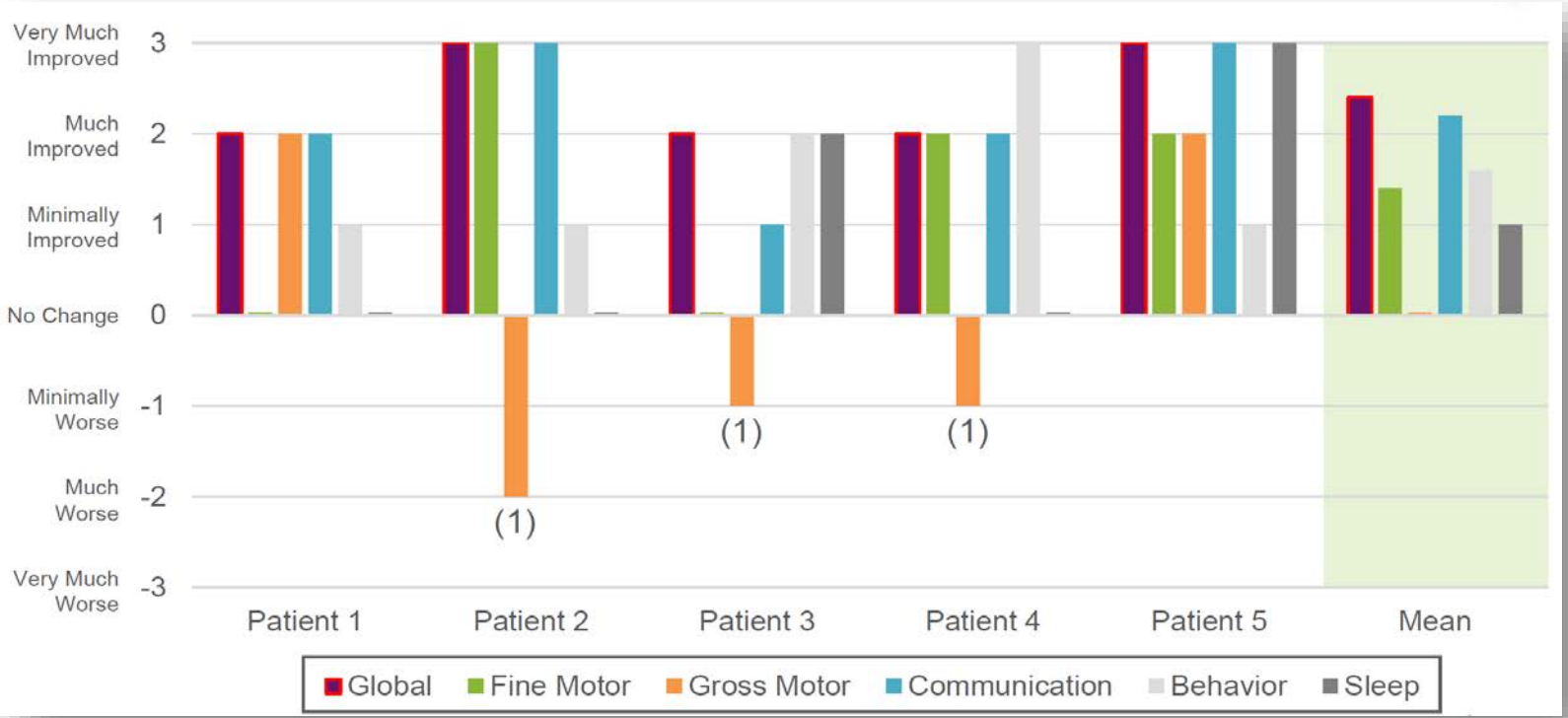
All patients had a positive response in at least 3 domains

Patient	Overall Global Rating	Sleep	Behavior	Communication	Gross Motor	Fine Motor
001	+2 Much Improved	0	+1	+2	+2	0
002	+3 Very Much Improved	0	+1	+3	-2*	+3
003	+2 Much Improved	+2	+2	+1	-1*	0
004	+2 Much Improved	0	+3	+2	-1*	+2
005	+3 Very Much Improved	+3	+1	+3	+2	+2

* (1) Significant lower extremity weakness due to AIP that had not yet resolved at the time of testing.
**Patient 005 had his Day 128 visit completed at Day 86 (12 Oct 2020) because he developed AIP after his first dose of GTX-102 but prior to his Day 128 visit.

