
ultragenyx

Welcome and Corporate Overview

- Emil Kakkis, M.D., Ph.D.
  President and Chief Executive Officer

Forward Looking Statements

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 operating results and financial performance, anticipated cost or expense reductions, plans with respect to commercializing our product and product candidates, our translational research program, expectations regarding our manufacturing capabilities, the expected timing of release of additional data for our product candidates, plans to initiate additional studies for product candidates and timing and design of these studies, plans regarding ongoing studies for existing programs, our liquidity position as of the most recent fiscal quarter end, 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, future regulatory interactions, and the value to be generated by our pipeline. 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 reliance on our third party partner, Kyowa Kirin Co., Ltd., for the supply of Crysvita, fluctuations in buying or distribution patterns from distributors and specialty pharmacies, the transition back to Kyowa Kirin of our exclusive rights to promote Crysvita in the United States and Canada and unexpected costs, delays, difficulties or adverse impact to revenue related to such transition, smaller than anticipated market opportunities for our products and product candidates, manufacturing risks, competition from other therapies or products, uncertainties related to insurance coverage and reimbursement status of our newly approved products, our evolving integrated commercial organization, uncertainties in the regulatory approval process and the timing of our regulatory filings, the uncertainties inherent in the clinical drug development process, including the potential for substantial delays and risk that earlier study results may not be predictive of future study results, risks related to adverse side effects, the ability for us to successfully develop our pipeline product candidates, our ability to achieve our projected development goals in the expected time frames, the potential for any license or collaboration agreement to be terminated, and other matters that could affect sufficiency of existing cash, cash equivalents and short-term investments to fund operations, the availability or commercial potential of our product and product candidates, 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.

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.

Ultragenyx is leading the future of rare disease medicine

5 commercial programs **generating revenue**

CRYSVITA® burosumab

Treatment for
XLH

DOJOLVI®

Treatment for
LC-FAOD

Mepsevii®

Treatment for
MPS VII, Sly syndrome

Evkeeza®

Treatment for
HoFH

CRYSVITA® burosumab

Treatment for
TIO

ultragenyx

programs that entered clinical trials have demonstrated **clinical success**

Ultragenyx is the most productive rare disease company in the industry…

Approvals since IPO exceeds many other successful rare disease companies

	Years from IPO to 1st approval^	# of approvals^ 10y post-IPO	# of approvals^ 15y post-IPO
Ultragenyx	**3**	**5**	**8-12***
BioMarin	4	3	5
Genzyme	5	2	3
Alexion	11	0	2
Alnylam	14	0	2
Vertex	21	0	0

^Approvals for rare disease indications
** Expected based on current pipeline*

Key to Our Success

Clear science that leads to our ***higher probability of success*** than other companies

Fastest development in the industry that leads to ***efficient spend***

Experienced management team with track record of novel study designs, new endpoints and rapid regulatory pathways

Innovative approach to commercialization has led to a **successful global commercial organization…**

Led commercialization efforts of **blockbuster product**

CRYSVITA® burosumab

Navigated **more launches of 1st ever treatments –**

including multiple indications with

DOJOLVI®

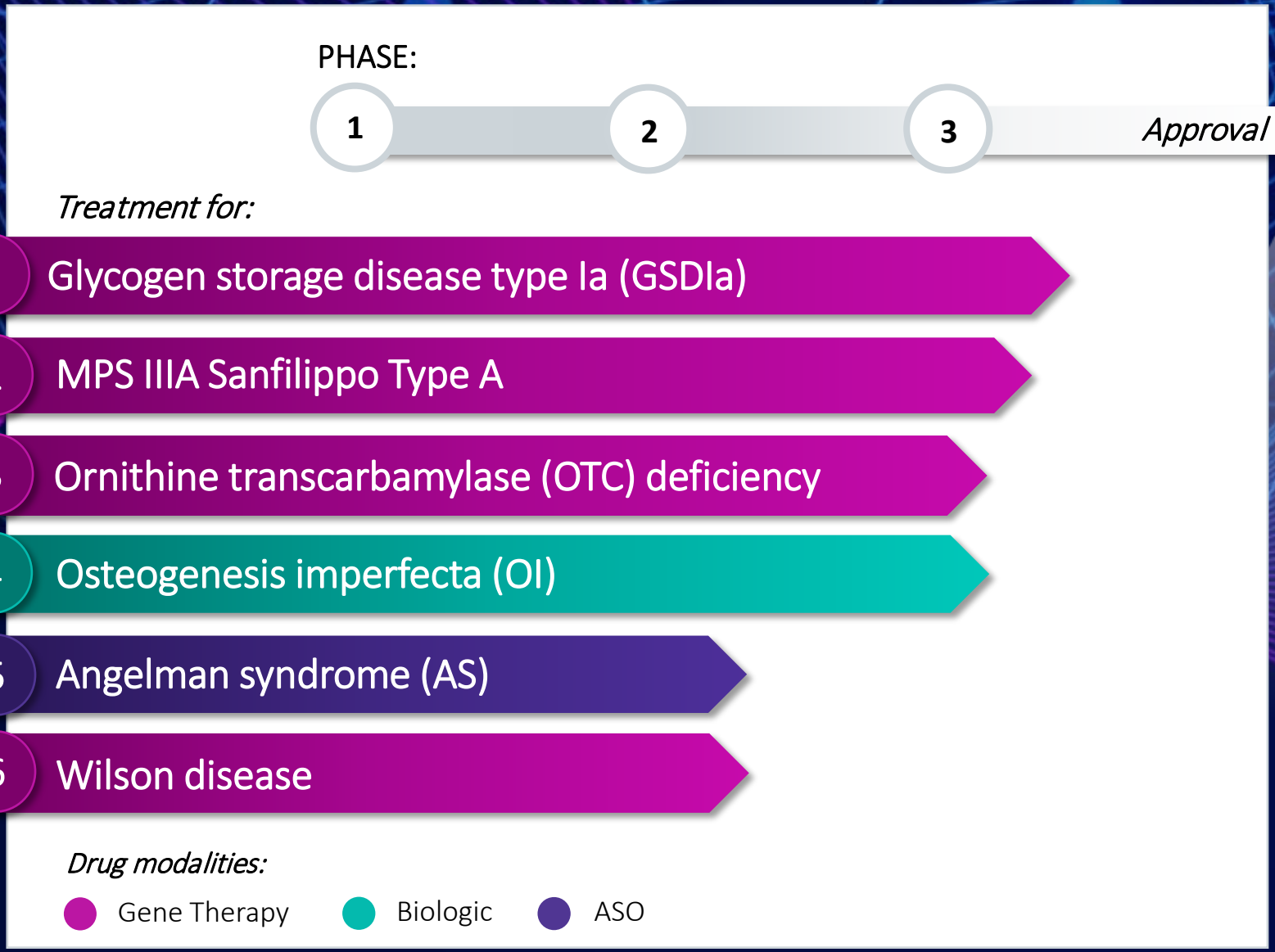
Reputation differentiators – with payors, doctors and patient community through **compassionate use policy and 100% co-pay Support / Access**

Global Commercial Operations Across North and South America, Europe and Japan

Treating patients in ~34 countries

6

in **later-stage** programs



3 **independent large opportunities** with substantial value – **and they are all working…**

	Osteogenesis Imperfecta	**~60,000** patients	**Phase 3**	**Monoclonal Antibody**
	Angelman Syndrome	**~60,000** patients	**Phase 2**	**Antisense Oligonucleotide**
	Wilson disease	**~50,000** patients	**Phase 2/3**	**Gene Therapy**

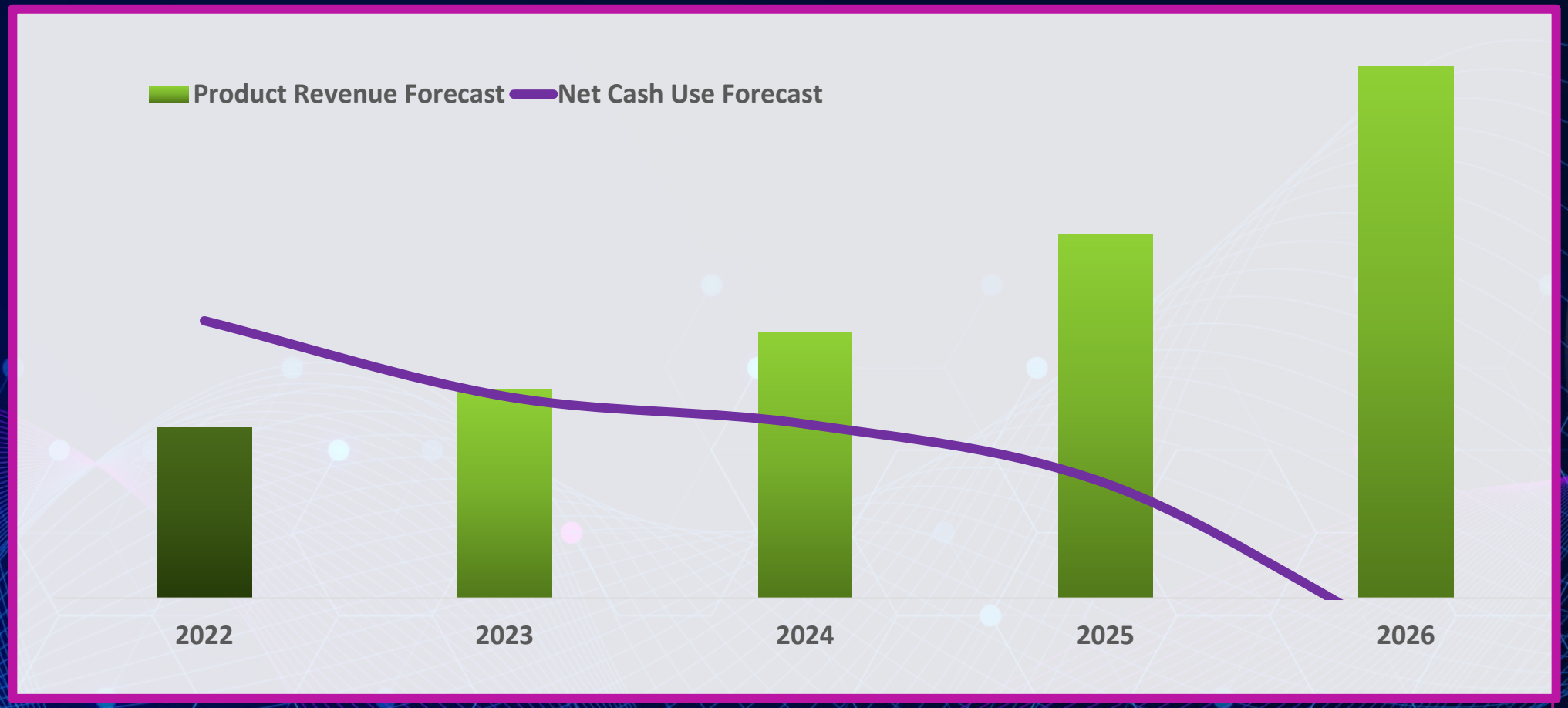
5 key clinical catalysts

	PROGRAM	OBJECTIVE	EXPECTED TIMING
1	**UX143** Osteogenesis Imperfecta	Phase 2 fracture data	Today!
2	**GTX-102** Angelman Syndrome	Extension & redosing data Expansion cohort data	Today! 1H24
3	**UX701** Wilson Disease	Cohort 1 data Cohorts 1-3 data	Today! 1H24
4	**DTX401** GSDIa	Phase 3 unblinding	1H24
5	**UX111** MPS IIIA	Regulatory discussions on filing	4Q23

Increased **financial discipline** over last 18 months to **drive priority programs**…

Strong revenue growth and decreasing cash use

Pathway to profitability in 2026 driven by new product approvals and continued operational leverage



A moment in time.

The future of rare disease medicine **is here**.

Multi-modality allows for independent **value creation with the right technology**

Major catalysts coming for **key programs**

Within **2-3 years expect multiple new product approvals**

Revenue projected to exceed $1B with a path to profitability

UX143 for Osteogenesis Imperfecta
Phase 2 Clinical Study Update

- Eric Crombez, M.D.
  Chief Medical Officer

Disclaimers

UX143 is an investigational drug and is not approved by any regulatory authority

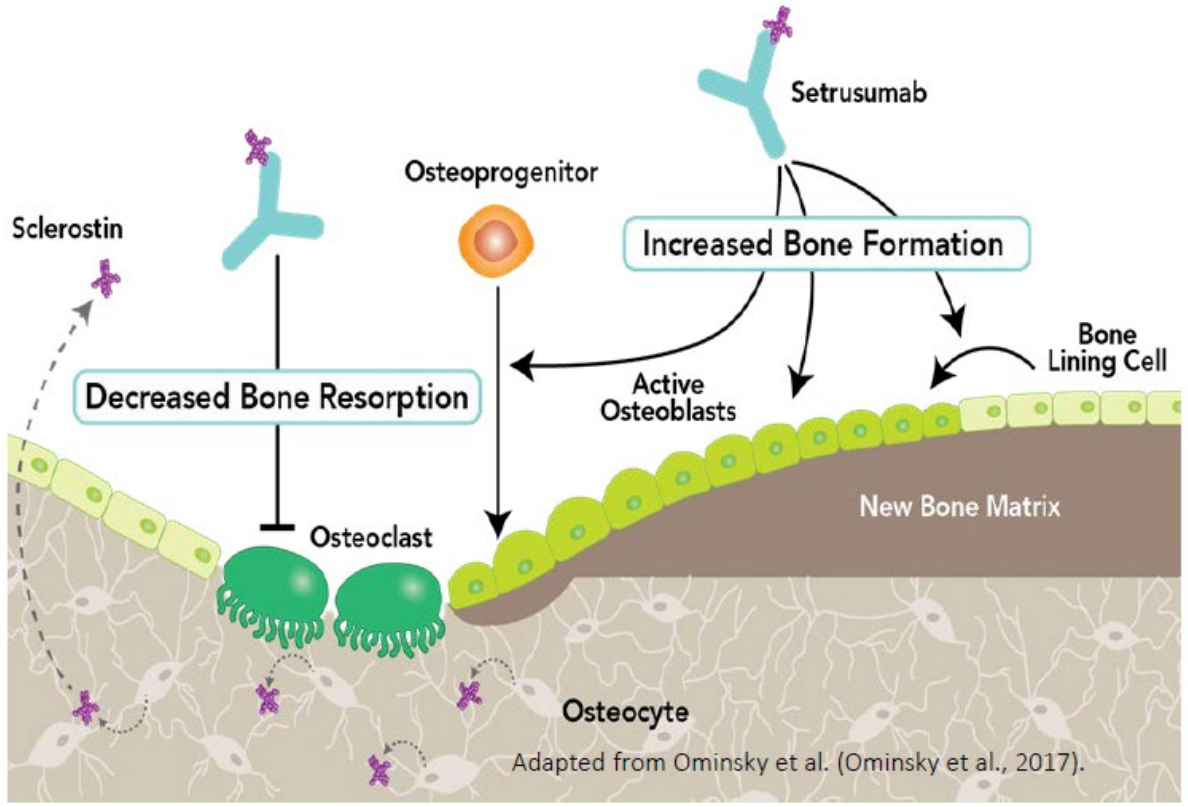
The data presented here are open-label interim data and do not provide definitive conclusions on efficacy or safety

UX143 Setrusumab for Osteogenesis Imperfecta

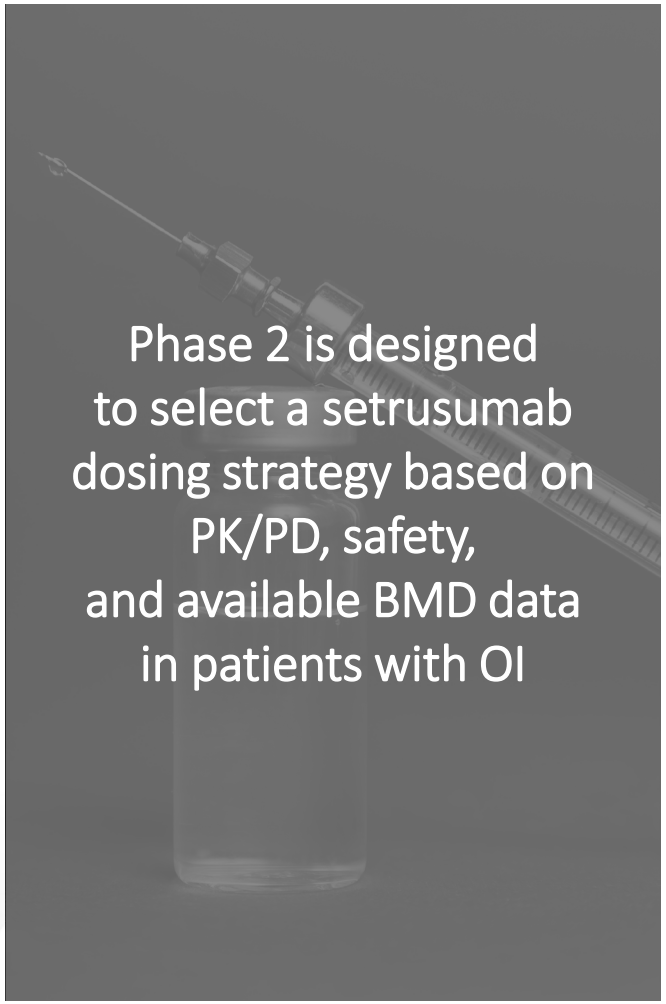
- **OI is a severe bone disease with high unmet need**
  - No approved treatments
  - Bisphosphonates used off label with modest effect
- **Prevalence of three OI types I/III/IV***
  - ~60,000 patients, more than XLH
- **UX143 Setrusumab**
  - Anti-sclerostin fully human antibody candidate
  - Improved bone mass and bone strength in preclinical OI models
- **Status**
  - Ongoing enrollment in pivotal *Orbit* Phase 2/3
  - Ongoing enrollment in supportive *Cosmic* Phase 3
- **Today**
  - Presentation of 6 months of bone mineral density and fracture data from the ongoing Phase 2

*prevalence in Ultragenyx commercial regions

Recruiting more bone cells to produce more bone
at the places where strength is needed



UX143-CL301 Phase 2 Study Design



24 patients with OI Types I, III, or IV and a confirmed COL1A1 or COL1A2 mutation enrolled in Phase 2

Phase 2 includes patients 5 to < 26 years of age and intended to enroll 12 patients with body weight ≤ 30 kg

Randomization ratio 1:1 to 20 mg/kg or 40 mg/kg of setrusumab administered IV QM

Randomization stratified by number of fractures in the previous 2 years (≤ 3 vs > 3) and age group

67% Reduction in Fracture Rate After at Least 6 Months of Treatment

Associated with continuous and meaningful improvements in bone mineral density (BMD)

Much lower incidence of fractures post-treatment vs. pre-treatment

- All patients (n=24) had at least 1 fracture (22/24 were radiographically confirmed) pre-treatment
- 20/24 (83%) had no radiographically confirmed fractures after at least 6 months of treatment

Dramatic reduction in radiographically confirmed fracture rate post treatment

- Median pre-treatment annualized fracture rate (AFR) of 0.72 was reduced to 0.0 (p=0.042) post-treatment

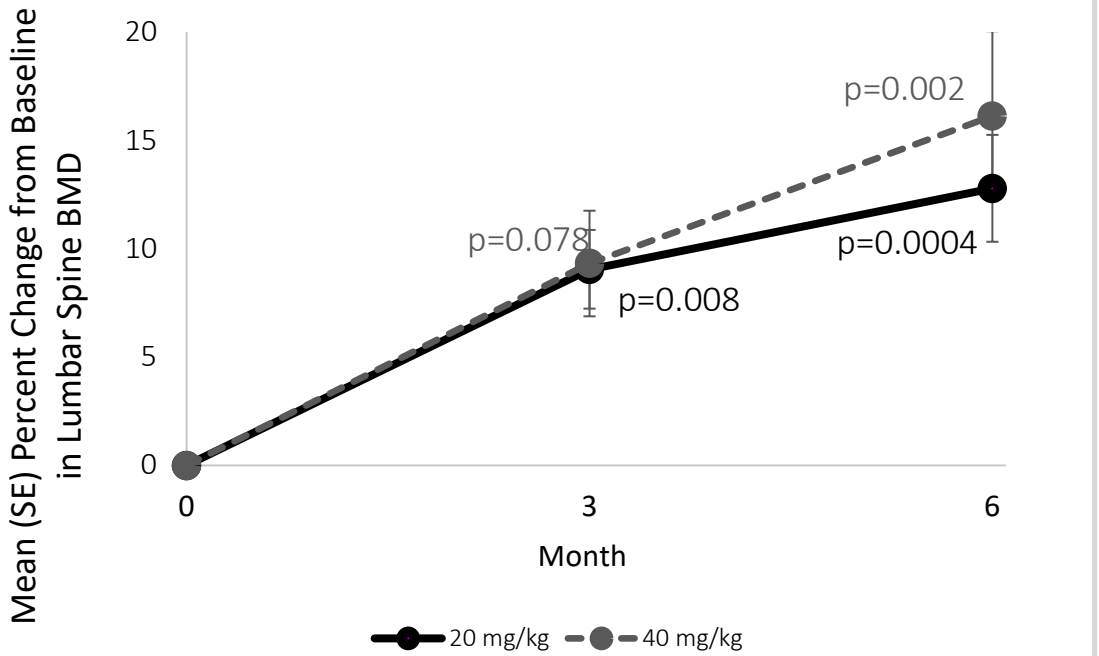
Significantly increased lumbar spine BMD and BMD Z-score from baseline

- 6M BMD % change from baseline of 14.19% (mean, n=19) and Z-score change of +0.85
- Greatest improvements for ages 5 to <12: 19.64 % change from baseline (mean, n=8)

