Arimoclomol for the Treatment of Niemann-Pick Disease Type C (NPC)

August 2, 2024

Zevra Therapeutics

Genetic Metabolic Diseases Advisory Committee

Introduction

Louise Himmelstrup

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Niemann-Pick Disease Type C (NPC)

- Ultra-rare, neurodegenerative lysosomal storage disease
- Impairs ability to transport cholesterol and other lipids inside cells
- Causes progressive dysfunction of nerves, brains, and other organs
- Typically diagnosed in early childhood
- Median age at death is 13 years[3]
- No approved therapies in United States

NPC in US
600 – 900 patients[1]

Ultra-rare Disease
< 6,600 patients[2]

Orphan Disease in US
< 200,000 patients

1. Burton et al., 2021; 2. Smith et al., 2022; 3. Bianconi et al., 2019

Arimoclomol for the Treatment of NPC

- Arimoclomol slows NPC progression
  - Clinically meaningful benefit for relentlessly progressive disease
- Well tolerated with acceptable safety profile
  - Long-term data through 5 years

Arimoclomol is indicated for the treatment of adult and pediatric patients (≥ 2 years) with Niemann-Pick disease type C (NPC)

Substantial Evidence of Effectiveness

Rare Disease Approach*

1 Adequate and well-controlled study

+

Confirmatory evidence

Standard Approach

2 Adequate and well-controlled studies

*FDA Guidance, 2023:
"*Disease- or condition-specific considerations (e.g., unmet need, size of the patient population) may be relevant to whether such an approach is appropriate.*"

Resubmission Demonstrates Substantial Evidence of Effectiveness that Arimoclomol Slows NPC Progression

1 Adequate and well-controlled study

- **Statistically significant result on pre-specified primary efficacy endpoint**
- **Consistent findings with FDA's recommended estimand**

+

Confirmatory evidence

Consistent and mutually reinforcing data across several domains

- ✓ **Clinical data**
- ✓ **Natural history data**
- ✓ **EAP Data**
- ✓ **NPC animal models**
- ✓ **Mechanism of action**

Presentation to Address Questions Posed by FDA

FDA Questions	Supportive Information
1. Uncertainties about primary endpoint	▪ Removed Cognition domain in agreement with FDA ▪ Revised Swallow domain scoring methodology based on qualitative study with swallow experts ▪ Validated domains using objective functional measures
2. Uncertainty of estimated treatment effect	▪ Met pre-specified endpoint with pre-specified analysis ▪ Met revised endpoint with FDA-recommended analysis ▪ Consistent treatment effect across sensitivity analyses
3. Strength of clinical and nonclinical confirmatory evidence when considered together	▪ Favorable outcomes in 4-year open-label study and EAP ▪ Supportive data from new in vitro and in vivo studies

Pivotal study and confirmatory evidence support conclusion of substantial evidence of effectiveness for arimoclomol

Clinical Background on Niemann-Pick Type C	**Marc Patterson, MD** Professor of Neurology, Pediatrics and Medical Genetics Emeritus Chair, Division of Child and Adolescent Neurology Mayo Clinic, Rochester, MN
Pivotal Efficacy	**Dan Gallo, PhD** SVP, Medical Affairs and Advocacy, Zevra Therapeutics
Confirmatory Evidence of Effectiveness	**Travis Mickle, PhD** Co-Founder, Senior Advisor, Zevra Therapeutics
Safety	**Christine í Dali, MD** VP, Clinical Science, Zevra Therapeutics
Clinical Perspective	**Kristina Julich, MD** Assistant Professor, Department of Neurology Chief, Pediatric Neurogenetics Center University of Texas at Austin

Additional Experts

Lisa LaGorio, PhD, MPH, CCC-SLP
Assistant Professor & Director SLP Faculty Research Lab
Rush University Medical Center

Jason Connor, PhD
President & Lead Statistician
ConfluenceStat

Clinical Background on Niemann-Pick Type C

Marc Patterson, MD

Professor of Neurology, Pediatrics and Medical Genetics

Emeritus Chair, Division of Child and Adolescent Neurology

Mayo Clinic, Rochester, MN

NPC: An Atypical Lysosomal Storage Disorder

- Characterized by relentless neurological progression
- NPC symptoms may begin as early as infancy, or as late as maturity
- Incidence: 1 in 100,000 births[1]

1. Geberhiwot et al., 2018

NPC: Very Heterogeneous and Highly Variable Disease

- Core symptoms and progression to death determined by age of onset[1-3]

Perinatal	▪ Severe liver involvement, may be accompanied by pulmonary involvement
Infantile	▪ Dominated by neurologic progression ▪ Children typically hypotonic with delayed development at first; signs of neurologic regression follow
Middle Childhood	▪ May present as difficulties concentrating, sometimes misdiagnosed as ADHD ▪ Others appear clumsy; experience uncontrollable seizures and sleep disorders
Teenage/ Adulthood	▪ Dominated by cognitive impairment; presenting as early onset dementia ▪ Many have traumatic psychiatric presentations

1. Imrie et al., 2007; 2. Patterson et al., 2012; 3. Vanier, 2010; ADHD = attention-deficit/hyperactivity disorder

Routine Clinical Care for NPC

- Symptom management by multi-disciplinary team
  - Neurologist or geneticist lead care team
  - Other experts as needed
- No FDA-approved therapies for NPC
- Routine care may include miglustat
  - Substrate reduction therapy approved for Gaucher disease
  - Used off-label in US
  - Some unable to tolerate due to known GI side effects

Heterogeneity of NPC Makes Disease Progression Difficult to Measure across Wide Range of Ages

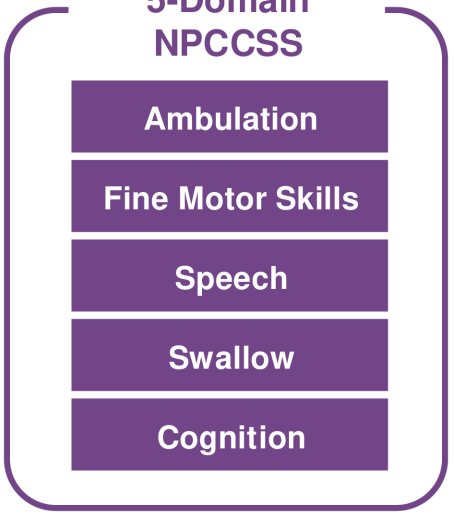
- No established surrogate endpoints or readily measurable biomarkers to assess progression
- Disease progression needs to be measured by composite clinical scales
  - Embrace breadth of disease
  - Measure progression in sufficiently granular fashion

Vanier, 2010

Niemann-Pick Type C Clinical Severity Scale (NPCCSS)

Development of NPC Clinical Severity Scale (NPCCSS)

- NIH developed 17-domain NPCCSS
- Simplified 5-domain scale developed to capture key symptoms most valued by patients, caregivers, and clinicians
- Clinicians score domains based on defined criteria, from 0 – 5
  - Higher scores indicate more severe impairment
- Simplified scale commonly used in clinical studies



Cortina-Borja et al., 2018; Patterson et al., 2021

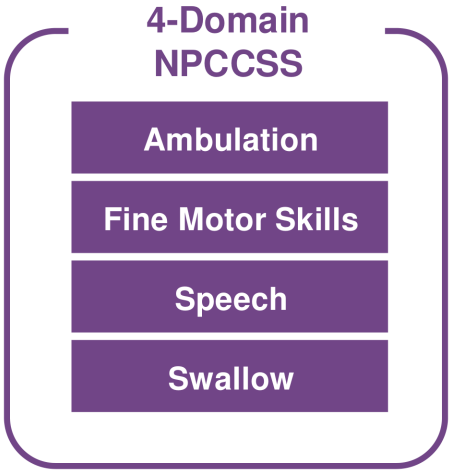
Zevra Adapted 4D-NPCCSS Based on FDA Recommendations

Cognition Domain Removed in Agreement with FDA

- FDA concerned that a single item unable to fully evaluate a broad concept like cognition

Swallow Domain Scoring Methodology Updated Based on Expert Recommendations

- FDA concerned scoring did not reflect linear progression
- Zevra enlisted experts to review scoring methodology for Swallow domain without access to study data
- Applied revised methodology to pivotal trial data



Original Scoring Methodology of Swallow Domain Could Yield Incorrect Equivalencies in Disease Severity

Original Swallow	Score	Patient A	Patient B
Normal, no dysphagia	0		
Cough while eating	1	1	
Intermittent dysphagia with liquids	+ 1		
Intermittent dysphagia with solids	+ 1		
Dysphagia with liquids	+ 2	+ 2	
Dysphagia with solids	+ 2	+ 2	
Nasogastric tube or gastric tube for supplemental feeding	4		
Nasogastric tube or gastric tube feeding only	5		5
		Total = 5	Total = 5

A patient who does not require feeding tube *at any time* ≠ to patient who requires feeding tube *all of the time*

Updated Swallow Domain Scoring Methodology Reflects Linearity of Disease Progression

Updated Swallow	Score
Normal, no dysphagia	0
Cough while eating	1
Intermittent dysphagia	2
Dysphagia	3
Nasogastric tube or gastric tube for supplemental feeding	4
Nasogastric tube or gastric tube feeding only	5

Scores clearly delineated

- **Each step-wise increase in swallow dysfunction matched with numeric point increase in score**

- Applied updated scoring methodology to data collected during pivotal trial

4D-NPCCSS Includes Clear Descriptions, Defines Each Scoring Level of Clinical Impairment from 0 – 5

Ambulation	Fine Motor Skills	Speech	Swallow (Revised)	Score
Normal				0
Clumsy	Slight dysmetria/ dystonia (*independent manipulation*)	Mild dysarthria (*easily understood*)	Cough while eating	1
Ataxic unassisted gait	Mild dysmetria/dystonia (*requires little to no assistance, able to feed self easily*)	Severe dysarthria (*difficult to understand*)	Intermittent Dysphagia	2
–	–	Non-verbal / functional communication skills for needs	Dysphagia	3
Assisted ambulation	Moderate dysmetria/dystonia (*limited fine motor skills; difficulty feeding self*)	–	Nasogastric tube or gastric tube for supplemental feeding	4
Wheelchair dependent	Severe dysmetria/dystonia (*gross motor limitation, requires assistance for self-care activities*)	Minimal communication	Nasogastric tube or gastric tube feeding only	5

More details provided in scoring manual

Trained Clinicians Collected NPCCSS

- Working with neurologically impaired children across broad age range
- Well-defined scoring criteria applied using flexible approach to accurately evaluate children
- Standardized procedures in arimoclomol trial included
  - Scoring manual
  - Same NPC experts evaluating patients at each visit
  - Rater training

NPCCSS Is the Only Validated and Appropriate Tool to Measure NPC Disease Severity and Progression

NPCCSS validity and reliability established at domain level

- Construct validity vs objective performance tests
  - Correlations range from 0.45 to 0.99
- High inter-rater reliability (ICC = 0.99)
- High intra-rater reliability (ICC = 0.94)

ICC = intraclass correlation coefficient

Two Approaches Determined that a 1-Point Change on the NPCCSS was a Clinically Meaningful Difference

- **Anchor-based approach**
  - Preventing 1-point worsening on the 5-domain scale was clinically meaningful
- **Patient- and caregiver-based judgement approach**
  - Collaborated with patients and caregivers to identify amount of change that would be clinically meaningful
  - Slowing progression in any domain meaningful
    - Eating by themselves vs needing caregiver to feed them
    - Sometimes having difficulty swallowing vs always
    - Walking with assistance vs needing a wheelchair