CGI-I-AS at Day 128

Graphical representation of global (purple/red) and individual domains



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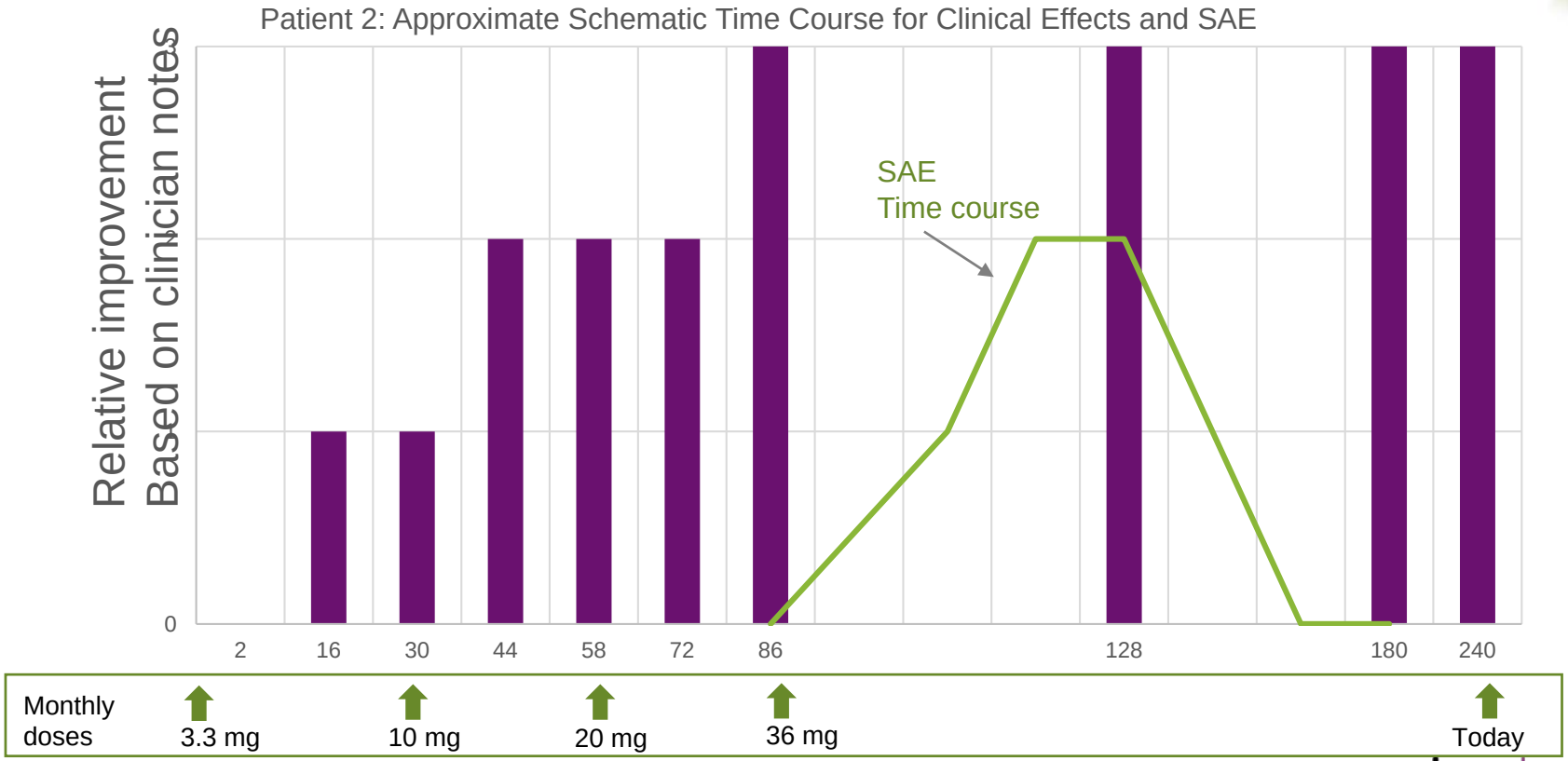
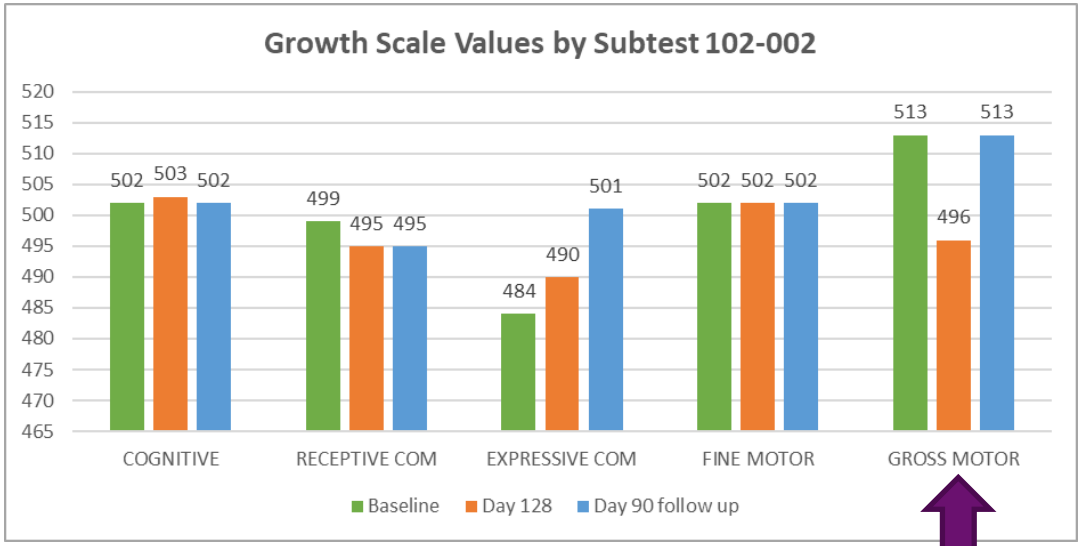
Schematic Time Course: Clinical Improvement Precedes and Continues Following SAE of LE Weakness