Increase in Lumbar Spine BMD and Z-score Observed at Month 6

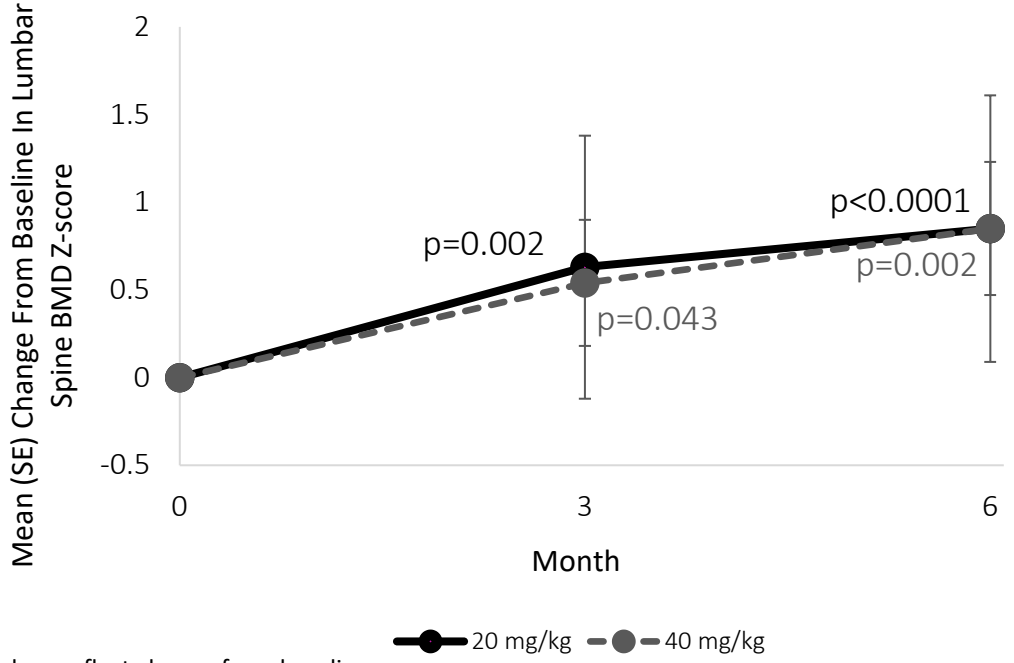
- No significant differences were observed between setrusumab dose groups (p value for comparison >0.05)
  - % change in BMD at M6, 20 mg/kg group=13%, 40 mg/kg group=16%
  - Change in BMD Z-score at M6: both dose groups = +0.85

Lumbar Spine BMD %Change from Baseline



P-values represent change from baseline

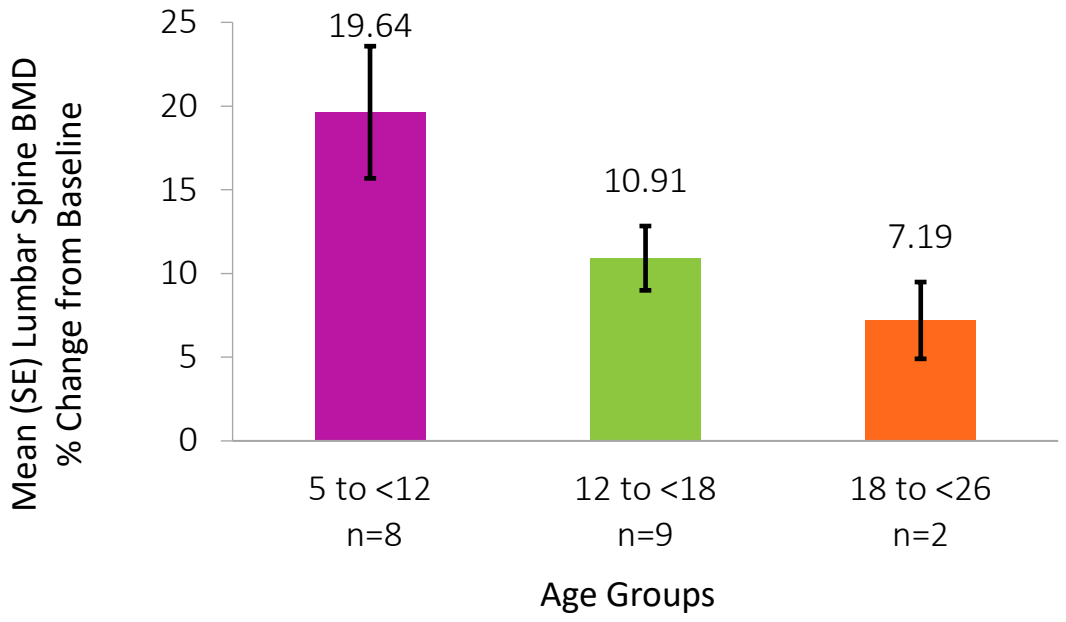
Lumbar Spine BMD Z-Score Change from Baseline



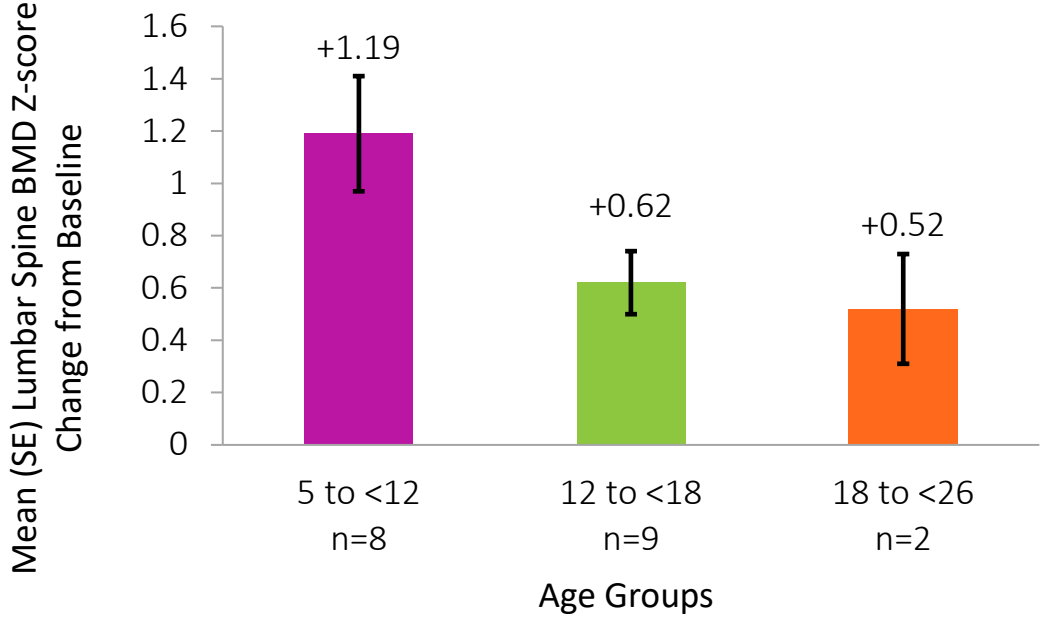
P-values reflect change from baseline

Increase in BMD Observed in all Age Group

Lumbar Spine BMD
Percent Change from Baseline to Month 6



Lumbar Spine BMD Z-score
Change from Baseline to Month 6

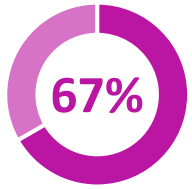


In 5 to <12 year olds, nearly 20% increase in BMD with Z-score change of +1.19

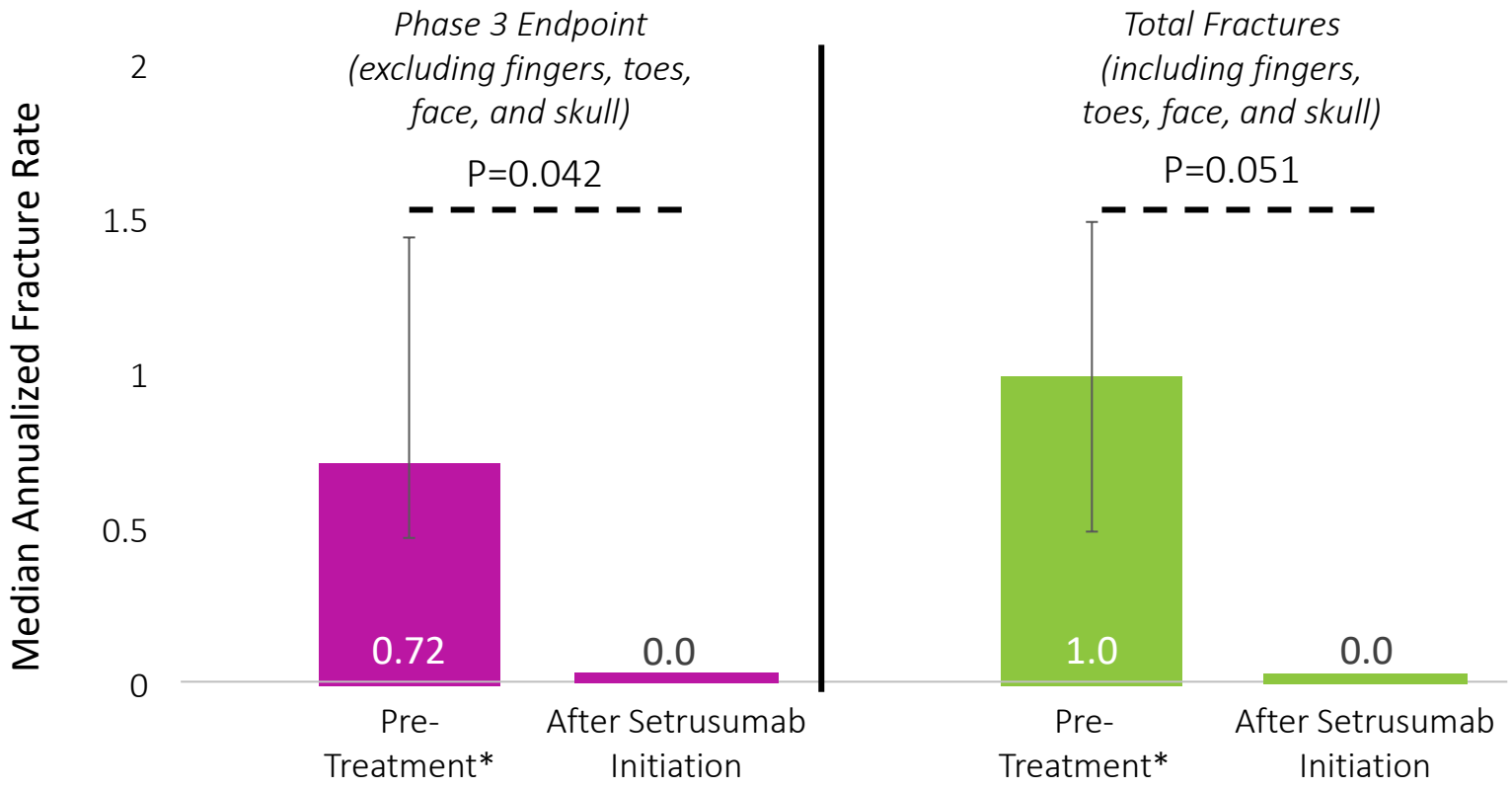
67% Reduction in AFR Observed Post-Treatment with Setrusumab

- Median total confirmed AFR post-treatment was 0.0
- 67% reduction in annualized fracture rate, excluding fingers, toes, face, and skull
  - Mean treatment duration of 9 months (6 - 16 months) in 24 patients as of data cut

$$\frac{\text{median(AFR post - AFR pre)}}{\text{median(AFR pre)}} = \frac{-0.48}{0.72} =$$



Radiographically Confirmed Fractures

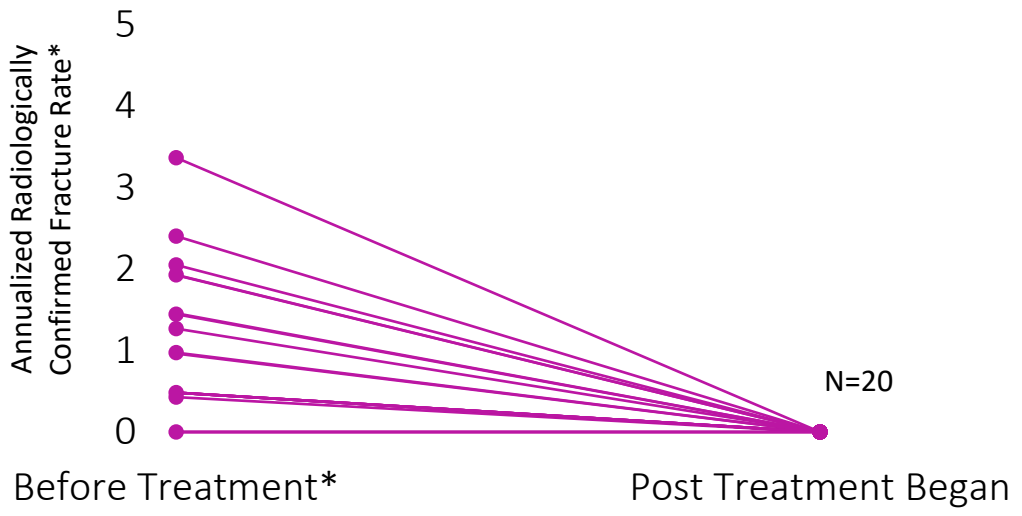


*Pre-Treatment period includes fractures in the two years before screening based on medical record review and patient report, and fractures between screening and first dose

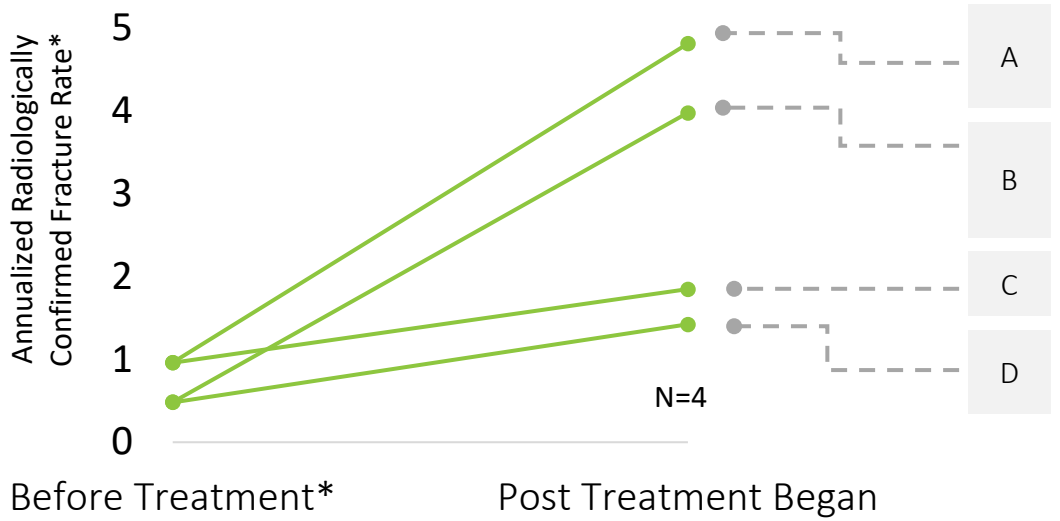
20/24 Patients Did Not Have Radiographically Confirmed Fractures After Treatment with Setrusumab

Radiographically Confirmed Fractures

Patients without Confirmed Fractures by Month 6



Patients with Confirmed Fractures by Month 6

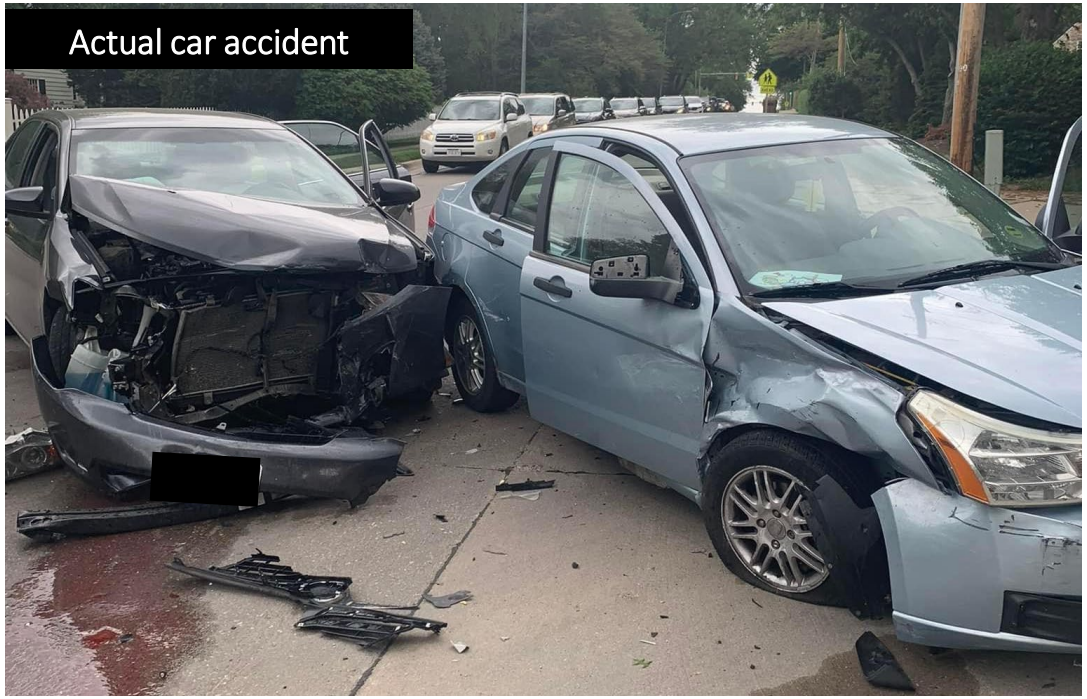


- 20/24 patients had no radiographically confirmed fractures despite meaningful historical fracture rates

A. Slipped on ice (2 fractures) [at 1.6 mo]; stubbed toe [at 6 mo]
B. Fell off tricycle (2 fractures) [at 5.5 mo]
C. Bending over in bed [at 1.1 mo]
D. Tripped and fell on hand [at 7.7 mo]

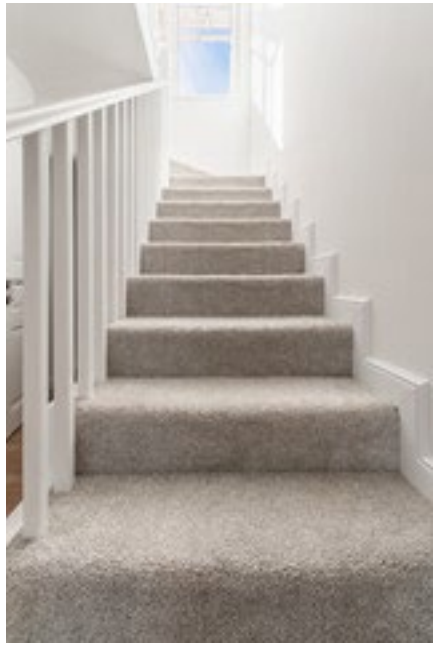
Some Major Traumatic Events Occurred Without Fractures

High-impact motor vehicle accident at Month 5.5 of treatment resulted in **no fractures**

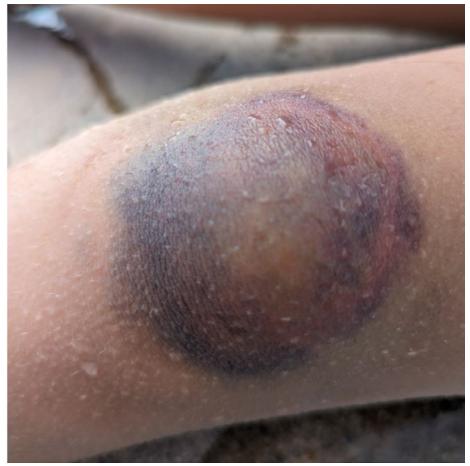


Patient “walked away unscathed” from accident totaling both cars

Patient fell down a flight of stairs at Month 4.7 of treatment **Evaluated: No fractures**



(Not the actual stairs)



Patient’s bruised knee after fall

Patient with Increased Mobility After 17 Months on Study

6-year-old male with Type IV OI

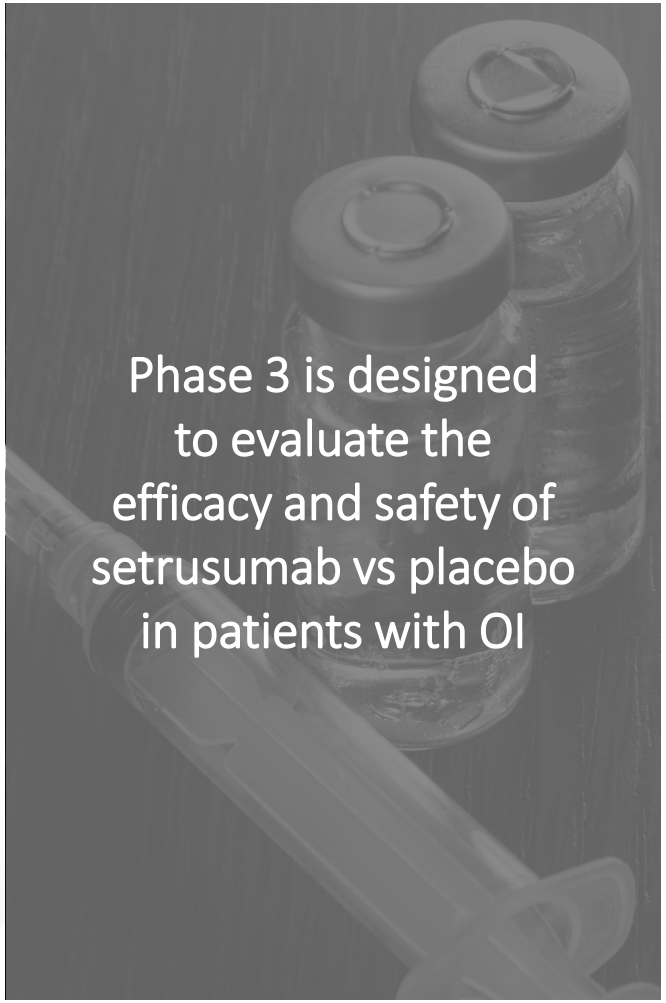
Interim Safety Evaluation

No treatment-related SAEs	No unexpected adverse events or safety concerns	No patient discontinued treatment for any adverse event	No drug-related hypersensitivity reactions

Most Common Adverse Events Reported	Phase 2 Patients (N=24)
Infusion-related event (not hypersensitivity)	7 (29%)
Headache	3 (13%)
Abdominal discomfort	1 (4%)
Infusion site pain	1 (4%)
Bone pain	1 (4%)
Upper respiratory tract infection	1 (4%)

Safety update as of August 04, 2023

Orbit: CL301 Phase 3



Approximately **195 patients** 5 to < 26 years of age with OI Types I, III, or IV and a confirmed *COL1A1* or *COL1A2* mutation will be enrolled in Phase 3.

Phase 3 patients will be randomized 2:1 to receive setrusumab (at the selected dosing strategy from the Phase 2 analysis) or placebo administered IV QM.

Primary efficacy endpoint: **annualized clinical fracture rate**

The Phase 3 treatment period is double-blind with respect to patients, Investigators and Ultragenyx.