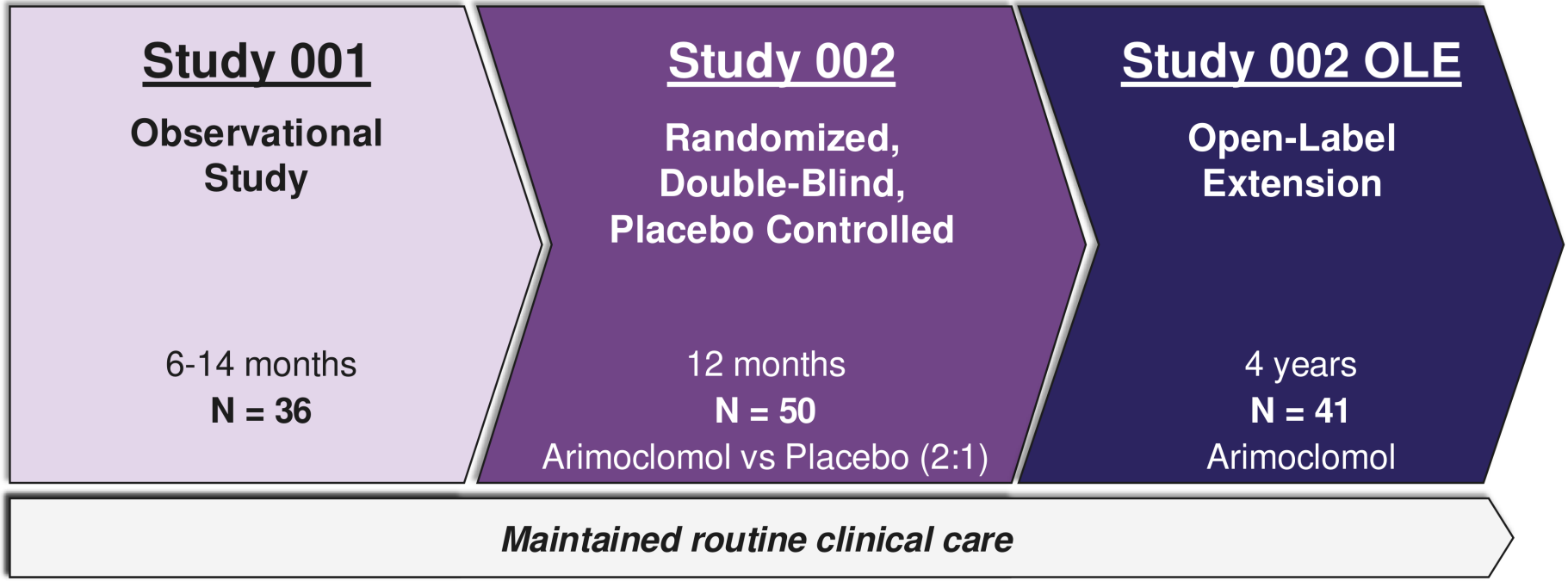
Patterson et al., 2021

Pivotal Efficacy

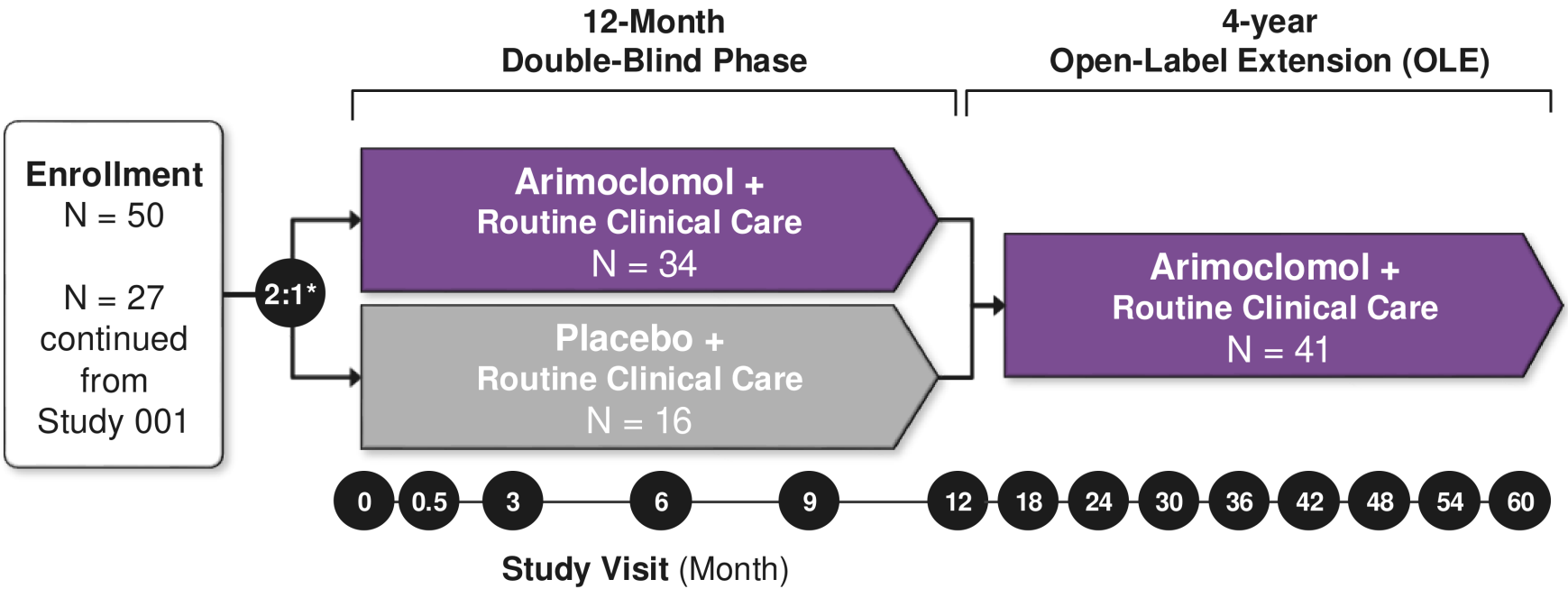
Dan Gallo, PhD

SVP, Medical Affairs and Advocacy
Zevra Therapeutics

Clinical Program Included 3 Studies in NPC



Design of Pivotal Study 002 and Open-Label Extension



*Stratified by miglustat use

Study 002 Baseline Demographic and Disease Characteristics

	Arimoclomol N = 34	Placebo N = 16
Age (years), mean (range)	**11.5** (2 – 19)	**10.2** (2 – 19)
Female	**50%**	**56%**
White	**94%**	**81%**
Years since first symptoms, mean (SD)	**7.6** (4.5)	**8.1** (3.8)
Baseline use of miglustat	**77%**	**81%**
Baseline 4D-NPCCSS (SD)	**9.2** (5.8)	**6.7** (5.2)
Double functional null mutation, n (%)	**3 (9%)**	**0**

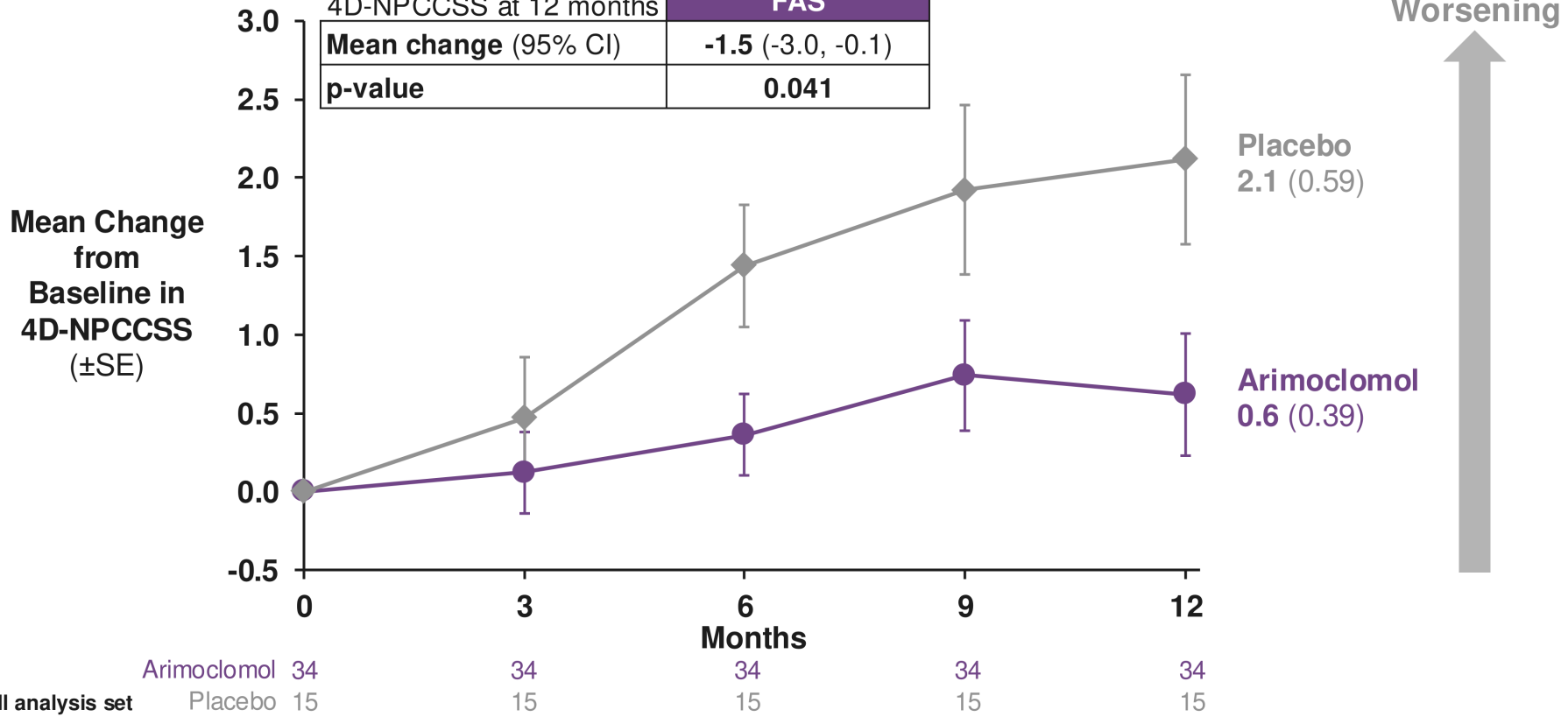
Study 002 Met Pre-specified 5D-NPCCSS Primary Endpoint

- Change from baseline in 5D-NPCCSS at Month 12 using MMRM model
- Treatment effect: -1.4 (95% CI: -2.8, -0.03; p = 0.0456)

MMRM = mixed model for repeated measures

Study 002 Met Primary Endpoint Using 4D-NPCCSS –
Used FDA-recommended Estimand (While-on-treatment)

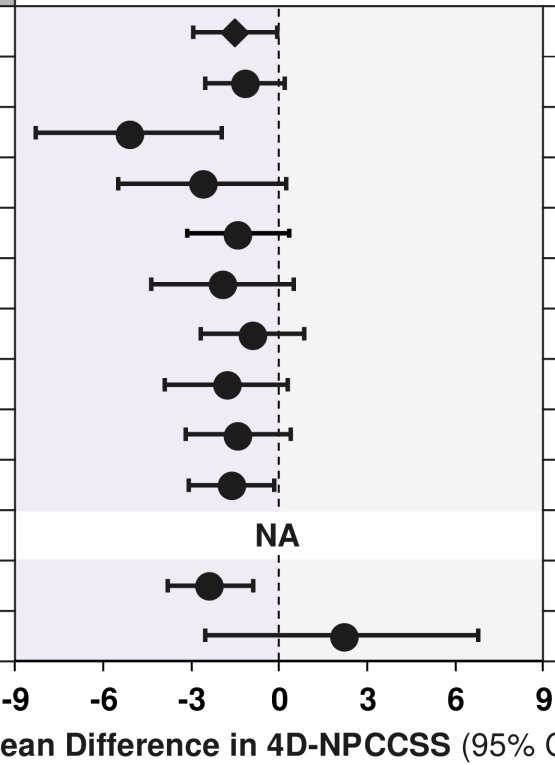
4D-NPCCSS at 12 months	FAS
Mean change (95% CI)	**-1.5** (-3.0, -0.1)
p-value	**0.041**



FAS = full analysis set

Consistent Arimoclomol Treatment Effect Across Subgroups

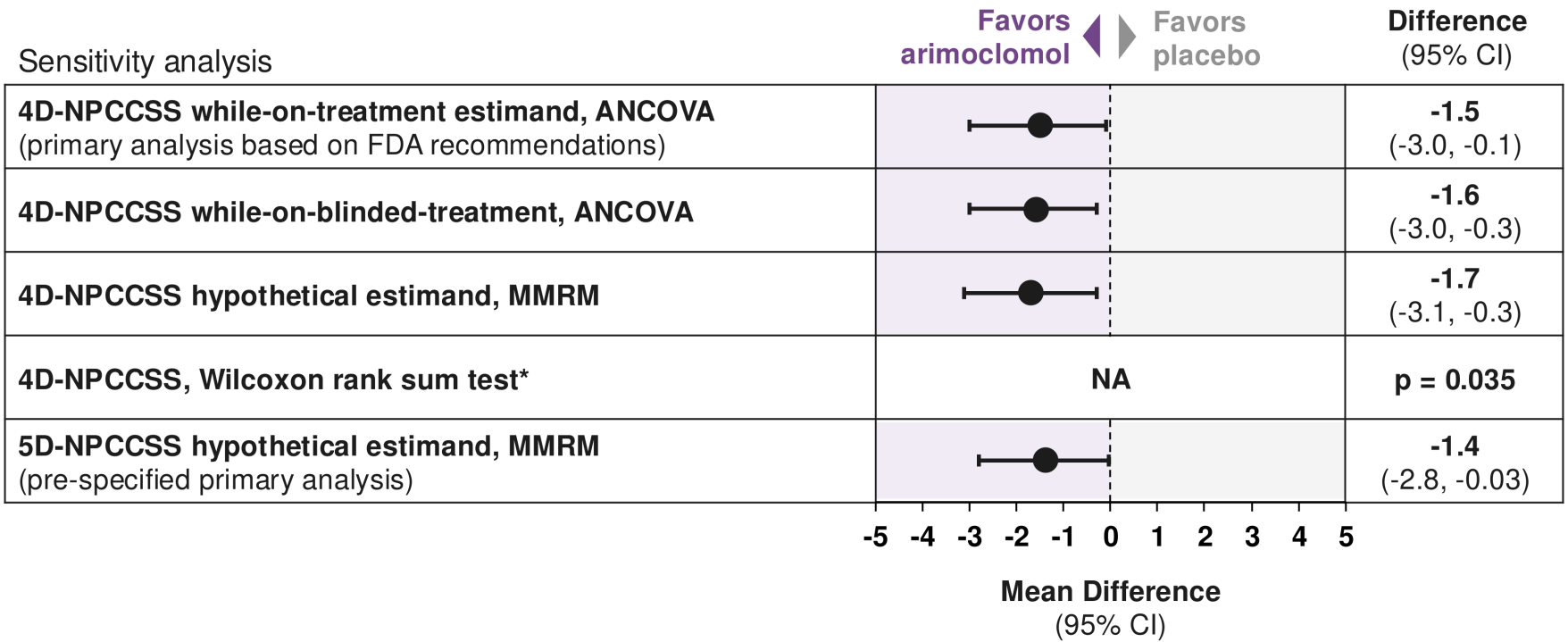
		Arimoclomol N	Placebo N	Difference (95% CI)
Overall		34	15	**-1.5** (-3, -0.1)
Age at baseline	**< 12 years**	16	10	**-1.2** (-2.5, 0.2)
	≥ 12 years	18	5	**-5.1** (-8.3, -1.9)
Age at first neurologic symptom	**< 2 years**	6	3	**-2.6** (-5.5, 0.3)
	≥ 2 years	28	12	**-1.4** (-3.2, 0.3)
Sex	**Female**	17	8	**-1.9** (-4.4, 0.5)
	Male	17	7	**-0.9** (-2.7, 0.8)
Baseline 4D-NPCCSS	**≤ 8**	17	11	**-1.8** (-3.9, 0.3)
	> 8	17	4	**-1.4** (-3.2, 0.4)
Double functional null mutation	**No**	31	15	**-1.6** (-3.1, -0.2)
	Yes	3	0	**NA**
Miglustat use	**On Miglustat**	26	12	**-2.4** (-3.8, -0.9)
	Off Miglustat	8	3	**2.2** (-2.5, 6.8)



Baseline Imbalances Confound Interpretation of Off Miglustat Subgroup

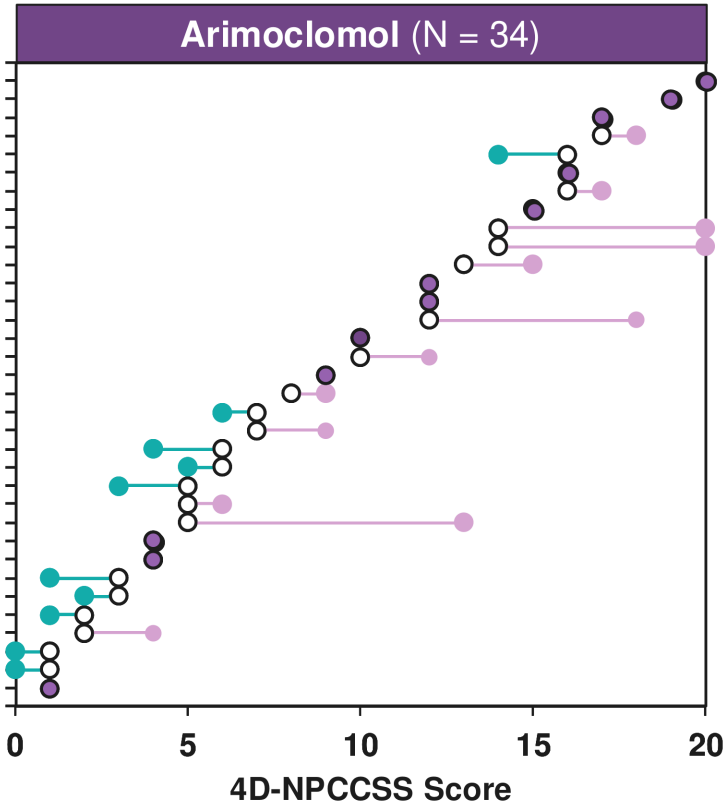
	On Miglustat		Off Miglustat	
	Arimoclomol N = 26	Placebo N = 12	Arimoclomol N = 8	Placebo N = 3
Age (years), mean (SD)	**12.9** (4.7)	**9.2** (3.8)	**7.0** (5.4)	**15.0** (1.7)
Age of neurological onset (years), mean (SD)	**5.3** (3.3)	**4.1** (3.3)	**4.4** (3.9)	**10.3** (1.5)
Baseline 4D-NPCCSS, mean (SD)	**8.9** (6.1)	**7.2** (6.0)	**10.1** (5.1)	**5.3** (0.6)
Double functional null mutation, n (%)	0	0	**3 (38%)**	**0**