Impact of SAE on Bayley over Time
Decrease in Gross Motor with SAE then Improves



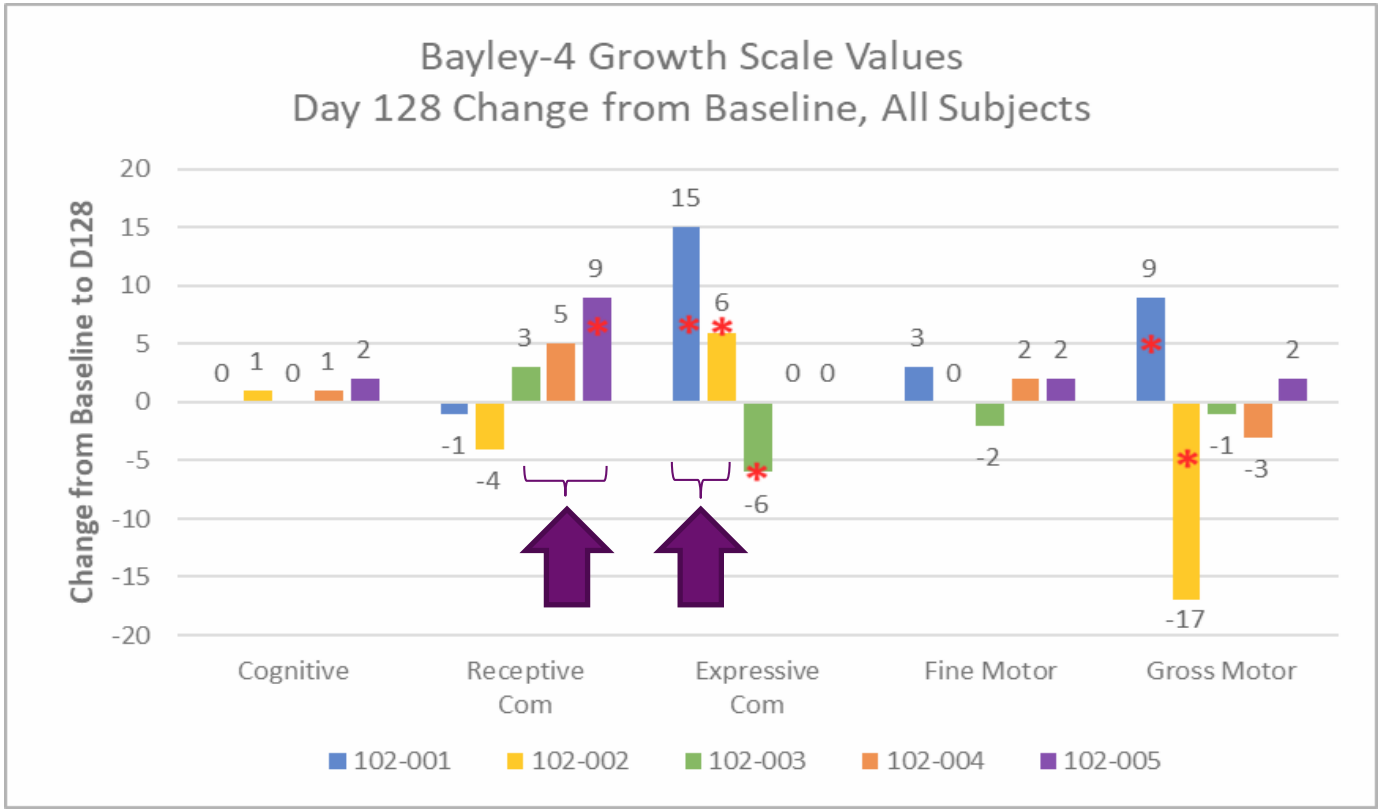
- Decrease at Day 128 due to SAE
- Repeat Bayley 90 days later demonstrates recovery
- Bayley is a viable measure