Conclusions and Next Steps

67% reduction in annualized fracture rate over 6 months

- Significantly increased lumbar spine BMD and BMD Z-score from baseline
- Improvements in bone strength without having to directly correct collagen defects

Higher pre-treatment fracture rate and larger treatment effect size could enable a faster path to study readout

- *Orbit* study updates in process that may accelerate timeline pending health authority agreement
- Two interim analyses added to statistical analysis plan to evaluate for overwhelming efficacy

Actively enrolling *Orbit* and *Cosmic* Phase 3 studies

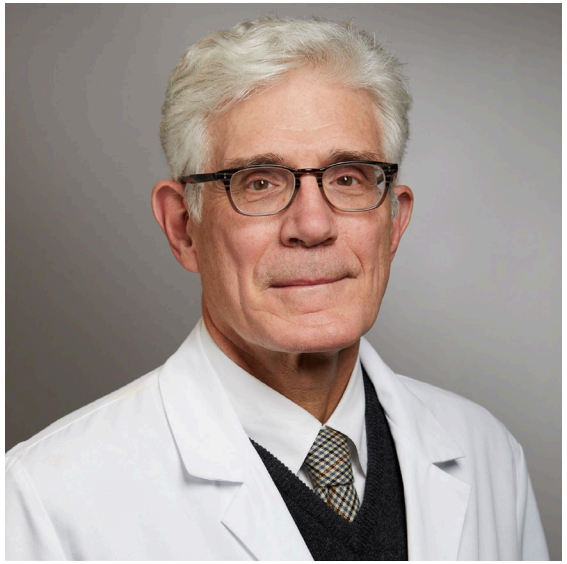
- *Orbit* is enrolling at 50 sites in 12 countries
- *Cosmic* is enrolling at 22 sites in 8 countries

Expect further Phase 2 data update in 2024

Osteogenesis Imperfecta KOL Panel

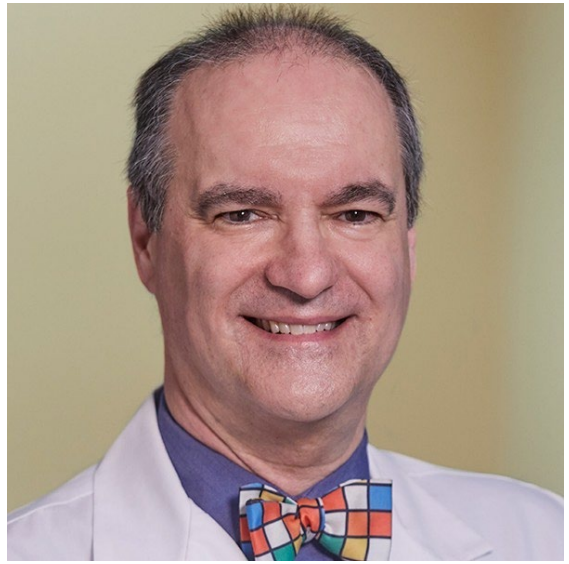
- Heather Byers, M.D.
  Ultragenyx Lead Physician, UX143

Osteogenesis Imperfecta KOL Panel



Thomas Carpenter, M.D.

- Professor of Pediatrics (Endocrinology) and of Orthopaedics and Rehabilitation and Clinical Professor of Nursing
- Director, Yale Center for X-Linked Hypophosphatemia
- Principal investigator for UX143 Phase 3 program



Gary Gottesman, M.D.

- Professor of Pediatrics and Medicine, Washington University School of Medicine in St. Louis
- Previously, Medical Geneticist in the Center for Metabolic Bone Disease and Molecular Research at Shriners Hospital
- Principal investigator for UX143 Phase 3 program

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

- Emil Kakkis, M.D., Ph.D.
  President and Chief Executive Officer

Disclaimers

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

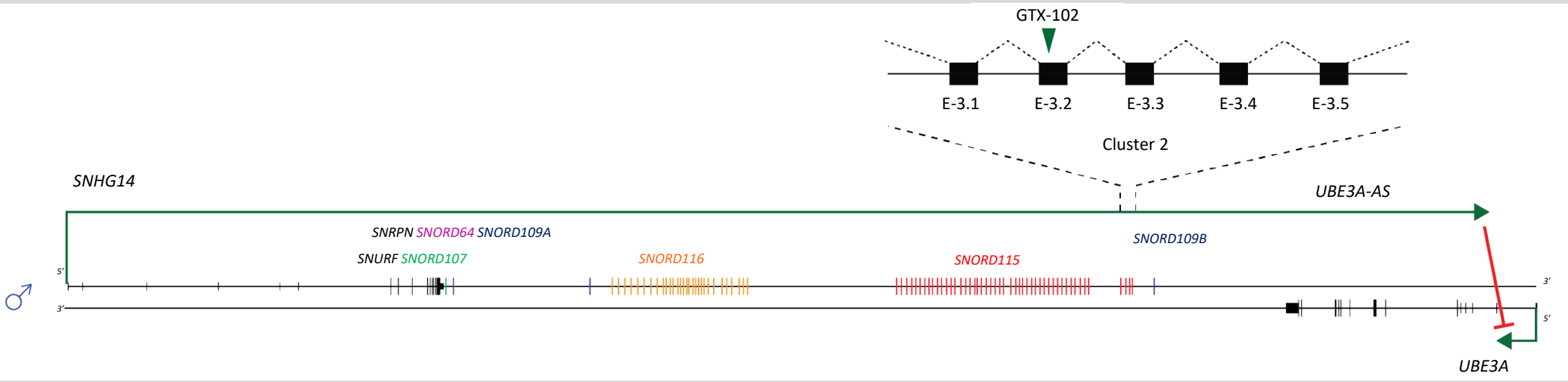
The data presented here are open-label interim data and do not provide definitive conclusions on efficacy or safety

GTX-102 for Angelman Syndrome (AS)

Antisense oligonucleotide (ASO) activates UBE3A

- Devastating neurodevelopmental disorder
- Prevalence*: ~60,000
- No approved treatments
- Phase 1/2: enrolling and dosing expansion cohorts
- Targeting highly conserved region across multiple species

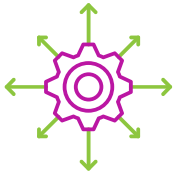
**Prevalence in commercially accessible geographies*



GTX-102 Phase 2 Update

Multiple domains improved in Loading and Maintenance Phase compared to natural history, where available

Clinical changes associated with quantitative changes in EEG



Extension cohorts and redosed patients have demonstrated clinically meaningful changes in quantitative scores and in emerging developmental gains as reported by caregivers

Discuss video examples of improvements

Key Angelman Syndrome Domain Evaluations

Domains	Evaluation	Natural History Comparison[1]
Cognition	Bayley-4	Yes
Sleep	Angelman Severity Assessment for Sleep (ASA)	--
Receptive Communication	Bayley-4	Yes
Behavior	ASA for Behavior	--
Gross Motor	Bayley-4	Yes
Overall	ASA for Overall	--

1: Not available for all endpoints and shown as representative comparisons

Angelman Severity Assessment (ASA) Rating Scales

ASA rate 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

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

A decrease in score represents an improvement or lessening severity

Interim Phase 2 Data on Extension Cohorts

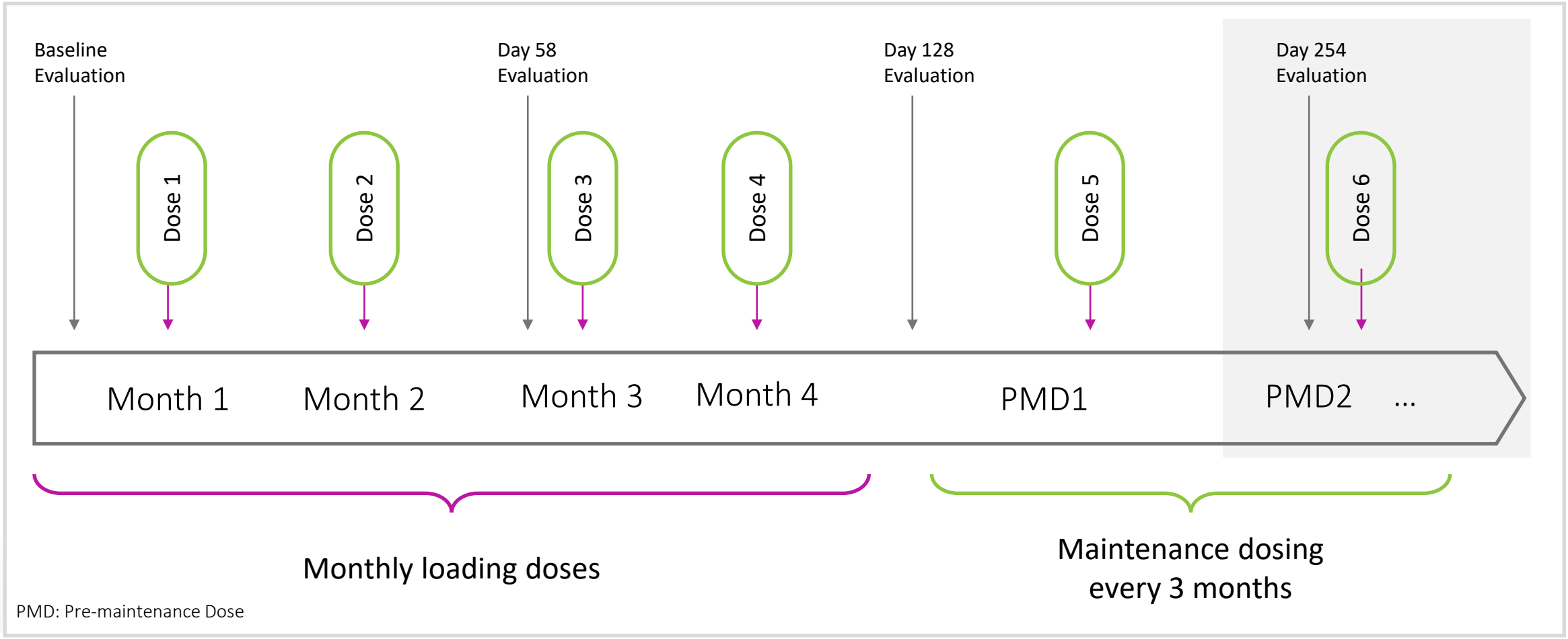
Cohorts 4-7
Enrolled outside of the U.S.
n=15 patients

Loading doses from 3.3 - 7.5 mg
Maintenance from 10 - 14 mg

11 patients on therapy greater than 12 months, with the longest approaching 2 years

No additional events of lower extremity weakness or other safety signals

Study Dosing Schematic for GTX-102
Loading phase through Day 254



PMD: Pre-maintenance Dose

Natural History as Comparator for GTX-102 Phase 2 Data

Comparable to GTX-102 study population age and genotype

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

Bayley-4 Cognition, Receptive Communication, and Gross Motor scores were compared across GTX-102 treated and natural history patients[2]

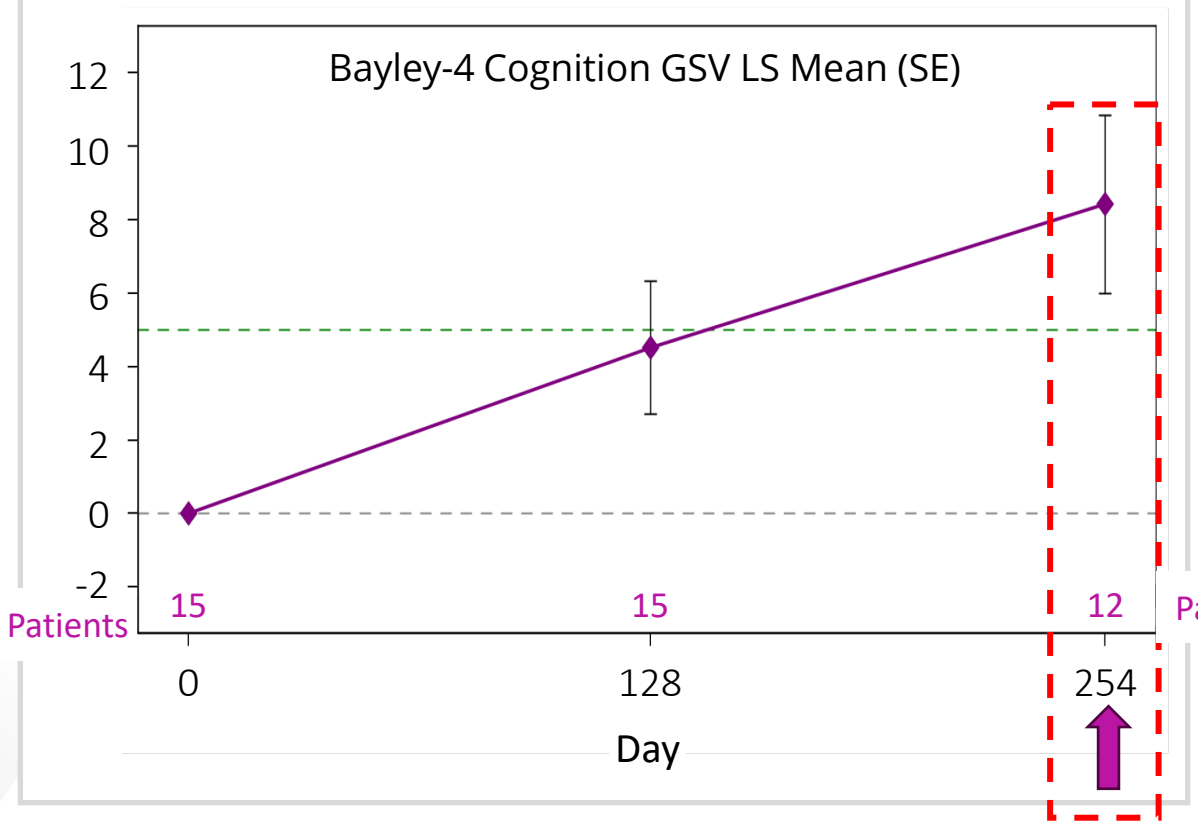
- 64 patients with deletion-type AS
- Ages 4 to 17 years
- At least 2 consecutive assessments

[1]Sadhwani et al., 2021; Keute et al., 2021; Gentile et al., 2010

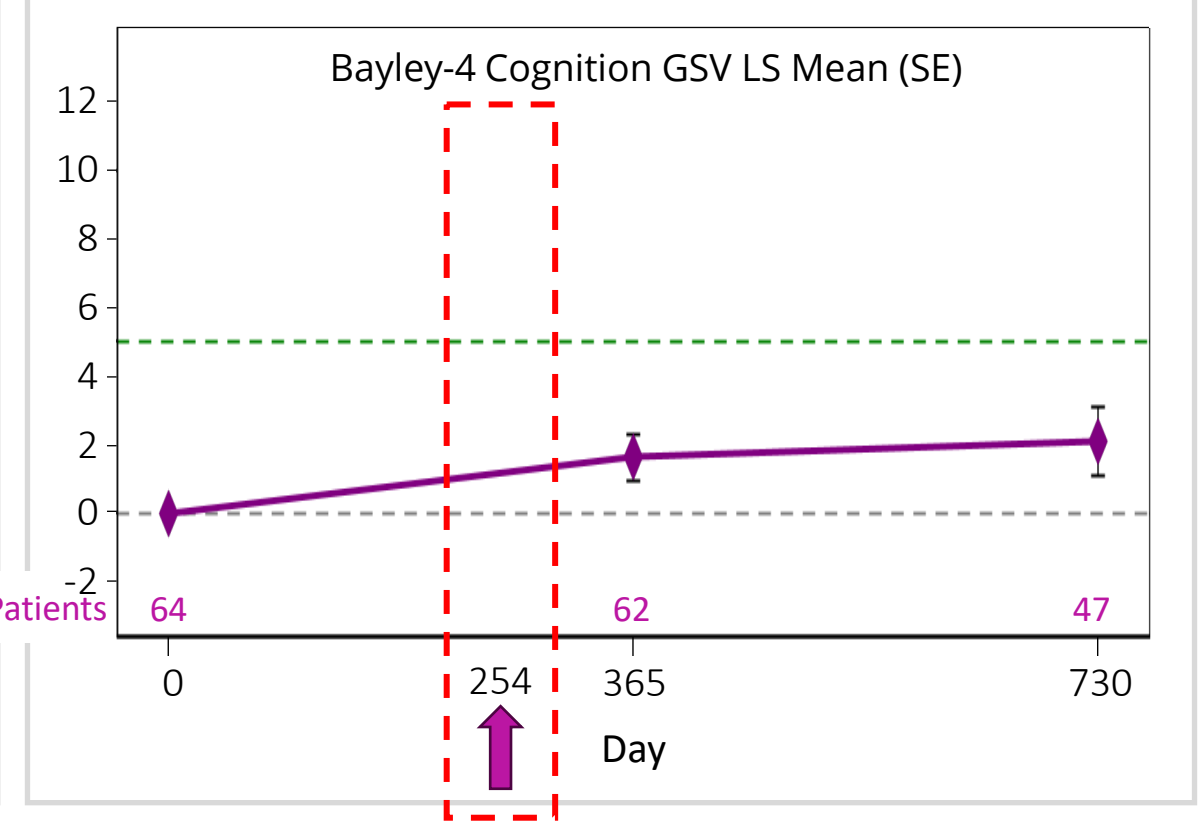
[2]Linking Angelman and Dup15q Data for Expanded Research (LADDER)

Cognition by Bayley-4 Improved Rapidly Compared to Natural History

GTX-102 treated patients showed positive response at Day 254



Natural history through Day 730

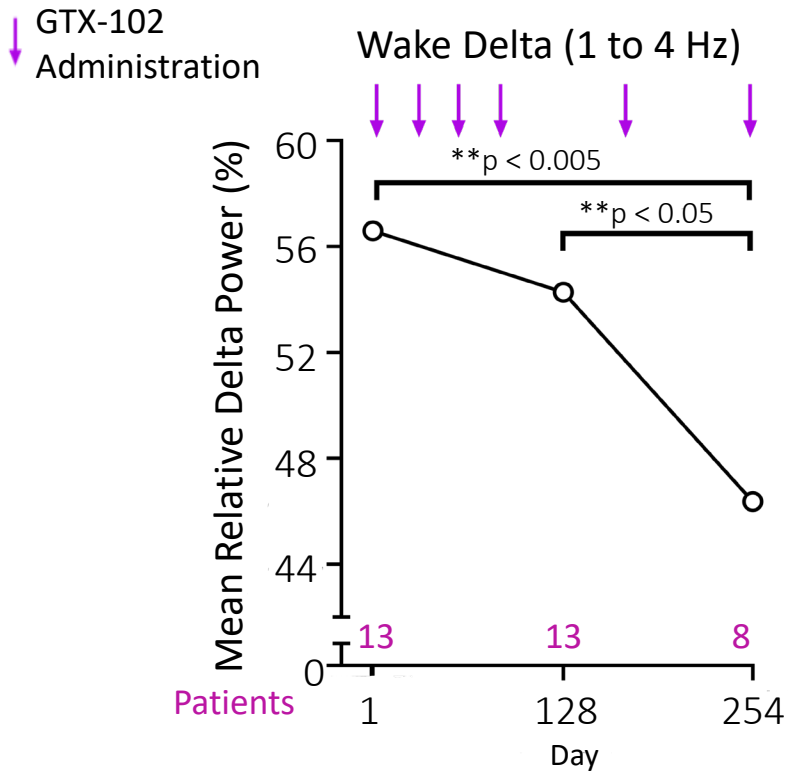


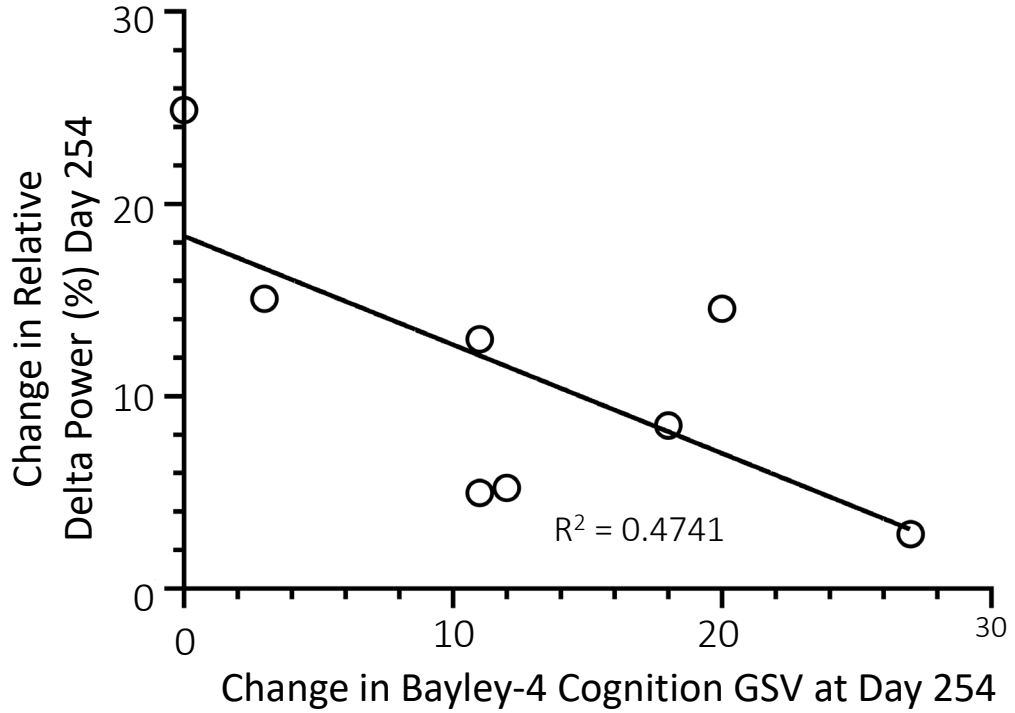
Response threshold of ≥5 based on Bayley-4 administration manual

The estimated values are from a GEE model which includes all available data as the dependent variable and baseline age as a covariate, with exchangeable correlation structure

EEG Showed Rapid Positive Change for Patients on GTX-102

Reduction in delta relative power while awake correlated with improvement in Bayley-4 Cognition scores