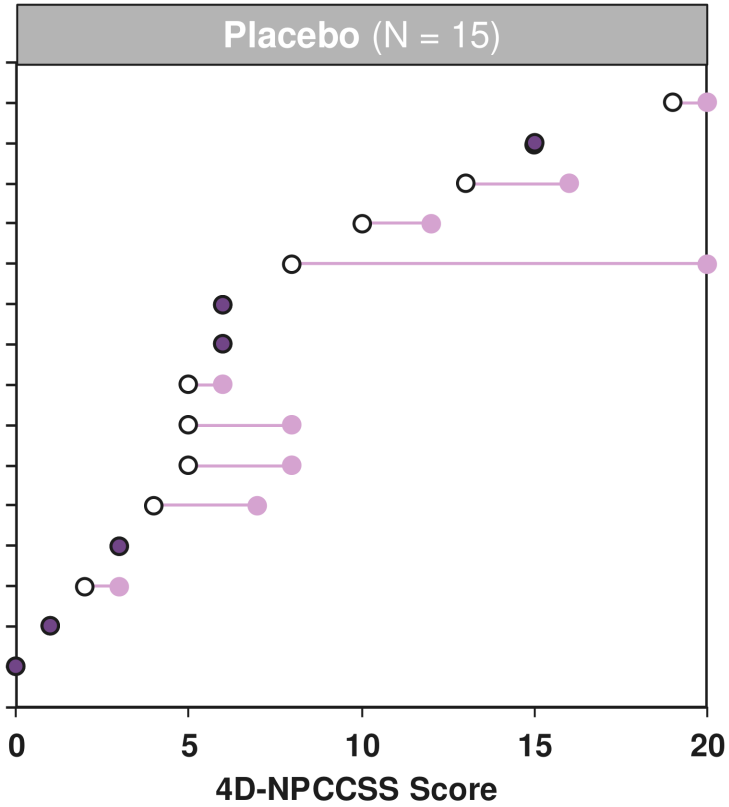
Consistent Arimoclomol Benefit in Sensitivity Analyses



*Nonparametric test does not produce treatment effect on same scale
ANCOVA = analysis of covariance; MMRM = mixed model for repeated measures

Study 002 Patient-level Analysis of 4D-NPCCSS Illustrates Arimoclomol Benefit





Score at Baseline

Score at 12 Months

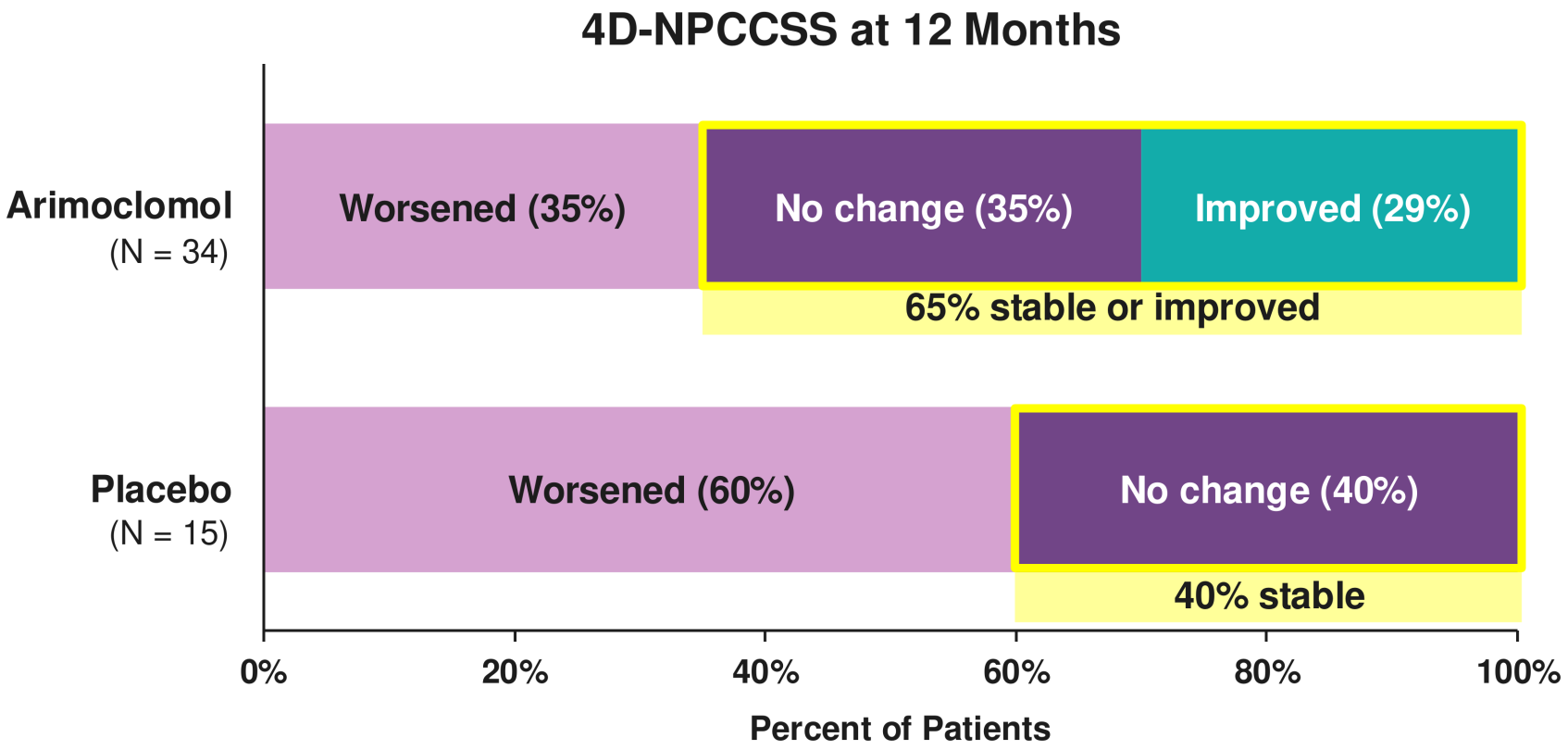
Improved

No Change

Worsened

Patients sorted by baseline score, followed by change from baseline

More Patients on Arimoclomol had Favorable Outcomes



Study 002 While-on-treatment estimand

Study 002 Efficacy Analyses Consistently Show Arimoclomol Slows Natural Course of NPC

1 Adequate and well-controlled study

+

Confirmatory evidence

- NPCCSS, a validated instrument created by NIH
- Primary endpoint domain scoring and statistical analyses revised based on FDA requests and recommendations
- Clinically and statistically significant treatment effect on NPCCSS endpoint at 12 months
  - Pre-specified analysis
  - FDA-recommended estimand and statistical approach
- Treatment effect robust to multiple sensitivity analyses

Confirmatory Clinical Evidence Supporting Effectiveness

Travis Mickle, PhD

Co-Founder, Senior Advisor

Zevra Therapeutics

Confirmatory Clinical Evidence Supporting Effectiveness

- ✓ **Additional Analyses from Studies 001 and 002 OLE**
- ✓ Natural History
- ✓ Expanded Access Program (EAP)

Studies 001 and 002 Enable Pre-Post Analyses of Arimoclomol Treatment

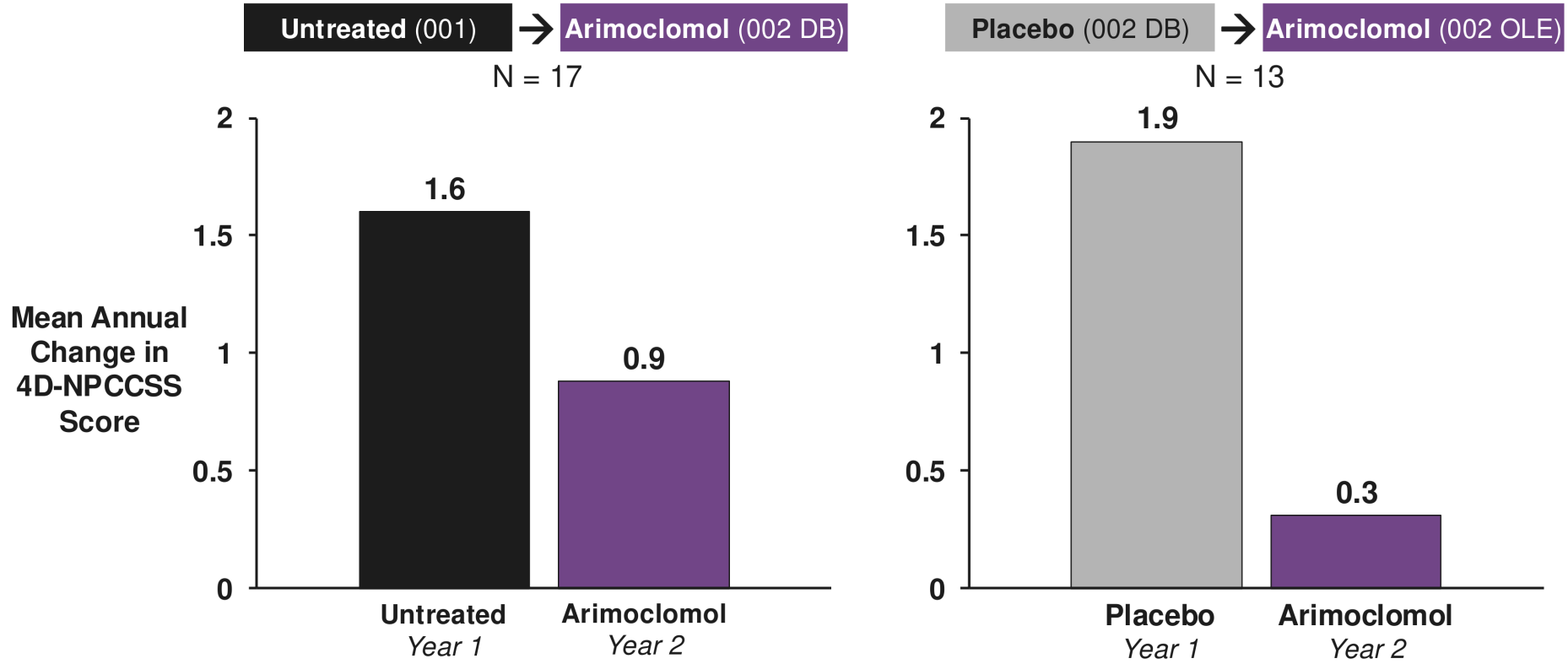
- Compared untreated or placebo to arimoclomol in paired analyses where patients served as their own control
  - Annual change in 4D-NPCCSS

Analysis #1 (N=17)	Year 1: untreated in Study 001	vs.	Year 2: arimoclomol in Study 002 DB
Analysis #2 (N=13)	Year 1: placebo in Study 002 DB	vs.	Year 2: arimoclomol in Study 002 OLE*

** Patients and physicians unaware of randomized assignment for first 2 years of OLE*

DB = double-blind; OLE = open-label extension

Slower Rate of Disease Progression After Initiation of Arimoclomol



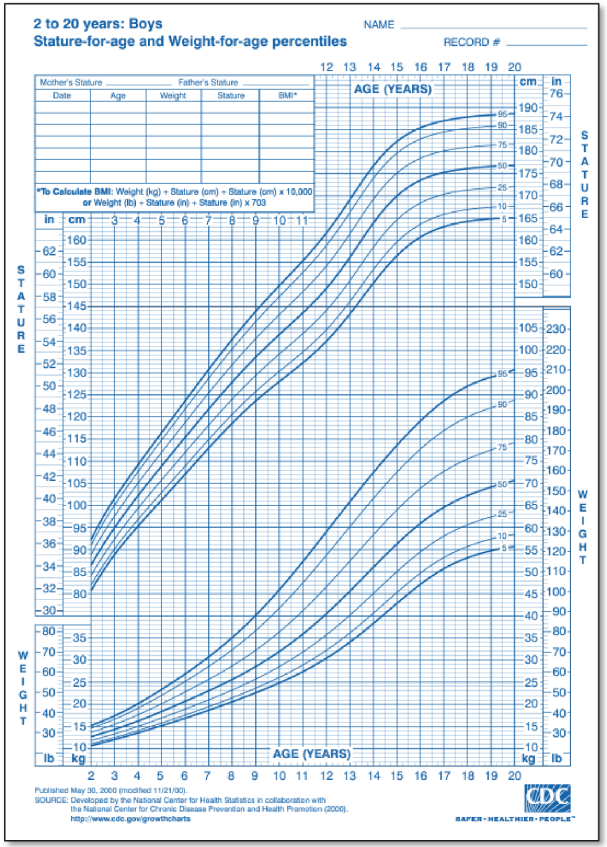
DB = double-blind; OLE = open-label extension

Evaluating Annual Weight Changes Using Z-Scores

- NPC can cause below-average weight gain in children due to swallowing issues and other complications[1]
- Patient weights compared to the respective CDC childhood growth curve for age and sex[2]
  - Z-score calculated for each time point

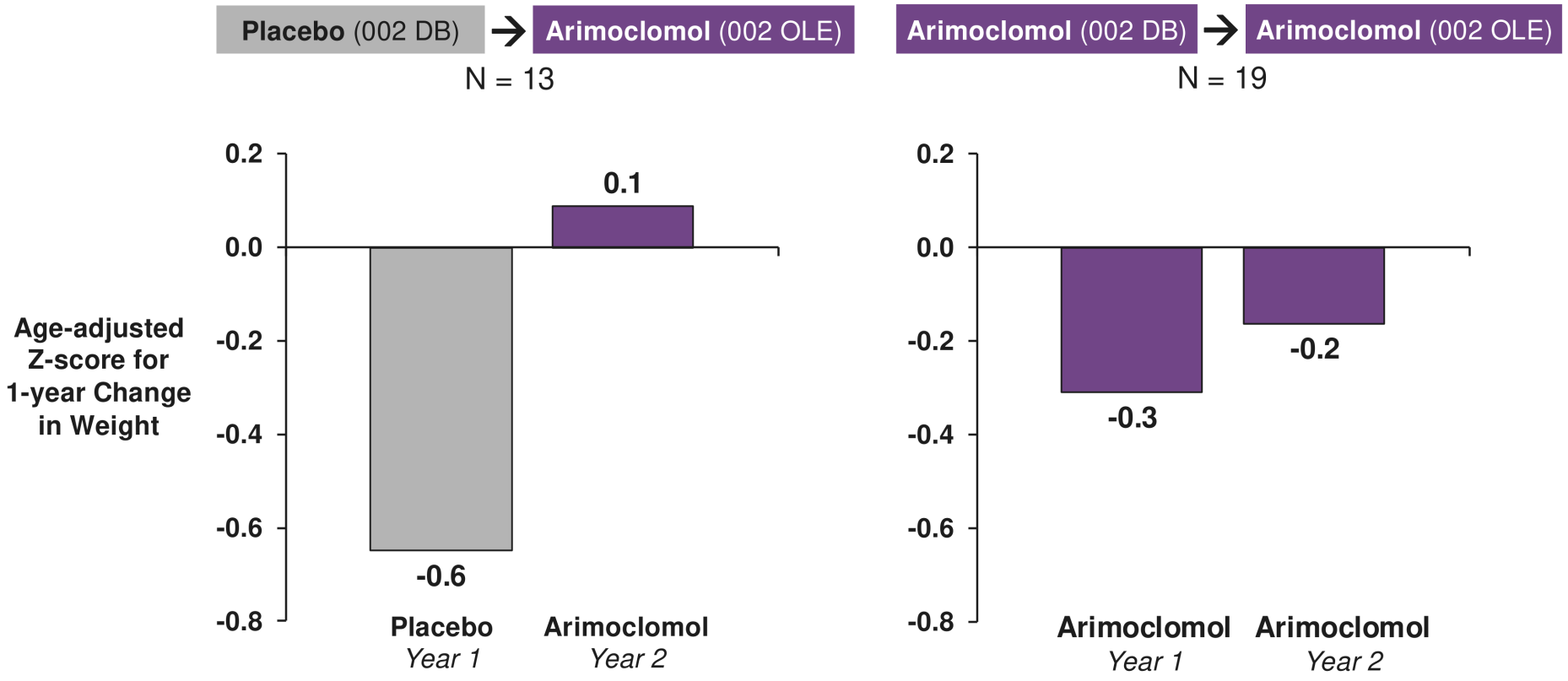
Annual Change in Weight = **Z-score after 1 year** − **Z-score at Baseline**

- *Zero change* indicates average growth
- *Negative values* indicate below-average growth in standard deviation units