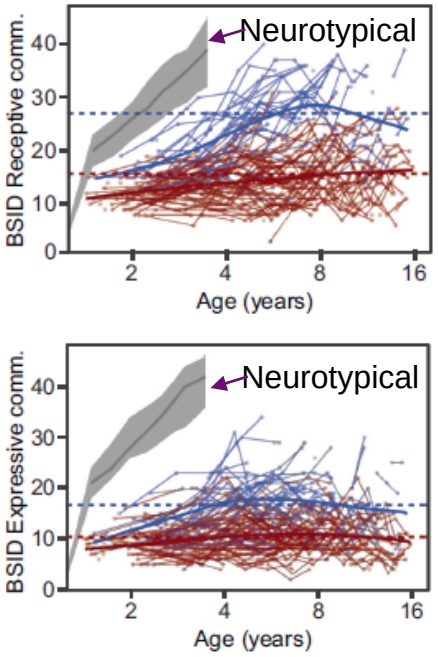
Low point during the SAE
Resolved before next assessment

Caregivers Reported a Range of Improvements
Patient ages between 5 and 15 years old

- Communication
  - Acquisition of spoken words, signs & gestures, and augmentative & alternative communication abilities
  - Ability to respond to their name, follow commands, and focus on tasks
- Motor, Fine or Gross
  - Acquisition of independent capabilities, such as self-feed with a fork
  - Increased abilities in physical activities, such as patients swimming on own and catching/throwing a ball
  - Improved gait and posture; going up hills, walking on sand without falling, stepping up curbs, more narrow based, stable, more upright, faster gait
- Sleep: Dramatically improved sleep for one with poor sleep at baseline
- Behavior
  - Decreased maladaptive behaviors
  - Increased social engagement

Bayley Scale of Infant and Toddler Development-4
Improvement in Receptive or Expressive Communication





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Observer-Reporter Communication Ability (ORCA)
Three Patients Show Relevant Improvement

- Standard deviation (SD) is 10
- Change > half a SD (>5 point change) indicates a response
- 2.3-2.9 indicates Standard Error (SE)

Patient	Baseline	Day 128	Follow-up	Change from Baseline
1	50.2	58.7	58.8 (Day 217)	***8.5***
2	47.4	54.9	55.2 (Day 196)	***7.9***
3	56.5	53.7	-	-2.9
4	50.6	57.3	-	***6.7***
5	43.8	42.2	-	-1.6