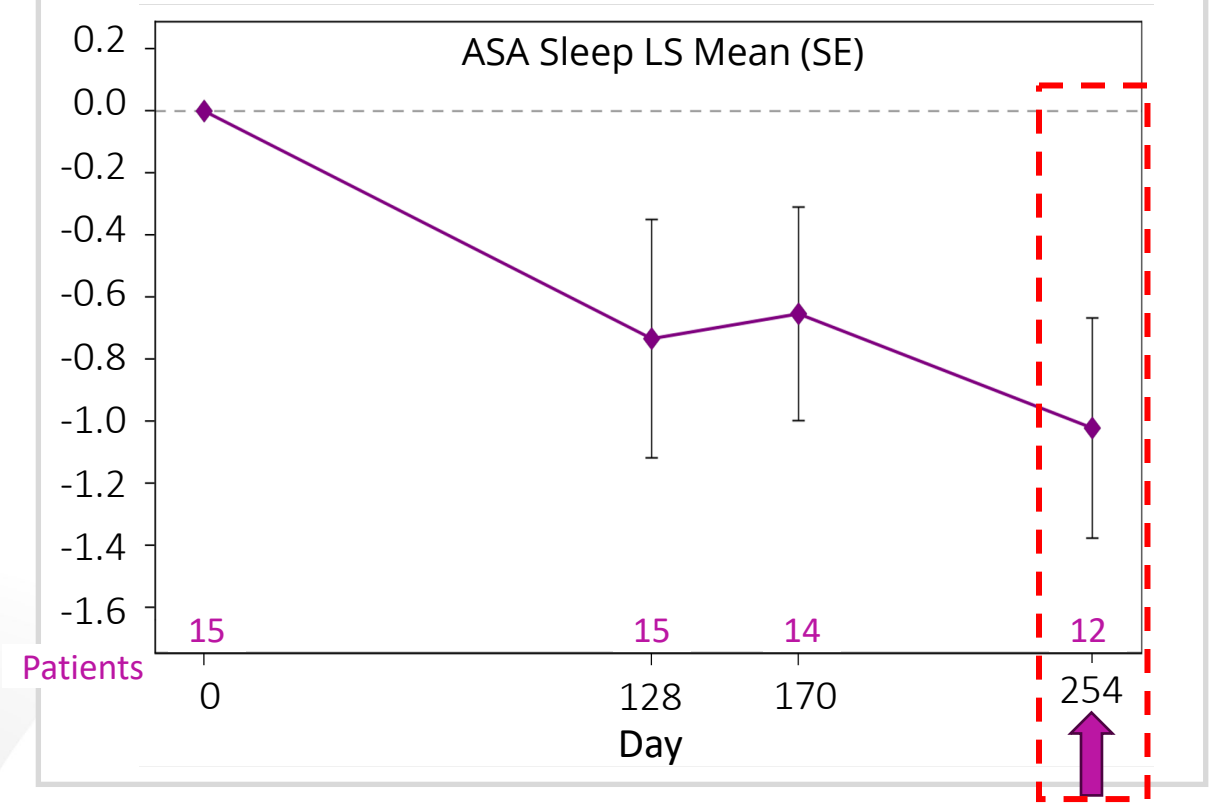


Natural History EEG data shows pathologically increased relative delta power (den Bakker et al., 2018)

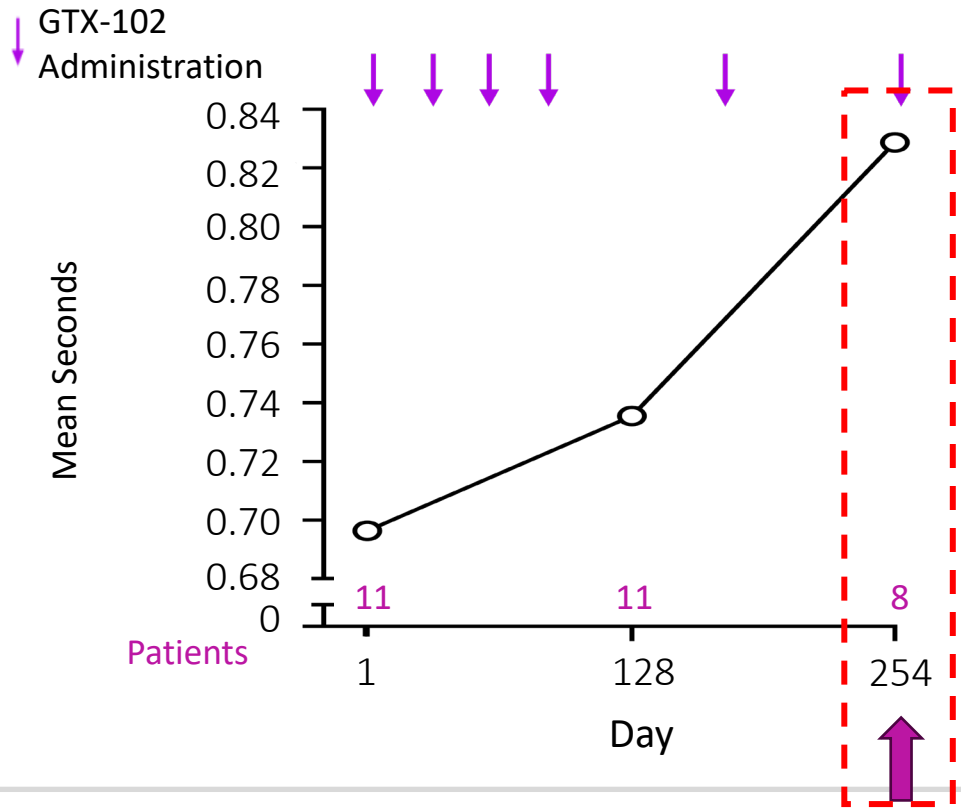
Relative delta power reliably predicts cognitive function, as assessed by the Bayley (Ostrowski et al., 2021)

Sleep by Angelman Severity Assessment (ASA) Scores Improved in Parallel with Increased Sleep Spindle Duration on EEG

ASA-Sleep improved for GTX-102 treated patients through Day 254



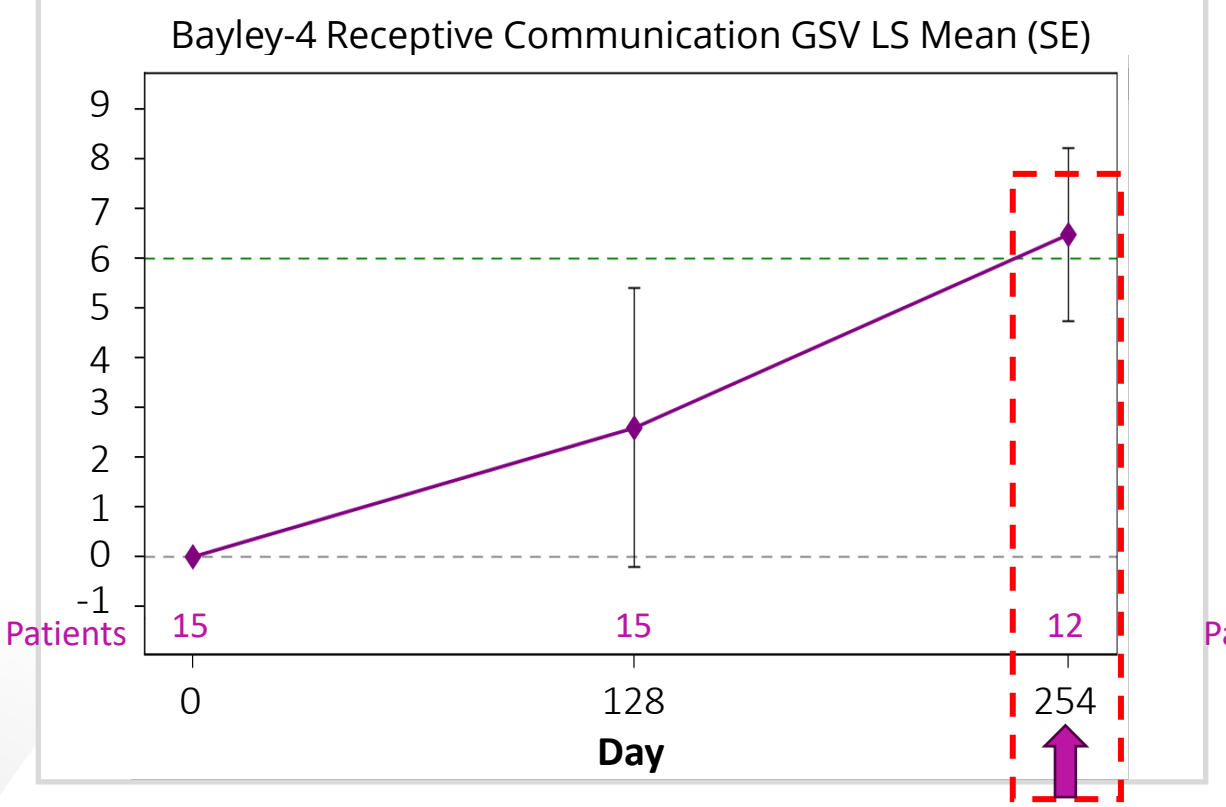
EEG showed increased sleep spindle duration through Day 254



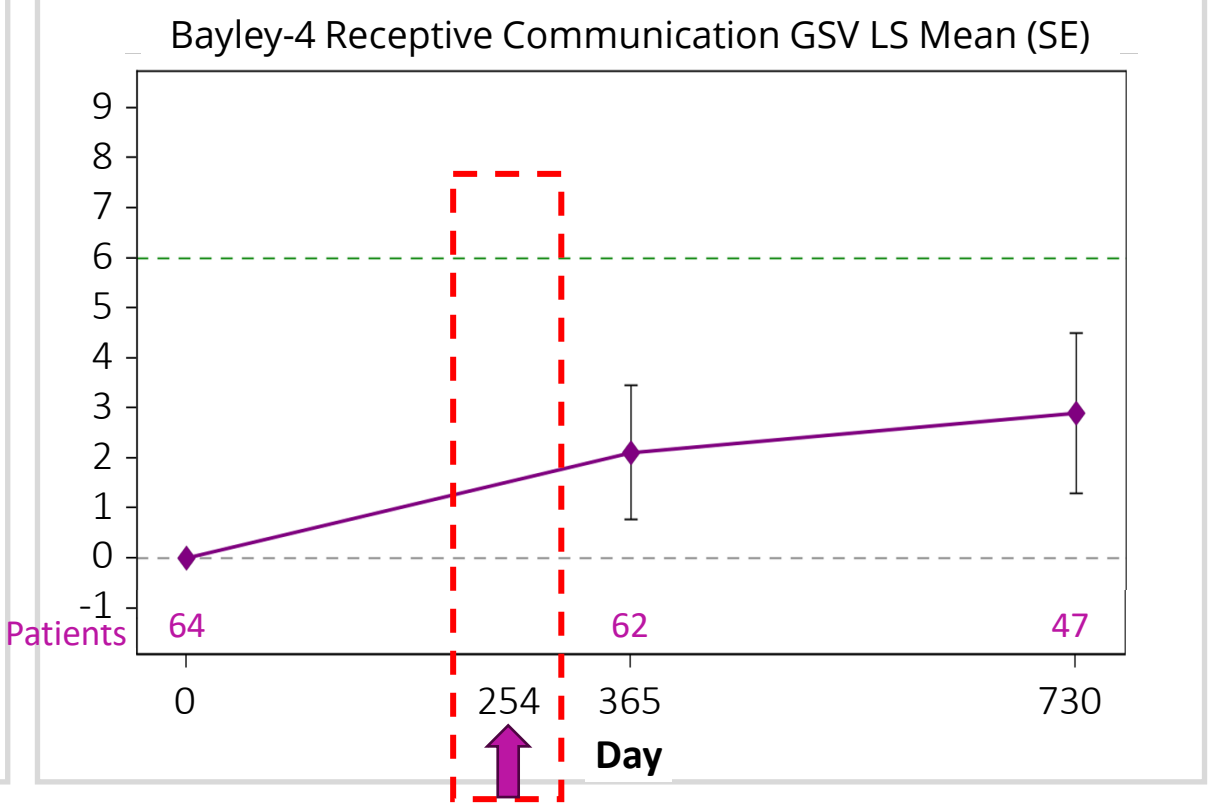
den Bakker H et al. (2018) *Mol Autism* 9: 32.
Ostrowski LM et al. (2021). *Ann Clin Transl Neurol* 8(7): 1433-1445.

Receptive Communication by Bayley-4 Improved Rapidly Compared to Natural History

GTX-102 treated patients showed positive response at Day 254



Compared with natural history at Day 730

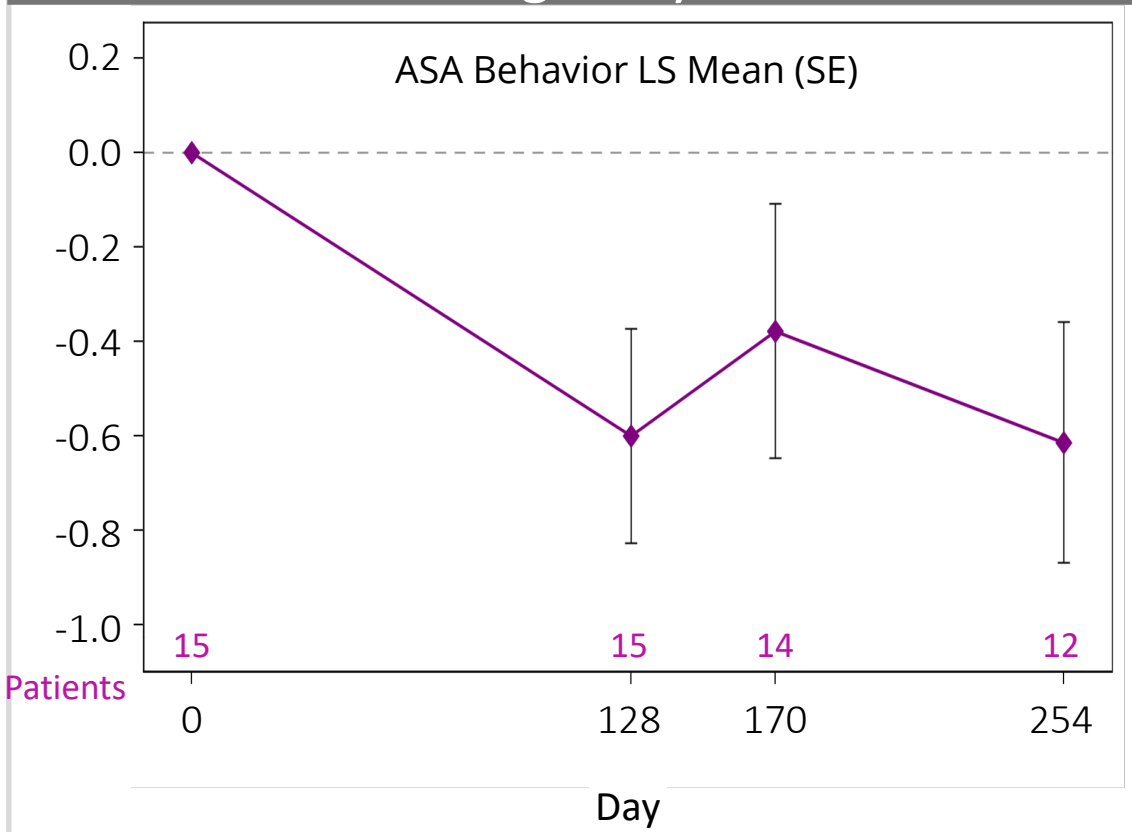


Response threshold of ≥6 based on Bayley-4 administration manual.

The estimated values are from a GEE model which includes all available data as the dependent variable and baseline age as a covariate, with exchangeable correlation structure.

Behavior by Angelman Severity Assessment (ASA) Showed Clinically Meaningful Changes

ASA-Behavior improved with GTX-102 through Day 254



Behavior Improvements anchored by changes in:

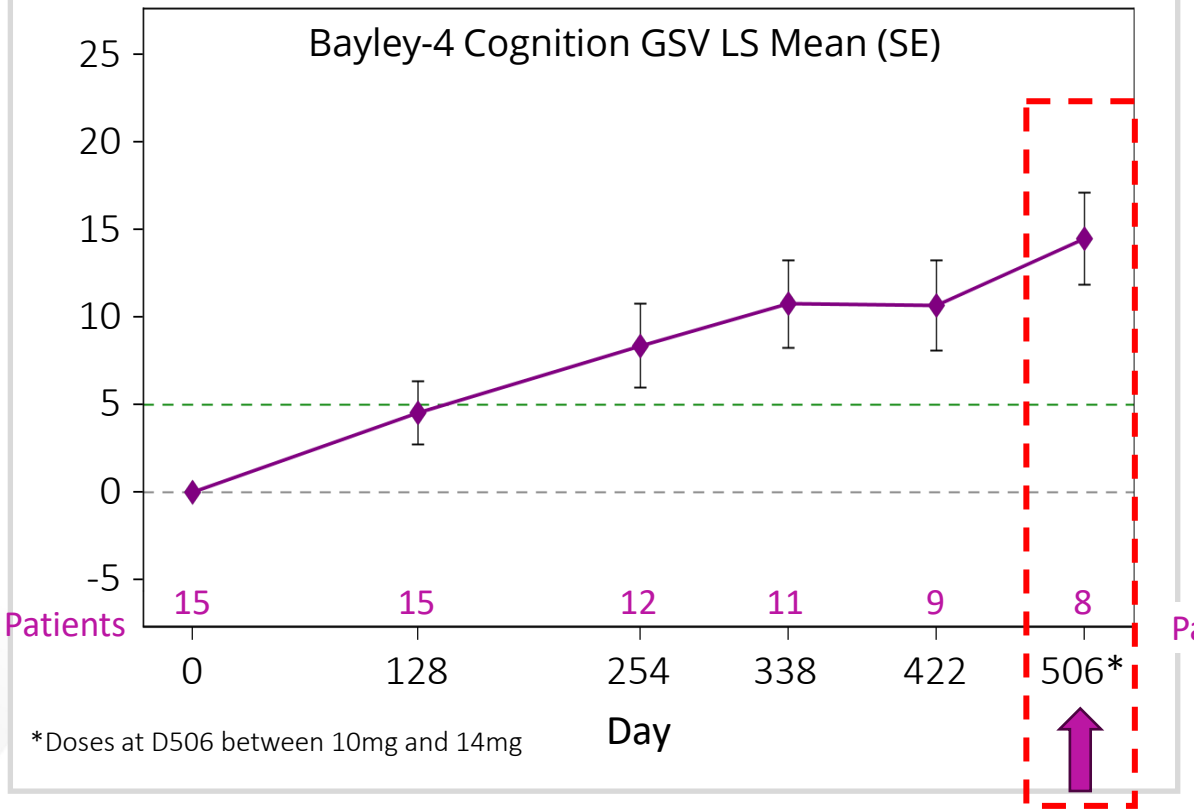
- Focus/Overexcitability
- Maladaptive Behavior
- Transitions
- Impulsivity

The estimated values are from a GEE model which includes all available data as the dependent variable and baseline age as a covariate, with exchangeable correlation structure.

GTX-102 Maintenance Phase

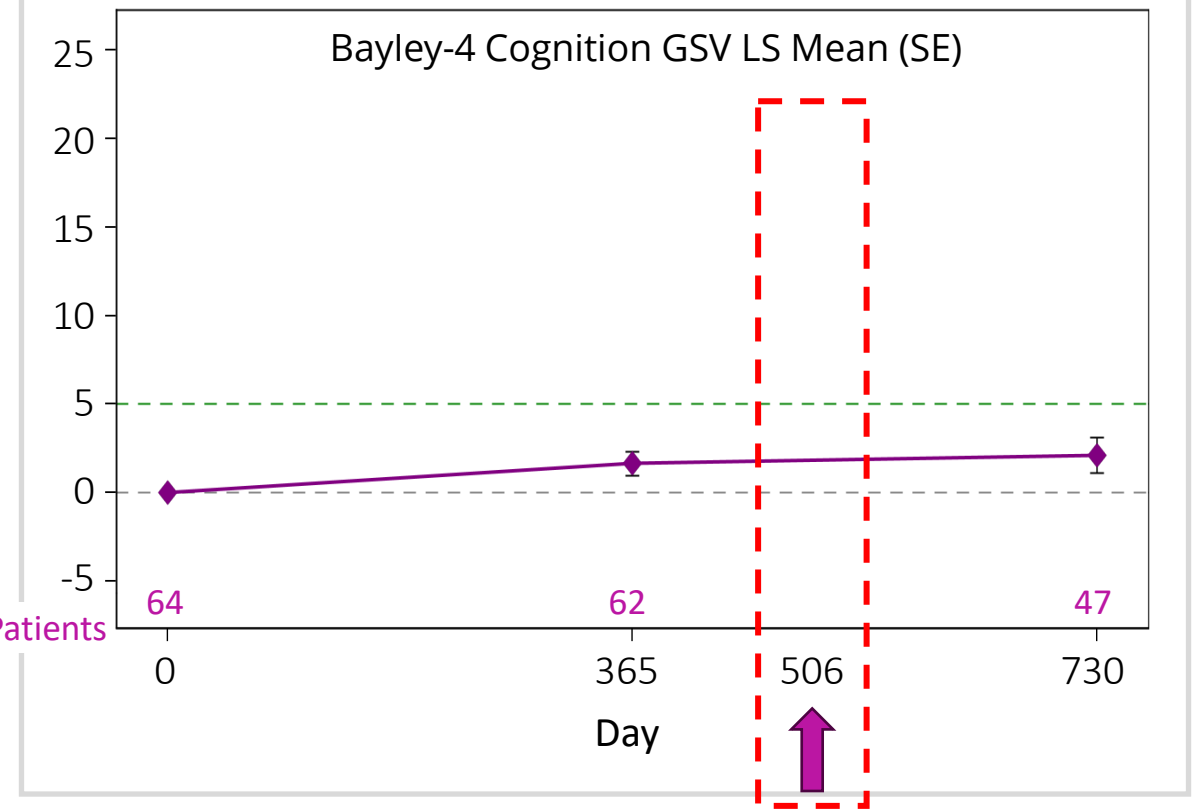
Cognition by Bayley-4 Continued to Improve During Maintenance Phase

GTX-102 treated patients showed positive response through Day 506



*Doses at D506 between 10mg and 14mg

Natural history through Day 730

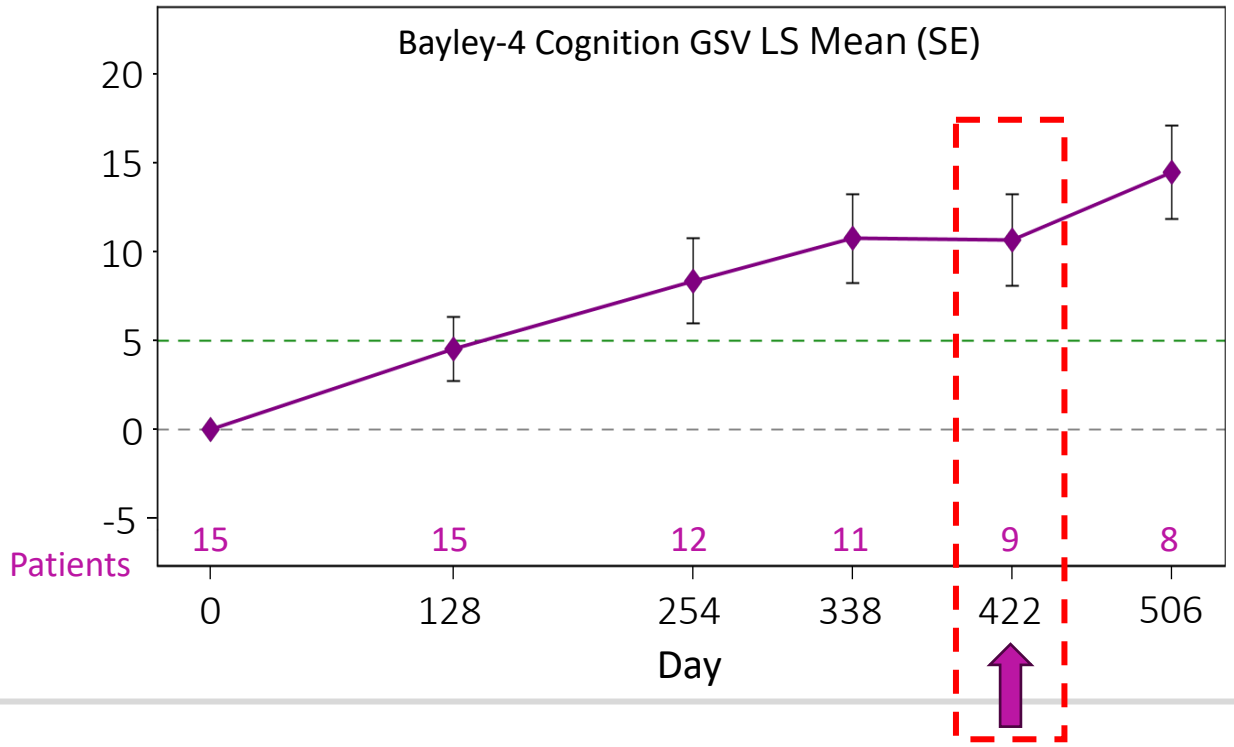


Response threshold of ≥5 based on Bayley-4 administration manual.