1. Geberhiwot et al., 2018; 2. https://www.cdc.gov/growthcharts/

Change in Age-Standardized Weight Consistent with Results on Primary Efficacy Endpoint



Confirmatory Clinical Evidence Supporting Effectiveness

- ✓ Additional Analyses from Studies 001 and 002 OLE
- ✓ **Natural History**
- ✓ Expanded Access Program (EAP)

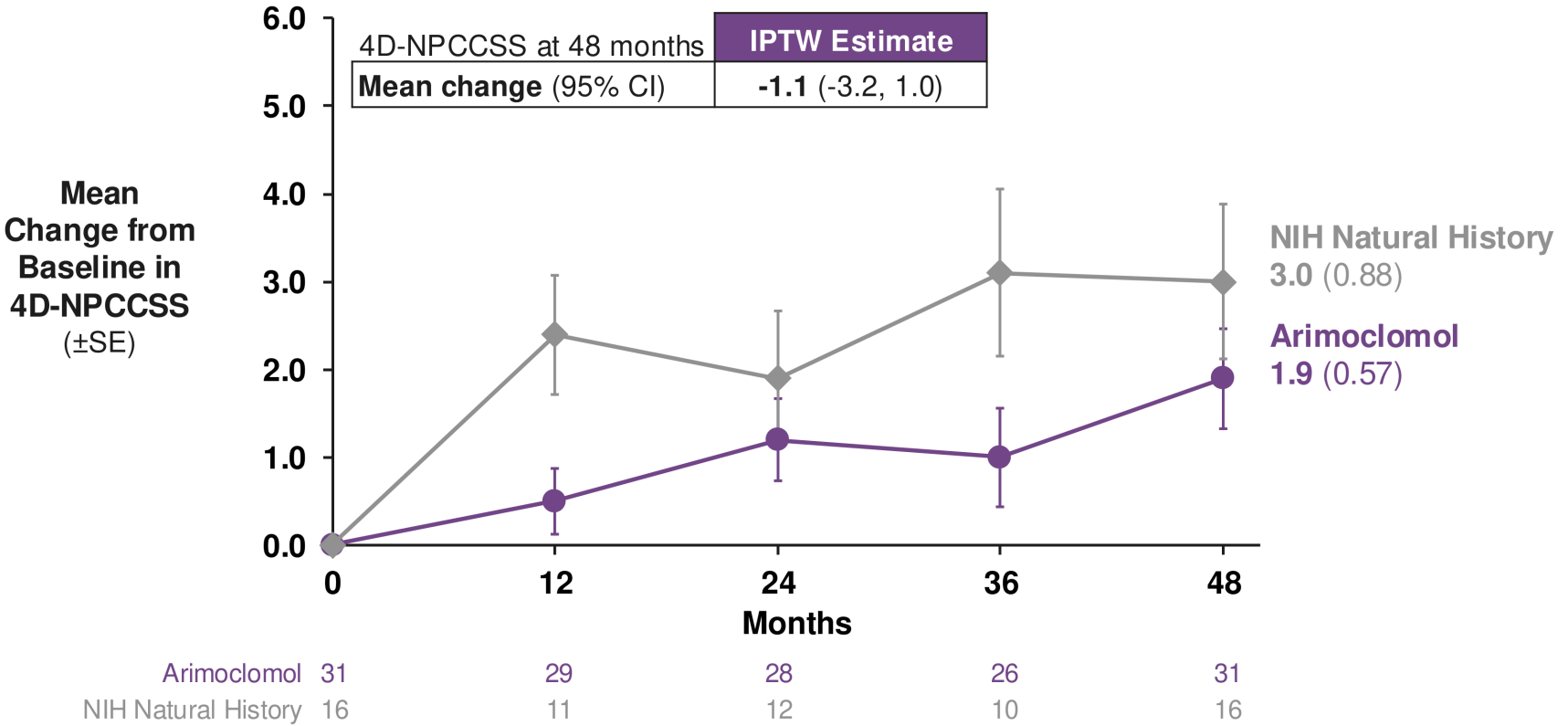
Analysis of Patients in OLE with External Comparators from NIH Natural History Study

FDA requested analysis comparing patients in OLE with NIH natural history cohort who had 4 years of follow-up data

Analysis	▪ Inverse probability of treatment weighted analysis
Inclusion Criteria	▪ Analyzed patients aged ≥ 4 years at baseline to enable matching
Matching Variables	▪ Weighted on baseline age, sex, miglustat use, age of symptom onset, baseline 4D-NPCCSS

NIH = National Institutes of Health

Arimoclomol Demonstrates Slower Disease Progression vs Natural History Patients

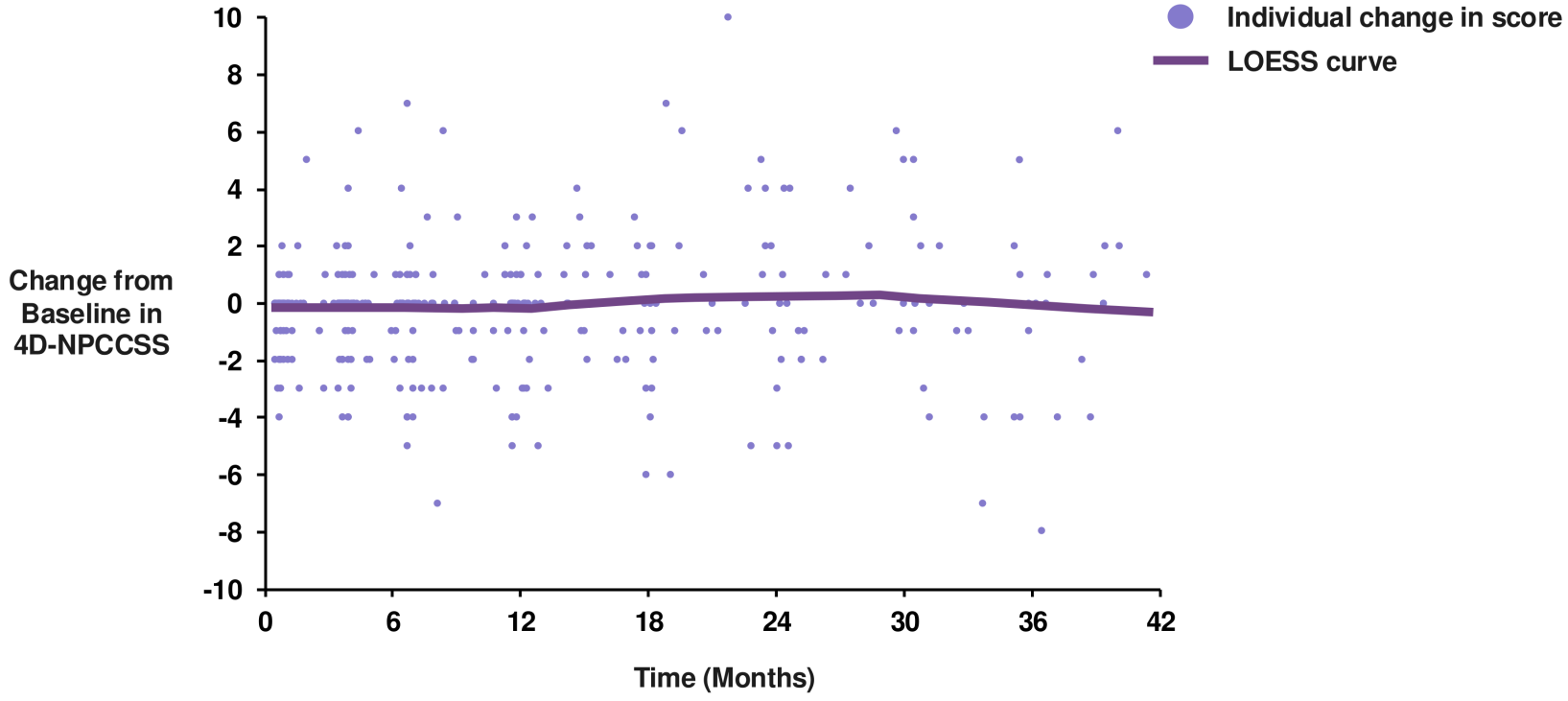


IPTW = inverse probability of treatment weighting; 4D-NPCCSS with original Swallow domain

Confirmatory Clinical Evidence Supporting Effectiveness

- ✓ Additional Analyses from Studies 001 and 002 OLE
- ✓ Natural History
- ✓ **Expanded Access Program (EAP)**

Change in 4D-NPCCSS in Arimoclomol Expanded Access Program (EAP)

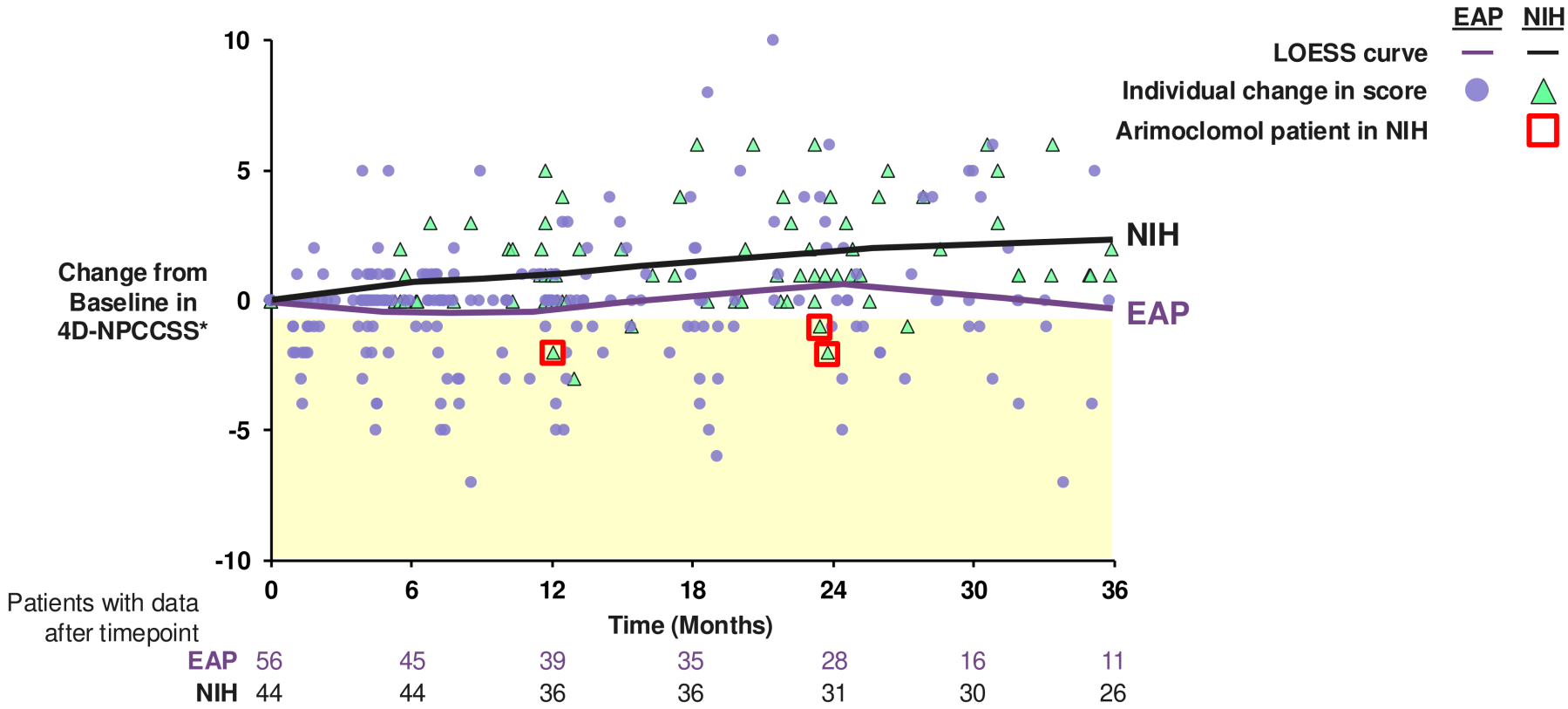


Analyses of EAP and NIH Natural History Data

- US data from EAP and NIH natural history cohort
- Analyzed patients aged 4 – 30 years to make datasets more comparable
- No other inclusion/exclusion criteria applied

	Patients Aged 4 to 30 years	
	EAP N = 56	**NIH N = 44**
Age (years), mean (range)	**16.5** (4 – 30)	**13.6** (4 – 30)
Baseline 4D-NPCCSS (SD)	**8.2 (5.1)**	**4.9 (4.2)**
Miglustat use, n (%)	**39 (70%)**	**21 (48%)**

Change in 4D-NPCCSS in Arimoclomol Expanded Access Program (EAP)