EEG: A Potential Biomarker of Drug Effect
Preliminary Results

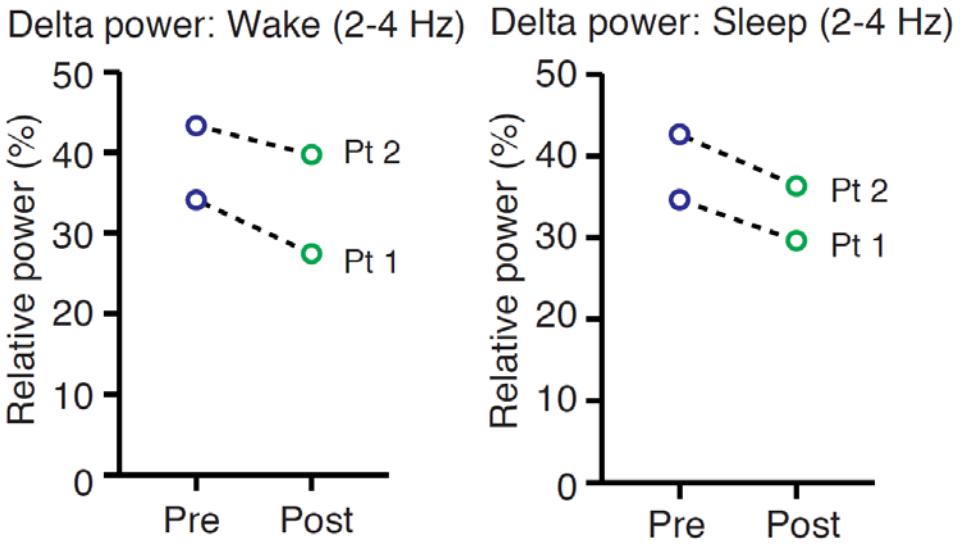
- Blinded independent central read of EEG by 2 expert pediatric clinical neurophysiologists/ epileptologists, readings then reconciled
- EEG differences in AS compared to neurotypical
  - Notched delta waves (an interictal epileptiform discharge) is a common finding in AS
  - Delta power is broadly increased and more dynamic relative to age-matched neurotypical controls
- Qualitative reading of EEGs reveal some potential trends
  - 3 of 4 have a reduction in notched delta waves
  - 3 of 4 have a reduction in epileptiform discharges (either sleep or wake)
- Normally there is significant variability in an EEG tracing; need to repeat EEGs after longer treatment with GTX-102

Seizures well controlled at baseline in all subjects & no seizure AEs were recorded during the study to date

Preliminary EEG Quantitation Showing Trends

More data and longer treatment evaluation needed

Patient	Notched Delta Wave Frequency from baseline	Epileptiform Discharges (wake or sleep)	Relative Delta Power (wake or sleep)
Patient 1	Minimal change to slight ↑	↓	↓
Patient 2	↓	↓	↓
Patient 3	↓	↓	pending
Patient 5	↓	Minimal change to slight ↑	pending