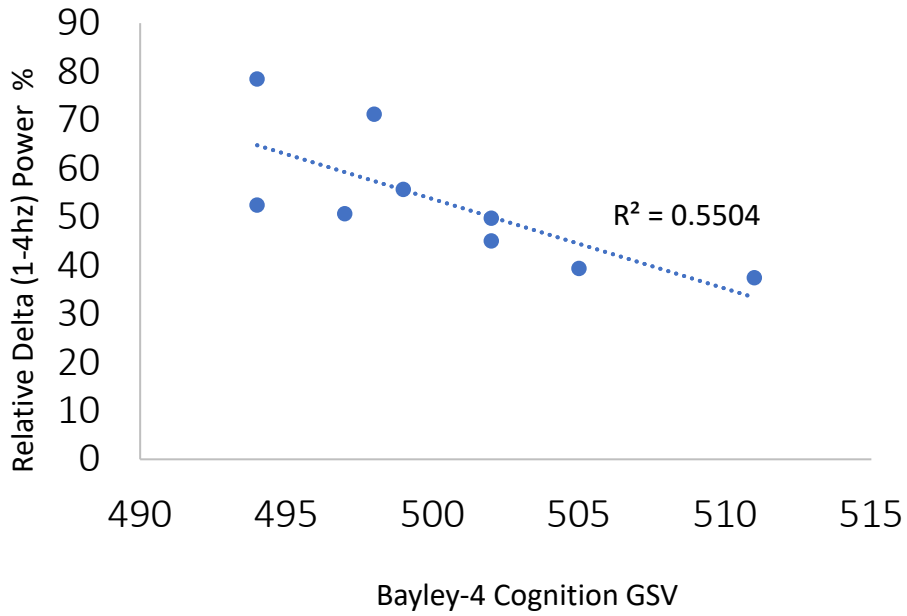
The estimated values are from a GEE model which includes all available data as the dependent variable and baseline age as a covariate, with exchangeable correlation structure.

Cognition by Bayley-4 Showed Rapid and Sustained Improvement Correlating with Positive EEG Change

GTX-102 treated patients showed positive response that continues after Day 422



Relative delta power compared to Bayley Cognition at Day 422

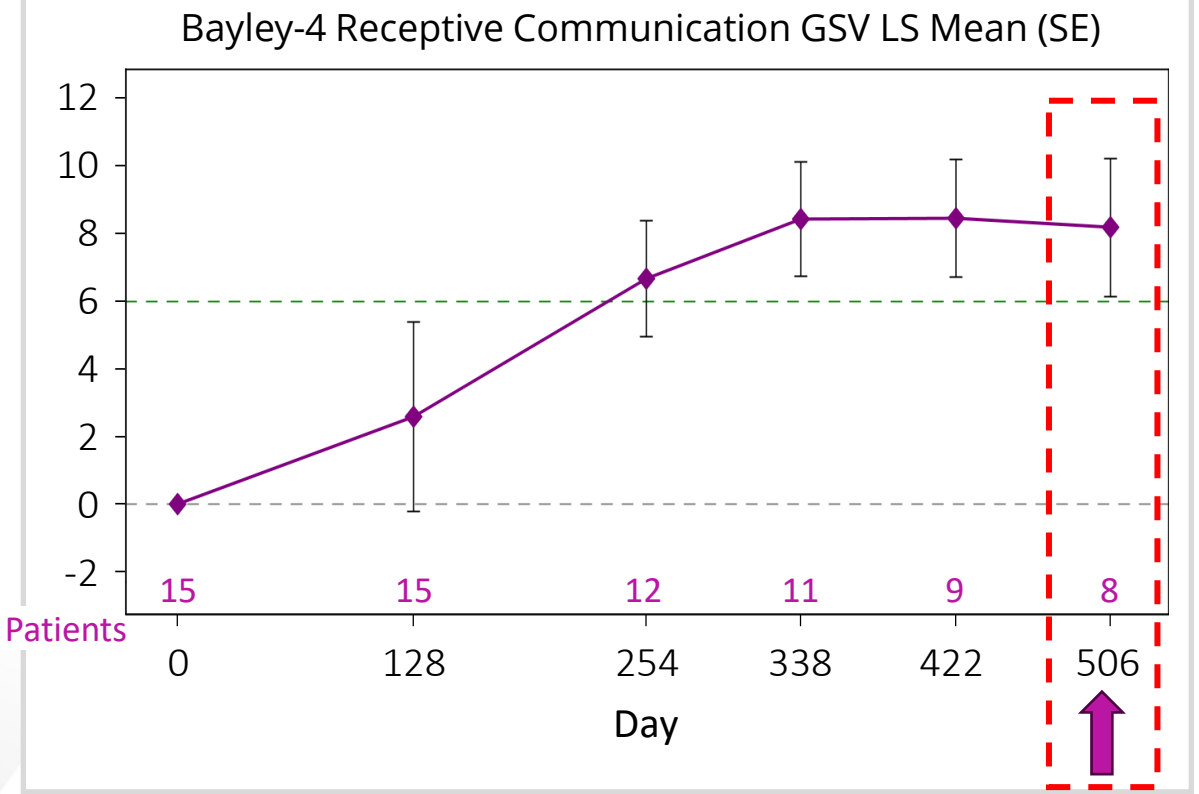


Relative delta power reliably predicts cognitive function, as assessed by the Bayley, in patients with AS (Ostrowski et al., 2021)

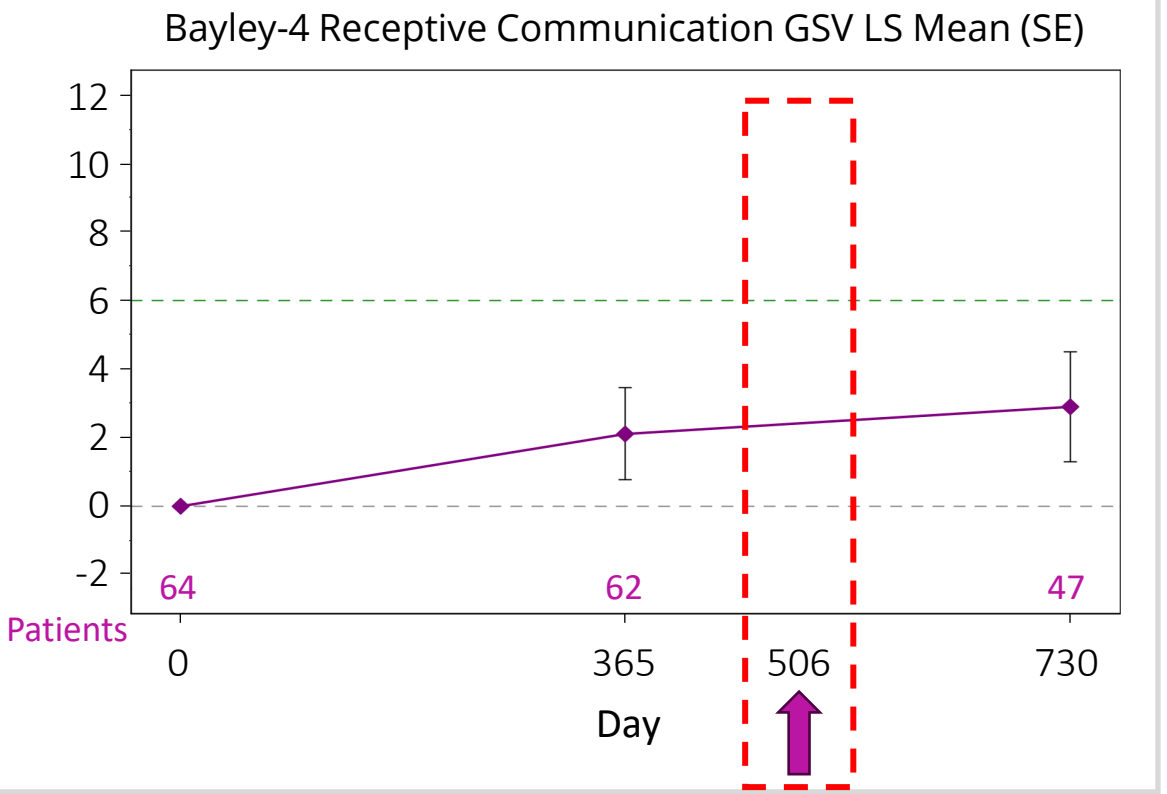
den Bakker H et al. (2018) *Mol Autism* 9: 32.
Ostrowski LM et al. (2021). *Ann Clin Transl Neurol* 8(7): 1433-1445.

Receptive Communication by Bayley-4 Showed Sustained Improvement During Maintenance

Treated patients showed sustained improvements through Day 506



Natural history through Day 730

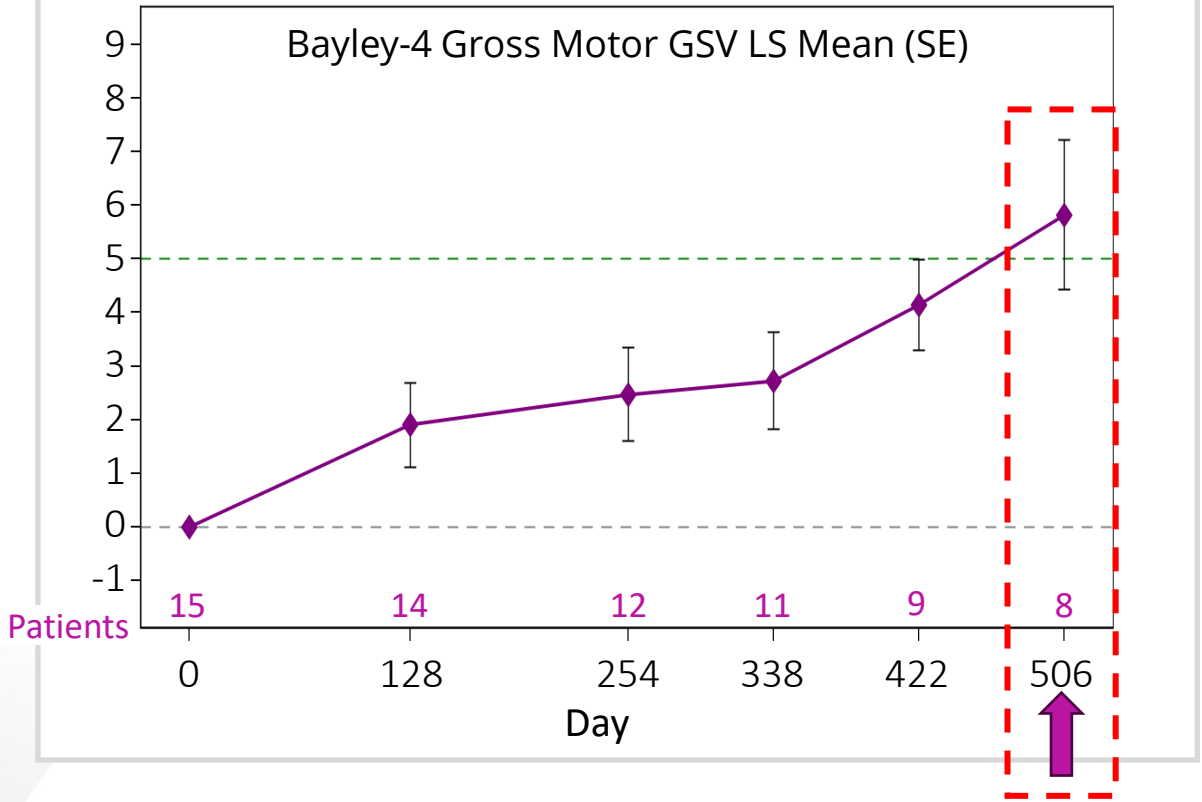


Response threshold of ≥6 based on Bayley-4 administration manual.

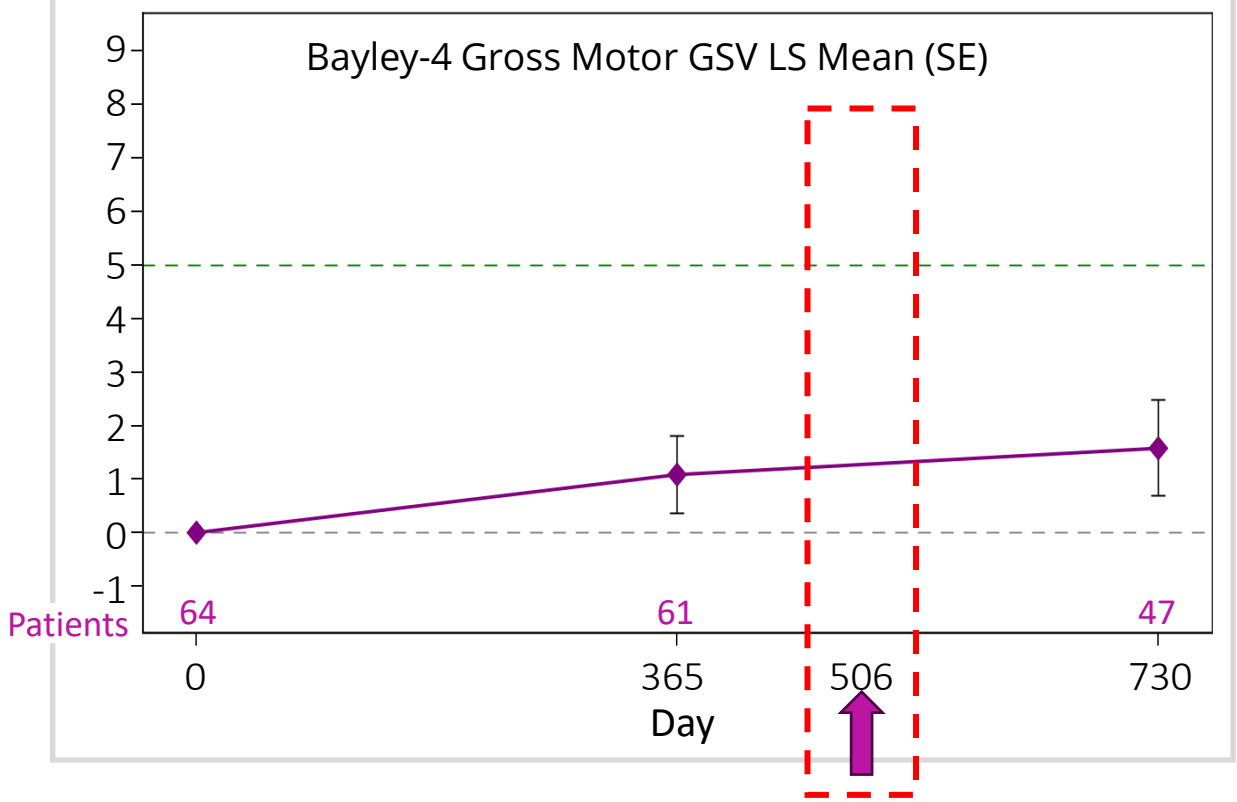
The estimated values are from a GEE model which includes all available data as the dependent variable and baseline age as a covariate, with exchangeable correlation structure.

Gross Motor by Bayley-4 Showed Continued Improvement Compared to Natural History

Gross Motor Bayley-4 showed steady improvement through Day 506



Natural history through Day 730

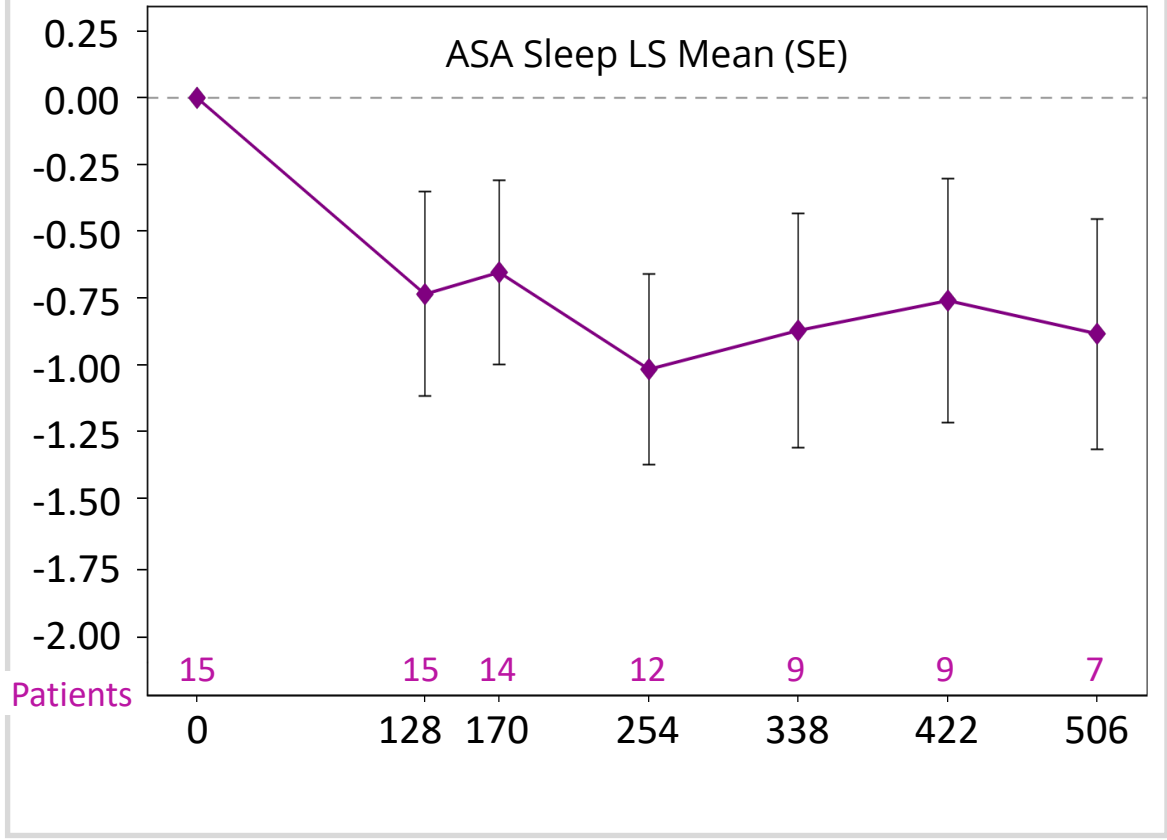


Response threshold of ≥5 based on Bayley-4 administration manual.

The estimated values are from a GEE model which includes all available data as the dependent variable and baseline age as a covariate, with exchangeable correlation structure.

Sleep by ASA Show Continued Improvement During Maintenance

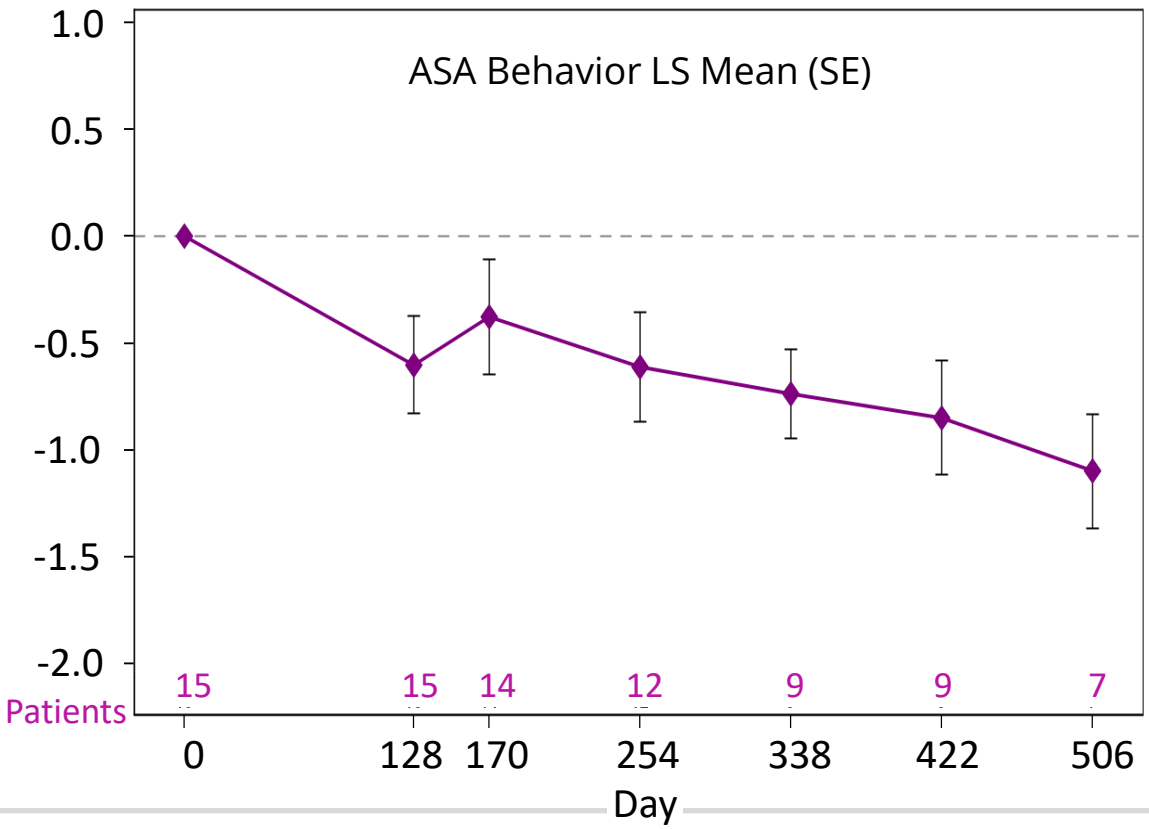
ASA-Sleep improved for patients treated with GTX-102 through Day 506



The estimated values are from a GEE model which includes all available data as the dependent variable and baseline age as a covariate, with exchangeable correlation structure.