* 4D-NPCCSS with original Swallow domain

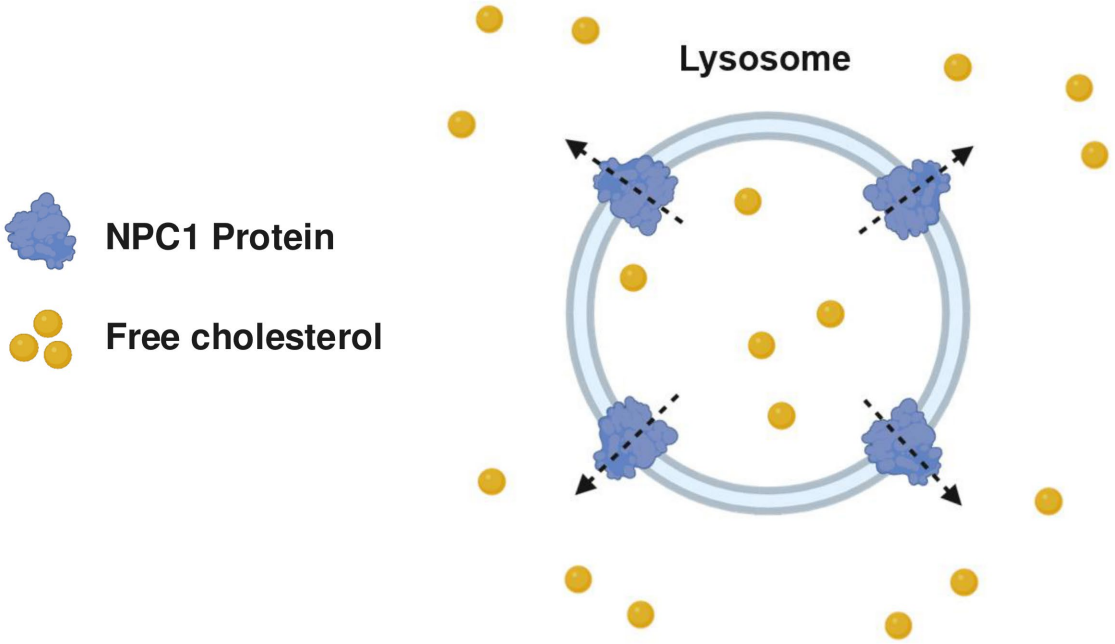
Nonclinical Confirmatory Evidence

- ✓ Mechanism of Action
- ✓ NPC Animal Data
- ✓ Effect of Miglustat

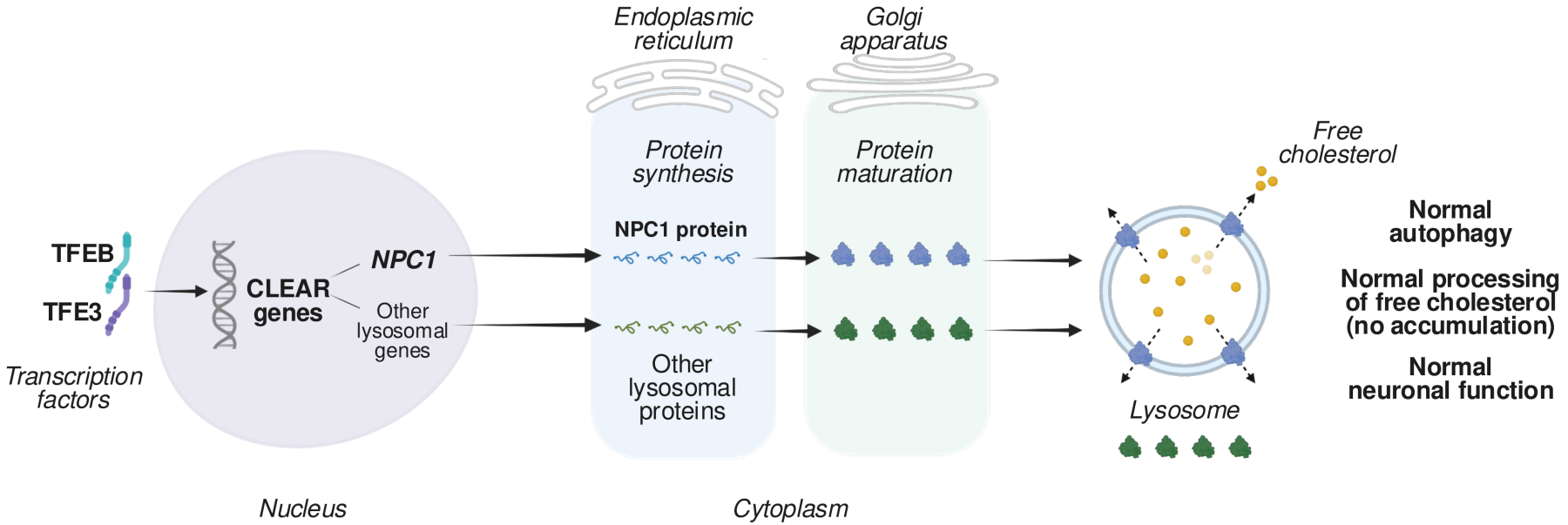
Nonclinical Confirmatory Evidence

- ✓ **Mechanism of Action**
- ✓ NPC Animal Data
- ✓ Effect of Miglustat

NPC1 Protein Clears Free Cholesterol From Lysosomes

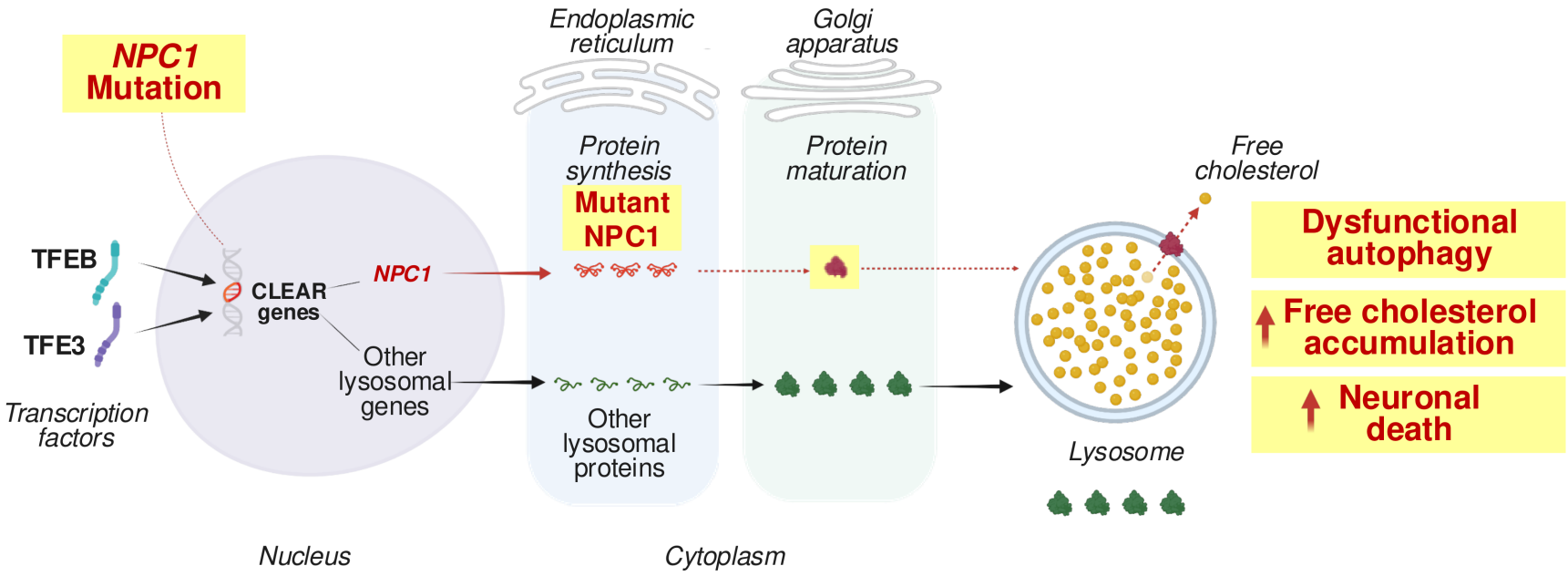


Healthy Lysosomal Function



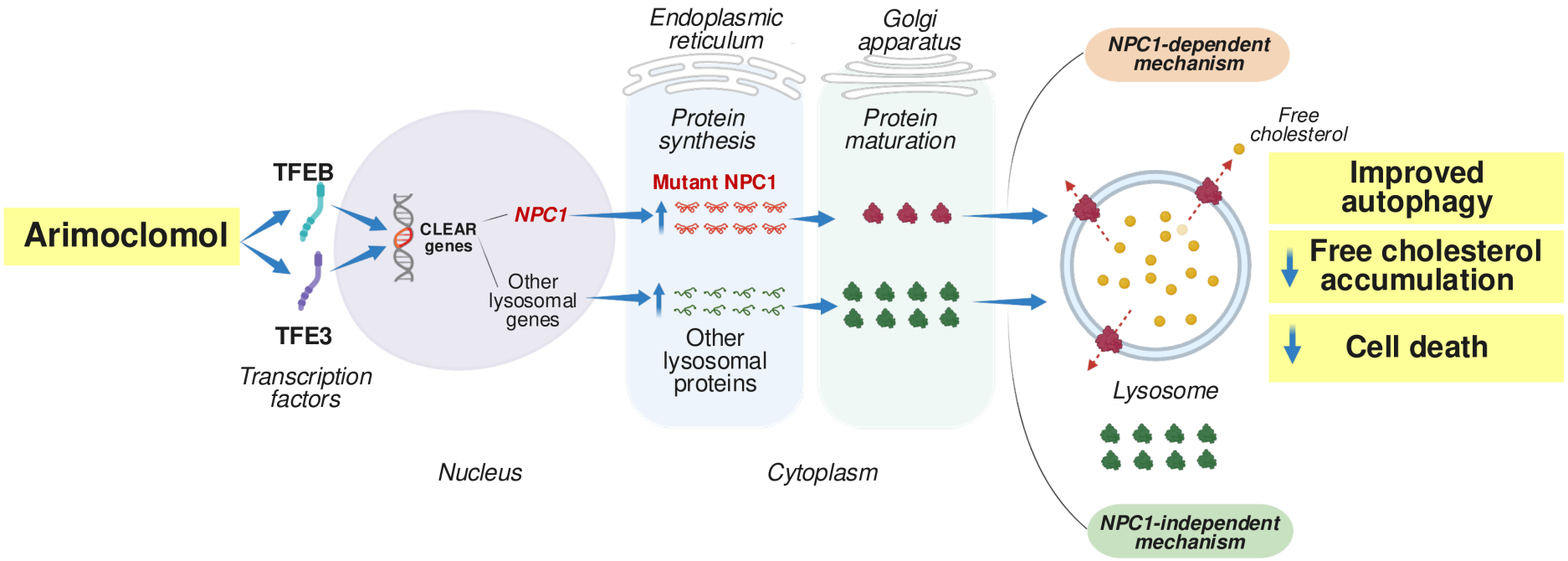
CLEAR = Coordinated Lysosomal Expression and Regulation

Untreated NPC Disease



CLEAR = Coordinated Lysosomal Expression and Regulation

Arimoclomol Improves Lysosomal Function in NPC Disease by Two Pathways



CLEAR = Coordinated Lysosomal Expression and Regulation

Rationale for *In Vitro* Assays and *In Vivo* Models

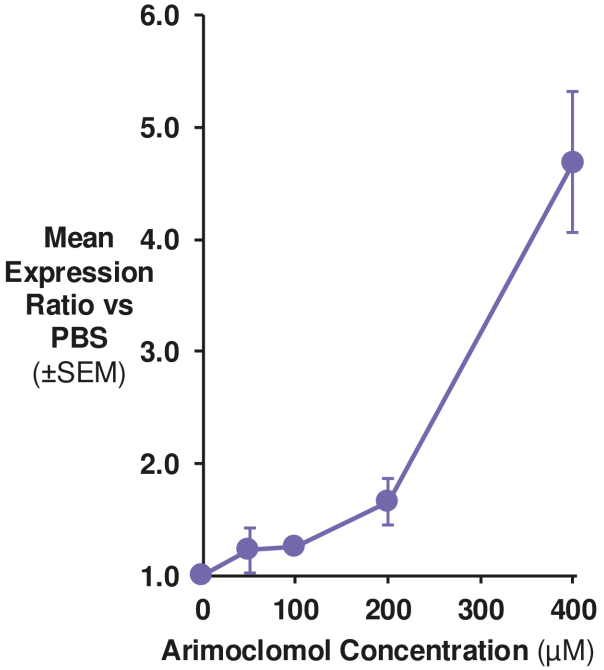
- *In vitro* models focused on studies in wild-type and mutant fibroblasts of various genotypes
- High concentrations required to measure effect due to high cellular and target turnover rate, so ratio of *in vitro* to human plasma concentrations difficult to interpret
- Dosing in clinical trials based on safety margin from animal toxicology models
- Patients achieved exposures higher than effective doses in NPC mouse models

Effective Mouse Doses (mg/kg/day arimoclomol citrate)	**Human Exposure Relative to Mouse** (dosed at 124 mg* arimoclomol TID)
30	**6.0-fold higher**
50	**3.6-fold higher**
100	**1.8-fold higher**

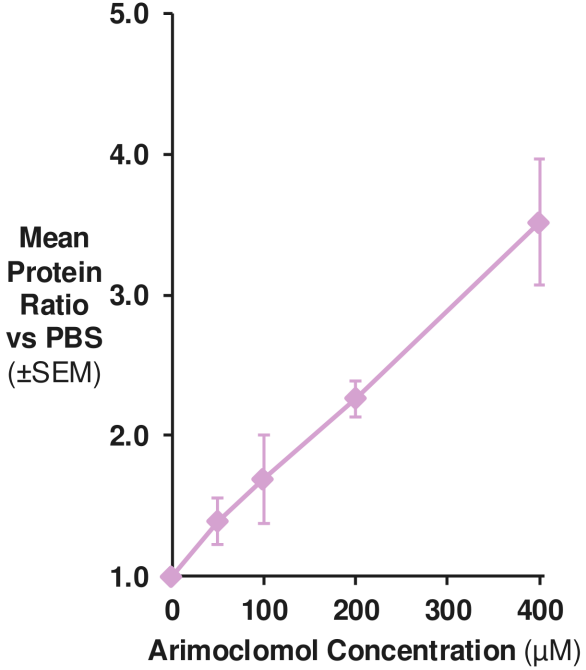
***Corresponds to 200 mg/day arimoclomol citrate**

Arimoclomol Upregulates CLEAR Network Genes, Leading to Increased NPC1 Protein and Improved Lysosomal Function

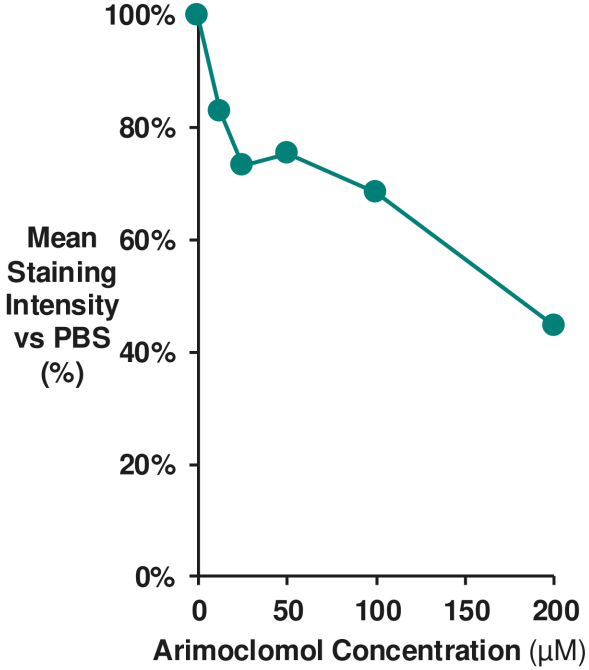
Increased *NPC1* Gene Expression



Increased NPC1 Protein Concentrations



Reduced Unesterified Cholesterol in Human NPC Fibroblasts



Test system in all 3 studies: NPC patient fibroblasts (I1061T/I1061T)

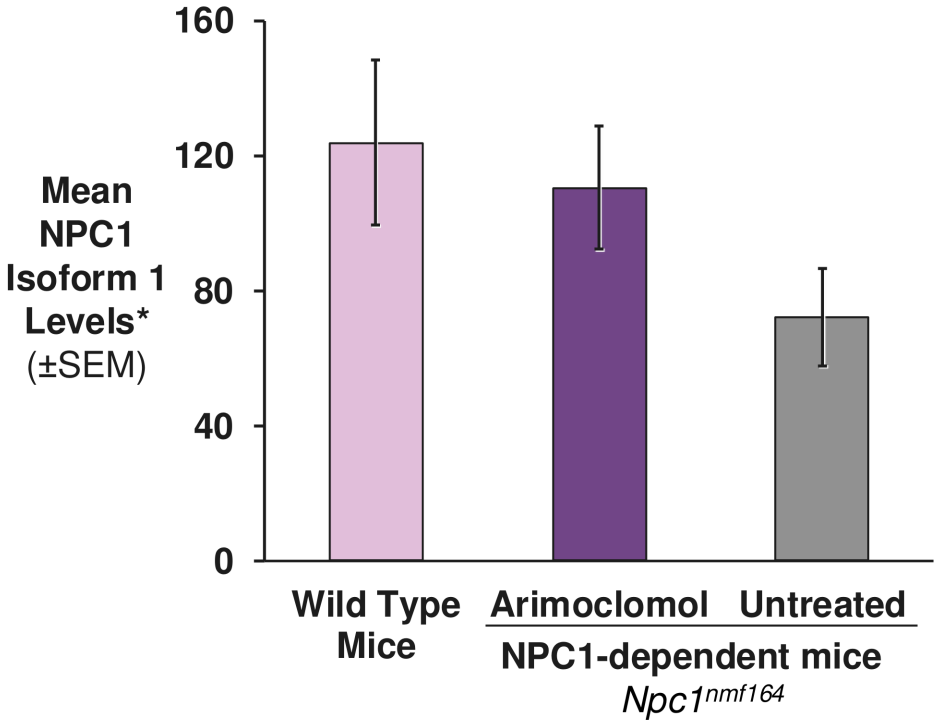
Nonclinical Confirmatory Evidence

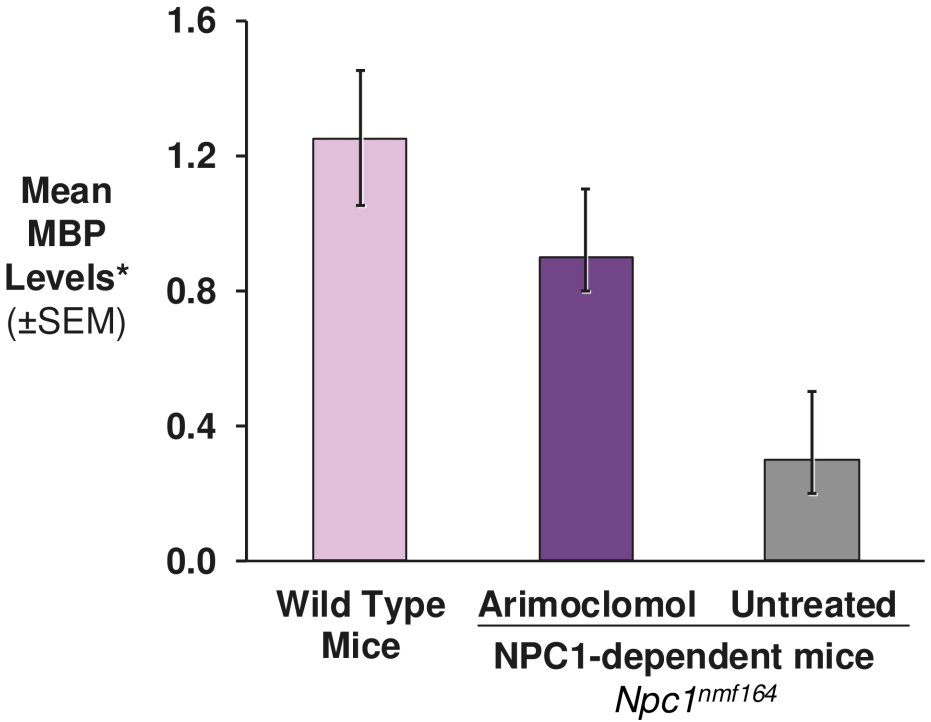
- ✓ Evidence of Mechanism of Action
- ✓ **NPC Animal Data**
- ✓ Effect of Miglustat