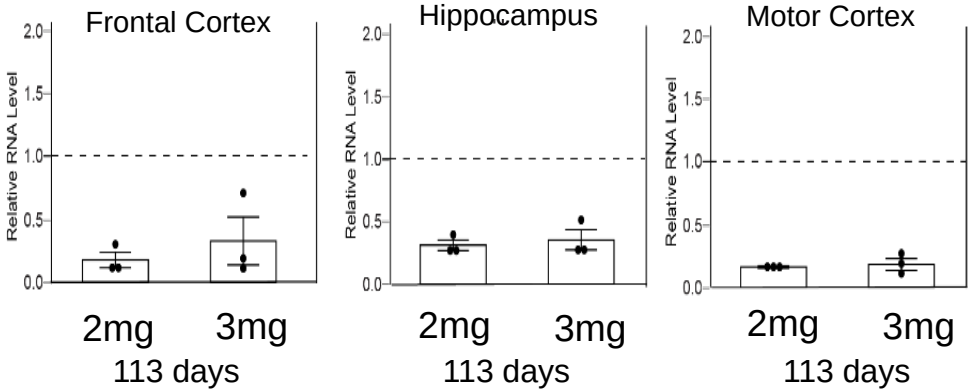


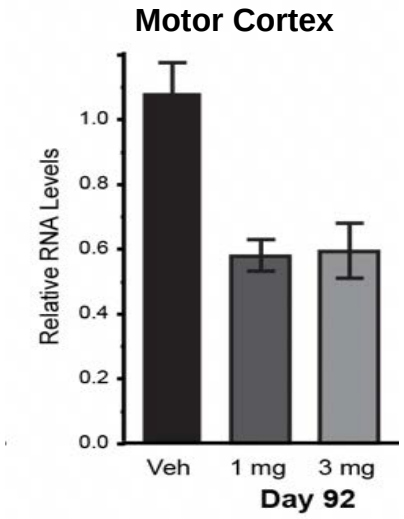
Summary clinical data and questions

- All five subjects with clinical improvement observed
  - Youngest two subjects, #2 and #5 with the very much improved CGI-AS
  - Other improvements captured in different domains
  - Improvements begin at lowest two doses 3.3mg and 10mg
- SAE occurred at the highest 36mg dose in four, and the 20mg dose in one (#5)
  - Most impaired in youngest/smallest patients #2 and #5
  - The site of the SAE appears local to lumbosacral nerve roots/meninges
- **Key questions**
  - Can a lower dose if applied repeatedly accumulate enough drug to gain the improvements while avoiding the SAE?
  - Are there adjustments to the dosing/administration to reduce local exposure and improve delivery to brain site of action?

GTX-102 at lower doses applied monthly (4 doses) can knockdown *UBE3A-AS* substantially in recent NHP data

- Single and repeat dose (4 to 7 monthly doses) applied to NHP
- Acute sporadic and transient weakness observed typically less than 24 hours
- Delayed-onset weakness similar to SAE **not** observed at doses as high as 10mg/dose (110mg HED) or 7 monthly doses of 4mg (313.6 mg HED accumulation)
- Knockdown of *UBE3A-AS* occurs at very low doses of GTX-102
  - Strong effect at 1, 2, 3 or 5 mg/dose on monthly basis in NHP
  - Measurable impact at 0.5 mg dose when applied with repeat doses





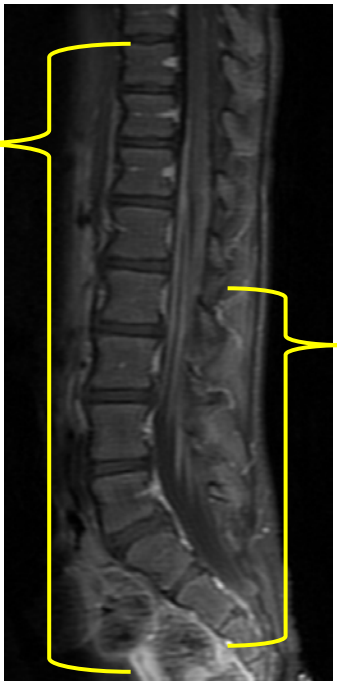
Further evaluation of the SAE pattern of impact

Local effect may be based on inadequate mixing and "settling"

- Drug SAE may have size/age based difference consistent with drug distribution
- Younger smaller patients with more severe impact and also greater improvement

Smaller Patients
#2 and 5

MRI findings cover lumbar *and* sacral levels



Larger Patients

MRI findings predominantly in sacral levels

NHP Tissue Concentration Data

Lumbar region = ~3x Brain regions consistent with inadequate distribution and mixing, leading to potentially higher local lumbosacral concentrations

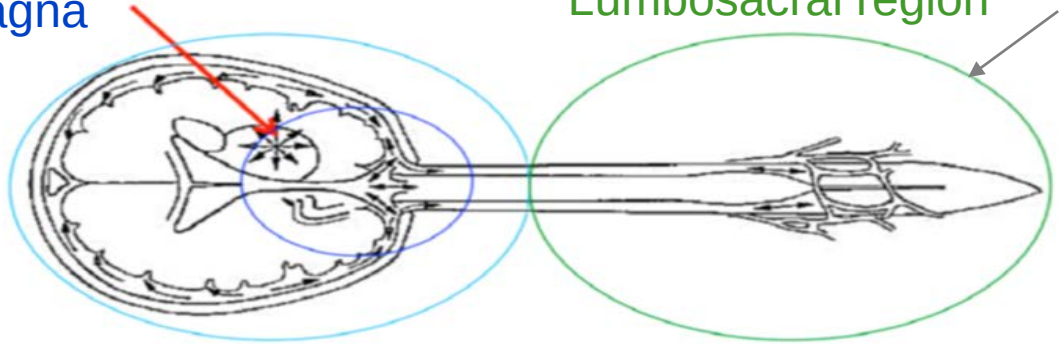
Suggests need for better distribution and mixing of GTX-102