Behavior by ASA Showed Continued Improvement During Maintenance

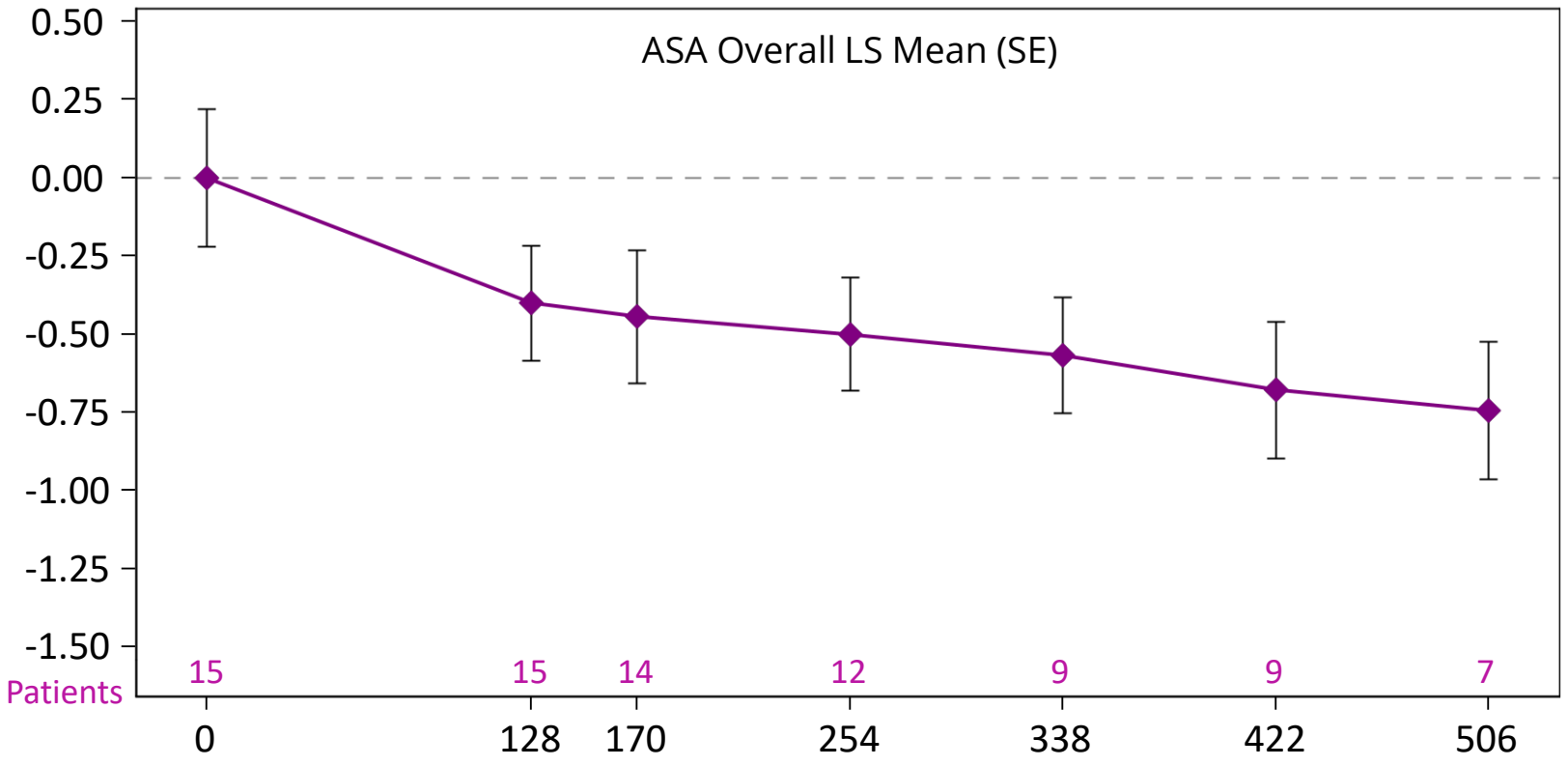
ASA-Behavior severity decreased with GTX-102 through Day 506



The estimated values are from a GEE model which includes all available data as the dependent variable and baseline age as a covariate, with exchangeable correlation structure.

Overall Angelman Severity Assessment (ASA) Score Continued to Improve During Maintenance

ASA-Overall severity decreases for patients treated with GTX-102 through Day 506



The estimated values are from a GEE model which includes all available data as the dependent variable and baseline age as a covariate, with exchangeable correlation structure.

Multi-Domain Responder Index (MDRI) to Tabulate Clinically Meaningful Changes Across Diverse Functional Domains

Choose 4-6 important clinical domains

- Sleep, behavior, receptive communication, gross motor, cognition

Score each patient on each domain

- Change assessed on Minimal Important Difference (MID)
  - >1 MID = +1 ; <1 to >-1 = 0 ; <-1 MID = -1

Only count the significant changes that exceed the MID

- Filter out small changes: no disease/no effect or no measure

Captures more potential points of benefit by assessing the “totality of the data”

Multi-Domain Responder Index (MDRI) Captures Broad Clinical Benefit Across Five Domains in Patients Treated with GTX-102

Patient (n=11)	ASA Sleep	ASA Behavior	Bayley-4 Receptive Comm	Bayley-4 Gross Motor	Bayley-4 Cognition	Total Net Responses*
1	**1**	0	1	0	3	**1**
2	**3**	**2**	**7**	3	**17**	**4**
3	**1**	**1**	**16**	**5**	**20**	**5**
4	0	0	**14**	3	**23**	**2**
5	**1**	**2**	**6**	1	4	**3**
6	**4**	0	**7**	1	1	**2**
7	**2**	**1**	**10**	**9**	**16**	**5**
8	**1**	**1**	**15**	**6**	**25**	**5**
9	2	0	**23**	**7**	**11**	**2**
10	n/a	n/a	2	1	**5**	**1**
11	0	0	3	4	**16**	**1**

Improvement Decline

*Day 338

Minimal Important Difference (MID)

- ASA-Sleep +/- 1
- ASA-Behavior +/- 1
- Bayley-4 Receptive Communication +/- 6
- Bayley-4 Gross Motor +/- 5
- Bayley-4 Cognition +/- 5

Median Total Net Responses +2

Net Responses ≠ 0 $p^{**} = 0.001$

** P-value is from a sign test

Quantitative Analysis of Multiple Domains Showed Meaningful Improvement

Improvements far exceeding natural history

- Cognition
- Receptive Communication
- Gross Motor

Improvements in other important domains

- Sleep
- Behavior

Supportive data from

- EEG delta power and sleep spindle

Powerful change in multiple domains as demonstrated by MDRI

Interim Safety Evaluation including Extension and Expansion Cohorts

No patients with lower extremity weakness events since Nov 2022	3 patients discontinued treatment for non-serious adverse events	No unexpected adverse events or safety concerns	Patients have received up to 11 doses of GTX-102

Most Common Adverse Events Reported	Phase 1/2 Patients (n=58)
Vomiting (anesthesia related)	18 (31%)
Pyrexia (Fever)	10 (17%)
Nasopharyngitis	8 (14%)
Coronavirus infection	6 (10%)
Fall	5 (9%)
Post-lumbar puncture syndrome	5 (9%)

Safety data as of October 3, 2023

Next Steps Phase 2 Expansion Cohort Update

>30 patients enrolled across Cohorts A-E (Expansion Cohorts)

25 sites active across 8 countries

No new lower extremity weakness

Next data update planned for at least 20 patients with 6 months of data by 1H24

Expected FDA interactions in early 1Q24 to discuss Phase 3 endpoints

Panel Discussion on GTX-102 for the Treatment of Angelman Syndrome

- Kemi Olugemo, M.D., FAAN
  Ultragenyx Lead Physician, GTX-102
- Elizabeth Berry-Kravis, M.D., Ph.D.
  Professor, Dept of Pediatrics
  Rush University Medical Center
  Principal Investigator for GTX-102 Phase 1/2

ultragenyx

Redosing of Three Original Patients

Emergence of New Developmental Skills Gained, Lost and Regained

	Patient A			Patient B			Patient C		
	Init dose	Off-tx	Re-dose	Init dose	Off-tx	Re-dose	Init dose	Off-tx	Re-dose
Receptive Communication									
Responds to name	*No issue*								
Follows 1-step directions									
Follows 2-step or complex directions									
Expressive Communication									
Babbles/consonant sounds									
Communicate wants or needs (gesture/device)									
Identifies or requests object(s)									
First word/approximation									
Multiple words									
Behavior									
Alertness									
Reduced hyperactivity							*No issue*		
Reduced disruptive behavior or irritability									
Reduced mouthing behavior				*Data N/A*					
Sleep									
Sleeping through the night	*No issue*			*No issue*					
Less frequent awakenings									
Fine Motor									
Pincer grasp									
Opening/closing doorknobs, lids									
Gross motor									
Throwing/catching a ball									
Walking up stairs or reciprocal climbing									
Reduced or eliminated falls				*Data N/A*					
Swimming independently									

Key

Skill gained

Issue, but no change

Skill lost

Emergence of New Developmental Skills Gained in Cohorts 4 to 7

Patient	1	2	3	4	5	6	7	8	9	10	11	12	12	14	15
Receptive Communication															
Responds to name															
Follows 1-step directions															
Follows 2-step directions															
Expressive Communication															
Babbles/consonant sounds															
Communicate wants or needs													.		
Identify object(s)															
First word/approximation															
Multiple words															
Behavior															
Alertness															
Reduced maladaptive behavior or impulsivity															
Reduced mouthing behavior															
Sleep															
Sleeping through the night															
Less frequent awakenings															
Fine Motor															
Pincer grasp															
Opening/closing lids															
Gross motor															
Throwing/catching a ball															
Walking up stairs or reciprocal climbing															
Reduced or eliminated falls															

Skill gained | No change

Closed Session:
Videos Played In Room Only

Q&A

Break

Gene Therapy Clinical Overview

- Eric Crombez, M.D.
  Chief Medical Officer

Largest Advanced Gene Therapy Portfolio in Rare Disease

Candidate	Description	Pre-Clinical	IND	Phase 1	Phase 2	Phase 3	Approved
DTX401	AAV8-G6Pase Gene Therapy	**Glycogen Storage Disease Type Ia (GSDIa)**					
UX111	AAV9-SGSH Gene Therapy	**Mucopolysaccharidosis Type IIIA (MPS IIIA)**					
DTX301	AAV8-OTC Gene Therapy	**Ornithine Transcarbamylase (OTC) Deficiency**					
UX701	AAV9-ATP7B Gene Therapy	**Wilson Disease (WD)**					
UX055	AAV9-CDKL5 Gene Therapy		CDKL5 Deficiency Disorder				
UX810	Microdystrophin Gene Therapy		Duchenne Muscular Dystrophy				

DTX401 for Glycogen Storage Disease Type Ia

Phase 3 fully enrolled with data in 1H24

Disease Overview

- Dysregulation of glycogen metabolism
- SOC: Diet and cornstarch
- Prevalence*: 6,000

GlucoGene Phase 3 Design

GlucoGene Gene Therapy for the Treatment of GSDIa

- ~50 patients, 1:1 placebo randomized
- 48-week duration
- Cornstarch reduction and control

Before After

Patient from Ph1/2
cornstarch when travelling

Phase 1/2 Data Summary

- 4+ years data
- 100% response rate
- 66% reduction of cornstarch
- No serious related TEAEs

Next Steps

- Phase 3 fully enrolled in 1Q23
- Phase 3 data in 1H24

**Prevalence in commercially accessible geographies*

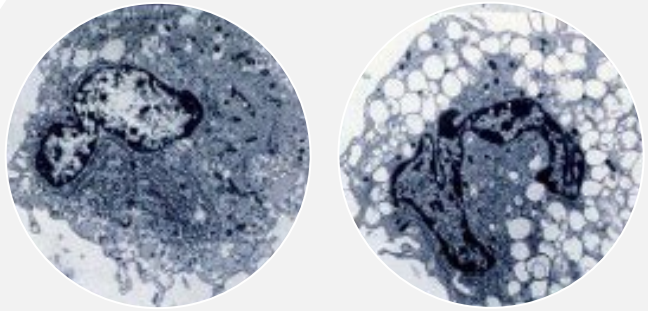
ultragenyx

UX111 for Sanfilippo syndrome (MPS IIIA)

Pivotal study fully enrolled, regulatory interactions for accelerated approval ongoing

Disease Overview

- Defect in heparan sulfate metabolism
- SOC: Supportive / symptomatic therapy
- Prevalence*: ~3,000 - 5,000



Normal cell

Cell with lysosome deficiency showing vacuolization

Phase 1/2 *Transpher A* Design

- 16 patients; 10 at highest dose
- Open label study up to 5 years of age

Phase 1/2 *Transpher A* Result

- Highest dose patients track along normal development range
- Observed stabilization in brain volume and reduction in liver volume
- Significant reduction in CSF heparan sulfate and urine GAGs

Next Steps

- Planning to meet with FDA in 4Q23
- Aiming to use biomarker data for premarket application to FDA

**Prevalence in commercially accessible geographies*

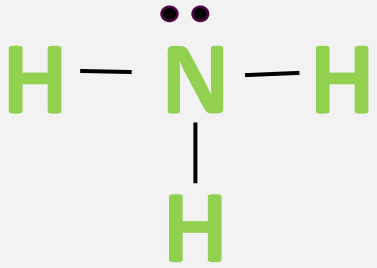
DTX301 for Ornithine Transcarbamylase Deficiency (OTC)

Phase 3 enrolling with LPI expected in 1H24

Disease Overview

- Defect in ammonia detoxification
- SOC: Diet and ammonia scavengers
- Prevalence*: ~10,000, 80% late-onset

Ammonia



Phase 1/2 Data Summary

- Up to 5.5 years of observed response
- 7 out of 11 showed metabolic control
- No treatment related SAEs

Phase 3 Design

Enhance™ Gene Therapy for the Treatment of OTC Deficiency

- ~50 patients, 1:1 placebo randomized
- 64-week duration
- Ammonia control and discontinuation of SOC

Next Steps

- Phase 3 dosing began in 1Q23
- Phase 3 LPI expected in 1H24

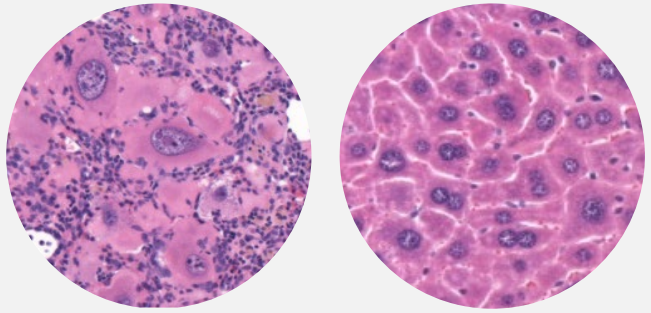
*Prevalence in commercially accessible geographies

UX701 for Wilson Disease: Pinnacle PCL Product Candidate

Stage 1 enrolling with LPI expected around the end of the year

Disease Overview

- Dysregulation of copper trafficking
- SOC: Diet and copper chelators / zinc
- Prevalence*: ~50,000



Untreated KO Mice

$1x10^{11}$ GC Treated Mice

Manufacturing Scale

- Leverages Pinnacle PCL™ platform
- Single run supported Stage 1 dosing

Phase 1/2 Design

Cyprus 2+ Gene Therapy for the Treatment of Wilson Disease

- 3 dose cohorts, 5 pts/cohort; open label
- 52-week duration
- Safety and tolerability, copper metabolism biomarkers, and reduction of SOC

Phase 3 Design

Cyprus 2+ Gene Therapy for the Treatment of Wilson Disease

- Seamless transition from Ph1/2
- 63 patients, 2:1 placebo randomized
- 52-week duration
- Urinary copper and reduction of SOC

**Prevalence in commercially accessible geographies*

UX701 for Wilson Disease

Four of five Cohort 1 patients tapering SOC, including two completely off chelators and/or zinc therapy

Cohort 1	Weeks on Study	Reduction of SOC [Chelator and/or zinc therapy]	Copper Trafficking
Patient 1	82	0%	Indeterminate
Patient 2	70	100%	Reduced urinary copper and improved trafficking by copper oxidase assay
Patient 3	44	100%	Reduced urinary copper and improved trafficking by copper oxidase assay
Patient 4	20	33%	Reduced urinary copper; pending trafficking assessment
Patient 5	16	50%	Reduced urinary copper; pending trafficking assessment

Data as of October 8, 2023

SOC reduction initiates 12-weeks after dose

No infusion related reactions and no serious TEAEs[1]

Cohort 2 dosing completed; all patients in Cohort 3 screened

Stage 1 data on three cohorts expected in 1H24

(1) Steroid regimen given from Day 1 to Day 60 post-dose, including taper

Gene Therapy
Pinnacle PCL Platform Overview

- Dennis Huang
  Chief Technical Operations Officer
  EVP, Gene Therapy R&D

Ultragenyx has Developed Multiple GT Manufacturing Processes

Each process optimized to match target indication

HEK293 Suspension

DTX401; DTX301

4 x 500 L

PINNACLE PCL™

UX701; UX055; UX810

2000 L

Future of Gene Therapy Manufacturing

- Reduced cost to manufacture
- Faster and more predictable supply during the full drug lifecycle

Enables

- Greater worldwide patient access
- Ability to use larger doses which could enable extra-hepatic delivery
- Address larger market opportunities

Pinnacle Platform Improves Speed and Provides Greater Control Over Quality and Cost

Manufacturing facility in Bedford, MA

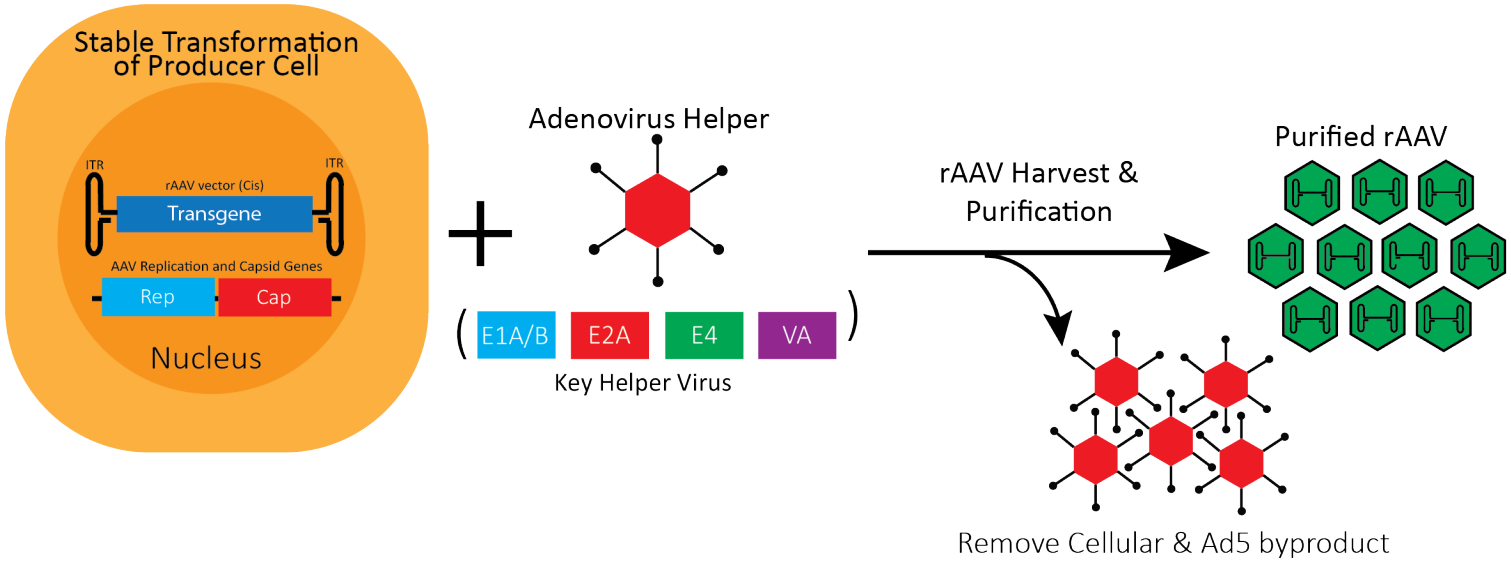
Gene Therapy Internal Capabilities

- Full gene therapy R&D capabilities with 500L Pilot Plant
- GMP QC laboratories (2019)
- GMP manufacturing facility (2023)
  - 110,000 sq ft
  - Drug substance
  - Drug product
  - Multi-product design
  - 2000L single use bioreactors

Pinnacle PCL Enables Treating Large and Extrahepatic Indications

	HEK293	PINNACLE PCL™
Scale	Adherent 500m^2 Suspension 500L or higher	Commercial scale 2000L+
Process	Triple plasmid transient transfection & more variable at commercial scale	Stable cell line, robust process
Quality	20-25% full capsids from the bioreactor	50-70% full capsids from the bioreactor
Cost of MFG	Traditionally high, worsened by lower scale and cost of GMP plasmids	Substantially lower MFG costs due to scale, high yield, inexpensive reagents

Pinnacle Producer Cell Line (PCL) Delivers High Titer and Commercial Grade Material