Overview of NPC Animal Study Designs

- **NPC mouse models**
  - NPC-independent (*Npc1*$^{-/-}$): represent double functional null mutations with no functional NPC1 protein
  - NPC-dependent (*Npc1*^{nmf164}): represent point mutations with some dysfunctional NPC1 protein
- **Key objective endpoints across *in vivo* studies**
  - NPC1 and myelin basic protein levels in brain
  - Survival

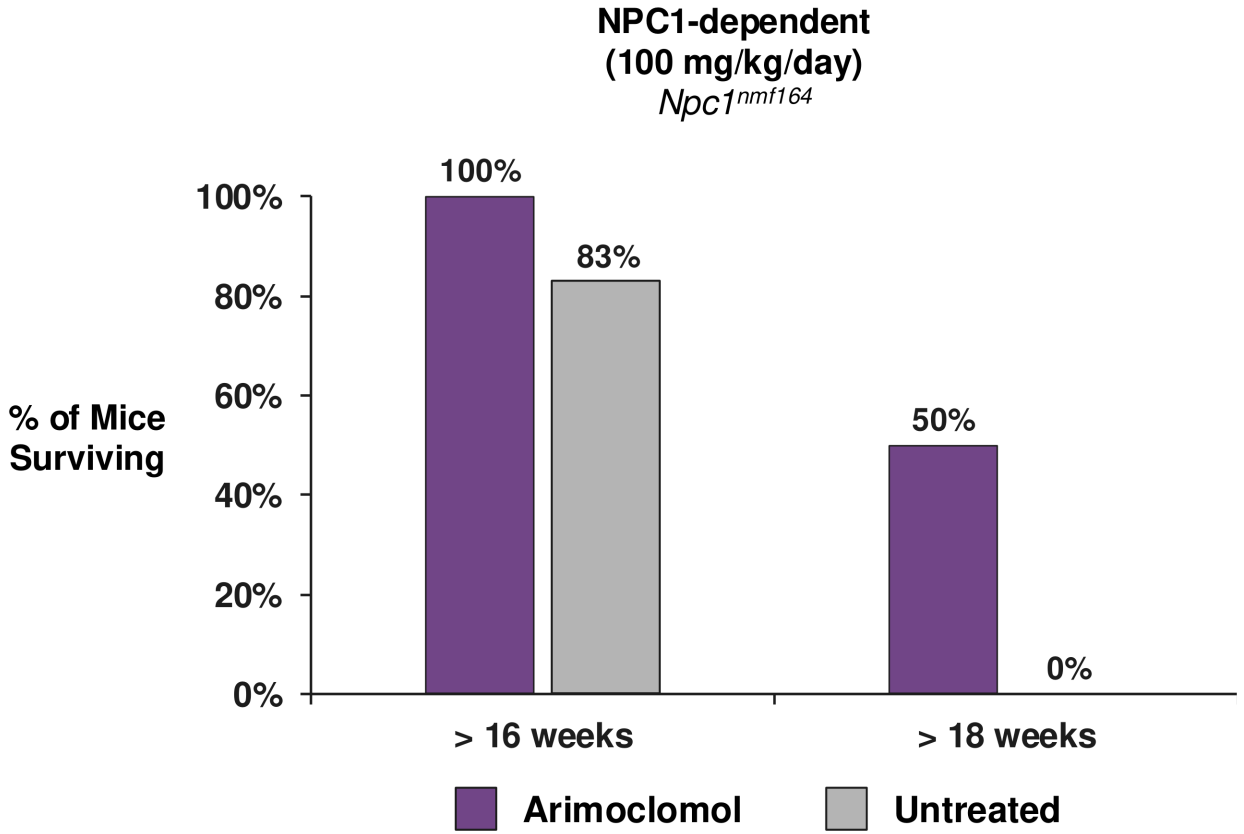
In Vivo NPC Mice Data Show Arimoclomol Increased Mature NPC1 Protein and Myelin Basic Protein in Brain





* Levels expressed as percentage relative to tubulin

In Vivo NPC Mice Studies Demonstrated Increased Survival With Arimoclomol

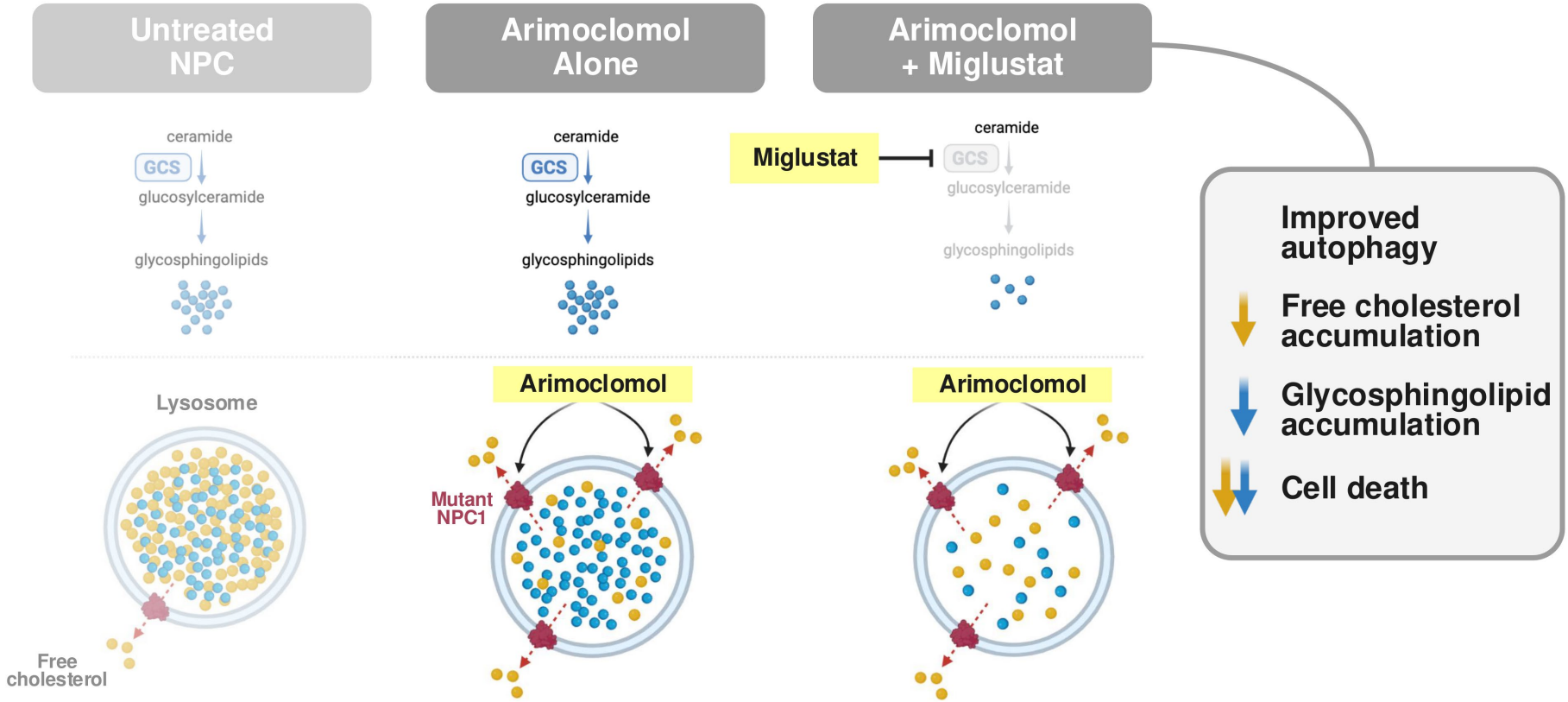


Mean Survival	
Arimoclomol	Untreated
18.3 weeks	16.7 weeks

Nonclinical Confirmatory Evidence

- ✓ Evidence of Mechanism of Action
- ✓ NPC Animal Data
- ✓ **Effect of Miglustat**

Arimoclomol and Miglustat Have Complementary Mechanisms of Action



Reduction in Cholesterol Achieved with Arimoclomol and Miglustat Measured Independently and in Combination

Percent Difference vs Vehicle Control in Unesterified Cholesterol in Human NPC Fibroblasts

14 Days of Treatment		Miglustat 0 µM	Miglustat 10 µM	Miglustat 30 µM	Miglustat 100 µM
Arimoclomol	0 µM	0%	-27%	-39%	-44%
	50 µM	-11%	-35%	-46%	-55%
	100 µM	-18%	-29%	-41%	-50%
	200 µM	-42%	-54%	-63%	-78%

Confirmatory Effects of Miglustat with Arimoclomol

In Vitro Data / Mechanism of Action	▪ Greater clearance of unesterified cholesterol ▪ Further enhancement of CLEAR gene upregulation
NPC Animal Data	▪ Improved survival
Clinical Data	▪ Treatment effect on 4D-NPCCSS for arimoclomol and miglustat

Confirmatory Evidence is Consistently Aligned, Mutually Reinforcing and Confirming Benefit from Pivotal Trial

1 Adequate and well-controlled study

+

Confirmatory evidence

Clinical	▪ Consistent evidence of slowing of disease progression ▪ Benefit consistent with objective measure of weight
Natural History and EAP	▪ Favorable treatment effect vs matched NIH cohort ▪ Sustained benefit over time observed in EAP
Mechanism of Action	▪ CLEAR gene upregulation ▪ Improved cholesterol clearance, lysosomal function
NPC Animal Model	▪ Increased NPC1 protein and MBP brain concentrations ▪ Beneficial effects on survival
Miglustat	▪ Positive effects of arimoclomol from *in vitro* and *in vivo* studies enhanced with miglustat

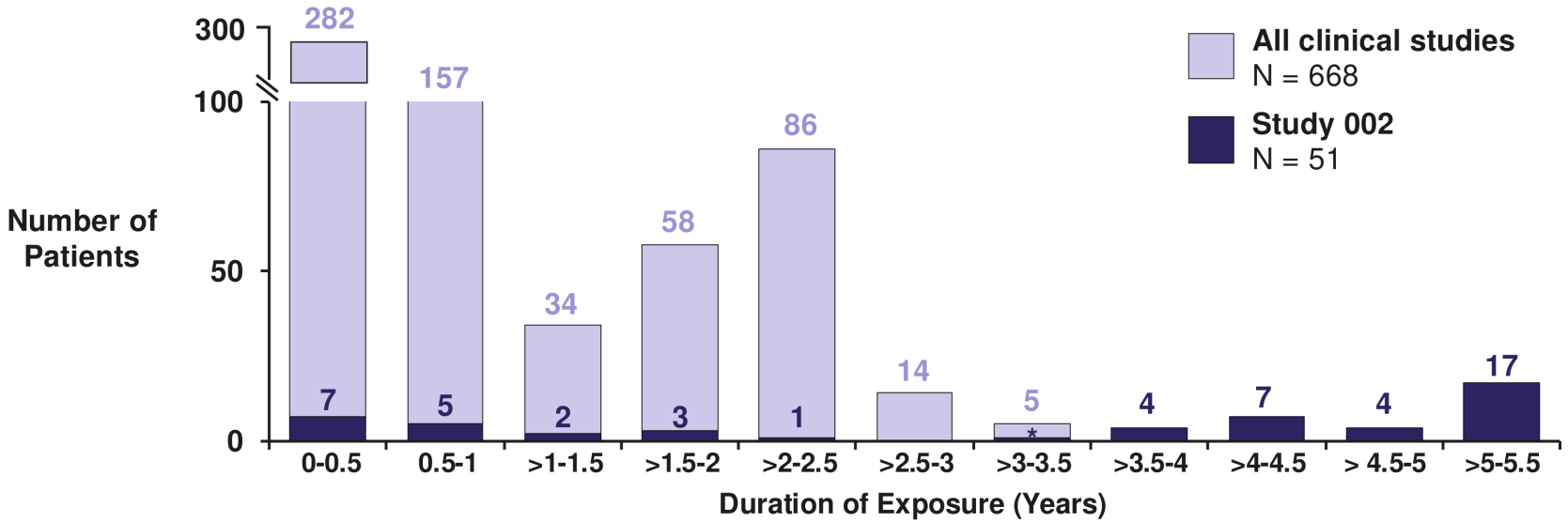
Safety

Christine í Dali, MD

VP, Clinical Science
Zevra Therapeutics

Considerable Safety Database for Ultra-Rare Disease

- 668 individuals in clinical studies across all clinical programs
  - Study 002 dosed 51 patients with NPC; 28 have > 4 years exposure



* 1 patient in Study 002 with a duration of exposure of >3 – 3.5 years

Study 002 (DB): Arimoclomol Safety Profile

	Arimoclomol N = 34	Placebo N = 16
AE	30 **(88%)**	12 **(75%)**
SAE	5 **(15%)**	5 **(31%)**
AE leading to discontinuation of study	3 **(9%)**	0
Deaths	1 **(3%)**	0

Study 002 (DB): 3 Patients Discontinued Arimoclomol Due to Adverse Events and Recovered

AE Leading to Discontinuation	Severity	Study Day Onset	Outcome
Blood creatinine increased	Moderate	177	Recovered
Urticaria / angioedema	Moderate	28	Recovered
Urticaria / angioedema	Moderate	28	Recovered

Arimoclomol is Well-tolerated

- Did not add to high patient burden of disease
- Similar incidence rates of AEs between treatment groups in DB
- No new safety signals in long-term follow-up
  - 4 years of OLE (N = 41)
  - 3.5 years of Expanded Access Program (N = 206)
- No significant safety concerns or risks identified with use of arimoclomol in patients with NPC