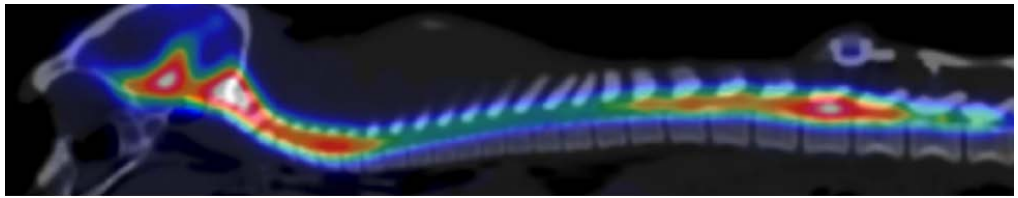
CSF mixing is not equal along the spine: Rapid pulsatile mixing in the cisterna magna

Rapid Pulsatile Mixing
Cisterna Magna

Lumbosacral region

Slower transport region 2-6mm/hr





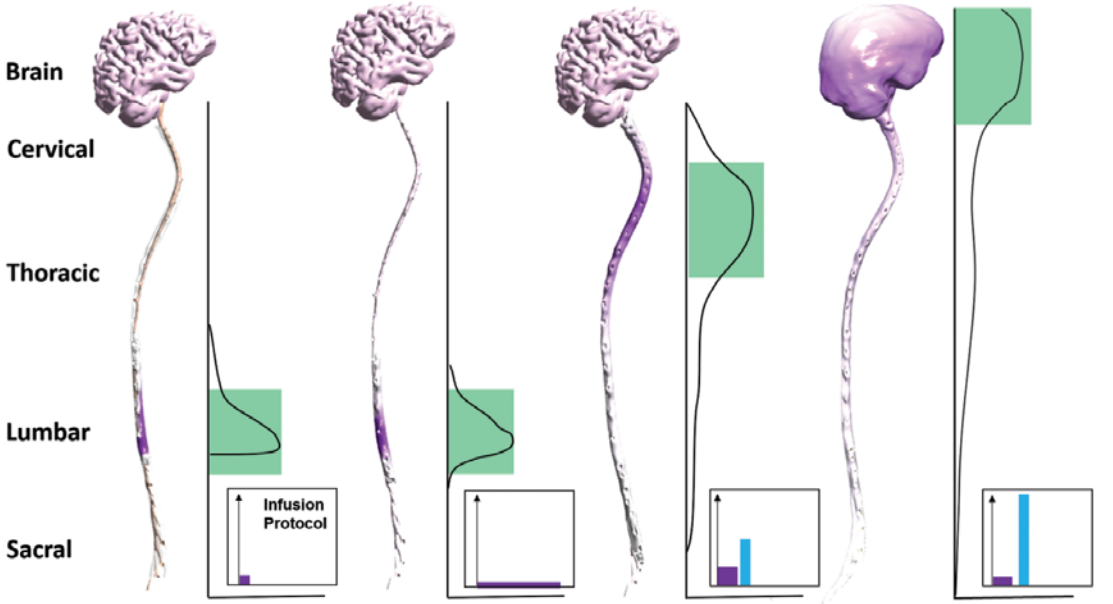
Applying Trendelenburg sufficiently could move drug toward CM for mixing

Physiology of the Intrathecal Bolus: The Leptomeningeal Route for Macromolecule and Particle Delivery to CNS Molecular Pharmaceutics

Mikhail I. Papisov,*,† Vasily V. Belov,† and Kimberley S. Gannon‡

Applying Trendelenburg with an artificial CSF Flush

Modeling shows the ability of a flush with a CSF to push drug toward the CM mixing



Time	10 minute	1 hour	1 hour	1 hour
Infusion Strategy	Single Bolus	Drug pump	Drug-Bolus aCSF flush	Drug-Bolus High volume
Infusion Parameters	1mL @ 1 mL/min. – Drug	0.016 mL/min. Drug	5mL @ 1mL/min. – Drug 5mL @ 10 mL/min – aCSF	5mL @ 1mL/min. – Drug 10mL @ 10 mL/min - aCSF
Total Infusion	1 mL – Drug	1 mL – Drug	10 mL – Drug/aCSF	15 mL – Drug/aCSF