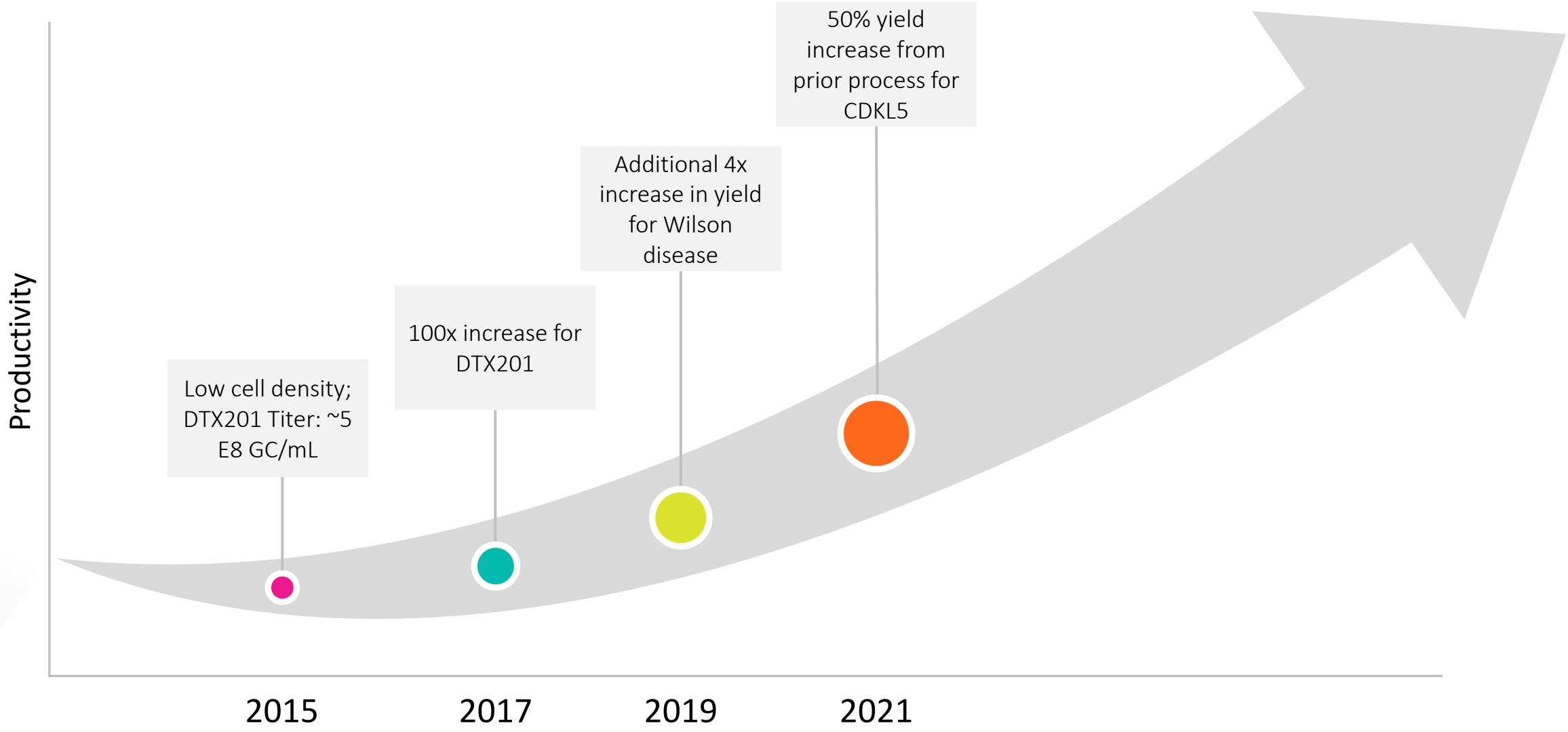


Stable Transfection of Rep/Cap and gene of interest into Producer Cells

AAV production is initiated with addition of Ad5 to the bioreactor

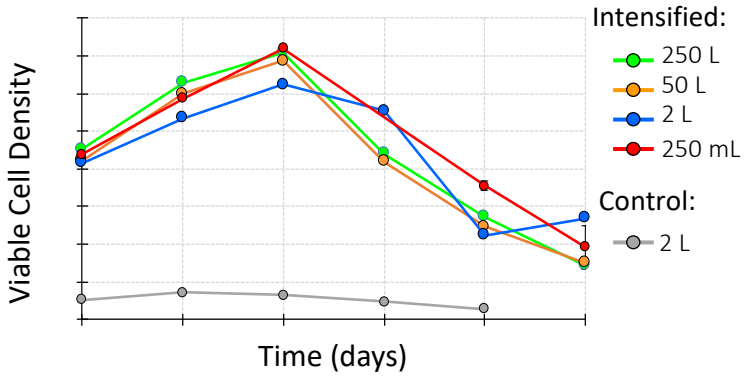
Downstream processing to purify final drug product

Productivity Improved Enabling Larger scale Clinical Programs Including UX701 for Wilson Disease



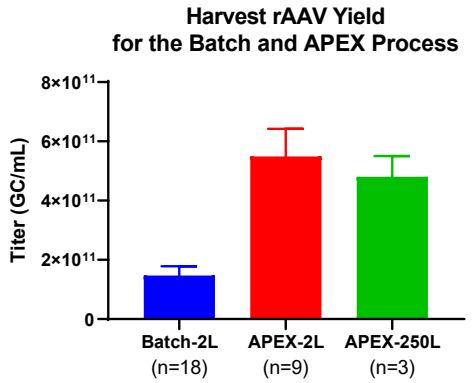
APEX (**A**AV **P**erfusion **E**nhanced e**X**pression) PCL Manufacturing Process Overcomes Batch Mode Limitations

Cell Density in Bioreactor



5X Cell Density achieved relative to batch culture.

Volumetric AAV Yield



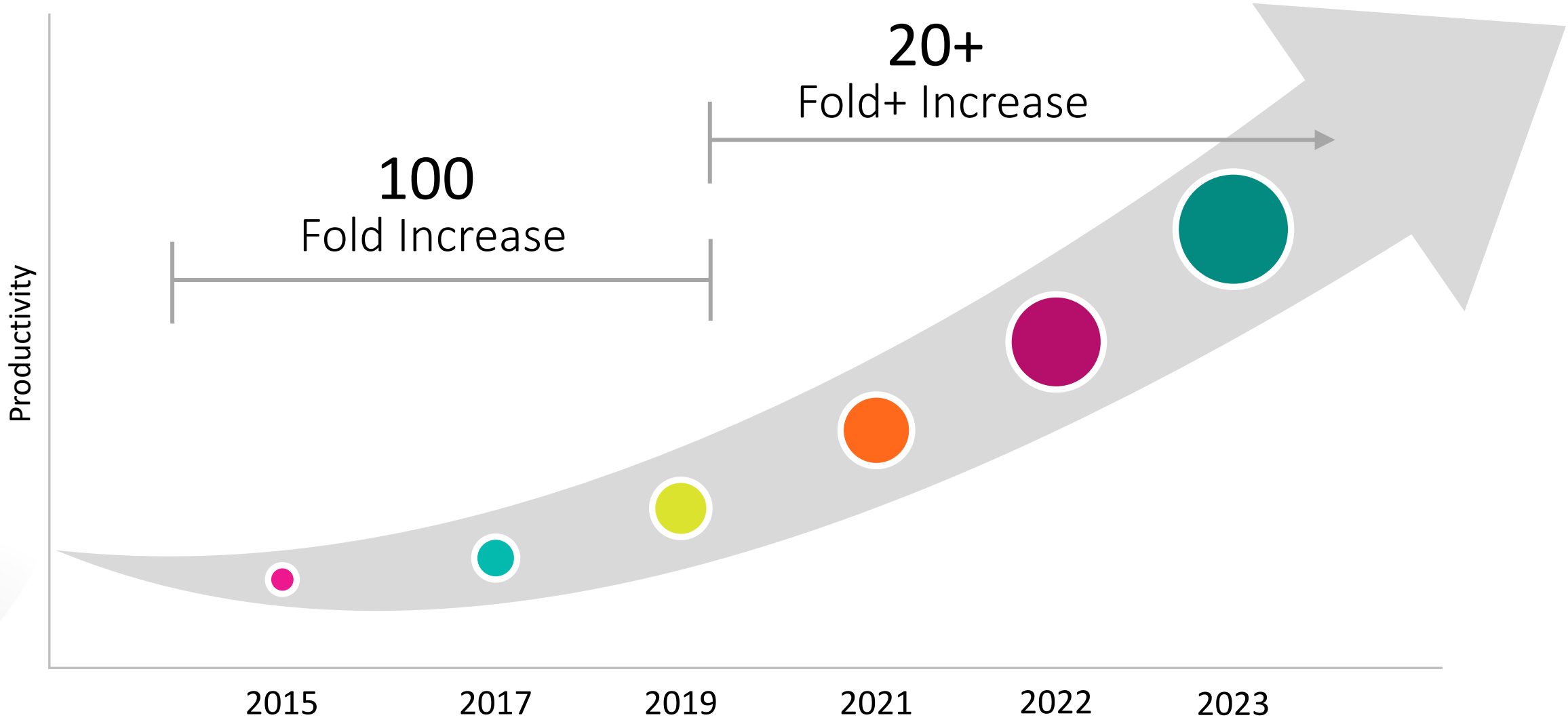
3.5X Productivity relative to batch, scaled to 250L

Benefits of APEX Process

- **Engineering control** over a historically "black box" production process
- Designed to operate at **2000L + scale**
- Perfusion rate can be customized to maintain very high cell density, accommodates high clinical supply for **larger patient populations**
- **Significantly lower COGS** changes the business model for AAV gene therapy products

Recent Advancements Enable Manufacture for Large Market Indications

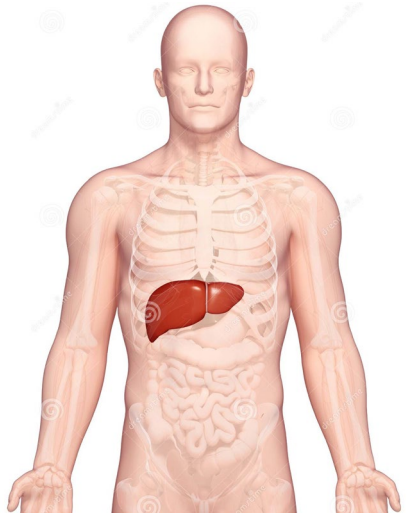
Higher productivity allows for lower COGS, moderated pricing, and biologic margins



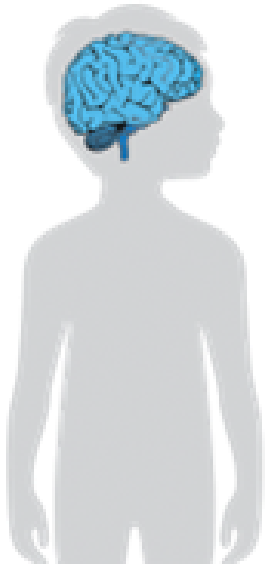
Pinnacle PCL is a Transformative AAV Manufacturing Technology

Enables treating with high dose or larger indications

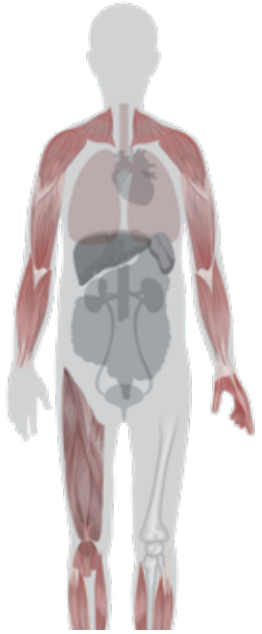
Liver



Neurologic



Musculoskeletal



Pinnacle PCL platform offers the titer and quality at a lower cost to address these disease with responsible commercial pricing

Pinnacle PCL Platform the New AAV Gene Therapy Manufacturing Process Standard

Standardizing key technology platforms has led to faster regulatory approvals and access for patients

- Monoclonal antibody therapeutics – Mammalian CHO (1990-2000's)
- mRNA – COVID vaccines (2020's)

Pinnacle PCL Platform has the right characteristics and maturity to be the AAV Gene Therapy manufacturing standard

- Clinically validated
- Cost effective
- Efficient development timelines
- Scalable and reliable
- High quality
- IP protected

A Novel Gene Therapy Therapeutic Approach to Targeting Beta-amyloid

- Emil Kakkis, M.D., Ph.D.
  President and Chief Executive Officer

ultragenyx

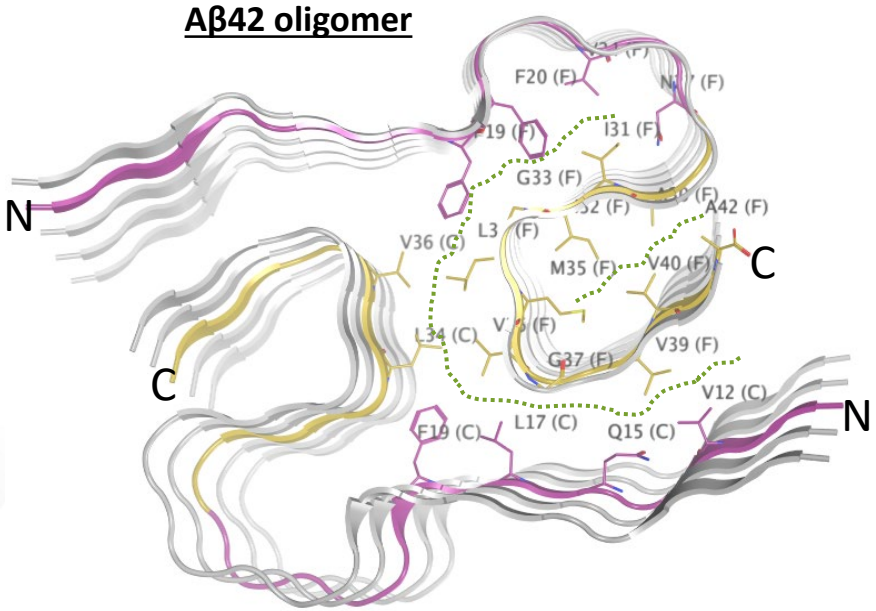
Executive Summary: The Use of a Lysosomal Enzyme to Reduce Aβ42

- Galactosialidosis (UX004) studies have led to an important discovery:
  - ***Protective Protein/Cathepsin A (PPCA) is a protease that can cleave Aβ42***
- Alzheimer's is complex, but the role of amyloids is resurgent due to Mab success & approvals
- Alzheimer's and Lysosomal Diseases share many parallels
- Ultragenyx research working with Dr. D'Azzo has shown that PPCA has special properties:
  - PPCA cleaves amyloid at is C terminus and prevents aggregation *in vitro*
  - Delivery of PPCA to the lysosome via an AAV gene therapy can prevent, reduce or reverse amyloid accumulation in the most severe 5xFAD mouse models of AD
- A special purpose vehicle was proposed to finance the progression of this high-risk, high return project that is beyond the accepted scope of Ultragenyx

Amyloid Hypothesis Validated, but Room to Improve Remains

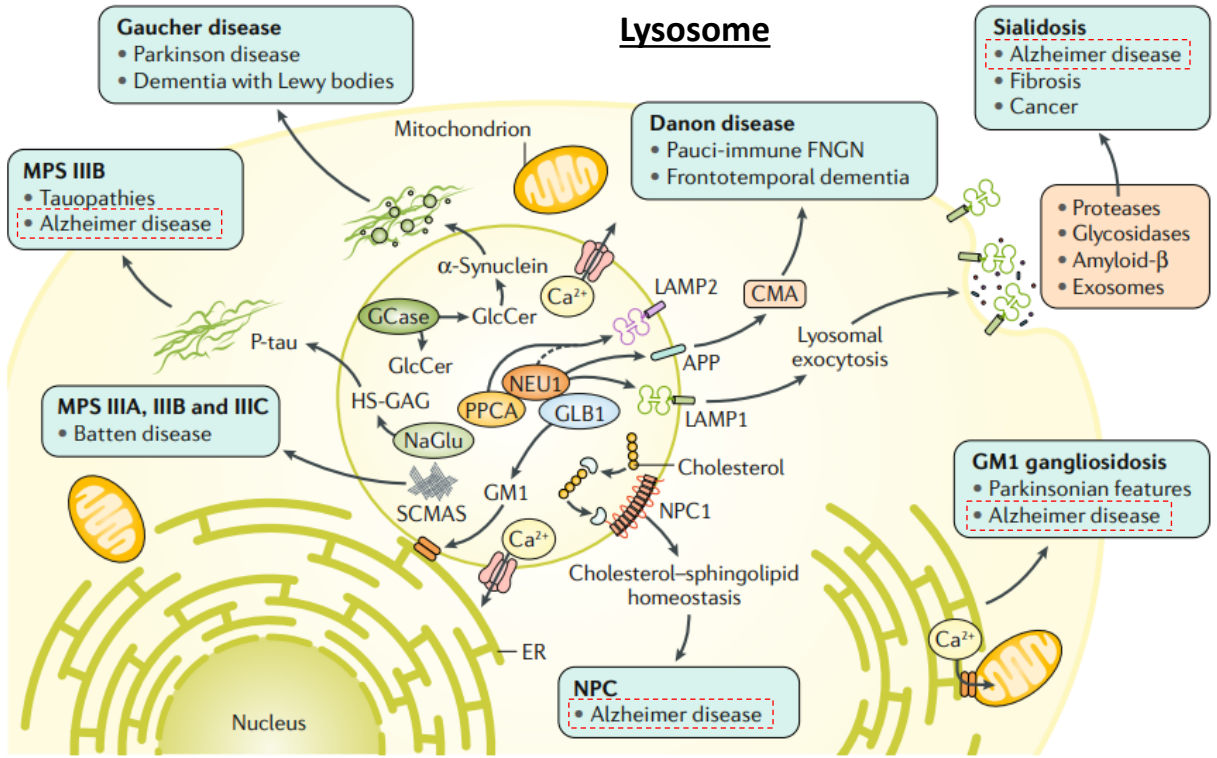
Recent approvals show amyloid's importance; relevance of lysosome to AD increasing

- Amyloid hypothesis has become predominant theory with promise to treat AD, but story is complicated
- Recent approvals of Mab against Aβ42 show amyloid matters but efficacy still is modest
  - (-27% decrease in rate of still continuing decline)
- Recent insights by scientists indicate growing association of amyloid disorders with the lysosome



Adapted from Yang et al. Science. 375. (2022)

Platt et al. Nature Rev. 4(1). (2018)



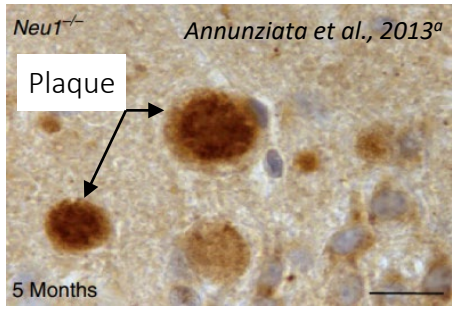
Lysosomal Diseases Share Many Pathologic Features with AD

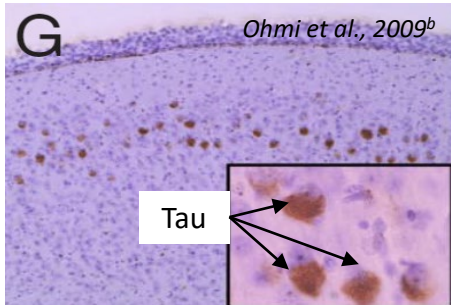
Various lysosomal diseases show Alzheimer biology and Aβ42 plaque accumulation

Alzheimer's Disease and Lysosomal Diseases have similar pathologic features as they are actually related diseases

Types of Protein Accumulation and Associated Diseases

Aβ-amyloid plaque	α-synuclein	Proteo-lipid amyloid	Tau
Sialidosis	Gaucher	CLN2 (Batten)	MPSIIIB
	MPSIIIA and B		
	Parkinson's		





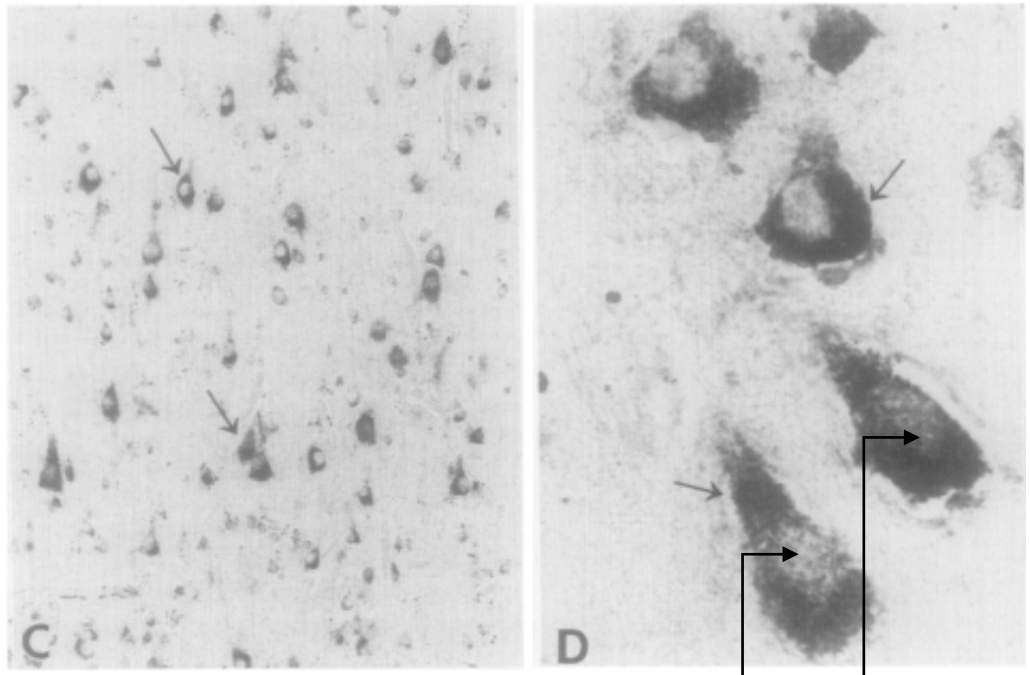
(a) I Annunziata, A Patterson, D Helton, H Hu, S Moshiach, E Gomero, R Nixon, A ***d'Azzo****, "Lysosomal NEU1 deficiency affects amyloid precursor protein levels and amyloid-b secretion via deregulated lysosomal exocytosis"; Nat Comm, 2013*

(b) K Ohmi, L Kudo, S Ryazantsev, H Zhao, S Karsten, E F ***Neufeld,*** *"Sanfilippo syndrome type B, a lysosomal storage disease, is also a tauopathy"; PNAS, 2009*

Is There Direct Evidence of Lysosomal Involvement in AD?