Clinical Perspective

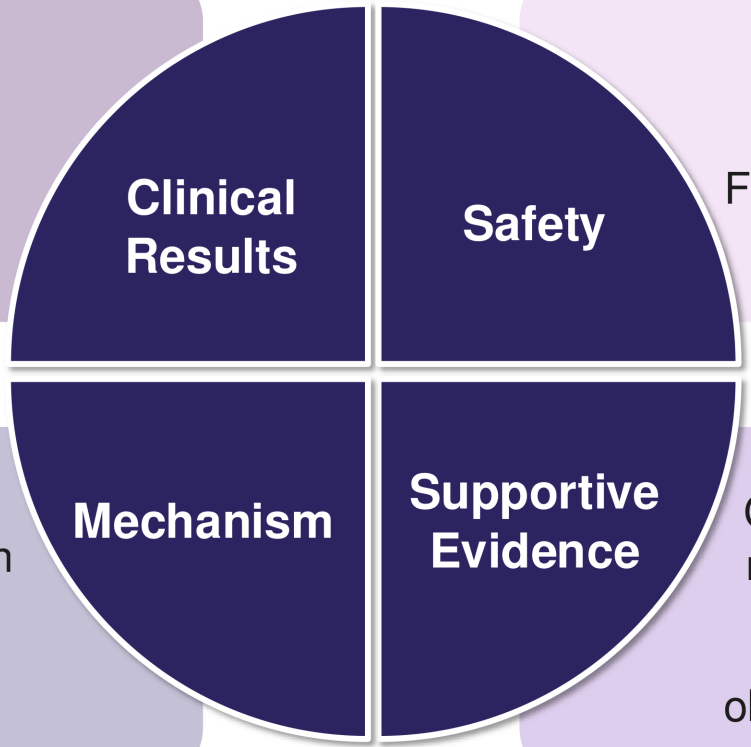
Kristina Julich, MD

Assistant Professor, Department of Neurology
Chief, Pediatric Neurogenetics Center
University of Texas at Austin

Arimoclomol is a Safe and Effective Treatment for Patients with NPC Based on 4 Important Points

NPCCSS evaluates meaningful changes in heterogeneous population

Pivotal study shows slowing of progression



Well tolerated therapy

Few AEs observed in EAP

Mechanism consistent with preservation of neurons in models of NPC

Consistent benefit across multiple lines of evidence

Sustained benefit observed in OLE and EAP

Arimoclomol for the Treatment of Niemann-Pick Disease Type C (NPC)

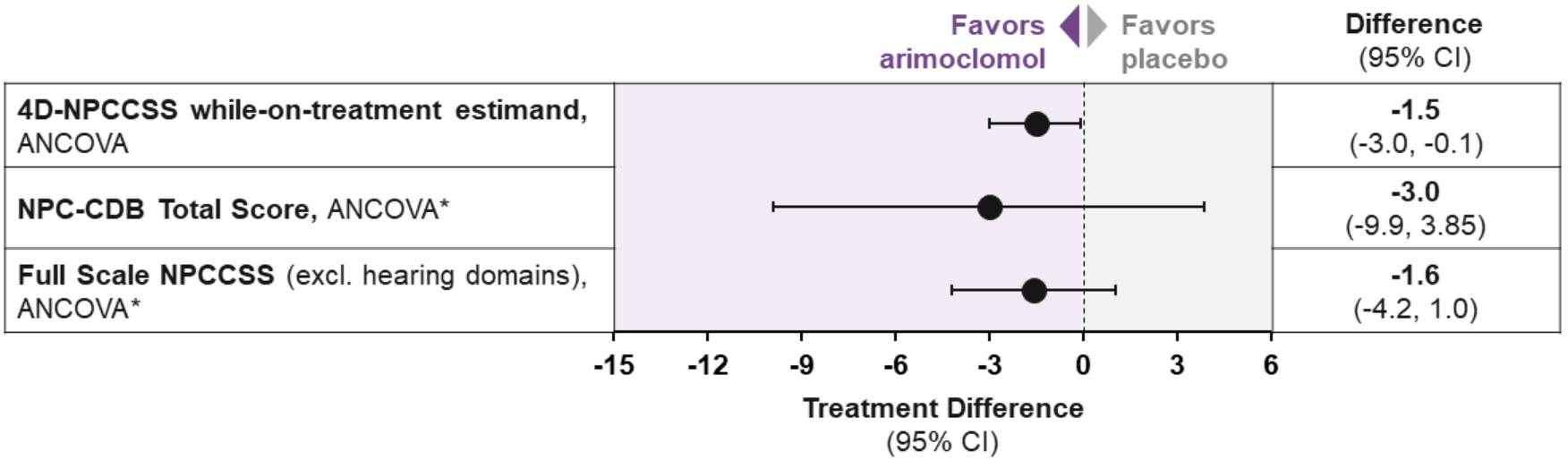
August 2, 2024

Zevra Therapeutics

Genetic Metabolic Diseases Advisory Committee

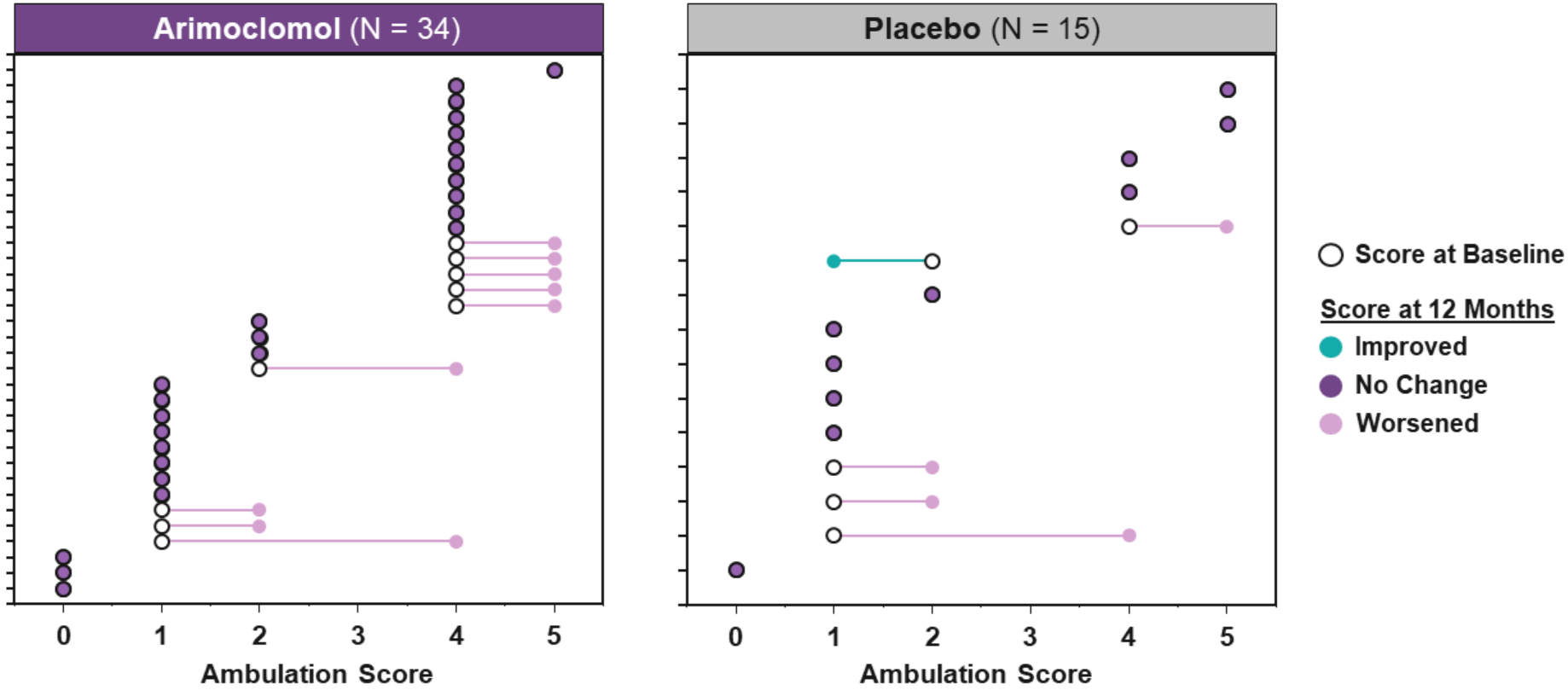
Back Up Slides Shown

NPC-Specific Secondary Endpoints: NPCCSS (excl. hearing domains), NPC-cdb



*ANCOVA was fitted with treatment, baseline value and miglustat use as covariates

Study 002 (DB): Patient-Level Changes in Ambulation



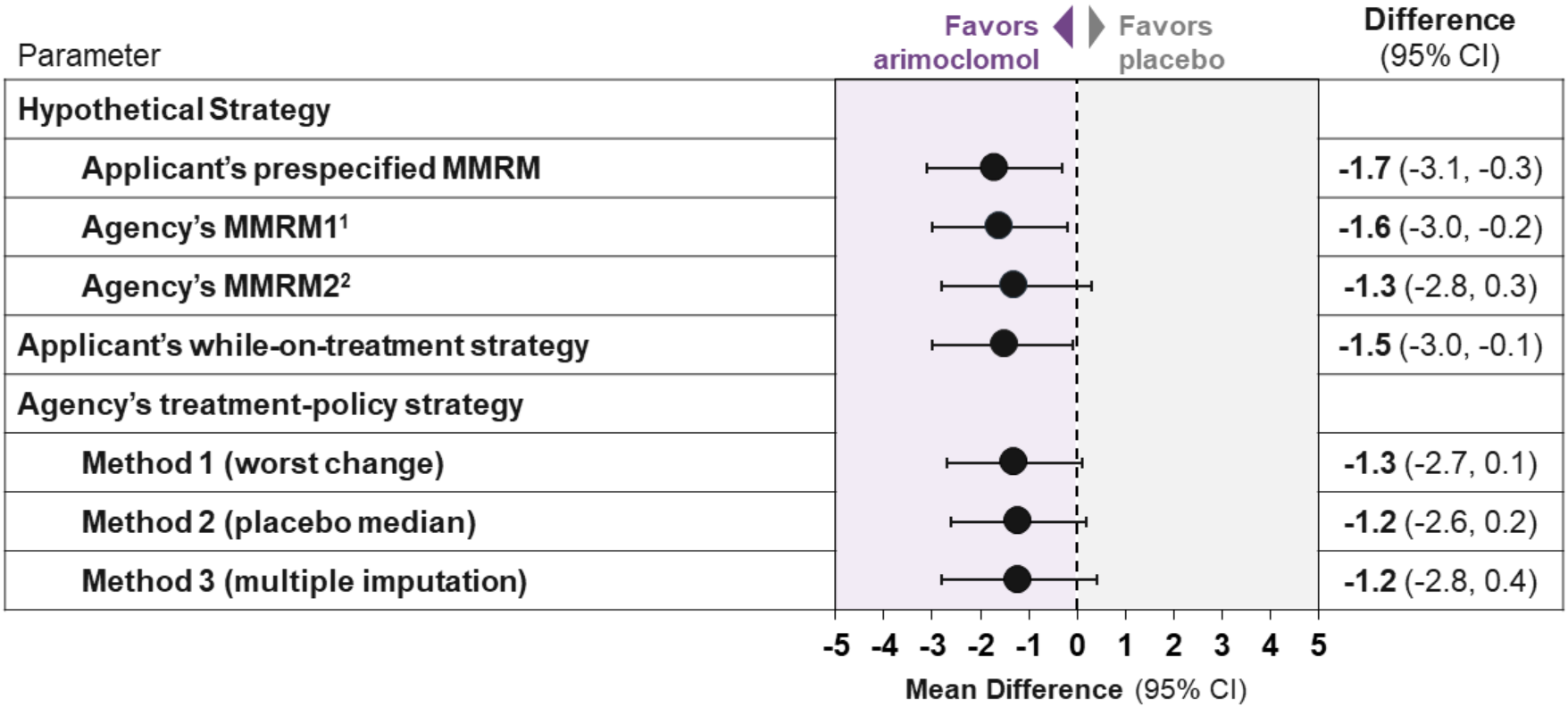
Patients sorted by baseline ambulation score, followed by change from baseline

Study 002 (DB): Baseline and Final Scores for 7 Early Withdrawals

- No pattern in disease severity or progression in early withdrawals

			4D-NPCCSS Score		
Patient	Reason for Withdrawal	Last Month of Follow-up	Baseline	Withdrawal	Difference
1	Withdrew consent	3	12	12	0
2	Urticaria	3	7	6	-1
3	Urticaria	3	5	3	-2
4	Early escape	12	5	13	8
5	Early escape	6	14	20	6
6	Urea/creatinine increased	8	2	1	-1
7	Patient died	6	12	18	6

Sensitivity Analyses for 4D-NPCCSS



1. Excludes data collected after early escape and uses the worst score of 20 as outcomes for visits after death
2. Includes data collected after early escape and uses the worst score of 20 as outcomes for visits after death

Revised swallow domain reduces scoring options by disregarding texture (liquid/solid)

- One modification of removing texture from the scoring options
- Confirmed by 9/12 clinicians in the FDA reviewed Qualitative Study

Swallow categories captured in the CRF

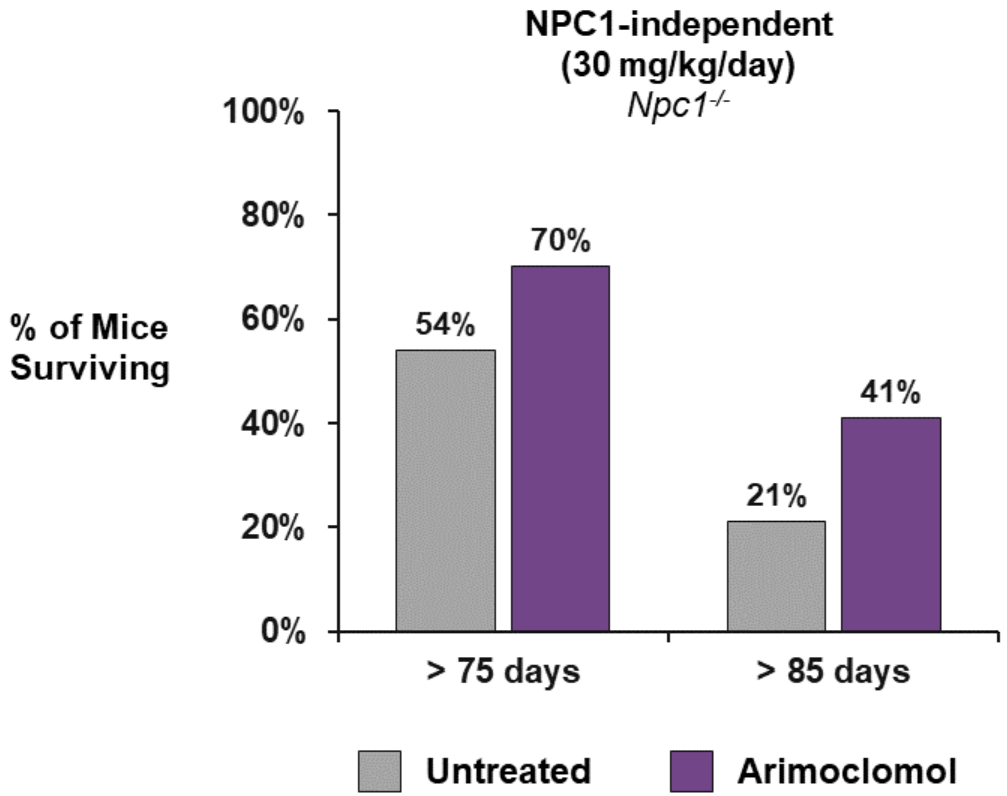
Intermittent dysphagia (liquids)	2
Intermittent dysphagia (solid)	2
Intermittent dysphagia (liquids) + Intermittent dysphagia (solids)	3
Dysphagia (liquids)	3
Dysphagia (solids)	3
Intermittent dysphagia (liquids) + Dysphagia (solid)	4
Intermittent dysphagia (solids) + Dysphagia (liquids)	4
Dysphagia (liquids) + Dysphagia (solids)	5

Updated Swallow	Score
Normal, no dysphagia	0
Cough while eating	1
Intermittent dysphagia	2
Dysphagia	3
Nasogastric tube or gastric tube for supplemental feeding	4
Nasogastric tube or gastric tube feeding only	5

Swallow Domain Scoring Details

0	Normal	No dysphagia. Eats and drinks without hesitation, **no signs of coughing and choking**. Appropriate for age.
1	Cough while eating	**Coughs more than expected** after eating/drinking vs same age on appropriate oral intake
2	Intermittent dysphagia with liquids/solids	**Coughs often** when drinking clear fluids, **but not always**. May be fine if they concentrate, take small sips or use a straw/drinking cup. May cough or choke on certain foods (e.g. meat not chopped small enough or white bread). Can manage food presented in appropriate size and if avoiding not-so-easily-swallowed food.
3	Dysphagia with liquids/solids	**Cough and splutter every time** they drink, particularly clear fluids - liquid may come back down the nose. **Struggles to swallow anything of solid consistency**, chokes often - food needs to be finely chopped or pureed for safe ingestion.
4	Nasogastric tube or gastric tube for supplemental feeding	Can **safely ingest thickened fluids/pureed food** but extra liquids and/or medications needed through nasogastric tube. Can manage some food and drink but takes very long time - sufficient calorie intake cannot be maintained without supplemental tube feeding.
5	Nasogastric tube or gastric tube feeding only	Tube feeding needed to maintain adequate intake and optimum weight. **Oral intake contraindicated** due to **high risk of aspiration** and subsequent **pneumonia** (assessed by speech and language therapist or clinician).