Goal:

Maximizing movement of ASO toward the CM mixing chamber to deliver to CNS and reduce local contact with lumbosacral region

Computational and In Vitro Experimental Investigation of Intrathecal Drug Distribution: Parametric Study of the Effect of Injection Volume, Cerebrospinal Fluid Pulsatility, and Drug Uptake

Tangen et al 2017

Plan to Resume the Clinical Trial

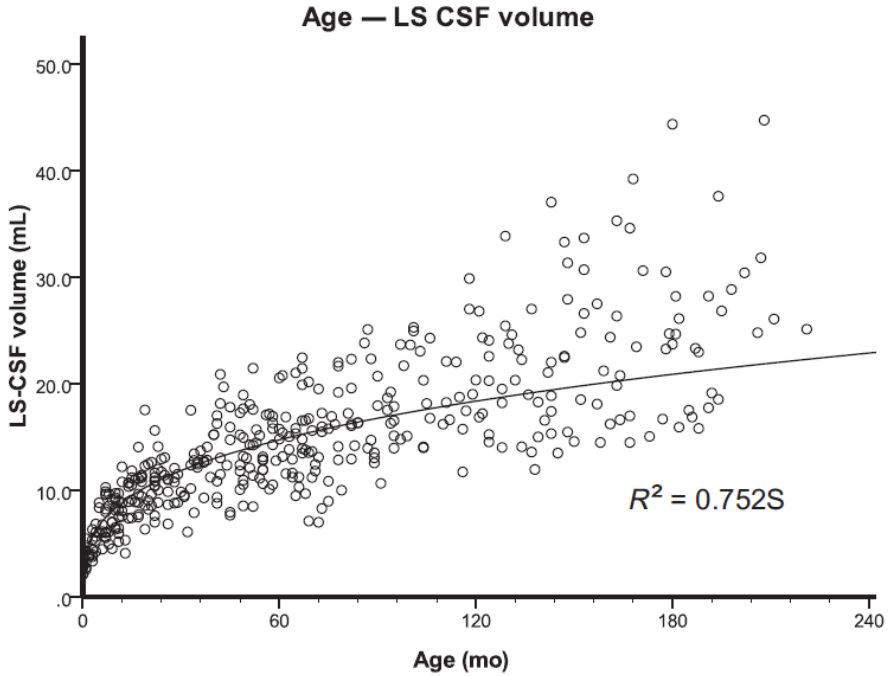
- Learnings
  - GTX-102 clinically active at lower doses
  - Higher doses associated with SAE of reversible leg weakness
  - SAE appears to be a localized effect of GTX-102 on lumbosacral spinal nerves
  - Clinical impact on communication and other measures lasts 3-5 months, longer than SAE
- Plan
  - Amend the protocol for dose and administration
  - Starting dose at lower 3.3 mg and 5 mg depending on age of individual
  - Individualized dose titration: increase dose slowly if not responding, if no safety findings
    - Cap dose at 14 mg: avoid 20 mg dose
  - Modify administration procedure to minimize duration of exposure at injection site
- FDA must review and approve protocol amendment prior to resuming dosing and enrollment

Acknowledgements

- Patients and families participating in the Phase 1/2 Trial
- Dr. Scott Dindot, for science and data of GTX-102
- GeneTx team, Paula Evans, Scott Stromatt, Allyson Berent and Jennifer Panagoulias for nonclinical data, clinical data and regulatory
- Ultragenyx team for support of the program

Lumbosacral CSF volume increases as patients age
Poor mixing from lumbosacral region may enhance SAE effect

Age Range (n=418)*	Mean LS volume / weight (mL/kg)	Mean LS Volume (mL)
Toddlers and preschoolers (1-<6yr)	0.86	12.5
Schoolers (6-<12yr)	0.71	18.3
Adolescents (12-18yr)	0.54	24.4



Lumbosacral and thoracolumbosacral cerebrospinal fluid volume changes in neonates, infants, children, and adolescents: A retrospective magnetic resonance imaging study

Jang et al, Pediatric Anesthesia. 2019;29:92–97.