Alzheimer's brains at autopsy indicate maximal lysosomal upregulation

Neurons from AD Brain



Cataldo et al., 1995

Marker for lysosomal activation

Lysosomal function is **maximally induced in AD brain**[a,b]

Implies that AD pathology is consistent with a **lysosomal / endosomal dysfunction** that cannot compensate for accumulating protein storage

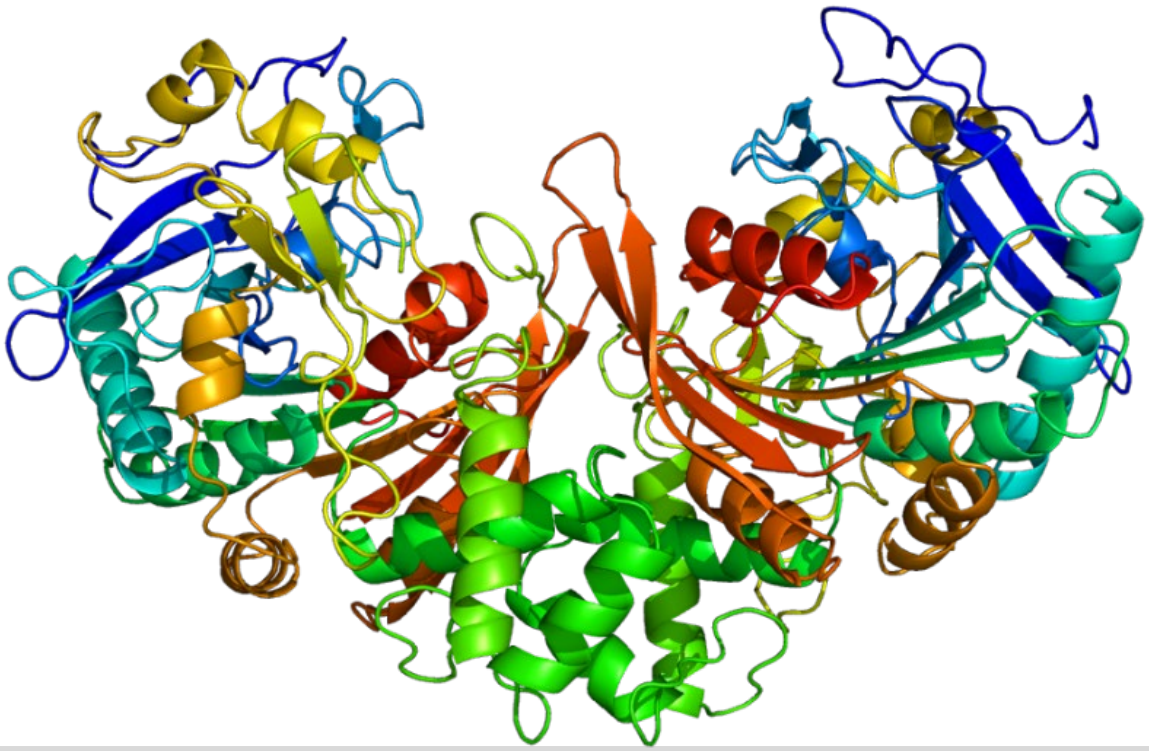
(a) A Cataldo, J Barnett, S Berman, J Li, S Quarless, S Bursztajn, C Lippa, R A Nixon, "Gene Expression and Cellular Content of Cathepsin D in Alzheimer's Disease Brain: Evidence for Early Up-Regulation of the Endosomal-Lysosomal System, Neuron, 1995

(b) J Lee, D Yang, C Goulbourne, E Im, P Stavrides, A Pensalfini, H Chan, C Bouchet-Marquis, C Bleiwas, M Berg, C Huo, J Peddy, M Pawlik, E Levy, M Rao, M Staufenbiel, R A Nixon, "Faulty autolysosome acidification in Alzheimer's disease mouse models induces autophagic build-up of Aβ in neurons, yielding senile plaques", Nat Neuro, 2022

PPCA Enzyme Supplementation as Potential Solution

Lysosomal enzyme to degrade hydrophobic peptides that form beta-pleated sheet structures

PPCA



PPCA is a carboxypeptidase with specificity for hydrophobic amino acid cleavage including the amino acids at the C-terminus of APP and Aβ42

PPCA recruits endogenous NEU1, which regulates lysosomal exocytosis and lengthens digestion time

The combination of more protease activity and delayed exocytosis can reduce excess Aβ42

PPCA Selectively Degrades Aβ42 and Prevents Oligomer Assembly

PPCA targets the C-terminus of Aβ42 and degrades/prevents assembly of larger oligomers

PPCA cleaves the C-terminus of Aβ42 that leads to amyloid disaggregation and prevents further oligomerization

Aβ42 sequence

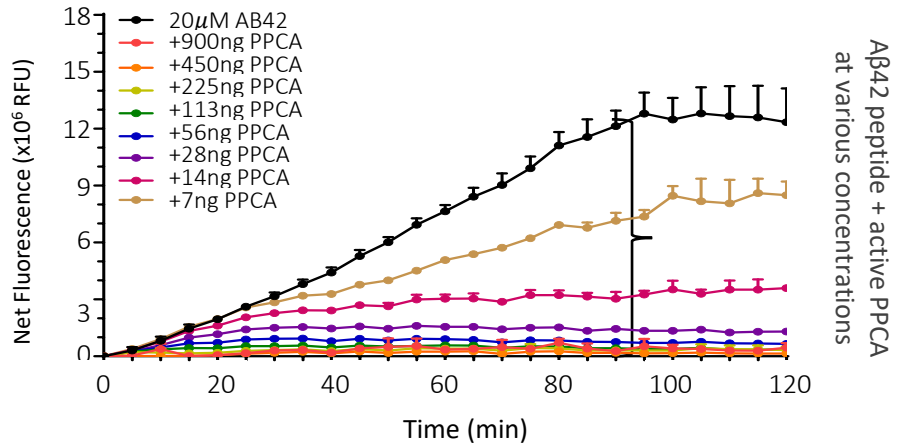
DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA

Potential target for PPCA hydrolysis

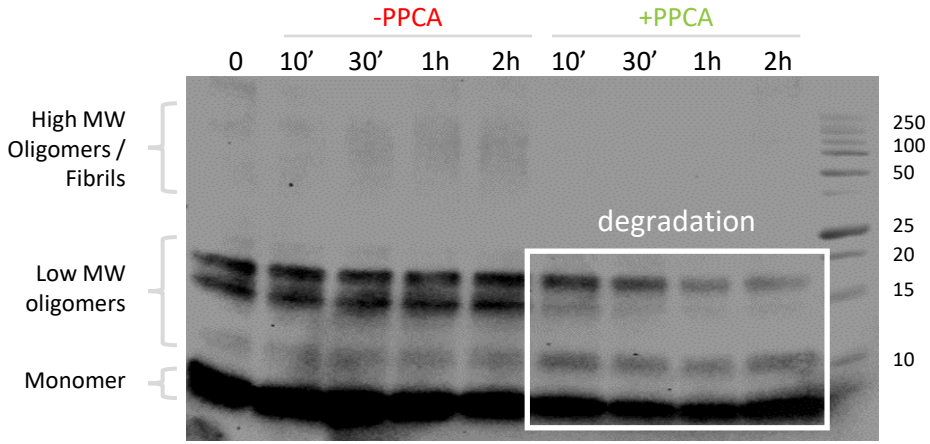
Verified C-terminal truncations after PPCA cleavage of Aβ42

Aβ42 peptide	…DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA
C-terminal truncations	…DAEFRHDSGYEVH
	…DAEFRHDSGYEVHHQKL
	…DAEFRHDSGYEVHHQK

Amyloid Aggregation Assay



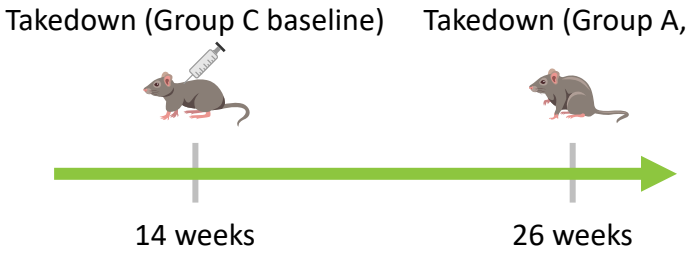
PPCA Digestion Assay



AAV-PPCA in 5xFAD Mice Shows Strong Therapeutic Effect

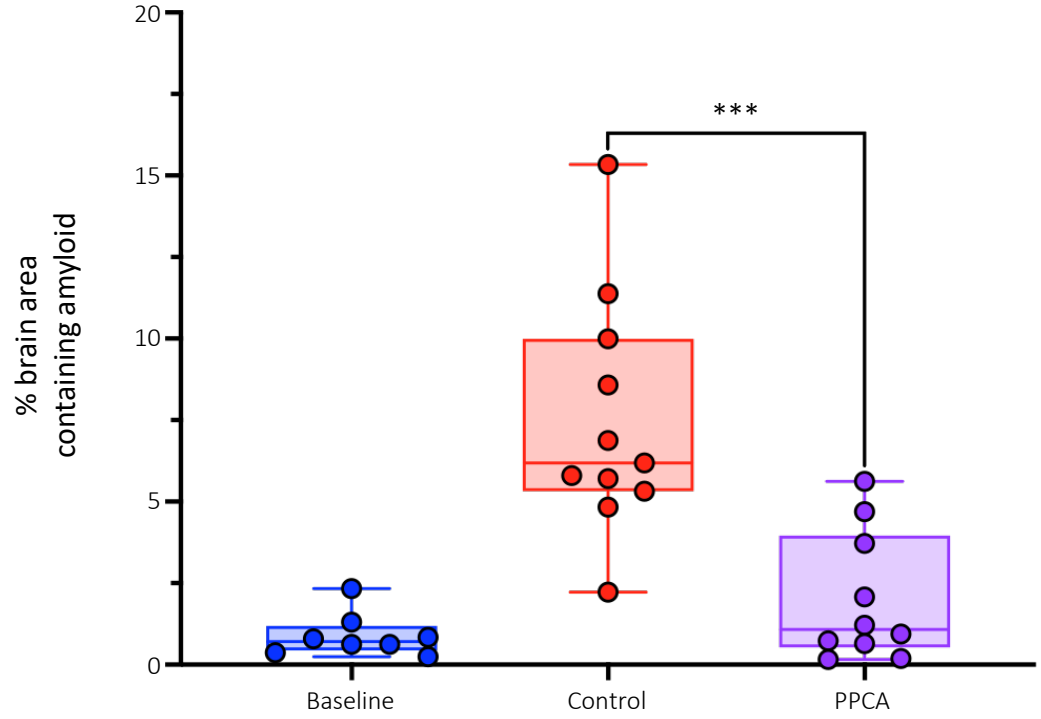
Significant reduction in the volume of Aβ42 plaques

Experimental design



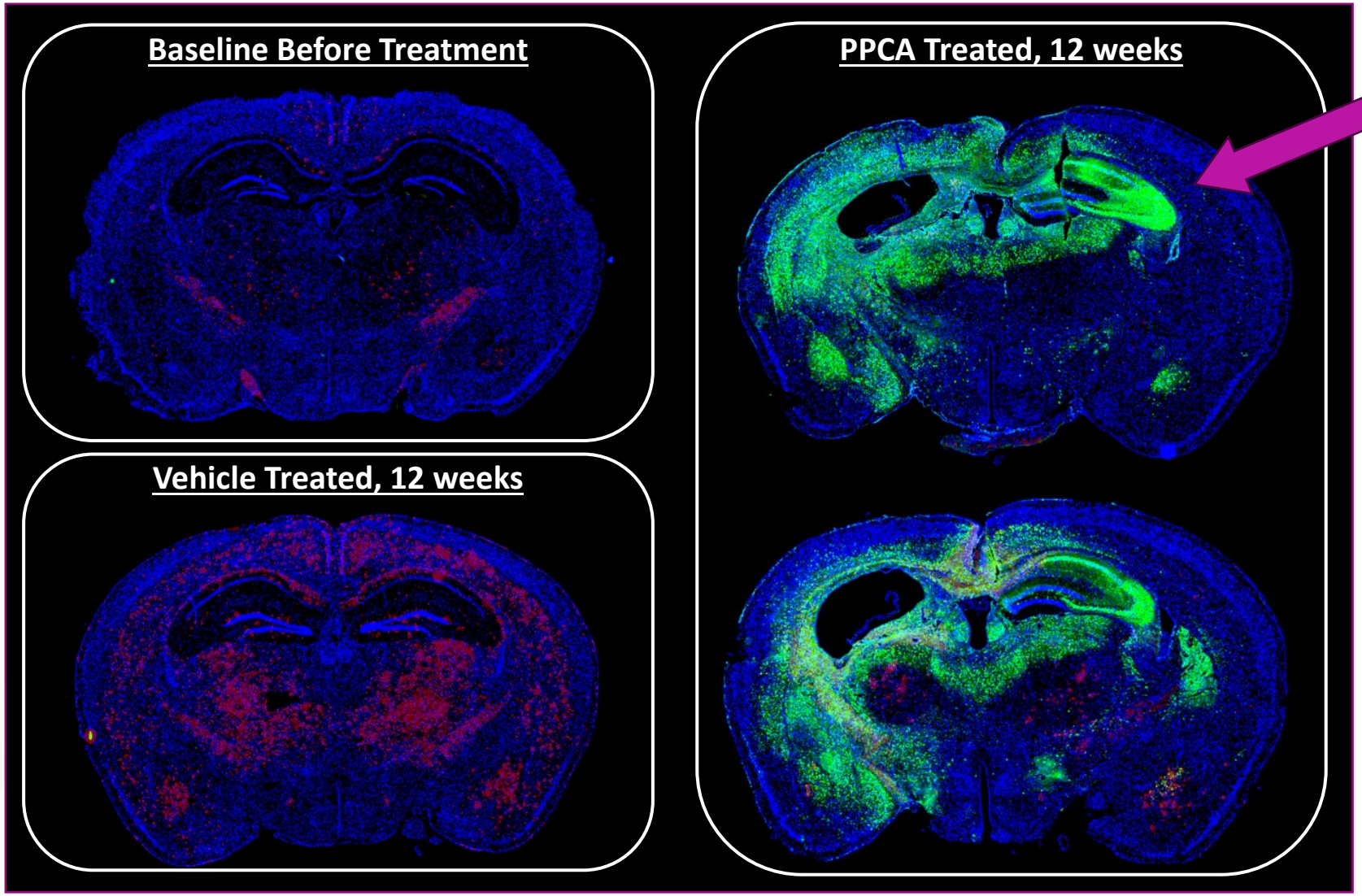
- Intracranial infusion of 1e12 total VG, AAV-PPCA
- Mice (5xFAD) dosed at 14 weeks of age
- In life duration was 3 months, study end at 26 weeks of age

Amyloid reduction



AAV-PPCA in 5xFAD Mice Shows Strong Therapeutic Effect

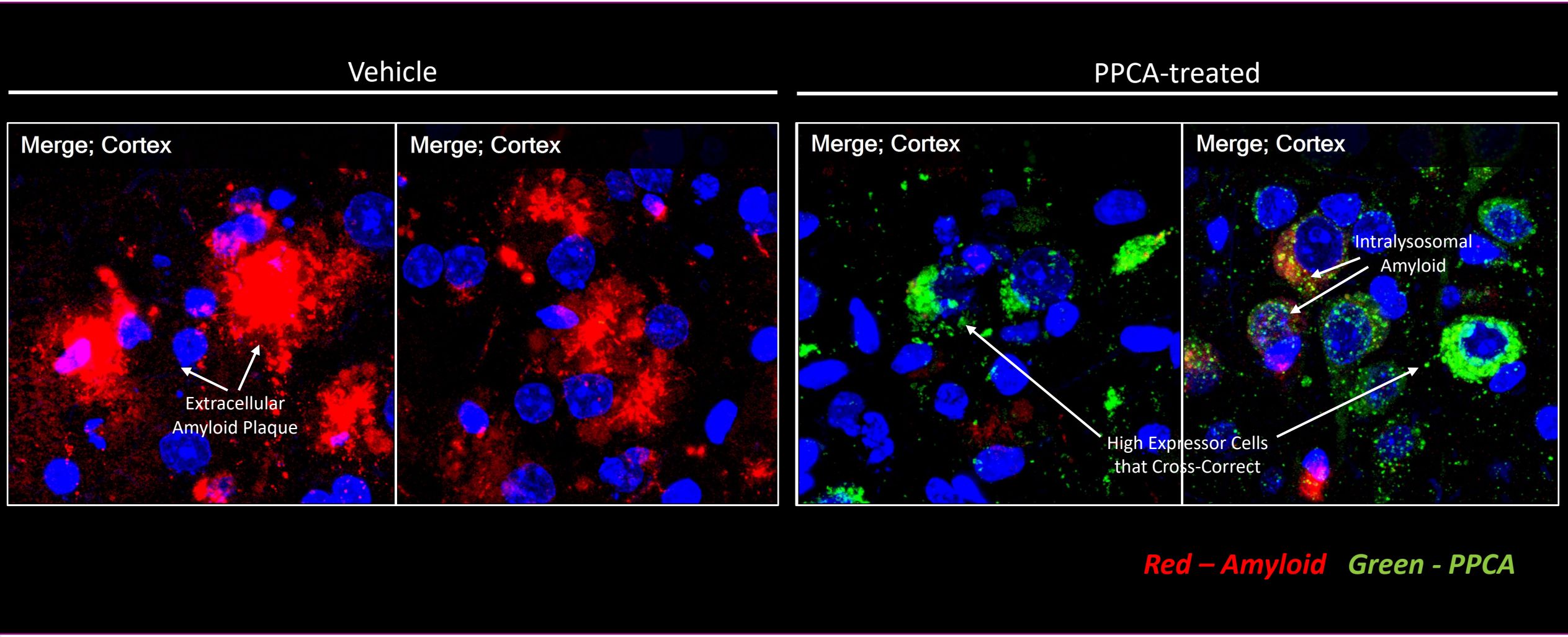
AAV-delivery of PPCA in treated brain shows dramatic amyloid clearance



Near complete reversal in some mice

AAV-delivered supplementation of PPCA (Green) in treated brain shows **significant reduction of amyloid** (Red, right panels)

Immunohistochemistry Staining Show PPCA's Ability to Cross-correct and Dramatically Reduce Amyloid Accumulation



PPCA Supplementation Reduces Amyloid via the Lysosome

Demonstration that Aβ42 plaque possesses an obligate step through the lysosome

Key Novel Insight:

Delivery of a lysosomal protease that is active only inside the lysosome is reducing the Aβ42 plaque accumulation outside the cell

Plaque outside the cell directly results from an **upstream lysosomal process**

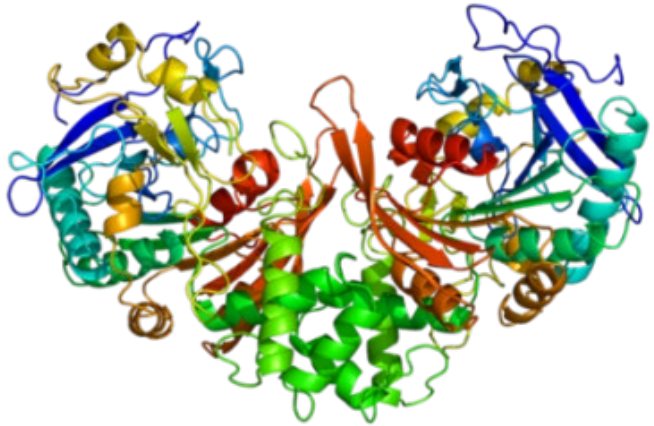
Connects the "toxic intracellular oligomers" with the lysosome

Enzymatic vs Antibody Approach: Which is Better?

Catalytic proteolysis with PPCA enables greater levels of Aβ42 degradation than antibodies

Catalytic Degradation

PPCA

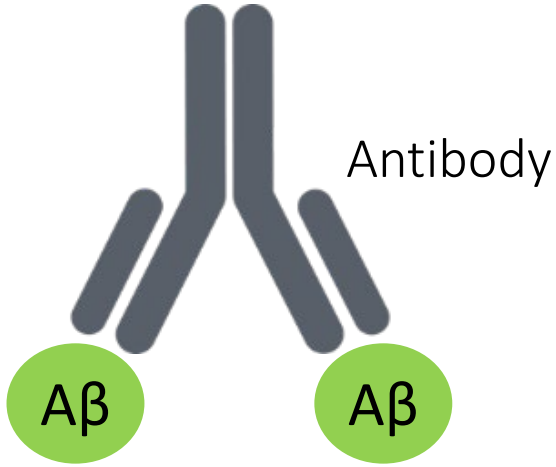


35 x Aβ per second

<u>Thousands</u> of 4.2 kd peptides per 54 kDa

VS

Stoichiometric Binding



<u>Two</u> 4.2 kd peptides or oligomers per 180 kDa

AAV-PPCA Shows Greater Plaque Reduction Using a More Aggressive AD Mouse Model Compared to Anti-Aβ42 mABs

Drug	Mouse model *(mutations[1])*	Age of mouse at first dose	Treatment regimen and duration	Aβ42 plaque reduction data
AAV-PPCA (Ultragenyx)	5xFAD (Swedish, Florida, London, PSEN1M146L, PSEN1L286V)	3-4 months	Single dose / 3 months	>60%+
Lecanemab (Eisai/Biogen)[a]	ArcSwe, 2X FAD (Swedish, Arctic)	11-13 months	Weekly dose / 3 months	29%
Donanemab (Eli Lilly)[b]	PDAPP (Indiana)	23-24 months	Weekly dose / 3 months	38%-53%
Aducanumab (Biogen)[c]	Tg2576 (Swedish)	9 months	Weekly dose / 6 months	40%

(1) List of mutations: Swedish - APPK670_M671delinsNL ; Florida - APPI716V ; London - APPv717I ; Arctic - APPE693G ; Indiana - APPv717F
(a) S Tucker, et al., "The Murine Version of BAN2401 Selectively Reduces Amyloid-ß Protofibrils in Brain and Cerebrospinal Fluid of tg-ArcSwe Mice", J Alzheimer's Dis, 2015
(b) R DeMattos, et al., "A Plaque-Specific Antibody Clears Existing ß-amyloid Plaques in Alzheimer's Disease Mice", Neuron, 2012
(c) J Sevigny, et al., "The antibody aducanumab reduces Aß plaques in Alzheimer's disease", Nature, 2016

Pinnacle PCL and Ultragenyx GT Capabilities Enable Large Scale GT Production at Lower COGS to Treat Large Market CNS Indications

Pinnacle PCL™ platform	Optimized CNS delivery
Producer cell line technology with scalable process that provides reliable production of high quality AAV with improved yields	Formulation and administration improvements greatly enhance CNS delivery and biodistribution

Enables gene therapies for large CNS indications, such as Alzheimer's disease

Summary on NewCo Amlogenyx and Next Steps

Ultragenyx is spinning out a new company, Amlogenyx

- Ultragenyx to retain majority ownership
- Ultragenyx to grant Amlogenyx license to required IP and know-how
- Amlogenyx to develop the novel therapeutic strategy using AAV delivery of a lysosomal protease

Seeking independent funding and working to close a Series A round by year-end

Program will be cash neutral to Ultragenyx and will not alter our commitment to our key value drivers

Closing Remarks

Well positioned to be the leader of rare disease medicine

Transformative treatment in our **UX143 OI program**

GTX-102 for Angelman is changing lives

UX701 for Wilson disease demonstrated clinical activity in lowest dose cohort

Pathway to profitability

We lead with purpose.
Every moment matters.

5 key clinical catalysts

	PROGRAM	OBJECTIVE	EXPECTED TIMING
1	**UX143** Osteogenesis Imperfecta	Ph 2 fracture data	Today!
2	**GTX-102** Angelman Syndrome	Extension & redosing data Expansion cohort data	Today! 1H24
3	**UX701** Wilson Disease	Cohort 1 data Cohorts 1-3 data	Today! 1H24
4	**DTX401** GSDIa	Phase 3 unblinding	1H24
5	**UX111** MPS IIIA	Regulatory discussions on filing	4Q23

Q&A

Thank You