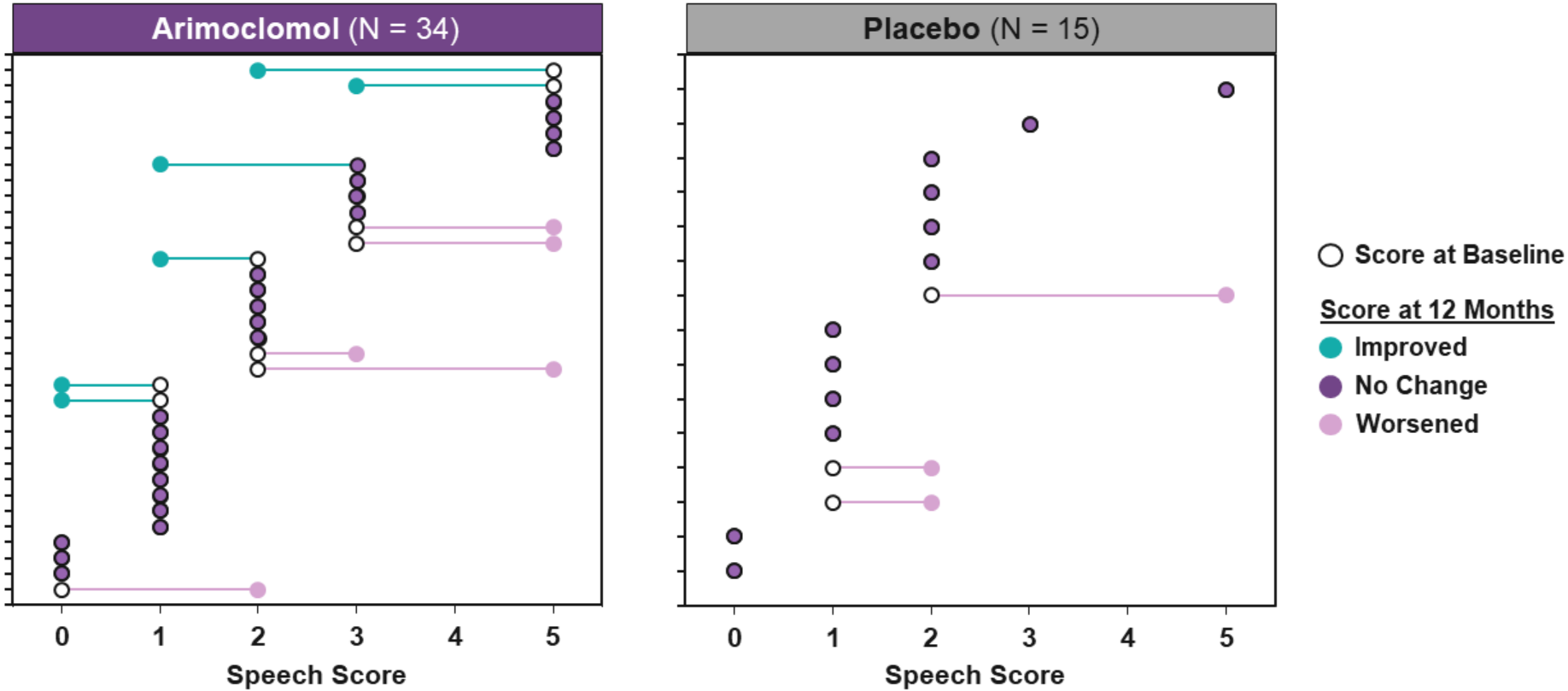
NPC Mice Studies Demonstrated Increased Survival With Arimoclomol in NPC1-independent Model



Study 002 (DB): Summary of Adverse Events

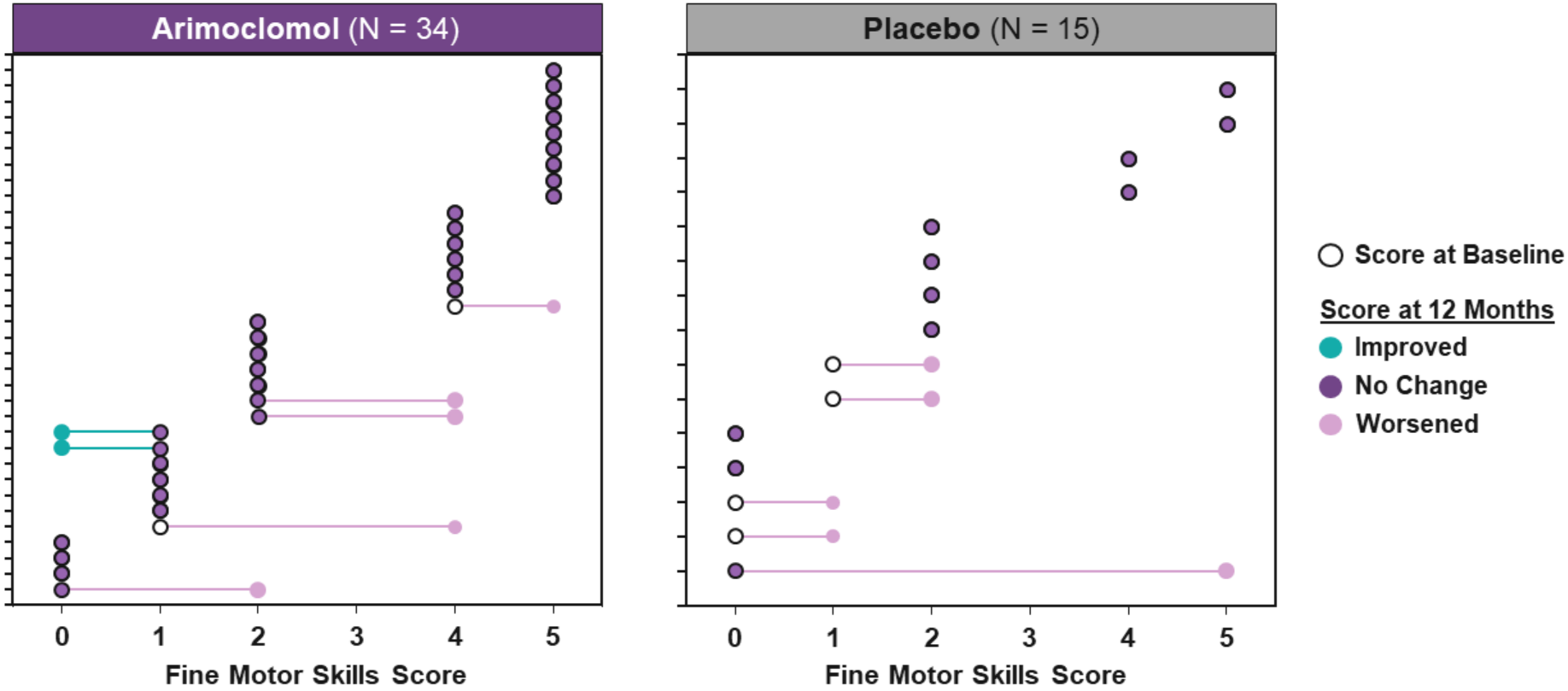
	Arimoclomol N = 34	Placebo N = 16
Any AE	30 **(88%)**	12 **(75%)**
Mild	27 **(79%)**	12 **(75%)**
Moderate	26 **(77%)**	9 **(56%)**
Severe	4 **(12%)**	3 **(19%)**
Serious AE	5 **(15%)**	5 **(31%)**
AE leading to treatment discontinuation	3 **(9%)**	-
AE with fatal outcome	1 **(3%)**	-

Study 002 (DB): Most Arimoclomol Patients Stabilized or Improved in Speech Domain



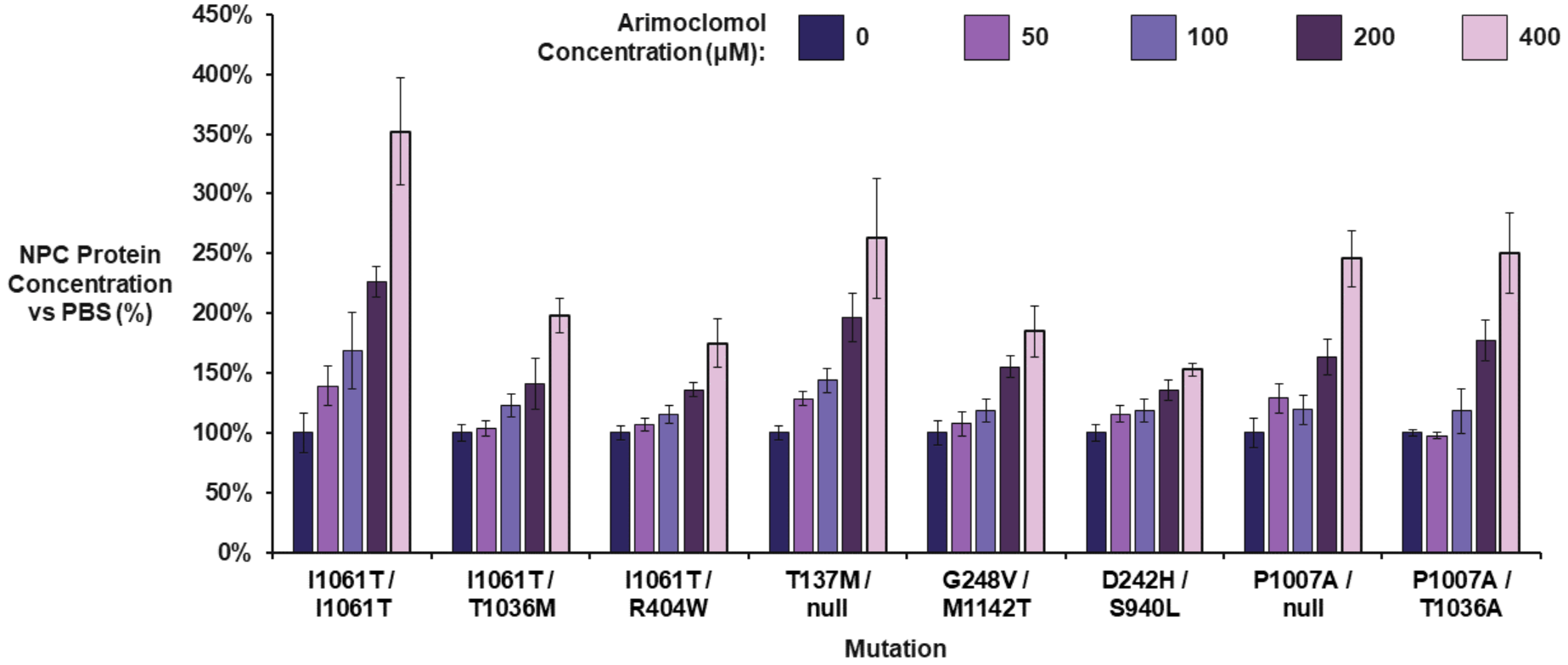
Patients sorted by baseline speech score, followed by change from baseline

Study 002 (DB): Most Arimoclomol Patients Remained Stable in Fine Motor Skills Domain

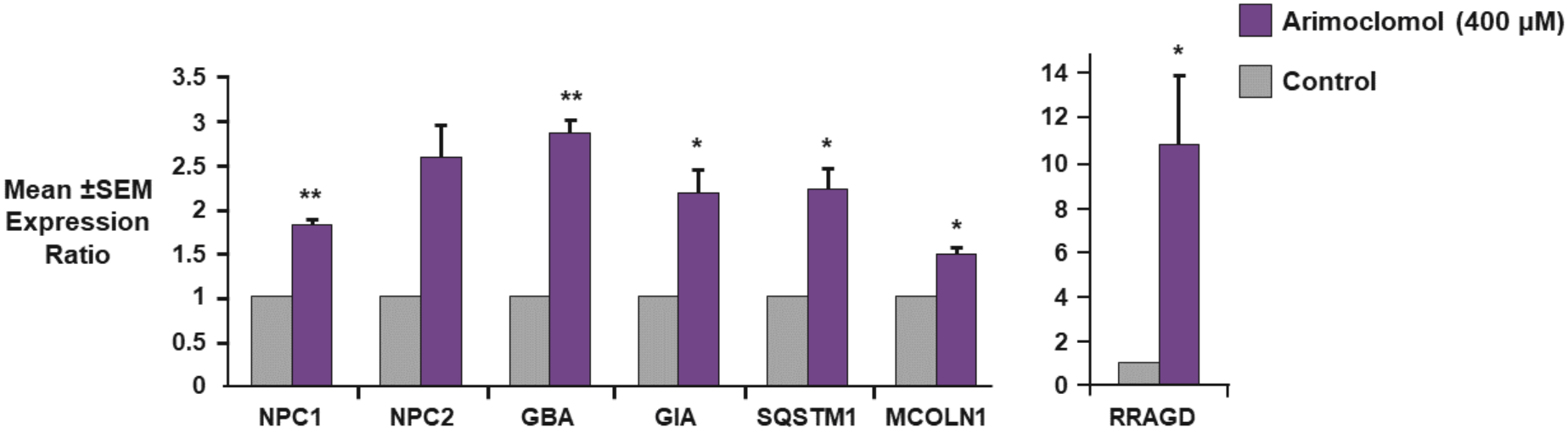


Patients sorted by baseline motor skills score, followed by change from baseline

Increased NPC1 Protein Concentration by Genotype in Human NPC Fibroblasts



Expression Levels of Selected CLEAR Network Genes After Treatment with Arimoclomol in Wild Type Fibroblasts



Original Swallow Domain Scoring Methodology

Original Swallow	Score
Normal, no dysphagia	0
Cough while eating	1
Intermittent dysphagia with liquids	+ 1
Intermittent dysphagia with solids	+ 1
Dysphagia with liquids	+ 2
Dysphagia with solids	+ 2
Nasogastric tube or gastric tube for supplemental feeding	4
Nasogastric tube or gastric tube feeding only	5